Contributions to Economics

Nezameddin Faghih
Amir Forouharfar *Editors*

Biopolitics and Shock Economy of COVID-19

Medical Perspectives and Socioeconomic Dynamics

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This book is dedicated to the following cherished philanthropists, devoted parents, grandparents, and great-grandparents, who served mankind and saved lives in difficult times of pandemics and wars in Estahban (Fars, Iran) and Neyriz (Fars, Iran), the lands of figs, saffron, pomegranates, walnuts, and almonds:

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An Introduction to Biopolitics and Shock Economy of COVID-19: Medical Perspectives and Socioeconomic Dynamics

Nezameddin Faghih and Amir Forouharfar

Since the causes of mortality are infinite,
which road, then, shall we bar?
A hundred windows and doors facing towards mordant death
are ever creaking as they are opened,
From greed for provision the ear of the covetous
does not hear the harsh creaking of those doors of death.
From the side of the body, pains are the noise of the door;
and from the side of enemies, maltreatment is the noise of the door.
My dear friend read for one moment the table of contents of Medicine
look at the flaming fire of diseases!
Through all those tumors there is a way into this house:
at every two steps there is a pit full of scorpions.
The people said, "O you company of impostors,
where is the evidence of knowledge of medicine and usefulness?
So that they compiled medical books.
and were relieving the body from pain.
Every part of you is an army of God.
in accord they are obedient to you now, not sincerely'.
Open the Medicine and read the chapter on diseases,
that you may see what is done by the army of the body.
The fine artifices of geometry or astronomy,
and the science of medicine and philosophy—
Which are connected only with this world
and have no way up to the Seventh Heaven
How shall the excellence of the art of medicine be made manifest
when there is no emaciated invalid?
So that they compiled medical books
and were relieving the body from pain.
What medicine are you? What are you? What is your name?

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To whom are you hurtful and for whom is your usefulness?"
Listen; come hither for the incurable disease!
We, one by one, are a medicine for the sick.
That such a medicine as this is suitable to such a desperate malady,
for the purpose of success
The usefulness of every external object is, indeed, internal:
it is latent, like the beneficial quality in medicines.
The people said, "O you company of impostors,
where is the evidence of knowledge of medicine and usefulness?
Open the Medicine and read the chapter on diseases,
that you may see what is done by the army of the body.
What medicine are you? What are you? What is your name?
To whom are you hurtful and for whom is your usefulness?"
When the Decree comes, the physician is made foolish,
and the medicine too loses its beneficial effect
Till he cleanses your humors with medicine,
how will the indisposition be removed? How will a cure be affected?
When your body falls ill it makes you seek medicine
and if it grows strong it makes you an outrageous devil.
(Rumi. 1207–1273iv, P. 195; iii, P. 171: iv, P. 82, 95; i, P. 204; iv, P. 81, 82; iii, P. 170; vi, P. 152,; iv, P. 181; iii, P. 171; iv, P. 51, 81; v,

112; vi, P. 148, 89)

Pandemics are large-scale phenomena which affect macro-economies and hence call for relevant biopolitics to mitigate the economic consequences and at least to help the economy bounce back to the previous economic balance. Macroeconomics deals with the large-scale economic factors of a state. Biopolitics is a broad political science term embracing the definitions of Rudolf Kjellén, Hans Reiter, Morley Roberts, Robert E. Kuttner, Michel Foucault, etc. for specific intentions, views, and perspectives. Thus, as Liesen and Walsh (2012, p. 2) put it, competing meanings of "biopolitics" are faced in political science. Rudolf Kjellén as a pioneer in this arena coined the term "biopolitics" in his two-volume work (in 1905) entitled "The Great Powers," and he developed and elaborated the term later in a 1916 book entitled *The State as a Form of Life*. However, due to Kjellén's organicist analogies, the biopolitical theory of the state can be considered as a form of "organicism" or "vitalism" in the contemporary biopolitics literature (Gunneflo, 2015, p.1). Later in Nazi Germany, or the German Reich, biopolitics was used with the racist connotations by Nazi ideologues. Moreover, the biopolitics of Morley Roberts in the same era was based on analogy. His biopolitics is metaphorical in a sense that he tries to draw an analogy between human society and the colony of insects with the organisms. He believed, "Whatever the groups, the laws of organic development which produce order, form, interdependence, and differentiation are everywhere the same" and he extended the analogy to the extent which he claimed "After what was said earlier on immunity, students of medicine will have no difficulty in thinking that sarcoma, or malignant revolt of various connective tissue elements, may be nearly matched by a revolt of the police" (Nature, 1938, p. 138). The biopolitics of Robert E. Kuttner as a biologist and white supremacist was also a racist approach to the application of the term. He defined his concept of biopolitics within a so-called scientific racism (see Jackson, 2005). In the late 1970s when the term biopolitics was first applied in the United States, it implied the advent of a subdiscipline for the incorporation of the life sciences theories and knowledge into the political and public studies. Before the mid-1990s, the term was adopted and used by postmodernist thinkers and theorists at the American Political Science Association's annual meeting after Foucault's works (Liesen & Walsh, 2012).

Straightforwardly, "biopolitics" is a term that refers to the intersection and mutual incorporation of life and politics. In literal terms, it signifies a form of politics that deals with life (Greek: bios)" (Laurence, 2016, p.1). There are two broad approaches to defining biopolitics: (1) naturalistic and (2) nonnaturalistic.

The first meaning was developed by scholars in the United States in the 1970s and seeks to use theories and data from the life sciences to achieve a more complete understanding of political behavior. This kind of "naturalistic" research begins from biological origins and factors and works outward in an effort to explain the causes of political behavior. For these scholars, biological life is understood as a foundation of politics. The second (and more prevalent) meaning took effect when Michel Foucault broke radically with this "naturalist" tradition by redefining the term in his writings and lectures in France in the late 1970s. For Foucault, life cannot be understood in terms of biological forces or determinants that exist outside of political processes. Instead, life must be understood as both an object and effect of political strategies and technologies. Biopolitics, he argues, refers to a historical transformation and development, beginning in the seventeenth century, whereby the sovereign right to seize, repress, and destroy life is complemented by a new form of power that aims to develop, optimize, order, and secure life. Foucault often uses the term biopower to denote this new form of productive power (Laurence, 2016, p. 1).

In general, Michel Foucault (1980) has had an implicitly metaphorical approach to the concept of power (e.g., he uses the expressions such as "mechanics of power," "wheels of power," "power skeleton," "a power with/without a bludgeon," etc., in his book *Power/Knowledge*. He introduces the concept of power to a broad arena from Truth to *Governmentality* – a term with positive connotations coined by him to reflect the concept of conducting the individuals' conduct through calculated means for the intention of increasing their well-being (see Li, 2007; Burchell et al., 1991). Foucault (1976, p. 93) assumes power as an omnipresent entity, "not because it has the privilege of consolidating everything under its invincible unity, but because it is produced from one moment to the next, at every point, or rather in every relation from one point to another. Power is everywhere; not because it embraces everything, but because it comes from everywhere." He attributed the characteristics "permanent," "repetitious," "inert," and "self-reproducing" to power; albeit on some occasions the attributions are controversial (e.g., he believed, "Power is not something that is acquired, seized, or shared, something that one holds on to or allows to slip away…. Power comes from below; that is, there is no binary and all-encompassing opposition between rulers and ruled at the root of power relations" (Foucault, 1976, p. 94); nevertheless, in contrary, power dynamics entail "the acquisition, maintenance, and loss of power" (Anderson & Brion, 2014, p. 67). Nonetheless, in his terminology, biopolitics is "a political rationality which takes the administration of life and populations as its subject: 'to ensure, sustain, and multiply life, to put this life in order'" (Adams, 2017, p. 1). Additionally, biopower in his writings and lectures implies "the way in which biopolitics is put to work in society and involves what Foucault describes as 'a very profound transformation of [the] mechanisms of power' of the Western classic age" (Adams, 2017, p. 1).

Concerning COVID-19, which is the underlying theme of the book chapters contributed to this volume, the application of the term biopolitics refers to the biopolitical governance practiced for the administration, betterment, and abatement of the pandemic in the public. The successful accomplishment of this biogovernance needed the exertion of biopower not exactly in the Foucauldian sense but as that sort of power which dealt with biologic issues and measures under the policy responses to COVID-19. During the pandemic, the biopower exercised by the governments or the supervisory bodies was an "emergency power." Emergency powers are exercised against public emergencies, and they "allow the government to introduce measures that may affect fundamental rights, such as the right to liberty. These measures can only be introduced in exceptional circumstances and should be temporary in nature" (Nice et al., 2021, p. 1). For instance, the nature of power, which was exercised by the British government to control COVID-19 based on the two acts, *Public Health (Control of Disease Act) 1984* and the new legislation, the *Coronavirus Act 2020*, was an emergency power in the biopolitical context, and hence the power begot from the abovementioned acts falls within our definition of biopower. Thus, the biopower originated from the UK *Coronavirus Act 2020* "… increases the powers of the government to restrict or prohibit events and gatherings and to close educational establishments beyond those set out in the Public Health (Control of Disease) Act 1984. Police and immigration officials will have the power to detain an individual who may be infectious" (Nice et al., 2021, p. 1).

Furthermore, the biopolitics which was emerged, molded, and exercised during the pandemic has profoundly justified the interventionist biopolicies and hence the exercise of biopower on the grounds that they are for the public good, although the policies have had numerous counter effects on the public life all over the world. However, "We are all statists now. Since the coronavirus pandemic struck and the global economy unraveled, we have looked to governments to mobilize medical resources, implement containment measures, and spend previously unimaginable sums to support workers and businesses. Out of these emergency policies could arise new institutions and ways of solving problems that will benefit us long after the pandemic" (Crabtree et al., 2020, p.1).

In sum, the term biopolitics has passed a four-stage metamorphosis from a broad metaphorical analogy (e.g., Rudolf Kjellén, Morley Roberts) to racist ethnic cleansing measures and policies (e.g., Hans Reiter) and white supremacy (e.g., Robert E. Kuttner, Eustace Mullins) and later to a more philosophical concept (e.g., Michel Foucault) to the more recent tangible biological policies exercised by the states for

Table 1 Connotation metamorphosis of the term *biopolitics*

Biopolitics		
Connotation	Epoch	Mainstream Authors/thinkers/users
Metaphorical	In the late 1900s to the 1920s	Rudolf Kjellén, Morley Roberts
Racist	1930s–1960s	Hans Reiter, Robert E. Kuttner
Philosophical	1970s–2010s	Michel Foucault
Biological	2020s	Post-COVID intelligentsia

Source: Authors' own work

the pandemic prevention, detecting, tracking, and controlling (Table 1). Our references to the biopolitics fall within the last category.

Furthermore, the COVID-19 economic shock was aggravated by the biopolitical measures employed against COVID-19 by the world governments such as social distancing, teleworking, movement restrictions, lockdowns, etc. There is not a consensus among the economists over a single definition of economic shock. However, an economic shock usually embraces four features:

(i) It should be *exogenous*; in other words, the shock must come from out of the economy. Nevertheless, there are some economists who do not accept this feature as a necessary feature for defining economic shock.
(ii) Economic shocks are *unexpected* and usually unpredictable.
(iii) The shocks are *large scale* embracing all or nearly all the economy.
(iv) They are *short-term* phenomena.

In respect to the COVID-19 pandemic, the subsequent economic shock consisted of three different shocks: (1) demand shock, (2) supply shock, and (3) financial shock (Triggs & Kharas, 2020). Thus, if the previous famous economic shocks targeted one of the above aspects, the demand or supply sides or the financial markets, COVID-19-originated economic shocks hit all the above. Therefore, this super economic shock needed much more elaboration which is addressed in this edited volume.

The book is divided into two parts and contains nine chapters (including this introductory chapter).

This chapter, as the introduction to the book, introduces the book and explains how this edited volume on the biopolitics and shock economy of COVID-19 crisis embraces a wide spectrum of topics such as shock economy; medical perspectives on COVID-19; application of geospatial technology; infectivity, immunity, and severity of the disease; as well as ontology of the disease emergence as important factors for adoption of relevant biopolitical measures, sociocultural obstacles, COVID-19-induced transaction costs, social support and resilience of inhabitants of marginalized areas, as well as business resilience factors, entrepreneurship, and digital transformation. Through each chapter of this book, the authors, with their expertise in the theme they picked, have attempted to unfold emerging aspects in the COVID-19 crisis which could benefit not only the academics but also the institutional, social, economic, developmental, and health policy-makers as well as the health practitioners on the ground. Thereafter, the book proceeds in two parts consisting of nine chapters.

Part I presents a medical and pandemic overview of COVID-19, in Chapters "Medical Perspective on COVID-19", "Advances in the Application of Geospatial Technology in the Mitigation of COVID-19 Pandemic", and "The Ontological Nature and Cause of COVID-19: A Philosophical Analysis".

Chapter "Medical Perspective on COVID-19" recalls that in December 2019, a series of acute respiratory illnesses were first reported in central China. Investigations have led to the identification of a novel coronavirus (2019-nCoV), subsequently designated as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), as the causative agent of the so-called coronavirus disease 2019 (COVID-19). Since its emergence, SARS-CoV-2 has spread rapidly across the globe, resulting in the current ongoing COVID-19 pandemic, which has claimed the lives of millions of people throughout the world and continues to do so. Beginning with a brief overview of different historical and contemporary theories of infectious diseases, this chapter moves on to review the most recent literature on the origin, structure, pathogenesis, host immune responses, viral evasion of the host immunity, and mutated variants of SARS-CoV-2. In addition, patients' clinical characteristics and risk factors, clinical trials, preventative measures, and the COVID-19 death toll among different countries are discussed. This chapter also overviews the utilization of various technologies in the battle against the pandemic, the impact of the pandemic on clinical research and trials, medical insurance, biomedical waste (BMW) generation and management, and the clinical lessons learned.

Chapter "Advances in the Application of Geospatial Technology in the Mitigation of COVID-19 Pandemic" explores geospatial technologies currently used by various researchers, industries, health professionals, etc. in the fight against the global pandemic of COVID-19. The use of dashboards is among the prominent innovative geospatial mapping technologies implemented by several bodies such as the Johns Hopkins University's Center for Systems Science and Engineering (JHU CSSE) dashboard, WHO dashboard, HealthMap dashboard, etc. Dashboards have been useful in providing information on the dynamics of the pandemic spread. The use of geospatial big data and Web map viewers has also gained much ground. The application of various statistical and epidemiological models and tools has equally been utilized to simulate the dynamics of the pandemic in new dimensions. Time series model forecast has played a major role in the modeling of medical facilities, while location/allocation modeling has contributed to resources management for best sites to situate testing centers, emergency units, medical centers, etc. ESRI industry has also developed a number of innovative solutions in the context of indoor assessment of facilities for the new normal, airport smart strategies and mobile tracking technologies, etc. Geospatial technology is critical in the fight against the pandemic, and it is imperative to state that efforts to maximize the technology should be advocated. The study provided limitations to the applications of geospatial technology and recommendation.

Chapter "The Ontological Nature and Cause of COVID-19: A Philosophical Analysis" investigates the ontological nature and cause of the coronavirus disease (COVID-19). The outbreak of the novel COVID-19, coupled with the fact that a global pandemic occurs virtually every century, has brought to the fore the need to interrogate the ontological nature and cause of the COVID-19 pandemic. There have been different conspiracy theories flying all over the globe about COVID-19 since its outbreak in Wuhan city of China and subsequent global spread. One matter of considerable public concern about the theories is the uncorroborated claim that the new coronavirus (SARS-COV-2) is manufactured in a laboratory at the Wuhan Institute of Virology as a biological weapon. This implies that the coronavirus is an artificial creation rather than a natural occurrence. Against this background, it is argued that the coronavirus is a natural phenomenon and that the resultant COVID-19, like other previous pandemics, is a privation of being. The study draws heavily on metaphysical works of Aristotle, Saint Augustine, and Thomas Aquinas to show that four types of cause, namely, material cause, formal cause, efficient cause, and final cause, are ontological components of every being in the natural world and that COVID-19 is not a being per se but rather a privation of being or good in a being. It is contended further that COVID-19 lacks a formal cause and thus it cannot exist in isolation from a being (a human person or an animal) that has a formal cause. COVID-19 and other pandemics originally occur when a being is corrupted or its good nature is deprived of. It is concluded that to forestall further pandemic outbreak, humanity must stop upsetting and disrupting the natural order of things by desisting from eating certain animals and birds that are unfit for human consumption, or eating foods contaminated by such animals and birds.

Part II considers the COVID-19 shock and socio-economy in Chapters "The Socio-Cultural and Economic Barriers of Self-Care Culture for COVID-19 Control in Developing Societies: The Case of Iran", "The COVID-19-Induced Transaction Cost Suggests Considerable Cost Effectiveness Resulting from the Prevalence of Universal Health Care in the United States", "Assessing the Social Support and Resilience of the Inhabitants of Marginalized Communities amid COVID-19 Pandemic in Iran: A Shiraz Metropolis Case Study", and "How the Pandemic Crisis May Affect Economic Systems: A Study on the Nexus Between COVID-19 and Entrepreneurial Activities".

Chapter "Digital Transformation: Prior to and Following the Pandemic" argues that COVID-19 has negatively affected businesses operations in addition to drastically threatening different ongoing organizational changes. Digital transformation has been considered as a unique way of improving the performance and business operations in the new digital world. However, the immediate shutdown caused by the pandemic and lack of preparation for implementing digital transformation influenced most industries. This chapter outlines the negative implications of COVID-19 on transferring to digital solutions as well as revealed prospects. In this regard, the outcomes of implementing digital transformation in several sectors are reviewed. Assessing these impacts addresses benefits and drawbacks associated with the digitalized solutions. The chapter highlights the beginning of the year 2020, announcement of the global pandemic, as an important timeline for evaluating contributions of published papers. Furthermore, it is emphasized that papers published following the epidemic in addition to considering the impacts should be included in the future research studies in this field.

Chapter "The Socio-Cultural and Economic Barriers of Self-Care Culture for COVID-19 Control in Developing Societies: The Case of Iran" considers that there are natural and unnatural problems for human beings. Communicable and incommunicable diseases are common issues in human life. The prevalence of COVID-19 since December 2019 is an ongoing and mysterious danger, and its control is a critical concern. According to the traits and dangerous consequences of COVID-19, self-care plays an inevitable role in its control. This chapter has reviewed the socio-cultural and economic barriers to self-care for COVID-19 control in developing societies with an emphasis on Iran. Using the documentary method, databases about concepts, research, theories, and economic, social, and cultural indexes were reviewed. The most databases used were PubMed., Magiran, Noormags, Google Scholar, Sid, Iran statistic Center, Trading Economics, and World Meters. Reviewing data on life expectancy, mortality, and other indexes among developed and less developed societies, the most barriers for developing societies such as Iran were introduced. Findings showed that the most important barriers are short-term (economic factors), medium-term (social factors), and long-term (cultural factors) barriers. In each time/subject period, two levels, micro and macro, are presented. The macroeconomic barriers are *Economic poverty*, economic recession, and inflation. The microeconomic barriers are malnutrition, lack of financial ability to use healthcare facilities, lack of living facilities, and the work time in epidemiological conditions. The macro-social barriers are social inequality, lack of attention to prevention, weakness of social organization, and family size in less developed areas, while the micro-social barriers are the weakness of education and socialization and unstable job conditions. The macro-cultural barriers are fate orientation, weakness of preventive insight, application of common beliefs, low social trust, social traps, and traditional habitus in health care, while the microcultural barriers are poverty of knowledge and living awareness, self-medication belief, self-healthy imagination, misunderstanding of disease risks, social indifference, and social irresponsibility. As a result, cultural factors are the most important barriers to the self-care culture for the control of pandemic diseases such as COVID-19.

Chapter "The COVID-19-Induced Transaction Cost Suggests Considerable Cost Effectiveness Resulting from the Prevalence of Universal Health Care in the United States" studies and models the US response to the COVID-19 pandemic from a transaction cost perspective, with the objective of considering the most efficient delivery of universal health care to the public. The neoclassical framing of production, price, and allocation does not consider the transaction costs resulting from the pandemic's broad effects on the entire economy. The intention of this study is to focus on transaction cost as a particular feature of cost-efficiency analyses. The study reveals the effect of pandemic conditions on transaction-specific healthcare assets. It considers the asset of registered nursing labor, specifically the changes in travel nurses' compensation during the period 2019 to 2020. This study finds that the doctrine of federal preemption instituting universal health care is economizing due to the lower transaction costs associated with the administrative control of transaction-specific assets and the advancement of collaboration between organizations. The COVID-19-induced transaction cost effects on travel nurse compensation reveal the extent to which the private healthcare system operates with implicit inefficiency. This study calculates a residual cost index using the US Bureau of Labor and Statistics and industry-sourced data.

Chapter "Assessing the Social Support and Resilience of the Inhabitants of Marginalized Communities amid COVID-19 Pandemic in Iran: A Shiraz Metropolis Case Study" argues that marginalized communities are extremely vulnerable to health, social, psychological, and economic consequences of the COVID-19 pandemic. Therefore, the aim of the present study is to investigate the relationship between resilience and provided social supports for the studied marginalized communities during the COVID-19 outbreak. This study was conducted by survey method. The study population belonged to the inhabitants of the suburbs of Shiraz (Iran), and people were selected from different neighborhoods by proportional cluster sampling. In order to collect data, a 67-item researcher-made questionnaire was used. Finally, results showed that among the dimensions of social support, the emotional and information support was above moderate, and the material support was at a moderate level. Thus, it can be assumed that the material support was insufficient to increase people's resilience, and it is necessary to make interventions to improve the situation. Measures to be taken to increase the level of social support in its various dimensions will strengthen and complement each other to increase the resilience of marginalized communities directly or indirectly. With regard to the information support, steps should be taken to increase people's awareness, besides a step to strengthen their self-worth through necessary training and the increase in awareness, which will in turn raise the level of emotional support. Therefore, people can strengthen capabilities for making decisions, solving problems, establishing effective relationships, as well as the abilities for self-awareness, empathy, and cope within emotions and stress, to be able to successfully do away with this crisis. Results of this study indicate that resilience can be increased through social support interventions. Strengthening the social support of the inhabitants of the marginalized areas as a method to increase their resilience seems to be an important strategy in controlling the pandemic. Assessing the social support and resilience of the inhabitants of marginalized communities amid COVID-19 pandemic allows us to design more targeted support programs for them during confrontation and virus infections.

Chapter "How the Pandemic Crisis May Affect Economic Systems: A Study on the Nexus Between COVID-19 and Entrepreneurial Activities" discusses that the world has experienced several great crises that have had a significant economic impact. The global crisis of the COVID-19 pandemic experienced worldwide has affected economies and production chains, harming millions of businesses and entrepreneurs. Economic resilience, an ability to adapt to change and responsiveness to exogenous shocks, is a scientific strategy in the business and economy sectors to analyze and deal with these crises. Undoubtedly, entrepreneurship is one of the important factors influencing the economy as a striking pillar of economic resilience. This study tries to identify factors for enhancing economic resilience that will help countries to be more viable when encountering exogenous or indigenous crises.

It is hoped that this book will appeal to a wide range of global audiences and academics and can provide a useful reference work on the shock economy and biopolitics of COVID-19. Academics, scholars, and researchers, from a wide spectrum of disciplines and through experienced approaches, have contributed chapters and addressed the most recent issues on COVID-19 crisis. Further, it is also hoped that the book can provide creative discussions and align with scholarly and intellectual interests in understanding current trends and mainstream research on the biopolitics and economic shocks of COVID-19 and hence add insight for better responses to changing and emerging future consequences and impacts.

It should also be noted that the facts, opinions, information, views, conclusions, findings, comments, strategies, and positions expressed by the contributors and authors of the chapters are theirs alone and do not necessarily reflect the opinions, views, strategies, or positions of the editors of this edited volume and do not constitute approval or endorsement by the editors. The contributors and authors are responsible for their citation of sources and the accuracy of their bibliographies and references. The editors of this volume cannot be held responsible for any errors or consequences arising from the use of the information contained in the chapters or for any lacks or possible violations of the rights of third parties. While every effort is made by the editors to see that no misleading or inaccurate data, statements, or opinions appear in this volume, the data, their use, interpretations, and the opinions appearing in the chapters are the sole responsibility of the contributors and authors concerned. The editors accept no liability whatsoever for the consequences of any such misleading or inaccurate data, opinion, information, or statements.

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Part I
Medical and Pandemic Overview of COVID-19

Medical Perspective on COVID-19

Pegah Hosseini-Nezhad, Sara Hosseini-Nezhad, and Ahmad Hosseini-Nezhad

Introduction

In recent decades, coronaviruses (CoVs) have been responsible for major worldwide outbreaks, including the 2002 severe acute respiratory syndrome (SARS) and the 2012 Middle East respiratory syndrome (MERS) (Liu et al., 2020a). In December 2019, a strain of CoV containing a not-previously-known genome sequence was first detected in Wuhan City, Hubei Province of China, and was hence named the 2019-nCoV; however, it was later called SARS-CoV-2 (Dhama et al., 2020). Although SARS-CoV-2 is considered to be less pathogenic, compared to the previously known MERS-CoV or SARS-CoV, it is more transmissible and, as a result, has led to the current ongoing COVID-19 pandemic (Dhama et al., 2020). In the chapter to follow, we begin with some historical and epidemiological information to call attention to the past understandings and theories of infectious diseases. Further, we review the most recent literature on various human coronaviruses (hCoVs), including SARS-CoV-2 and its origin, structure, mechanisms of cell entry, host immune evasion, mutations, and the emerged variants, as well as the COVID-19 risk factors, signs, and symptoms, clinical trials, preventative measures (e.g., quarantine and social distancing), the death toll, and the role of innovative technologies (e.g., artificial intelligence, etc.) in controlling the pandemic.

Moreover, we discuss COVID-19 impact on biomedical wastes (BMWs) generation and management, medical insurance, and research, among others. We ultimately end the chapter by highlighting some of the clinical lessons learned from the pandemic. We have used several databases, such as PubMed, Google Scholar, ResearchGate, and Cochrane Library, to collect the relevant literature, using the

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search terms “SARS-CoV-2 pathogenesis,” “SARS-CoV-2 origin,” “SARS-CoV-2 variants,” “COVID-19 and genetic polymorphism,” as well as “COVID-19 risk factors” and “COVID-19 clinical symptoms,” “COVID-19 radiological findings,” “COVID-19 histopathological features,” and so forth. It is noteworthy to mention that COVID-19 and its causative virus are new and unknown phenomena, and numerous ongoing research are being conducted across the globe, which will contribute to the current understanding. As a result, this chapter is only a glimpse of the medical perspectives of COVID-19 and is not representative of all related published papers.

Historical Views and Theories of Infectious Diseases

Since the beginning of time, humans have always coexisted with diseases, which have sparked creative thinking in disease prevention and treatment (Tulchinsky & Varavikova, 2014a). Childhood fever has been the most serious issue afflicting humans, and in the last 10,000 years, mortality by the age of 15 has been about 50%, with fever being by far the most common cause of death, killing far more people than war and famine (Casanova & Abel, 2013). Throughout history, several theories have been postulated in order to explain the etiologies of infectious diseases. In order to explain phenomena such as disease outbreak that lacked a clear scientific or psychological explanation, people in pre-germ theory societies often invoked the presence of supernatural forces, energies, power, or spirits in order to explain phenomena such as disease outbreak that lacked a clear scientific or psychological explanation (Bastian et al., 2019). The primitive mystical or religious theories stated that diseases are either brought about by demonic spirits or delivered by the gods as a way of punishment for committed sins and thus must be subdued via exorcism (Karamanou et al., 2012). For instance, in Ancient Rome, Febris (fever) was the goddess who protected people against fever and malaria and had three temples located in Palatine Hill, Vicus Longus, and Sacra, and demonology was highly valued in ancient Persia (Karamanou et al., 2012). Using mystical or religious rituals, as well as herbal remedies, shamans or witch doctors sought to cure maladies (Tulchinsky & Varavikova, 2014a). The term “moral vitalism” is given by Bastian et al. (2019) to describe such beliefs in contaminating and contagious evil forces, and moral vitalists believed that individuals are susceptible to being possessed (infected) by evil spirits and that these forces are communicable (transmitted) among people (Bastian et al., 2019).

The pre-Socratic philosophers from the sixth century BC heralded the beginning of an era in science during which it was claimed that the environment had a significant impact on health and illness (Karamanou et al., 2012). The Hippocrates’ treatise *Airs, Waters, Places* by Hippocrates linked a variety of symptoms and diseases, including malaria, catarrh, and diarrhea to geographical and meteorological conditions, such as climate changes impact on stagnant water or marshy area, which eventually evolved further into the “miasma theory” of contagious disease

(Karamanou et al., 2012). According to this theory, diseases are produced by the noxious vapor from decaying organic matter that contaminates the air, and in order to prevent such infectious diseases, sanitary measures such as clearing the streets of trash, sewage, animal corpses, and wastes were required (Tulchinsky & Varavikova, 2014a). Traditional Persian Medicine described flu-like respiratory pandemics using the terms, such as *háwāy-e vábāī* (polluted air) or "polluted wind," from which numerous infectious diseases (e.g., smallpox, typhoid, plague, and respiratory illnesses), and their associated symptoms (i.e., fever, dyspnea, palpitations, and syncope), as well as high death rate, would result; thus, in order to control such pandemics, Persian Medicine recommended distancing oneself from the pandemic area and practicing self-quarantine (Iranzadasl et al., 2021). Avicenna, the Persian medicine scholar, acknowledged the contagiousness of tuberculosis (TB), the transmission of illnesses via water and soil, and the connection between psychology and health (Hajar, 2013), and in his book, *The Canon of Medicine*, he uses the word vábā (a term for cholera in modern medicine) to refer to the pandemic spread of any diseases in general (Iranzadasl et al., 2021). During the sixteenth century, the "contagious theory" of infectious diseases was postulated by Girolamo Fracastoro, which stated that illnesses are spread by contaminated fomites, such as clothing that have come into contact with the infected individual, or by transmissible chemicals (i.e., not living microorganisms) evaporating and diffusing through the atmosphere (i.e., seed-like entities, seminaria, or germs); each condition had its own distinct germ multiplying in host's tissue producing disease by chemical putrefactive changes, and the transmission of certain diseases, such as syphilis and gonorrhea, was only possible through direct close contact, while others such as TB and smallpox are capable of traveling through air and be transmitted (Karamanou et al., 2012). Antonie van Leeuwenhoek's invention of the microscope in 1676 enabled the first visual observation, description, and discovery of "little animals"—bacteria and protozoa (Tulchinsky & Varavikova, 2014a).

Prior to the clinical-pathological paradigm in Parisian hospitals during the French Revolution, physicians struggled to come up with precise descriptions and a suitable nosology for the various types of fever they encountered, and any early accounts failed to address the issue of whether fever and disease were intrinsic or extrinsic (Casanova & Abel, 2013). Later scientists such as Antoine Lavoisier, François Magendie, and Claude Bernard opposed vitalism theory by stating that laws of physics apply to all living organisms and that any alteration in physiology brings about the diseases, and that diseases including fever are intrinsic; however, the internal environment—"milieu intérieur"—of living organisms protect them against environmental changes (Casanova & Abel, 2013). Moreover, work by other scientists, such as Semmelweis and Lister, elucidated the mechanisms these microorganisms spread and further enhanced the science of public health and preventative medicine (Ryan, 2004); however, despite their excellent findings, they were unable to convince people that fevers were transmissible (Casanova & Abel, 2013).

The breakthrough came in around 1870 when the French scientist Louis Pasteur, who lost three of his children to fever, first postulated the "germ theory" (Casanova & Abel, 2013), which states that living microorganisms are the etiology of infectious diseases (Karamanou et al., 2012). German scientist Robert Koch (1843–1910) was the one who further expanded the germ theory by claiming that there exists a specific microorganism for every infection, and this was the beginning of the modern concept of disease transmission (Karamanou et al., 2012). Koch, together with Loeffler (1852–1915), described the "Koch postulate," which explains the relationship between bacteria and diseases by stating that a diseased person must have a higher number of the infectious agent compared to non-diseased ones; such agents can be isolated and grown in culture; healthy individuals must lack such specific agent; microorganism introduction and inoculation elicit the same disease in healthy people, from whom the same microorganism can be re-cultured and re-isolated (Karamanou et al., 2012). During the twentieth century, more details were discovered regarding the structure, physiology, genetics, and molecular basis of different microorganisms, including bacteria, fungi, parasites, and, eventually, viruses, leading to the development of antimicrobial medication and the subsequent emergence of antimicrobial resistance among pathogens (Ryan, 2004). However, the fundamental conundrum in the field of infectious disease is the enormous clinical variability among individuals throughout the course of an infection (Casanova & Abel, 2013). The germ theory failed to explain why microbes predominantly cause asymptomatic infections and why there is interindividual variability of clinical presentation and outcome, ranging from asymptomatic, carriers, symptomatic, to fatal (Casanova & Abel, 2013). This led to the emergence of four other complementary and overlapping theories, including immunological, microbiological, and genetic, among others (Casanova & Abel, 2013). Previously, using attenuated microbes to immunize children against cholera and anthrax, Louis Pasteur prevented such infections, which subsequently resulted in the implicit idea that previous natural infection by a less virulent pathogen or lower quantity of the same pathogen would result in natural acquired immunity, which would protect or help the afflicted person survive against future infection (Casanova & Abel, 2013). Pasteur's vaccine discovery, together with three other groundbreaking discoveries, including antigen-specific antibody (Ab) responses,[1] serological diagnosis,[2] and sero-therapy,[3] by Paul Ehrlich, Fernand Widal, and Charles Richet/Emil von Behring, respectively, were the foundation of the immunological theory of infectious diseases. However, while these observations were able to account for interindividual variability partially, they were unable to explain the so- called infection enigma, that is, why the most virulent pathogen can be harmless to some individuals, yet the least virulent ones can be lethal to others (Casanova & Abel, 2020). For instance, findings by Charles Nicolle's

[1] Upon microbe (antigen) entry into the host body, host immune cells are stimulated to produce antibodies (Abs), such as immunoglobulin M and/or G that are specific to the corresponding antigen (Clem, 2011).

[2] Detection of antigen-specific Abs in patient serum, using various serological immunoassays (Vainionpää & Leinikki, 2008).

[3] Serotherapy is a type of passive immunization against numerous infectious diseases, using purified serum of infected or vaccinated individuals that contain specific Abs against the disease in question (Hifumi et al., 2017).

that some infected individuals with typhus pathogen may remain healthy and asymptomatic, yet still able to transmit the disease (Casanova & Abel, 2013), or in the infamous Lübeck disaster, only 72 of the 251 neonates died after being accidentally given a vaccine contaminated with highly virulent TB bacteria (Fox et al., 2016). These could be explained in part by the microbiological and immunological theories, which take into account microbial and human host variability. For example, microorganism's inherited[4] or acquired virulence,[5] and route of entry, or the host inherited or acquired immunodeficiencies, all of which alter infection outcome (Casanova & Abel, 2020). The pathogenicity of a microorganism is measured by its virulence, which refers to the organism's capacity to produce a disease and is influenced by a variety of parameters, including the quantity of microorganism present, route of entry into the host body, host immune system response, as well as pathogen virulence factors (Sharma et al., 2016). These virulence factors enable microorganism to enter the host body, evade host defense mechanisms, and produce disease (Sharma et al., 2016). During the period 1920–1949, human geneticists came to the conclusion that an individual's genetic makeup has a significant impact on his or her susceptibility and resistance to an infectious disease. This was the beginning of the germline genetic theory of infectious diseases, which was developed on the basis of studies on TB infection in twins (Casanova & Abel, 2013), that found the concordance of certain infections is much higher in monozygotic twins than in dizygotic twins[6] (Casanova & Abel, 2018). In addition, a simple or complex pattern of genes inheritance may result in susceptibility or resistance to certain illnesses. For example, the one infection-multiple genes phenomena (Casanova & Abel, 2007) describes that a single gene mutation (Mendelian traits) will produce rare primary immunodeficiency, which is often linked with numerous and recurring infections caused by weakly virulent opportunistic microorganisms (Picard et al., 2006). On the other hand, the one infection-multiple genes refers to the polygenic inheritance of several susceptibility genes, resulting in common infections (Casanova & Abel, 2007). For instance, multigene mutations of membrane attack complex (MAC) of complement pathways of the innate immunity, and IL-12- and IL-23-dependent interferon-gamma (IFN-γ)-mediated pathways, will predispose individuals to recurrent invasive bacterial infections by Neisseria species (e.g., meningitis by Neisseria meningitidis), and weakly virulent mycobacteria or *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) vaccines, respectively (Picard et al., 2006). Similarly, X-linked recessive lymphoproliferative disease (XLP) due to mutations of genes

[4] For example, the production of new strains of influenza virus due to genetic drift and the drastic genetic shift are responsible for the seasonal and pandemic influenza, respectively (Casanova & Abel, 2020).

[5] Antimicrobial substances can select for and result in the emergence of new strains of microbe that are resistance to antimicrobial agents (Casanova & Abel, 2020).

[6] In contrast to monozygotic twins, who are genetically identical, dizygotic twins are genetically distinct in that they only share approximately about half of their genetic material (Burgner et al., 2006).

responsible for natural killer (NK) and CD8+ cytotoxic[7] activation pathways will increase susceptibility to Epstein-Barr virus infection (Picard et al., 2006). In contrast, resistance to human immunodeficiency virus-1 (HIV-1) infection is induced by mutations in the chemokine receptor (CCR5) (Picard et al., 2006). It was not until the early 1950s that the study of human genetics of infectious diseases transitioned into the current molecular and cellular era (Casanova & Abel, 2013).

The "major histocompatibility complex" (MHC) genes were discovered in the 1930s in the context of posttransplantation tissue rejection; however, it was not until many decades later that the function of proteins encoded by MHC genes, in the adaptive and innate immune responses, was recognized (Mak et al., 2014) (Blackwell et al., 2009). Inherited in a Mendelian fashion, the human MHC is also called human leukocyte antigen (HLA) (Choo, 2007), with loci including MHC-I (HLA-A, -B, -C, -E, -F, and -G), II (HLA-DR, -DQ, -DM, and -DP), and III (tumor necrosis factor (TNF), complement factors C2 and C4b) (Blackwell et al., 2009). HLA genes are known to be the highest polymorphic human genes, especially at the antigen-binding site, thus altering the binding specificity to antigens (Choo, 2007). These polymorphisms and variants are believed to be evolutionary selected in order to present antigens of the most prevalent infectious pathogen in various geographic regions (Choo, 2007). MHC-I, located on almost all nucleated cells, facilitates innate and adaptive immune response against intracellular pathogens, such as viruses (Blackwell et al., 2009). On the other hand, MHC-II is expressed on antigen presenting cells (APC) (e.g., B-lymphocytes, dendritic cells (DC), macrophages, etc.) and is primarily engaged in defense against extracellular microbes, including bacteria and parasites (Abbas et al., 2015). Furthermore, due to their involvement in both the innate and adaptive immune responses, human HLA alleles play critical roles in host susceptibility to autoimmune disorders, diabetes, ischemic heart disease, as well as a wide range of infections (Blackwell et al., 2009) and the severity of such infections (Naemi et al., 2021). For instance, individuals with heterozygous HLA-I alleles are less likely to acquire AIDS following HIV infection and thus have lower mortality, whereas those with HLA-II alleles heterozygosity have a greater chance of clearing and overcoming hepatitis B virus infection (Blackwell et al., 2009).

Epidemiology

The occurrence spectrum of an infectious disease in a population can be described using several terms, including sporadic, endemic, epidemic, or pandemic. A "sporadic" disease occurs randomly and at irregular times (Straif-Bourgeois et al., 2014). Hippocrates was the first to use the terms "epidemic" and "endemic" (Swaroop,

[7] NK cells and CD8+ T cells, components of innate and adaptive immune systems, respectively, each have distinct mechanisms to recognize and kill infected cells (Rosenberg & Huang, 2018).

Table 1 Major pandemics throughout history

Pandemic name (time)	Death number	References
Plague of Galen (165–180)	5m	LePan (2020)
Japanese Smallpox (735–737)	1m	
Plague of Justinian (541–542)	30–50m	
Black Death (1347–1351)	200m	
New World Smallpox (1520–onward)	56m	
Italian Plague (1629–1631)	1m	
Cholera Pandemics (1817–1923)	1m+	
Third Plague (1885)	12m	
Russian Flu (1889–1890)	1m	
Spanish Flu (1918–1919)	40–50	
Asian Flu (1957–1958)	1.1m	
Hon Kong Flu (1968–1970)	1m	
HIV/AIDS (1981–present)	25m	
Swine Flu (2009–2010)	200,000	
SARS (2002–2003)	770	
MERS (2015–present)	850	
COVID-19 (2019–present)	4,777,503 as of October 1, 2021	WHO (2021a)

Authors' Own Table
Abbreviations: *HIV/AIDS* human immunodeficiency virus/acquired immunodeficiency syndrome, *SARS* severe acute respiratory syndrome, *MERS* Middle East respiratory syndrome, *m* million

1957). "Endemic" either refers to an area where a disease is common ("endemic area") or to a disease that is common and that exists at a constant rate among certain populations ("endemic disease") (Swaroop, 1957). "Epidemic" is used when a disease occurs at a higher rate than is typically expected in a specific area, compared to the previously observed baseline level, and if the disease spreads to several countries affecting a large number of people worldwide, it is referred to as a pandemic (Tulchinsky & Varavikova, 2014b). Several major pandemics have occurred throughout history (Table 1), killing millions worldwide (LePan, 2020). The recent COVID-19 pandemic, which started as an epidemic in Wuhan city, China, in December 2019 (Khafaie & Rahim, 2020), was declared a public health global emergency on January 31, 2020, and later a global pandemic on March 11, 2020, by the World Health Organization (WHO) (Dhama et al., 2020). As of October 01, 2021, the COVID-19 pandemic has affected 233,503,524 individuals and killed 4,777,503 people, worldwide (WHO, 2021a).

Human Coronaviruses (hCoVs)

Coronaviruses (CoVs) are enveloped non-segmented positive single-stranded ribonucleic acid (+ssRNA) viruses, which contain the largest genome among RNA viruses and are surrounded by crown-like surface projections under the electron microscope (EM) (Ye et al., 2020). They belong to the Coronaviridae family, which is divided into the subfamily Coronavirinae, which is in turn subdivided into four

CoV genera, alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV (Shors, 2021). Alpha and beta-CoVs are known to infect mammals (including bats, humans, etc.), while gamma and delta-CoVs infect birds and mammals (Shors, 2021). There are seven known hCoVs up until now, two in the alpha-CoV (HCoV-229E and HCoV-NL63) and five in the beta-CoV genera (HCoV-OC43, HCoV-HKU1, SARS-CoV, MERS-CoV, and SARS-CoV-2) (Ye et al., 2020). The low-pathogenic hCoVs predominantly cause mild (except in infants, elderly, and immunocompromised patients) upper respiratory tract (URT) infections (i.e., the common cold), while the highly pathogenic hCoVs (SARS-CoV, MERS, and SARS-CoV-2) cause lower respiratory tract (LRT) infections (i.e., pneumonia), as well as gastroenteritis, nephritis, hepatitis, etc. (Shors, 2021). Interestingly, for thousands of years, CoVs have been known to be transmitted from species to species, allowing for the emergence of pathogenic hCoVs (Ye et al., 2020). The RNA recombination[8] is extremely common among various strains of CoVs, which results in host ranges being expanded, and new CoV with higher pathogenesis and virulence being emerged (Wang et al., 2021a). For instance, this may occur if species carrying distinct CoVs come into close contact and exchange their viruses, and SARS-CoV-2 might have emerged during such occurrences (Singh & Yi, 2021).

SARS-CoV-2 Virion Structure

The spherical or ellipsoid SARS-CoV-2 virion seen under the EM is approximately 70–110 nm (Menter et al., 2020). It contains 4 structural glycoproteins, spike (S), membrane (M), nucleocapsid (N), and envelope (E), as well as 9 accessory proteins and 16 nonstructural proteins (NSPs); the E and M glycoprotein make up the viral envelope, while the N-glycoprotein is bound to viral RNA genome (Al-Horani et al., 2020). The S-glycoprotein is composed of two subunits, S1 (the receptor-binding fragment) and S2 (the fusion fragment) (Zhang et al., 2021). S1 is composed of four domains, including N-terminal domain (NTD), receptor-binding domain (RBD), and C-terminal domains (CTD1 and CTD2), while S2 is made up of fusion peptide (FP), fusion-peptide proximal region (FPPR), heptad repeat 1 (HR1), central helix (CH), connector domain (CD), heptad repeat 2 (HR2), transmembrane segment (TM), and the cytoplasmic tail (CT) (Zhang et al., 2021). The S glycoprotein is a trimer attached to the viral membrane by its transmembrane fragment, and its apex is composed of three RBDs, forming *up* and *down* conformations indicating receptor-accessible and or receptor-inaccessible states, respectively (Zhang et al., 2021). The surface of the spike protein is heavily covered by N-linked glycan molecules derived from the host cells (Watanabe et al., 2020), and it is the S-glycoprotein

[8] Recombination refers to the transfer genetic materials, as well as harmful traits between same virus, but different strains, which allows for the emergence of a novel virus that the host has never encountered or acquired immunity against have not previously been encountered by the host population (Gibson et al., 2015).

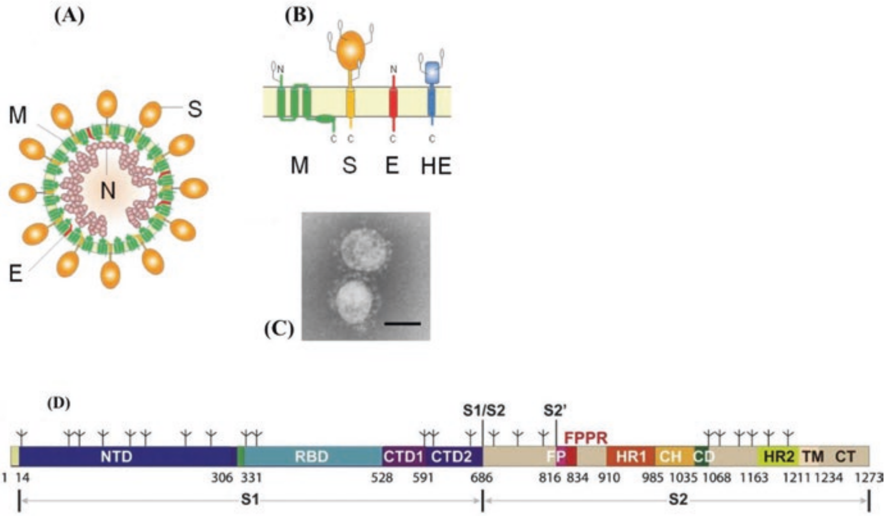

Fig. 1 Schematic diagram and electron microscopic image of coronaviruses (CoV), such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). (**a**) Virion structure of coronaviruses (CoV), such as SARS-CoV-2, which contains four structural glycoproteins, including spike (S), membrane (M), nucleocapsid (N), envelope (E). The viral positive single-stranded ribonucleic acid (+ssRNA) is associated with N-glycoproteins. (**b**) The four envelope structural glycoproteins and their topology (**c**) CoV (e.g., SARS-CoV-2) and the S-glycoprotein crown-like surface projections under the electron microscope. (**d**) The S-glycoprotein is composed of S_1 and S_2 subunits; S_1 is made up of four domains, N-terminal domain (NTD), receptor-binding-domain (RBD), and two C-terminal domains (CTDs), while S_2 is made up of fusion peptide (FP), fusion-peptide proximal region (FPPR), heptad repeat-1 (HR1), central helix (CH), connector domain (CD), heptad repeat-2 (HR2), transmembrane (TM), and the cytoplasmic tail (CT) domains. The S_1/S_2–S2′ is the cleavage site for viral entry into host cell. The surface of the spike protein is heavily covered by N-linked glycan molecules (tree-like structures) derived from the host cells and protrude from the viral envelope giving each virion a crown-like appearance under the EM. *Note*: SARS-CoV-2 lack the hemagglutinin-esterase (HE), which is present in some Beta-CoVs. (*Sources*: (**a**–**c**) Ujike and Taguchi (2015); (**d**) Zhang et al. (2021))

protruding from the viral envelope that gives each virion a crown-like appearance (corona—Latin for crown), and hence the name coronavirus (Sahu et al., 2021). Figure 1 shows the *Schematic diagram and electron microscopic image of coronaviruses (CoV), such as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).*

Viral Entry

The spike glycoprotein recognizes the angiotensin-converting enzyme-2 receptor (ACE2-R), which is expressed on various host cell membranes (Alanagreh et al., 2020). According to one research, small intestine, testicular, renal, cardiac, thyroid, and adipose cells had the greatest levels of ACE2 expression, whereas the blood, spleen, bone marrow, brain, muscular, and vascular endothelial cells had the lowest levels of ACE2 expression. On the other hand, cells other tissues, such liver, colon, bladder, and suprarenal gland were shown express moderate level of ACE2-R (Li et al., 2020b). Interestingly, in spite of the fact that lung inflammation is the most common symptom in COVID-19 patients, ACE2-R was found to be moderately expressed in pulmonary tissues (Li et al., 2020b).

Viral membrane and host cell membrane fusion occur upon binding of the S1-RBD to ACE2-R, followed by the conformational changes in the S2 subunit (Xia et al., 2020). Viral entry requires S-protein cleavage and activation (i.e., priming) at S1/S2 region, which occurs through two different pathways, namely, the direct fusion or the endocytotic entry pathway. In the direct fusion pathway, the priming occurs by viral use of the host transmembrane protease serine 2 (TMPRSS2) and/or furin, while the clathrin-mediated endocytosis takes place intracytoplasmically and by the action of furin and later cathepsin B and L in the acidic environment of endolysosome (Al-Horani et al., 2020). Both of these pathways result in the intracytoplasmic release of the viral RNA, followed by genomic replication, translation, and the subsequent release of new virions (Al-Horani et al., 2020). These two pathways are shown in Fig. 2. The presence of furin-cleavage site leads to a more

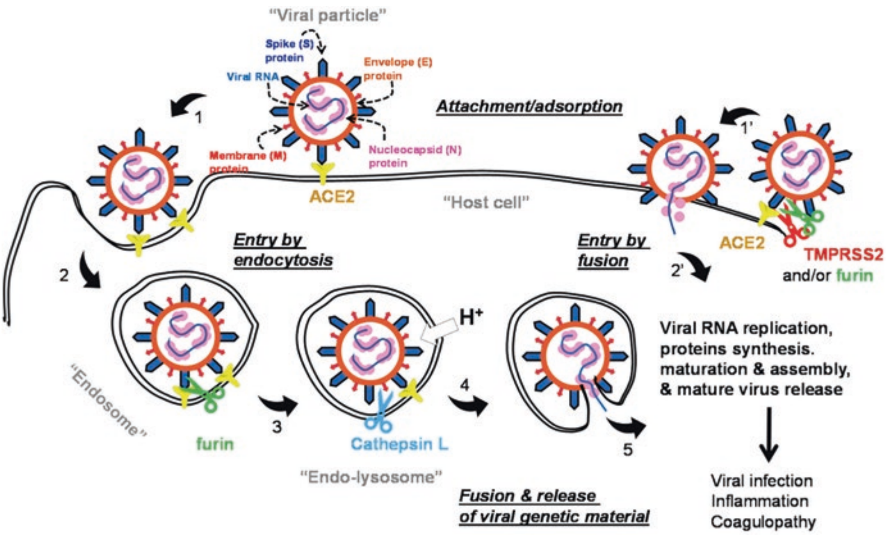

Fig. 2 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cell entry pathways. *Notes*: SARS-CoV-2 host cell entry occurs via two pathways, endocytosis or direct fusion, upon binding of viral spike (S) protein to host cell angiotensin-converting enzyme 2 (ACE2) receptors. Both pathways result in intracytoplasmic viral genome release (2′ and 5). The endocytosis pathway is mediated by furin-induced spike cleavage and subsequent cathepsin L or B (not shown) and acidic (H+) endolysosome action (1–4), while direct fusion is mediated by host transmembrane protease serine (TMPRSS2) and/or furin (1′), leading to spike cleavage. (*Modified from*: Al-Horani et al. (2020))

effective viral entry into human cells, which may account for the increased infectivity of SARS-CoV-2 (Kaina, 2021). Recently, it is revealed that viral entry can also occur when the already-cleaved SARS-CoV-2 at the furin cleavage site binds neuropilin-1 (NRP1) on olfactory endothelial and epithelial cells (Cantuti-Castelvetri et al., 2020). Another study reported a new possible mode of entry via high-density lipoprotein (HDL) scavenger receptor B type 1 (SR-B1) expressed on cells of LRT, as well as retina, testis, ovaries, metabolic organs, and other extrapulmonary organs, and that the co-expression of ACE2-R and SR-B1 makes these cells more susceptible to SARS-CoV-2 infection (Wei et al., 2020).

Life Cycle

Viruses are obligate intracellular microorganisms, and in order to translate, replicate, and assemble into new virions, they must use host cell machinery (Banerjee et al., 2020) and thus halt the host cell protein synthesis (Lapointe et al., 2021). SARS-CoV-2 has an unusually large genome (~29.0–30.2 kb) (Al-Horani et al., 2020), composed of six open reading frames (ORF); at the 5′-end is the ORF1a-ORF1b region which makes up two-thirds of the genome, while the other one-third of the genome is at the 3′-end, containing the remaining ORFs (Alanagreh et al., 2020). Upon SARS-CoV-2 entry and viral RNA release into the host cell cytoplasm, the ORF1a-ORF1b regions encode two polypeptides (pp1a, pp1ab), which are further cleaved by viral proteinase (i.e., Papain-like protease [PL-pro aka NSP3] and chymotrypsin-like proteinase [3CL pro aka NSP5]) into a total of 16 nonstructural proteins (NSP1-NSP16) (Sahu et al., 2021). Other ORF regions encode viral accessory proteins, such as ORF3a, 6, 7a, 7b, 8, and 10, as well as the structural glycoproteins (Majumdar & Niyogi, 2020). The viral RNA and the N-protein are synthesized and associated together in the host cell cytoplasm, and the nucleocapsid is then assembled with the M, E, and S proteins and bud into RER-Golgi lumen, forming mature virions which are eventually released from the host cell (Patocka et al., 2021). Figures 3 and 4 represent SARS-CoV-2 genome replication and life cycle, respectively.

Transmission Mode

Viruses causing respiratory tract infections are mainly transmitted via direct physical contact, indirect fomites, droplets, and/or airborne (Leung, 2021). Traditionally, droplets were identified as being too large (i.e., larger than 5 μm) to remain in the air and thus unable to traverse distances greater than 1 m, thus requiring close proximal contact between the infected carrier and the susceptible host (Fennelly, 2020). In contrast, the small airborne agents (usually less than 5 μm) would travel distances greater than 1 m and maintain their infectivity and virulence while suspended in the

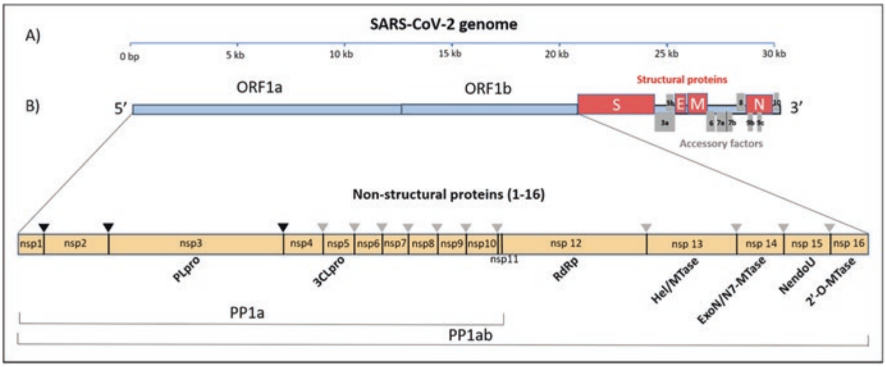

Fig. 3 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) genome replication. *Notes*: (**A**) SARS-CoV-2 genome (~30 kb) (**B**) The genome contains the 5′-end $ORF1_a$ and $ORF1_b$ regions, encoding two polypeptide (pp1a, pp1ab) that are further cleaved into nonstructural proteins (nsp1–nsp16) by papain-like protease (PLpro aka. nsp3) and chymotrypsin-like proteinase (3CLpro aka. nsp5) (cleavage sites are shown with black/grey triangles), and the 3′-end encoding the structural glycoproteins, spike (S), envelope (E), memberane (M), nucleocapsid (N) (red), and accessory proteins, 3a-10 (gray). *Abbreviations*: RdRp, RNA-dependent RNA polymerase (aka. nsp12); Hel/MTase, helicase and RNA ATPase (aka. nsp13); ExoN/N7-MTase, exonuclease methyl transferase (aka. nsp14); NendoU, endoribonuclease (aka. nsp15); 2′-O-MTase, 2′-O-methyl transferase (aka. nsp16). (*Sources*: Romano et al. (2020))

air (Fennelly, 2020). Originally, the person-to-person transmission of SARS-CoV-2 was thought to be impossible (Kaina, 2021). It was later shown to have the ability to be transmitted by direct contact and large droplets but was subsequently discovered to have the potential for airborne transmission (Patel et al., 2020). The airborne transmission was especially reported in places with ventilation-induced airflow (Tellier et al., 2019) or during procedures like endotracheal intubation, bronchoscopy, and manual ventilation (Jayaweera et al., 2020).

The reproduction number (R0), defined as the number of newly infected cases produced by each infected individual, is used to determine the transmissibility of a virus, which for SARS-CoV-2 was first estimated by the WHO to be between 1.4 and 2.5 (Rahman et al., 2020a). Other values of R0 have been reported, ranging from 2.2 to 6.47, especially in the initial phase of the pandemic (Shaw & Kennedy, 2021). A value of one or less for R0 suggests that the total number of new infections is gradually declining, and the pandemic will ultimately resolve; however, R0 greater than one implies that the virus is spreading rapidly, and more public health measures are required to limit its transmission (Rahman et al., 2020a). Moreover, using different R0 values from several countries (Brazil, Japan, Iran, Italy, and South Korea), Rahman et al. (2020a) estimated the mean R0 for SARS-CoV-2 to be 2.71.

There is, however, significant variability in the transmissibility of the virus. One observed that 69% of infected individuals do not infect other people, while 15–24% of cases accounted for 80% of all SARS-CoV-2 transmission (Adam et al., 2020).

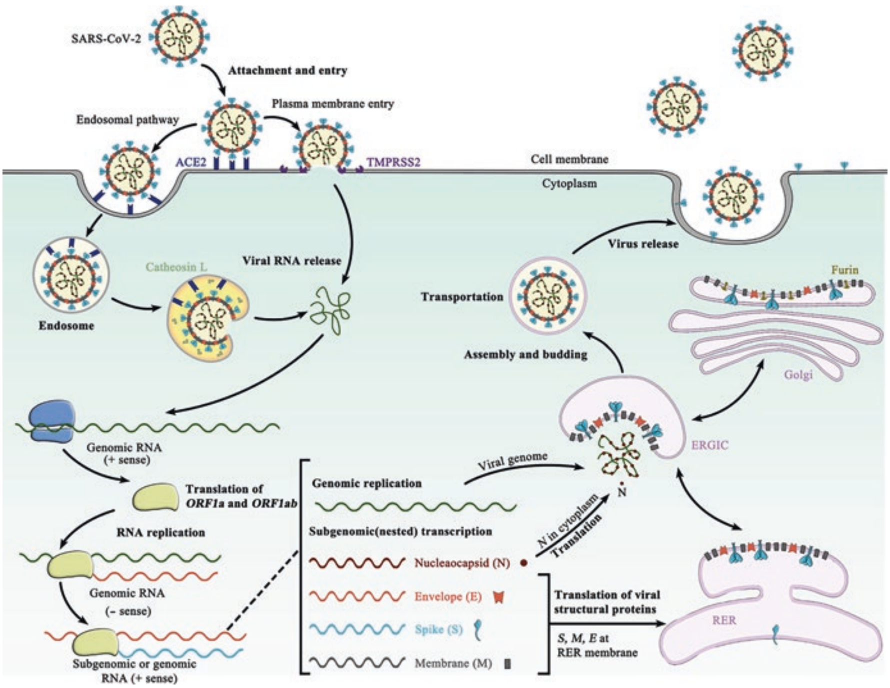

Fig. 4 Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) life cycle. *Notes*: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) binds angiotensin-converting enzyme 2 (ACE2) receptor and enters host cells via two pathways: endocytosis (endosome-cathepsin L) and direct fusion (TMPRSS2). Viral positive sense RNA is released and replicated and translated into viral proteins (N, E, S, and M) in the cytoplasm. The replicated viral RNA and the N-protein are associated together in host cell cytoplasm (forming nucleocapsid), while S, M, and E proteins are translated and undergo posttranslational modification (i.e., surface glycosylation) in the host endoplasmic reticulum (ER)/Golgi intermediate compartment (ERGIC); the nucleocapsid is then assembled with the M, E, and S proteins and bud into RER-Golgi lumen forming mature virions which are eventually released from the host cell via exocytosis. *Abbreviations*: ACE2, angiotensin-converting enzyme 2; TMPRSS2, transmembrane protease serine 2; RBD, receptor-binding domain; RNA, ribonucleic acid; ORF, open reading frame. (*Source*: Duan et al. (2020))

However, recent studies suggest that several factors play a role in the transmission, including contact patterns, viral load, and environmental factors. For example, it is reported that within the same household, individuals with very close contacts had an increased risk of transmission (43.4% for spouse vs. 18.3% for other contacts); the viral transmission is found to be higher within the first 5 days of symptoms onset due to higher viral load; and based on contact tracing studies, the indoor transmission is reported to be approximately 19-fold greater than outdoor transmission (Cevik et al., 2020). Moreover, based on the findings that certain countries with high temperatures and humidity, like Brazil, India, and Malaysia, are seeing more cases, compared to countries with lower temperatures, such as Japan and South Korea, such environmental variables are thought to have an impact on the spread of

SARS-CoV-2 (Islam et al., 2020a). Moreover, in contrast to SARS-CoV, which mainly replicates in the lung alveolar cells and macrophages, SARS-CoV-2 replication predominantly occurs in the epithelial cells of the URT, making it more transmissible (V'kovski et al., 2020), as new virions are actively shed from the nasopharynx (Cantuti-Castelvetri et al., 2020). Furthermore, recent study has also shown that the SARS-CoV-2 spike glycoprotein has a 10–20 times higher affinity for the ACE2-R receptor when compared to SARS-CoV, which contributes to its greater infectious capacity (Alanagreh et al., 2020).

More recently, United Health Professionals[9] have referred to the COVID-19 pandemic as the "Biggest Health Scam of the 21st Century." They reject the claim that SARS-CoV-2 is highly transmissible, saying that one infected person can only transmit the virus to only two or three other individuals, which makes the virus moderately contagious, as opposed to someone who is infected by the extremely transmissible measles virus who can infect up to 20 people. They further argue that there are other infectious diseases that infect and kill more people worldwide, yet they are underreported by the media compared to COVID-19 (United Health Professionals, 2021). For instance, the influenza virus infects and kills 1 billion (30 times more than SARS-CoV-2) and 650,000 people a year, respectively (i.e., globally infects 3 million and kills 2000 people daily), and TB bacteria that infects and kills 10.4 and 1.8 million people annually, respectively (i.e., infects 30,000 and kills 5000 people daily worldwide) (United Health Professionals, 2021).

Other possible routes of transmission have also been reported for SARS-CoV-2, including fecal-oral, vertical, etc. For example, compared to SARS-CoV-1, SARS-CoV-2 has higher affinity to bind intestinal ACE2-R, thus more transmissible, and also difficult to rule out fecal-oral transmission (Gavriatopoulou et al., 2020). Recently, fecal-oral transmission has been considered a possibility after an investigational study (Xu et al., 2020) revealed persistent positive real-time reverse transcription-polymerase chain reaction (RT-PCR) result from rectal swabs of eight out of ten infected children even after negative nasopharyngeal swabs RT-PCR. Vertical transmission refers to prenatal transplacental or intrapartum[10] maternal-fetal transmission, and although it is uncommon, it has been reported; however, these terms are misleading, and it has been recommended to use more accurate terms for fetal or newborn infection, such as intrauterine transplacental or neonatal, acquired intrapartum neonatal, or acquired postpartum neonatal infection (Konstantinidou et al., 2021).

[9] United Health Professionals has more than 1500 members, who are professors of medicine, intensive care unit doctors, and infectologists (United Health Professionals, 2021).

[10] Transplacental and intrapartum refers to viral transmission across placenta and direct contact of the baby with the genital tract during vaginal delivery, respectively (Konstantinidou et al., 2021).

Immunology

Immune Response Against Viruses

The nonspecific host innate immune system is the first line of defense against microbes, including viruses, followed by activating the more specific adaptive immune system (Abbas et al., 2015). The pathogen-associated molecular patterns (PAMPs) (e.g., viral RNA, etc.) are recognized by various host innate immunity pattern recognition receptors (PRR), such as toll-like receptors (TLRs), leading to the downstream signaling cascade and the activation of interferon regulatory factor 3/7 (IRF3/7) and NF-κB pathways (Lei et al., 2020). For instance, segments of ssRNA of RNA viruses are recognized by TLR7 and 8 leading to the production of type I and type III interferons (IFNs) as well as pro-inflammatory mediators via IRF7 and NF-κB pathways, respectively (Lester & Li, 2014). In fact, when it comes to ssRNA viral infections, greater levels of TLR7 expression may result in a better prognosis since it stimulates a stronger immune response (Khanmohammadi & Rezaei, 2021). Furthermore, in both experimental organisms and human investigations, it is reported that TLR3 deficiency is linked with increased vulnerability to RNA virus infection (Dhangadamajhi & Rout, 2021).

Viral infections, including CoVs, will also activate another component of the innate immunity called the inflammasome, a multi-protein complex composed of the sensor protein NLR (e.g., NLRP3, etc.), or an adaptor protein ASC, and caspase-1 (de Rivero Vaccari et al., 2020). These cascades will result in the synthesis of pro-inflammatory cytokines, interleukin (IL)-1, 6, 8, 12, TNFα, IFN-III (Belizário, 2021), IL-1β, IL-18, and type-I IFN (IFN-α/β) (Lee et al., 2020), as well as a form of cell death called pyroptosis (de Rivero Vaccari et al., 2020). In addition, pyroptosis integrated with other inflammatory cell death pathways is also activated, leading to cell death via PANoptosis (i.e., pyroptosis, necroptosis, and apoptosis). However, these cell death pathways act as a "double-edged sword" with both anti-inflammatory and pro-inflammatory effects; the former is typically beneficial in restricting viral replication and facilitating viral clearance, while the latter will release more intracellular cytokines and PAMPs, leading to cytokine storm and extensive tissue damage (Lee et al., 2020). Another major component of innate immunity is the complement system, composed of various transmembrane and soluble serum proteins, which are activated by viral antigens or by attached Abs to viruses (Abbas et al., 2015). These proteins neutralize viruses by various mechanisms, including the formation of a MAC that mediates lysis of viruses or via viral opsonization,[11] promoting phagocyte recruitment to the site of infection (Abbas et al., 2015). The opsonization results in the formation of neutrophilic extracellular traps (NETs) that will lead to another type of programmed cell death, termed NETosis, while the recruitment of other inflammatory cells contributes to more pro-inflammatory

[11] Opsonization is an immunological process that involves the attachment of opsonins, such as preformed Abs, to tag invading pathogens and then allowing them to be destroyed by phagocytes.

cytokine production, as well as create a pro-thrombotic state via damaging the vascular endothelial cells (Java et al., 2020).

In an ideal situation, the components of the host's innate immunity immediately recognize the virus and release cytokines (within a few hours) which limit intracellular viral replication and recruit other immune cells, creating an antiviral state that will eventually prime the adaptive immune system (Sette & Crotty, 2021). IFN-I recruits and activates other innate immunity cells, such as dendritic cells (DC) and natural killer (NK) cells, neutrophils, monocytes, and macrophages, as well as the repertoire of T and B lymphocytes (cells of the adaptive immune system) (Subbian, 2021), which stimulate the production of other cytokines (e.g., IFN-γ, a type-II IFN) (Costela-Ruiz et al., 2020). The APCs of innate immunity present the viral antigens to CD8+ cytotoxic T cells (CTLs) or CD4+ T-helper lymphocytes (Th1 and Th2 cells) via MHC-I and II molecules, respectively, resulting in the formation of long-lasting antigen-specific memory Th-cells and CTLs (Belizário, 2021). The produced innate cytokines will mostly shift the balance toward Th1 cells, specific to intracellular pathogens, like viruses (Belizário, 2021). In addition, B-cells are also activated indirectly by CD4+ cells or directly by viral antigens, leading to the formation of long-term memory B-plasma cells that will secrete neutralizing Abs, including high-avidity immunoglobulin (Ig)-M and high-affinity IgG, 3–5 days and 2 weeks postinfection, respectively (Belizário, 2021). The clearance of all viral infections depends on the more specific adaptive immune response and its components (Sette & Crotty, 2021), which upon activation, will typically increase host lymphocytes count; however, the failure of proper adaptive immune response will result in a state of constitutively active innate immunity with a detrimental impact on multiple organs (Moutchia et al., 2020).

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[12] Opsonization is an immunological process that involves the attachment of opsonins, such as preformed Abs, to tag invading pathogens and then allowing them to be destroyed by phagocytes.

Immune Response in COVID-19 Patients, SARS-CoV-2 Pathogenesis and Evasion of Host Immune Responses

It is reported that the innate and adaptive immunity in COVID-19 patients is dysregulated. This dysregulation is thought to cause a delayed IFN-I antiviral response (Subbian, 2021), resulting in overactive innate immunity and underactive adaptive immunity, leading to an extensive cytokine storm state (Moutchia et al., 2020). Autopsies of patients who died of COVID-19 showed high viral loads in the respiratory tract, as well as other tissues, implying ineffective immune responses (Mathew et al., 2020). The hallmark of severe COVID-19 is low lymphocyte count (lymphopenia), with low CD4+ and CD8+ T-cell counts (Cox & Brokstad, 2020), which implies a defective adaptive immune response (Neumann et al., 2020). It is demonstrated that lymphocyte depletion predominantly affects CD8+ T cells (Mathew et al., 2020). It is believed that the direct binding of SARS-CoV-2 to ACE2-R on cells of the reticuloendothelial system, such as spleen and lymph nodes, leads to lymphoid follicles atrophy and thus lymphocytes depletion (Gubernatorova et al., 2020). Studies on the humoral and cellular response in COVID-19 patients demonstrated contradictory findings. For instance, a study on 96 critically ill ICU-admitted patients identified three heterogeneous phenotypes: type 1 phenotype (35% of patients) had a deficient humoral immune response (i.e., lymphopenia with low NK and B cells and low Igs), but preserved T-lymphocyte count, and a moderate level of Il-6 and IL-1β; type 2 (21% of patients) demonstrated a hyper-inflammatory response and cytokine release syndrome (CRS) (IL-1β, Il-6, IL-8, and TNFα) with decreased CD4+ and CD8+ T cells, and discrete elevated soluble complement MAC (C5b-9); type 3 was the complement-dependent response patients, with high C3 level, profound C5b-9 elevation (Dupont et al., 2020).

Another research by Gao et al. (2021a) demonstrated a "dichotomous pattern" of the humoral and cellular immune response, which induced in asymptomatic/mild or moderate/severe COVID-19 cases. They indicated that peripheral blood of such cases contains low SARS-CoV-2-specific IgG, as S1- or S2-specific B-cell responses are transient, with no formed long-lived memory B cells, and IgG-secreting plasma cells; however, they reported a profound and sustained IFN-γ-secreting CD4+ Th and CD8+ cell response in these patients, all of which implying the failure to mount humoral immunity in the presence of a strong cellular immunity that might probably prevent them from progressing to severe COVID-19. On the other hand, moderate and severe COVID-19 patients had defective Th1 and IFN-γ-producing CD8+ T-cell responses, while they produced more sustained B cells and humoral responses (Gao et al., 2021a).

In addition, genes for TLR-7 and 8 are located on X chromosome, which may explain such gender-dependent immune response to SARS-CoV-2 (Khanmohammadi & Rezaei, 2021). In fact, when it comes to ssRNA viral infections, greater levels of TLR7 expression may result in a better prognosis since it stimulates a stronger immune response (Khanmohammadi & Rezaei, 2021). This is supported by a case series involving a pair of previously healthy young brothers from two unrelated families who developed severe COVID-19, requiring mechanical ventilation in the ICU, in which distinct loss-of-function variants in the TLR-7 gene X- were identified (van der Made et al., 2020). Moreover, a greater testosterone level is also responsible for the increased synthesis of TLR4 in men, which may account for the higher levels of pro-inflammatory cytokines (e.g., IL-6) in men as compared to females (Khanmohammadi & Rezaei, 2021). Moreover, significant positive correlation was reported with TLR3 deficiency and mutation (rs3775291) with SARS-CoV-2 susceptibility and COVID-19 mortality, but no correlation was found with percentage recovery of patients (Dhangadamajhi & Rout, 2021). In addition, such deficiency and mutant allele in TLR3 raise the chance of developing pulmonary hypertension and diabetes which increase the likelihood of progressing to severe COVID-19 and eventual dying in such individuals (Dhangadamajhi & Rout, 2021).

The pathogenesis of SARS-CoV-2 depends on S-protein interaction with host cells ACE2-R, expressed on type II alveolar epithelial cells (responsible for surfactant synthesis and regeneration of epithelial cells in damaged lungs) (Ortega et al., 2020), as well as many other human cells, including pulmonary macrophages, cardiovascular, intestinal epithelial, renal tubular, testicular, and brain cells, among others (Verdecchia et al., 2020). Severe COVID-19 is believed to occur via viral-induced direct cytotoxic damage, imbalance of the renin-angiotensin-aldosterone system (RAAS), and dysregulation of the immune system (Gupta et al., 2020). SARS-CoV-2 direct infection and replication in lung type II alveolar and vascular endothelial cells and its subsequent release and spread will infect and activate lung immune cells (i.e., macrophages, neutrophils, DC, etc.), leading to release of IL-6, IL-1, TNF, and other pro-inflammatory cytokines, and further viral spread (Gubernatorova et al., 2020). Moreover, the presence of IL-1β, IL-18, and LDH (a marker of cell death) in the sera of COVID-19 patients is believed to be due to the activation of inflammasome (Rodrigues et al., 2020). It is known that IL-1β and TNFα are the principal activators of IL-6, all of which play a critical role in CRS (Zhang et al., 2020a). IL-6 further induces the liver to synthesize acute phase reactants (APRs), such as C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, and α1-antitrypsin, while decrease fibronectin, albumin, and transferrin synthesis (Costela-Ruiz et al., 2020). Lung injury and function loss are attributed to elevated IL-1 (IL-1α), while IL-1β is believed to be responsible for COVID-19 hypercoagulation state and disseminated intravascular coagulation (Costela-Ruiz et al., 2020). The high blood glucose level in COVID-19 patients is caused by elevated IL-2 levels; G-CSF and GM-CSF stimulate bone marrow hematopoietic stem cells to undergo proliferation and maturation into monoblasts, promonocytes, monocytes, macrophages, eosinophils, neutrophils, monocytes, DC, etc. (Costela-Ruiz et al., 2020). MCP-1 mediates inflammatory cell infiltrates in various tissues by recruiting and regulating monocytes, memory T cells, and NK cells migration, while HGF is released by necrotic tissue (Costela-Ruiz et al., 2020). The imbalance in RAAS in COVID-19 patients is due to SARS-CoV-2-induced ACE2-R downregulation, which leads to an increase in angiotensin-II (AT-II), which has vasoconstrictive, pro-inflammatory, and pro-thrombotic and tissue remodeling effects (Verdecchia et al., 2020). Moreover, increased production of clotting factors (e.g., Factor VIII) and certain auto-Abs, such as anticardiolipin (aCL) and/or anti-β2 glycoprotein 1 (aβ2GP1) auto-Abs, have been shown to contribute to the hypercoagulable state in critically ill COVID-19 patients (Halpert & Shoenfeld, 2020). In a normal immune response against viruses, cytokine storm is resolved; however, in severely ill patients, this state persists, leading to thrombo-inflammation, and disseminated intravascular coagulation (DIC) (Gupta et al., 2020), tissue injury, multi-organ failure (MOF), and eventually death (Olbei et al., 2021). Moreover, it is reported that complement system activation, in combination with neutrophilia and dysregulated NETosis, is linked with ARDS, hyper-inflammation, and microthrombi formation leading to MOF (Java et al., 2020).

A virus must possess a minimum of one mechanism to evade the human immune responses in order to be able to cause disease; otherwise, it will cause no harm (Sette & Crotty, 2021). It is reported that CoVs escape the host's innate immune response during the first 10 days of infection, which leads to extensive systemic inflammation (cytokine storm) and high viral load as a result of robust viral replication, release, and spread (Sa Ribero et al., 2020). Studies are underway, but it is believed that SARS-CoV-2 has the same mechanisms as SARS-CoV for the evasion of host immune responses (Nikolich-Zugich et al., 2020). It has been demonstrated that viral NSPs and structural and accessory proteins disturb host innate immune response (Lei et al., 2020), with ORF3b, ORF6, and N protein of SARS-CoV-2 inhibiting IFN-type I synthesis by counteracting the IRF3 and NF-κB signaling pathways (Lee et al., 2020). It is also believed that in coronavirus-infected pulmonary cells, the PAMP-PRR interactions will activate the inflammasome via ORF3a, ORF8b, and E protein. Moreover, NSP1 is the first protein to be encoded by the SARS-CoV-2 genome, which is believed to bind to host cell 40S ribosomal subunit and prevent host cell protein translation (Lapointe et al., 2021), and hence inhibiting type-1 IFN synthesis (McGill et al., 2021). Furthermore, NSP3 is thought to be responsible for the weakening of the host IFN-I immune response by cleaving the IFN-stimulated gene (Yoshimoto, 2021). The posttranslational modification of the SARS-CoV-2 genome by NSP13-NSP16 allows the virus to escape the host innate immune response recognition, while the heavy glycosylation of spike is also responsible for the peptide folding and further evasion (Yoshimoto, 2021). In addition, the ORF3a accessory protein and nsp6 are reported to decrease the size of autophagosome or prevent its maturation, respectively, thus inhibiting the host cell autophagy mechanism toward infected cells (Miao et al., 2021).

Griffin et al. (2021) have divided stages of COVID-19 into different periods (pre-exposure, incubation, viral replication/detectable viral replication, and the inflammatory periods) and phases (symptomatic, early inflammatory, secondary infection, the multisystem inflammatory, and tail phase). The pre-exposure period ends when a susceptible individual is exposed to SARS-CoV-2, followed by the incubation period beginning at the time of exposure (T_E) which results in an asymptomatic carrier state in the majority of people. However, if infection occurs, the detectable viral replication phase starts at the time of detectable viral replication (T_{DVR}) when viral copies start rising. The viral symptom phase corresponds to the peak of viral RNA copies, which is at the time of symptom onset (T_S), followed by the early inflammatory phase (7–14 days after T_S) at time of early inflammation (T_{EI}). The coagulopathy, as well as a rise in inflammatory markers (cytokines, D-dimer, etc.), starts at T_{EI}. The cytokine storm will result in microvascular endothelial dysfunction, thrombosis, and later macrovascular manifestations. A minimum of one thrombotic complication (TC) was reported in 22.7% of cases within the first 14 days of ICU admission, and 52% of these developed pulmonary embolism (PE), which was also similar to the previous result of 42.7% and 16.7% of TC and PE, respectively (Tacquard et al., 2021). If untreated, the secondary infection phase can occur at the time of secondary infection (T_{SI}), which is due to immune dysregulation and result in fungemia, bacteremia, and the development of pneumonia and other bacterial superinfections (Griffin et al., 2021). The next phase, a hyperinflammatory state called multisystem inflammatory phase beginning at T_{MI} (time of multisystem inflammation), is when the IgG level is at its maximum and the secondary bacterial infection and autoimmune features are manifested (Griffin et al., 2021).

Other researchers have classified COVID-19 stages differently. For example, in the three-stage disease classification, stage I is associated with mild disease and is when the innate and adaptive immunity is activated. This stage corresponds to TLR-3,7, and 8 stimulation; IgM and IgG Abs production against S and N protein; and the onset of signs and symptoms of fever, dry cough, and lymphopenia. Stage I will progress to stage II if the host is not able to eliminate SARS-CoV-2 (e.g., in elderly and those with comorbidities), which will then spread and involve multiple organs (Ortega et al., 2020). In this stage, referred to as macrophage activation syndrome (i.e., hyper-inflammatory response and cytokine storm), the patient will present with dyspnea (IIA) and severe hypoxia (IIB), as well as detectable radiological findings, abnormal liver function test, lymphopenia, and elevated levels of APRs. If therapeutic measures are not effective, stage III will culminate with severe inflammatory response syndrome (SIRS), shock, and MOF, including acute respiratory distress syndrome (ARDS) (Ortega et al., 2020).

The pathophysiology behind COVID-19 extrapulmonary manifestations might predominantly be through widely expressed ACE2-R in various tissues, direct viral cytotoxic effect, or molecular mimicry, among others. For instance, the high expression of ACE2-R in cardiac and smooth muscle cells, as well as fibroblasts and endothelial cells, is responsible for SARS-CoV-2 direct extrapulmonary and atypical symptoms (Gupta et al., 2020). Moreover, the molecular mimicry between SARS-CoV-2 spike glycoprotein and human proteins is reportedly the pathomechanism behind autoimmune diseases seen in COVID-19 patients. For example, the shared peptide sequence between a peptide in S-protein (the major SARS-CoV-2 antigen) and human proteomes will result in the already-formed immune responses against the virus to also cross-react with these human proteins leading to the manifestations of autoimmune disorders (Kanduc & Shoenfeld, 2020). Similarly, molecular mimicry is hypothesized to facilitate peripheral neuropathy since SARS-CoV-2 surface glycoproteins are identical to human neural tissue glycoconjugates (Ramani et al., 2021). The pathophysiology for muscle involvement (e.g., autoimmune myositis and rhabdomyolysis) in COVID-19 patients has also been suggested to be the result of homology between SARS-CoV-2 antigens and human myocytes (Ramani et al., 2021). It has recently been found that several auto-Abs (e.g., antinuclear, anti-β2 glycoprotein-1 Abs, anticardiolipin Abs, etc.) are produced in SARS-CoV-2-infected patients resulting in new-onset autoimmune diseases, including Guillain-Barré syndrome, Miller Fisher syndrome, antiphospholipid syndrome, immune thrombocytopenic purpura, systemic lupus erythematosus, KD, large vessel vasculitis/thrombosis, psoriasis, and type I diabetes mellitus (DM), among others (Halpert & Shoenfeld, 2020). It is revealed that HLA gene polymorphism is responsible for such autoimmune diseases, and hence auto-Abs are developed in genetically susceptible individuals (e.g., those with HLA-DRB1, etc.) (Halpert & Shoenfeld, 2020).

The HLA alleles and COVID-19 severity might also be related, based on the previously reported relationship between these alleles and the severity of clinical manifestations of SARS cases, and the fact that in silico, the affinity of SARS-CoV-2 peptide varies for each HLA alleles (Amoroso et al., 2020). Research that investigated the relationship between the HLA genotype polymorphism and the severity of COVID-19 among 95 patients reported a high frequency of HLA class I, including HLA-B*51 in those who had fatal COVID-19 infections and that of HLA-B*35 in patients with mild infection (Naemi et al., 2021). Even though limited data is available regarding HLA class II, the same study found a high frequency of HLA-DRB1*13 in the fatal group, compared to the mildly infected patients. Comparing HLA alleles between healthy individuals and COVID-19 cases, as well as non-survived and survived patients, Lorente et al. (2021) reported higher HLA-A*32 in healthy individuals and higher HLA-A*03, HLA-B*39, and HLA-C*16 in COVID-19 patients; however, HLA-A*11, HLA-C*01, and HLA-DQB1*04 were found to be greater in non-surviving patients. Additionally, due to some unknown mechanisms, a positive correlation was reported between polymorphisms in CCR5 (i.e., deletion mutation) and SARS-CoV-2 infection and death (Mehlotra, 2020). In addition, the possibility of correlations between TMPRSS2 and ACE2 DNA polymorphisms with COVID-19 susceptibility and severity and outcomes was proposed in a comparative genetic study of 81,000 human genomes (Hou et al., 2020). For instance, the level of TMPRSS2, which is expressed on type I alveolar epithelial cells, is elevated with aging, and ACE2 polymorphisms and cardiovascular and pulmonary diseases (risk factors for COVID-19) are linked. This may explain the decreased risk of SARS-CoV-2 in infants and children relative to adults (Hou et al., 2020).

SARS-CoV-2 Origin

The origin of the majority of hCoVs is considered to be bats or rodents (natural hosts), where they are maintained and propagated yet remain nonpathogenic; they then spill over to the human host (and become pathogenic) via an amplifying intermediate reservoir host within which the virus undergoes transient replication (Shors, 2021). The intermediate host(s) are known for some hCoVs, while it is unknown for others. For instance, the CoVs of the 2003 SARS and 2012 MERS pandemics are believed to have been transmitted via the civet and camel as their intermediate hosts, respectively (Shors, 2021). As previously mentioned, the recombination among various strains of CoVs is reported to lead to the emergence of a novel virus, such as SARS-CoV-2 (Singh & Yi, 2021). Throughout their evolution, the genetic diversity of beta-CoVs, such as SARS-CoV-2, is increased via mutations and recombination, which is also reported to occur within other species (Rastogi et al., 2020). For example, evidence has shown sequence identity between SARS-CoV-2 and horseshoe bat CoV (RaTG13), as well as Malayan pangolins (Singh & Yi, 2021). As a result, bat and pangolin are considered to be the natural and intermediate hosts of SARS-CoV-2, respectively (Singh & Yi, 2021). In fact, the SARS-CoV-2 genome is thought to be a "mosaic" genome, made up of fragments from at least two previously known CoVs (Sallard et al., 2021), and is assumed to be likely a recombinant of those zoonotic viruses (Rastogi et al., 2020).

The unique feature of SARS-CoV-2, compared to any other alpha and beta-CoVs, is the presence of furin-cleavage site, as well as six major amino acid sequences in the RBD domain that is optimized for binding to the human-like ACE2-R (Andersen et al., 2020). It is reported that the SARS-CoV-2 genome is 96% identical to RaTG13, with the RBD domains being only 85% similar, sharing just one of the six major amino acid sequences (Rastogi et al., 2020). On the other hand, RBD regions of the SARS-CoV-2-related virus in pangolin share 92.4–99.8% sequence identity with the RBD of SARS-CoV-2 (Rastogi et al., 2020). Moreover, some studies indicate that all six main amino acids in the RBD regions of SARS-CoV-2 are identical to those in pangolin CoV (Andersen et al., 2020), whereas other studies claim this to be five out of six (Rastogi et al., 2020). This is supported by analyzing pangolin samples from two separate provinces in China, where researchers were able to identify two distinct clusters of SARS-CoV-2-related viruses, one of which shared greater amino acid identity (97.4%) with SARS-CoV-2 in RBD than did the bat CoV RaTG13 (89.2%); however, bat CoV shared more sequence identity (89.2%) with other non-RBD genome regions of SARS-CoV-2 than did pangolin CoV (Han, 2020). Furthermore, since bats have been ecologically separated from the human population, it is possible that SARS-CoV-2 has acquired its adaptive modifications in an intermediate host (e.g., pangolin) prior to its transmission to human (Rastogi et al., 2020). Further support pointing to pangolin as the intermediate host comes from pangolins or their scales being consumed as a source of food or in traditional Chinese medicine, respectively (Shors, 2021). Similarly, analysis of lung samples from two pangolins that died of pulmonary fibrosis, and the subsequent identification of CoVs that were nearly 90.5% and 91% similar to SARS-CoV-2, provided more evidence for this hypothesis (Shors, 2021). However, it is important to note that both bat and pangolin CoVs lack a furin-cleavage site (Andersen et al., 2020). In addition, concluding wild pangolins to be the intermediate host for SARS-CoV-2 is still controversial since the pangolins used in research studies were those from illegal smuggling activities and not wild ones (Singh & Yi, 2021). In addition, in order to get a more accurate estimate of the similarity and the "time to the most recent common ancestor (tMRCA)" of two different CoV strains (e.g., SARS-CoV-2 and bat CoV), it is preferable to utilize synonymous mutations, which are more prevalent in the genome since they are less likely to be subject to natural selection as they do not alter the properties of resulting proteins (Singh & Yi, 2021). For example, comparing such mutations, only 83% similarity is seen between bat RaTG13 CoV and SARS-CoV-2, and thus implying a distant relationship, compared to the initial report of 96% (Singh & Yi, 2021).

Sallard et al. (2021) explained that the similarity between pangolins CoV and SARS-CoV-2 is still considerably lower than the 99.52% similarity reported in the previously known SARS-CoV and its last intermediate host during the previous past zoonotic transmissions. In addition, they stated that human ACE2-R utilized by SARS-CoV-2 is more identical to farm animal proteins than that of wild pangolins and bats. On the other hand, genetic findings unequivocally suggest that SARS-CoV-2 is not generated from any previously known viral backbone (Andersen et al., 2020). Additionally, if pangolin is assumed to be the intermediate host, then the first detected case of SARS-CoV-2 infection would have to have acquired the virus when coming in contact with the intermediate host sold at Wuhan market; in fact, the first infected case did not even visit the market, which possibly excludes pangolin as the reservoir (Sallard et al., 2021).

In the absence of an intermediate host, some scientists have speculated that SARS-CoV-2 could have been synthetically developed in a laboratory, while others suggested it might have been adapted to laboratory animals or to a human, while it was being cultured on human cells (for study purposes) and have accidentally escaped these laboratories (Sallard et al., 2021). Additionally, CoVs are listed in Group 3 of potential bioterrorism agents that require Biosafety Level 3 (BSL-3) laboratories, where generally airborne agents that potentially cause fatal infections are kept (Kaufer et al., 2020). Hence, two circulating conspiracy theories have accused the USA or China of genetically engineering SARS-CoV-2 (Nie, 2020). Further controversies were brought about when the US CDC reported the presence of SARS-CoV-2 Abs in the blood of individuals from France, Italy, and the USA long before the virus was identified in Wuhan (Lew, 2020), as well as when CDC director Robert Redfield in a video interview stated that patients who were previously thought to have died of influenza might, in fact, have died from COVID-19 (Hall, 2020).

SARS-COV-2 Variants

Owing to their lack of proofreading capacity and as part of their evolution to increase genetic diversity, RNA viruses persistently go through recombinations and mutations (Rastogi et al., 2020). The change in the amino acid sequence of the viral protein is referred to as mutation (Lauring & Hodcroft, 2021), and one of the most significant ways in which viruses evolve in nature, is considered to be nucleotide substitution (Phan, 2020). These substitution mutations can be non-synonymous, resulting in the alteration of an amino acid sequence of a protein, as opposed to synonymous ones (silent mutations), which cause no such changes (Chu & Wei, 2019).

The synonymous mutations are heavily influenced by the viral mutation rate (Singh & Yi, 2021), and in general, mutations could occur upon human-to-human or human-to-animal viral transmission (Garry, 2021) or due to chronic infections of immunocompromised patients (Williams & Burgers, 2021). Viruses with different genomic sequences are called variants,[13] and when viral variants have a clearly distinct phenotype, including antigenicity,[14] transmissibility, or virulence, they are called strains (Lauring & Hodcroft, 2021).

The mutation rate of SARS-CoV-2 is around 23.6 mutations per year (Yao et al., 2020), resulting in the accumulation of mutations at 9.8×10^{-4} substitutions per site annually (Khateeb et al., 2021). Throughout the pandemic, several SARS-CoV-2 variants have evolved and are continuously emerging and spreading throughout the globe (Centers for Disease Control and Prevention (CDC), 2021b). The most variable region of SARS-CoV-2 to undergo mutational changes, including deletions, mutations, and recombination, is the S-protein region (Singh & Yi, 2021), which can alter viral infectivity or reactivity to neutralizing Abs (Li et al., 2020c). However, it is also stated that a single mutation in spike is not likely to cause resistance to neutralizing Abs, as the surface area of RBD is large enough for the Abs to bind (Sette & Crotty, 2021). Other regions, including structural protein (e.g., N) and NSP regions (i.e., ORF1a, ORF1b, ORF3, ORF8) of the SARS-CoV-2 genome, have also been reported to accumulate mutations (Wang et al., 2021a). The spike substitution mutations can occur in the RBD (S1 subunit) and non-RBD domains, as well as the S1/S2 furin-cleavage site. For example, the major substitutions in the RBD (N501Y, E484Q, E484K, T478K, L452R, K417T, K417N) as well as non-RBD (D614G)[15] regions will increase SARS-CV-2 immune evasion (both host and vaccine-acquired immunity) and affinity toward human ACE2-R (Khateeb et al., 2021). Table 2 summarized major SARS-CoV-2 spike protein mutations and their effects.

The SARS-CoV-2 Interagency Group (SIG) has established a classification system that categorizes SARS-CoV-2 variants into three categories, namely, variant of interest (VOI), variant of concern (VOC), variant of high consequence (VOHC), and variants being monitored (VBM). A variant is termed a VOI when any mutations in the viral genome might reduce neutralization by Abs (produced from previous infection or vaccine), decrease treatment efficacy, affect the diagnostic tests, or possibly increase transmissibility or disease severity (CDC, 2021a). On the other hand, the SARS-CoV-2 variant is classified as a VOC when genetic mutations result in substantial evidence of high transmissibility, severe COVID-19 (hospitalization or

[13] The term variant is misleading, as two viral variants may vary by a single mutation or by a large number of mutations (Lauring & Hodcroft, 2021).

[14] An antigen ability to elicit a cellular and humoral immune response is termed immunogenicity, whereas the ability to be recognized by antigen-specific antibodies is called antigenicity (Ilinskaya & Dobrovolskaia, 2016).

[15] In the substitution mutations, one amino acid (first letter) is replaced at a specific position in the protein sequence (middle number) with another amino acid (second letter). For example, D614G refers to a substitution of aspartic acid (D) to glycine (G) at amino acid position 614 of the spike glycoprotein (Khateeb et al., 2021).

Table 2 Major spike mutations in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and their effects

Spike mutations	ACE2-R affinity	Immune evasion[a]	Transmissibility	Virulence	Reference
RBD region					Khateeb et al. (2021)
K417N	↑	↑	↑	↑	
K417T	↑	↑	↑	↑?	
L452R	↑	↑	↑	↑	
T478K	↑	↑	↑	↑?	
E484K	↑	↑	↑?	↑?	
E484Q	↑	↑	↑?	↑?	
N501Y	↑	↑	↑	↑	
Non-RBD					
D614G	↑	↑	↑	↔	
S1/S2 furin cleavage site					
P681H	↔	↑?	↑	↑?	
P681R	↔	↑?	↑	↑?	

Author's Own Table
Abbreviations: *RBD* receptor-binding domain, *ACE2-R* angiotensin-converting enzyme-2 receptor
[a]Both host and vaccine-induced immunity

death), significantly low Ab neutralization, decreased treatment efficacy, and/or failure of viral detection by diagnostic tests. In contrast, a variant of high consequence, which has not yet been detected for SARS-CoV-2, as of July, 2021, is one that has obvious evidence of a significant reduction in the efficacy of public health preventative measures and medical interventions, compared to the previously known variant, mandating its report to WHO (CDC, 2021a). VBM refers to those variants for which there is adequate evidence of high transmissibility, increased disease severity, and obvious or potential effect on approved therapeutic measures, but which are not currently circulating in the USA and do not represent a major and immediate danger to public health. Any of the VOI and VOC may later be placed in this category, if their proportions have decreased significantly and consistently over time and they no longer represent a significant threat to public health in the USA (CDC, 2021a).

In late January and early February 2020, a new D614G mutation in the non-RBD region of spike appeared (Khateeb et al., 2021; WHO, 2021b). This was the first detected mutation of concern, which has spread globally, and by the end of June 2020 was present in the majority of circulating SARS-CoV-2 variants worldwide (Hossain et al., 2021), that is 99% of all variants (Khateeb et al., 2021). This mutated virus is reported to have increased affinity for olfactory epithelium (Khateeb et al., 2021), be ten times more infectious than the original virus (Li et al., 2020c), with higher ACE2-R affinity, viral load, and hence more transmissibility; however, it has no impact on disease severity (Zhang et al., 2020b) or on the efficacy of therapeutic drugs, diagnostic tests, vaccines, and public health preventative strategies (WHO, 2020). It is also reported that the affinity for ACE2-R is not limited to human but can also target other species, including horseshoe bat, Malayan pangolin, cat, and dog

(Wang et al., 2021a). However, it is still unclear which animal is capable of successfully transmitting SARS-CoV-2 to humans. For instance, more than 40 bat species susceptible to SARS-CoV-2 were recently identified in the USA. It is also stated that cat can acquire SARS-CoV-2 and transmit it to other cats, while ferrets develop URT infections but are unable to transmit the virus within their species (Solis & Nunn, 2021).

Between August and September 2020, a mink-associated variant named "Cluster 5" emerged in Denmark and the Netherlands, with the RBD mutations Y453F (the most widespread), del69_70, I692V, and M1229I (Lauring & Hodcroft, 2021). This variant has also been shown to include additional RBD mutations, such as F486L and N501T, which together with Y453F enhance viral affinity to both human and mink ACE2-R, thus making SARS-CoV-2 adaptable to both host species (Salleh et al., 2021). It was originally believed that such mutations would result in viral Ab-neutralization escape (Goodman & Whittaker, 2021); however, recent research in mice models suggests that they have no impact on the neutralizing Abs, and moreover, this variant is not circulating anymore and has already disappeared (Salleh et al., 2021). Following the discovery of an ORF8-deficient lineage with N501T mutations among humans and farmed-mink in Denmark, it has been suggested that ORF8-deficient lineages, which may have emerged as a result of the rapid transmission of SARS-CoV-2 within the mink population, are capable of interspecies spillover (Sharun et al., 2021).

In September 2020, having acquired 17 mutations, indicating a considerable period of evolution and natural selection, perhaps in a host with chronic SARS-CoV-2 infection, the UK VoC 202012/01 (B.1.1.7 lineage aka. Alpha variant) was detected (Lauring & Hodcroft, 2021). The mutations include 14 non-synonymous point mutations, and 3 deletions, with 8 of these being in the S-protein, and the variant is estimated to have a 43–90% higher R0 than the previous variants (Davies et al., 2021). The Alpha variant contains D614G, 69–70del, and 144del in NTD, N501Y in RBD, and P681H at the furin cleavage site, among others (Wang et al., 2021b). The deletion (del69_70) mutation is reported to affect the performance of real-time RT-PCR diagnostic tests (WHO, 2021b) and to help the virus evade the host immune responses. In addition, the N501Y mutation increases viral human-murine ACE2-R affinity (Rambaut et al., 2020) and infects children easily (Hayashi et al., 2021), while the P681H that is exponentially increasing worldwide may enhance systemic infection (Maison et al., 2021). Moreover, this variant is reported to increase hospitalization and disease severity, as well as produce 50% enhanced transmissibility, yet has no impact on neutralization by mAbs, or Abs from vaccinated or convalescent sera (CDC, 2021b). Furthermore, there is speculation that variant B.1.1.7 is responsible for the cases of myocarditis in pets; however, there is little evidence to support this hypothesis (Sharun et al., 2021). Moreover, according to retrospective observational studies, there is 35% higher risk of death linked to the Alpha variant (Farinholt et al., 2021). In addition, in a recent study, the effectiveness of NVX-CoV2373 (by Novavax), a protein subunit vaccine containing the S protein from the original Wuhan virus, against B.1.1.7 variant in 18–84 years old individuals is 85.6%, compared to 95.6% for the original Wuhan virus (Gómez et al., 2021).

In January of 2021, two new variants (Lineage B.1.427/B.1.429), with mutations at NTD (S13I and W152C) and RBD (L452R and D614G) regions, were first detected in California and have rapidly spread across the USA, as well as many other countries (McCallum et al., 2021), hence were initially considered VOCs in March 2021 (Martin Webb et al., 2021). A VOC, classified as the B.1.351 lineage (variant Beta), was first identified in South Africa, which possesses N501Y, K417N, and E484K, and is 50% more transmissible, with significant resistance to polyclonal/monoclonal Abs (mAbs), and Abs of convalescent and post-vaccination sera (CDC, 2021a). It is reported that the Beta variant is 6.5 and 8.6-fold more resistant to neutralization by polyclonal Abs obtained from people who have been vaccinated with Pfizer or Moderna, respectively (Gómez et al., 2021). However, the efficacy of NVX-CoV2373 was reported to be 49.4% against B.1.351 variant among more than 4400 participants, and this value increased up to 60% in the preventing of mild, moderate, and se-vere COVID-19 (excluding human immunodeficiency virus (HIV) positive individuals) (Gómez et al., 2021).

The other variant circulating in Brazil (P1 lineage) was first identified in January 2021 in Japan among people who had visited Brazil (Faria et al., 2021), harboring similar mutations to Beta variant (Faria et al., 2021), and is considered a VOC (Gamma variant) due to its potential impact on infectivity, immune escape, and reinfection (Resende et al., 2020). Reinfection is defined as a second positive PCR at least 28 days after the previous positive PCR (Colson et al., 2020). Furthermore, it is believed that IgG to anti-SARS-CoV-2 are unlikely to give long-lasting protection (Fang et al., 2020), and in fact, several reports have already presented cases of SARS-CoV-2 reinfection (e.g., with the Brazilian variant); however, unless the second infection is caused by a different viral variant (Resende et al., 2020), it is still unknown whether a second positive PCR implies reinfection or it is merely the persistence of COVID-19. In case it is truly reinfection, the management of the pandemic would be challenging, and no herd immunity would develop with either natural infection or vaccination (Falahi & Kenarkoohi, 2020). It is noteworthy to mention that the shared mutations between variants P.1, B.1.1.7, and B.1.351 reportedly emerged independently of each other (Faria et al., 2021).

In December 2020 and during the second wave of the pandemic in India, two other variants, including delta (B.1.617.2) and kappa, have emerged (B.1.617.1). They both have E484Q and L452R, while delta also carries T478K mutation, and are considered VOC (Khateeb et al., 2021). Moreover, reports indicate that compared to the alpha variant, the Delta variant is more transmissible (60% more than Alpha variant), increases hospitalization rate, and has intermediate resistance to the vaccine, especially in those who only had their first dose (Callaway, 2021). It must be mentioned that both the CDC (2021a) and Public Health Agency of Canada consider Variant Kappa a VOI (CDC, 2021a; Government of Canada, 2021). A recent study reports that vaccine-induced antibodies provide low immunity to Delta variant.

Harboring common mutations in their S1 subunit, the major circulating SARS-CoV-2 VOC includes alpha, beta, gamma, and delta, each having a global frequency of 48%, 7%, 7%, and 14%, respectively (Khateeb et al., 2021). As of July 21, 2021, there have been several SARS-CoV-2 VOI, including Epsilon (B.1.427 and B.1.429), Zeta (P.2), Eta (B.1.525), Theta (P.3), Iota (B.1.526 and B.1.526.1), Kappa (B.1.617.1), Lambda (C.37), B.1.1.318, and B.1.617.3 (WHO, 2021c). However, as of September 21, 2021, and according to CDC, there is no VOI, and Alpha, Beta, Gamma, Epsilon, Eta, Iota, Kappa, Mu, and Zeta are classified as VBM (CDC, 2021a). On the other hand, as of October 12, 2021, WHO considers both Lambda and Mu a VOI, while the remaining variants (except theta and zeta) are considered variants under monitoring (VUM), which was previously referred to as "Alerts for Further Monitoring" (WHO, 2021c). Evidence of increased transmission is reported in Epsilon, Eta, Iota, and Kappa, while almost all of them might have reduced sensitivity to neutralization by polyclonal Abs in convalescent sera or to mAb therapy (Epsilon) (Government of Canada, 2021) (Table 3 summarizes WHO and PANGO-lineage classification systems of major variants of SARS-CoV-2 and their characteristics).

Table 3 WHO and PANGO-lineage classification systems of major variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and their characteristics

WHO label	Alpha	Beta	Gamma	Delta and Kappa[c]	References
PANGO lineage	B.1.1.7 Q.1-Q.8	B.1.351 B.1.351.2 B.1.351.3	P.1 P.1.1 P.1.2	B.1.617.2 B.1.617.1	CDC (2021a)
Date of designation	**VOC:** December 29, 2020 **VBM:** September 21, 2021	**VOC:** December 29, 2020 **VBM:** September 21, 2021	**VOC:** December 29, 2020 **VBM:** September 21, 2021	**VOC:** July 20, 2021 (Delta) **VOI:** May 7, 2021 (Kappa) **VBM:** September 21, 2021 (Kappa)	CDC (2021a) Government of Canada (2021)
Main spike mutations	• **N501Y** • **D614G** • A570D • P681H • T716I • S982A • D1118H • E484K[a] & S494P[a] • H69-V70del • Y144del	• **N501Y** • **D614G** • L18F • D80A • D215G • R246I • K417N • E484K • A701V • LAL 242–244 del	• **N501Y** • **D614G** • L18F • T20N • P26S • D138Y • R190S • K417T • E484K • H655Y • T1027I • V1176F	• E484Q • L452R • T478K (Delta) • D614G • P681R	Gómez et al. (2021)
Transmissibility[b]	↑ By 56%	↑	↑	↑ (by up to 60% more than (B.1.1.7) variant)	Gómez et al. (2021) Callaway (2021)

(continued)

Table 3 (continued)

WHO label	Alpha	Beta	Gamma	Delta and Kappa[c]	References
Disease severity[b]	↑	↑	↑	↑	Government of Canada (2021)
Reinfection rate	↑	↑	↑	N/A	Gómez et al. (2021)
Neutralization by polyclonal antibodies	↓	↓	↓	↓	Government of Canada (2021)
Neutralization by convalescent sera or post-vaccination sera	↓	↓	↓	↓	Government of Canada (2021)
Host immune response	↓	↓	↓?	↓?	Khateeb et al. (2021)
Vaccination efficacy	Moderate ↓	Significant ↓	Significant ↓	N/A	Gómez et al. (2021)
Diagnostic method	↔	↔	↔	↔	Khateeb et al. (2021)

Authors' Own Table

Note: As of September 21, 2021, variants Alpha, Beta, Gamma, and Kappa have been downgraded to variants being monitored (VBM) by Centers for Disease Control and Prevention (CDC) in the USA (CDC, 2021a)

Note: N/A, not available; ↔, no change; ↓, decreased; ↑, increased; ↓?, might decrease

Abbreviations: *SARS-CoV-2* severe acute respiratory syndrome coronavirus-2, *WHO* World Health Organization, *PANGO* Phylogenetic Assignment of Named Global Outbreak, *VOC* variants of concern, *VBM* variants being monitored, *VOI* variants of interest

[a]Not detected in all sequences

[b]Compared to wild type

[c]Both Delta and Kappa variants originate from the same emerging lineage, B.1.617

Clinical Characteristics

Signs and Symptoms

The typical symptoms of COVID-19 appear after an average incubation period (interval between viral exposure to symptom onset) of 2–14 days (Griffin et al., 2021) but can also occur within a minimum of 1 day to a maximum of 20 days post-exposure (Qu et al., 2021). SARS-CoV-2 replication starts before the onset of symptoms; thus, in the majority of cases, COVID-19 is recognized when viral RNA copies have already reached their maximum level, which is during the symptom phase at the time of symptom onset (TS) (Griffin et al., 2021). These clinical presentations can range from asymptomatic, mild, moderate, severe, to critical respiratory symptoms (Table 4), but the majority of cases remain asymptomatic or only develop mild symptoms (Gao et al., 2021b).

Table 4 Clinical characteristics of different types of coronavirus disease 2019 (COVID-19)

COVID-19 types	Clinical findings	Reference
Asymptomatic	Clinical symptoms: none Chest radiological findings: none RT-PCR: positive	Gao et al. (2021b)
Mild	Clinical symptoms: mild (e.g., fever, cough, dyspnea, headache, fatigue, etc.) Chest radiological findings: none RT-PCR: positive	
Moderate	Clinical symptoms: mild/moderate Chest radiological findings: mild pneumonia RT-PCR: positive	
Severe	Clinical symptoms: suspicious for pulmonary disease and any of the dyspnea RR ≥ 30 breaths/min at rest $SaO_2 \leq 93\%$ (at rest) Pa02/Fi02 ≤ 300 mmHg (at rest) Chest radiological findings: significant progression (>50%) of lesions within 24–48 h RT-PCR: positive	
Critical	Rapid disease progression with any of the following: Respiratory failure requiring mechanical ventilation Shock MOF requiring ICU admission RT-PCR: positive	

Authors' Own Table

Abbreviations: *RT-PCR* reverse transcription-polymerase chain reaction, *RR* respiratory rate, SaO_2 oxygen saturation, PaO_2/FiO_2 ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen, *MOF* multi-organ failure, *ICU* intensive care unit

The initial signs and symptoms of hypoxemia and increased respiratory rate in the early inflammatory phase might require airway support, and if untreated, this can lead to cardiac disorders, renal failure, neurological symptoms, and MOF (Griffin et al., 2021). Hypoxia, a common and yet atypical feature of ARDS seen in the early disease stage, is surprisingly well-tolerated and is thus called "silent hypoxia" (Gavriatopoulou et al., 2020). According to a systematic review and meta-analysis (Rodriguez-Morales et al., 2020), 32.8% of patients developed ARDS with shock (6.2%), and 20.3% needed intensive care unit (ICU) admission, while 13.9% had fatal consequences. Moreover, diaphragm muscle can be involved in COVID-19 patients secondary to critical illness myopathy, ventilation-associated diaphragm dysfunction, phrenic nerve damage, or direct viral injury (as diaphragm express ACE2-R); this will further exacerbate respiratory distress (Ramani et al., 2021). Moreover, severe dyspnea and tachypnea were mostly reported by elderly patients who died of COVID-19, while fever and headache were present mostly in recovered elderly patients (Perrotta et al., 2020).

A systematic review and meta-analysis study (Grant et al., 2020) of 24,410 laboratory-confirmed COVID-19 adults revealed the most prevalent symptoms to be fever (78%), cough (57%), fatigue (31%), dyspnea (23%), rigors (18%), wheeze (17%), myalgia (17%), arthralgia 11%, headache (13%), confusion (11%), and diarrhea (10%), among others. This is consistent with Li et al. (2020a) meta-analysis result that found the most prevalent symptoms, in decreasing order of prevalence, to be fever (88.5%), cough (68.6%), fatigue or myalgia (35.8%), expectoration (28.2%), dyspnea (21.9%), headache or dizziness (12.1%), diarrhea (4.8%), and nausea and vomiting (3.9%). A few cases of acute arthritis secondary to COVID-19 and within a couple of weeks of SARS-CoV-2 infection have also been reported (Ramani et al., 2021).

COVID-19 patients can also present with loss of smell (anosmia) and taste (dysgeusia). In a meta-analysis among 20,451 patients, Ibekwe et al. (2020) reported anosmia and dysgeusia in approximately 49% and 41% of cases, respectively. This was in agreement with a global meta-analysis (Agyeman et al., 2020) among 8438 cases that reported the loss of smell and taste in 41.0% and 38.2% of patients, respectively. Anosmia and dysgeusia are more prevalent in mild and moderate cases, although the latter is more associated with severe disease (Mullol et al., 2020), and both are strongly suggestive of COVID-19 (Griffin et al., 2021).

Compared to mild COVID-19 cases, gastrointestinal (GI) symptoms occur more predominantly in patients with severe COVID-19 (8.1% vs. 23%) (Gavriatopoulou et al., 2020), and the most common reported GI symptoms in decreasing order were anorexia (21%), nausea and/or vomiting (7%), diarrhea (9%), and abdominal pain (3%) (Gupta et al., 2020). A retrospective study reported that 16% of 1141 patients solely developed GI symptoms (Gavriatopoulou et al., 2020), and in other cases, digestive symptoms occurred prior to the typical respiratory signs and fever (Philips et al., 2020). Moreover, it is stated that about 14–53% of critically ill hospitalized patients will have findings of hepatocellular injuries (Gupta et al., 2020). However, there has not been a convincing report on the direct involvement of the hepatobiliary system in COVID-19 cases, and it is believed that hepatic injury is mainly secondary to the disease itself or the result of hepatotoxic therapeutic agents used in these patients (Philips et al., 2020), including remdesivir, lopinavir, and tocilizumab (Gupta et al., 2020). In addition, earlier studies done prior to the pandemic have reported that ACE2-R expression was more than 30-fold higher in the liver of cirrhotic patients, which might explain the increased hepatotropism of SARS-CoV-2 in those with chronic liver disease (Marjot et al., 2021). Furthermore, during the pandemic social isolation, alcohol consumption has increased significantly, leading to alcoholic liver disease (ALD) (Marjot et al., 2021). For instance, it is reported that 17% of individuals who had previously abstained from alcohol but had a history of alcohol use disorder were shown to relapse during lockdown (Marjot et al., 2021). A study conducted at a single center in the UK found that the number of ALD referrals and the percentage of critically ill inpatients with ALD (without COVID-19) increased by more than twofold in June 2020 when compared to June 2019 (Marjot et al., 2021).

Dermatological manifestations of COVID-19 are present in approximately 20% of COVID-19 patients, and the cutaneous lesions range from urticaria, vesicles, purpura, papulosquamous, as well as purpuric eruptions and livedo reticularis (Gavriatopoulou et al., 2020). These skin lesions are thought to be due to hypersensitivity reactions to the SARS-CoV-2 genome, CRS, and vasculitis with microthrombi formation (Gupta et al., 2020). The endocrine system can also be affected by SARS-CoV-2; however, the information available on the impact of COVID-19 on the endocrine system, including the hypothalamic-pituitary-adrenal (HPA), is very limited (Alzahrani et al., 2021). It is reported that SARS viruses can impair the HPA axis, and research on the previous SARS pandemic revealed that 40% of cases had signs and symptoms of secondary adrenal insufficiency (SAI) 90 days after their recovery (Alzahrani et al., 2021). Moreover, the molecular mimicry between a SARS-CoV amino acid and adrenocorticotropic hormone (ACTH) results in a host immune response against SARS to cross-react with ACTH residue and induce adrenal insufficiency, hence decreased cortisol level (Alzahrani et al., 2021). Recent autopsy findings of SARS-CoV-2 patients have demonstrated microscopic changes in 46% of these cases, with evidence of suprarenal cortical necrosis, cortical lipid degeneration, focal inflammation, hemorrhage, and vascular thrombosis, were seen in these patients; however, no adrenal insufficiency was reported (Alzahrani et al., 2021).

On the other hand, an investigation on the response of the HPA axis in COVID-19 patients detected no normally expected robust cortisol response in any of the acute COVID-19 patients (Alzahrani et al., 2021). The cortisol and ACTH levels were in the low/normal low, which were diagnostic of SAI, while low dehydroepiandrosterone sulfate (DHEAS) levels in these patients were indicative of chronic ACTH deficiency. Interestingly, with except for one, none of the patients exhibited signs or symptoms of adrenal insufficiency (Alzahrani et al., 2021). It is noteworthy to mention that the nonspecific signs and symptoms of adrenal crisis, such as fever, nausea, vomiting, extreme fatigue, weakness, myalgia, postural hypotension, and abdominal pain, are similar to those of acute COVID-19 and thus are difficult to differentiate (Alzahrani et al., 2021).

COVID-19 can also present as atypical symptoms (Philips et al., 2020), with elderly patients more likely to present with these symptoms, such as falls, reduced mobility, generalized weakness, and delirium (Gan et al., 2020). Several case reports have also presented patients with other rare atypical symptoms, such as persistent hiccups (a reflex inspiratory movement) in patients with no travel history or sick contact. For example, the first reported case was a 62-year-old man with a previous history of hypertension (HTN), diabetes mellitus (DM), and coronary heart disease, who presented with unintentional weight loss and 4-day persistent hiccups but lacked the typical symptoms of cough, fever (though he later developed a fever in the hospital), sore throat, dyspnea, and so on (Prince & Sergel, 2020). In another case report, a 48-year-old man with a history of HTN visited the hospital complaining of persistent hiccups for 1 week, which started after he developed a fever 7 days earlier (Bakheet et al., 2020).

The systemic inflammatory response, CRS, and hypoxemia can also cause arrhythmia, myocardial ischemia, and myocardial infarction (MI), which are exacerbated in those with the previous history of heart conditions (Philips et al., 2020). For example, CRS is thought to disrupt the already existing atherosclerotic plaques via macrophage activation and leukocyte adhesion molecule expressions on vascular endothelial cells. In major arteries of the heart, this leads to an acute coronary syndrome, myocardial ischemia, and MI (Gavriatopoulou et al., 2020). Furthermore, hypotension, which is a clinical hallmark of CRS and sepsis, together with fever and systemic infection, causes an imbalance between the oxygen supply and demand of cardiomyocytes, leading to further cardiac damage and eventual left ventricular systolic dysfunction and cardiogenic shock (Gavriatopoulou et al., 2020).

Other cardiac manifestations included sinus tachycardia or bradycardia, pulseless electrical activity, atrial fibrillation, and atrial flutter (Gupta et al., 2020). Moreover, in a Chinese center, approximately 6% of 187 patients treated for COVID-19 developed sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF) (Guo et al., 2020). The inflammation of cardiac muscle cells (myocarditis) is thought to be responsible for heart dysfunction (Gupta et al., 2020), with ventricular arrhythmias being a common clinical finding of acute myocarditis (Gavriatopoulou et al., 2020). Moreover, some of the therapeutic agents, such as chloroquine (CQ), hydroxychloroquine (HCQ), and azithromycin that are used in COVID-19 patients, are pro-arrhythmic and may result in a long QT interval and the resultant torsade de pointes (Gavriatopoulou et al., 2020). COVID-19 may also affect the reproductive glands, such as male testes via ACE2-R on spermatogonia, leydig, and sertoli cells, leading to testis orchitis and infertility (Deshmukh et al., 2021).

Laboratory Findings and Diagnosis

Severe and critical COVID-19 cases are more likely to have abnormal laboratory parameters (Moutchia et al., 2020), while asymptomatic patients might have both normal and abnormal results (Zhang et al., 2020c). However, the lack of specific laboratory parameters in the early disease stage has made it difficult to establish an early diagnosis (Ebrahimi et al., 2020). A systematic review and meta-analysis among 4663 COVID-19 patients demonstrated the most prevalent abnormal laboratory findings to be an elevated level of CRP, erythrocyte sedimentation rate (ESR), IL-6, and lactate dehydrogenase (LDH), and decreased albumin, eosinophils, and lymphocytes (Zhang et al., 2020d). The elevated level of ESR, CRP, and LDH, as well as ferritin, D-dimer, and fibrinogen in COVID-19 patients implies dysregulation of immunity and hyper-inflammation (Gupta et al., 2020).

Several other pro-inflammatory cytokines and chemokines, including IL-1α, 2, 4, 7, 9, 10, G-CSF, GM-CSF, M-CSF, IP-10, MCP-1, MIP 1-α, HGF, PDGF, and VEGF, were also reported to be elevated in COVID-19 patients (Costela-Ruiz et al., 2020). Moreover, severe COVID-19 patients were shown to have elevated alanine aminotransferase and aspartate aminotransferase (ALT/AST), creatinine kinase (CK), total bilirubin, gamma-glutamyltransferase (GGT), myoglobin, blood urea nitrogen (BUN), and creatinine, while albumin is found to be lower in severe COVID-19 (Danwang et al., 2020). The complete blood count (CBC) in COVID-19 patients demonstrated mild thrombocytopenia, elevated total white blood cells (WBC) counts, with neutrophilia, but lymphopenia; thus increased neutrophil to lymphocyte ratio (NLR) (Gupta et al., 2020). Furthermore, abnormal coagulation markers were reported, including elevated D-dimer, fibrinogen, prothrombin time

(PT), and activated partial thromboplastin time (aPTT) (Gupta et al., 2020). However, interestingly, unlike patients with DIC due to bacterial sepsis or trauma who have high PT and aPTT, DIC in severe COVID-19 cases show minimal prolongation of aPTT and/or PT (Wool & Miller 2020). D-dimer is elevated to a greater extent and out of proportion than other parameters such as PT/INR, aPTT, fibrinogen, or platelets (Al-Samkari et al., 2020). Abnormal glucose metabolism in COVID-19 patients presents with high blood glucose level, euglycemic ketosis, and classic diabetic ketoacidosis, while patients with acute kidney injury demonstrated high blood urea nitrogen (BUN), creatinine, proteinuria, hematuria, metabolic acidosis, and electrolyte imbalance (e.g., hyperkalemia, hypo/hypernatremia) (Gupta et al., 2020). Furthermore, interestingly, a study among 129 patients with various COVID-19 reported significantly high levels of lung cancer tumor markers, such as carcinoembryonic antigen (CEA), cytokeratin 19 fragment (CYFRA21-1), neuron-specific enolase (NSE), squamous cell carcinoma antigen (SCCA), and pro-gastrin releasing peptide (ProGRP) (He et al., 2020).

The gold standard test for the diagnosis of SARS-CoV-2 infection is using real-time RT-PCR to detect viral genome from swab samples of deeper anatomical sites, such as nasopharynx, oropharynx, or upper and lower respiratory tract aspirates and bronchoalveolar lavage (Yüce et al., 2021). A successful SARS-CoV-2 infection will result in viral genome replication shortly after viral exposure (i.e., is detectable as early as 1-day postexposure) and peak 3–4 days postexposure; however, the currently used technologies are not able to detect viral replication in the immediate postexposure time, as viral RNA copies can range from undetectable to millions 1–3 days prior to the onset of symptoms (Griffin et al., 2021); thus, false-negative (FN) results might be generated, as RT-PCR sensitivity is not high (Falahi & Kenarkoohi, 2020), and a negative RT-PCR result in the initial stage of infection cannot rule out SARS-CoV-2 infection (Adams et al., 2020). A retrospective study on 280 hospitalized patients diagnosed with COVID-19 reported a positive RT-PCR in 39.6% of them (Özel et al., 2021); as high as 29% FN rate for RT-PCR of nasal swabs samples had been reported (Sasisekharan et al., 2021). Furthermore, the majority of mild COVID-19 patients will have their viral RNA copy number decreased to values under an infectious level by day 10; however, in immunocompromised and severe COVID-19 cases, the value may stay above infectious level until day 20, or in some cases to 3 weeks post-discharge (Griffin et al., 2021).

Other methods, including both lateral flow type assays (LFA) and enzyme-linked immunosorbent type assays (ELISA), can be utilized to detect either serum antiviral Abs (IgM/IgG) or viral antigens (S, M, or N glycoprotein antigens) (Yüce et al., 2021). Abs against SARS-CoV-2 appear 1–2 weeks after the onset of symptoms (Fang et al., 2020), and as previously explained, the humoral response to SARS-CoV-2 demonstrates heterogeneity among different cases. Thus, low levels produced in cases of viral evasion of the immune system (Shang et al., 2020), short-lived Abs in asymptomatic and mild cases, and late Ab response will give FN results (Fang et al., 2020).

Radiological Features

Pulmonary Findings

Computed tomography (CT) is a technique that combines X-rays and computer technology to produce sharp images of the lungs (Zahan et al., 2021). It is the most sensitive modality to detect early COVID-19 pneumonia and is predominantly used for patients with strong clinical suspicion of COVID-19 (Campagnano et al., 2021); however, CT exact sensitivity and specificity for COVID-19 are not known, and currently, it is not recommended for routine screening of COVID-19 pneumonia (Simpson et al., 2020). Furthermore, it is reported that CT has higher sensitivity compared to RT-PCR in suspected COVID-19 patients (Yau et al., 2020), but the patterns found on CT scans are nonspecific and do not differentiate between viral and bacterial pneumonia (Sun et al., 2020). Moreover, it is more accurate than conventional chest X-ray (CXR) in identifying lung abnormalities, especially in cases of false-negative RT-PCR (Zahan et al., 2021). Although more sensitive than other modalities, CT cannot rule in or rule out the diagnosis (Gavriatopoulou et al., 2020).

A systematic review and meta-analysis of chest CT and CXR (Garg et al., 2021) in COVID-19 pneumonia patients reported the pooled prevalence of 66.9% ground-glass opacity (GGO), 32.1% only consolidation, 44.9% GGO plus consolidation, 29.1% crazy paving, 23.6% halo sign, 8.9% nodules, 5.6% pleural effusion, and 2.7% lymphadenopathy on chest CT. Moreover, they found the most common lung areas involved on CT in decreasing order to be peripheral (58.5%), central plus peripheral (19.4%), and central (16%); bilateral lung involvement was seen in 44% of CT scans, while unilateral involvement was seen in 9.1% images (Garg et al., 2021). Regarding the CXR findings, more consolidation (46.9%) than GGO (38.7%) was observed in the radiographs of these patients (Garg et al., 2021); however, CXR has lower sensitivity in detecting abnormalities (Sun et al., 2020). Similarly, in another systematic review and meta-analysis of CT findings (Cao et al., 2020), in 46,959 patients with COVID-19 pneumonia, more bilateral involvements (75.5%) were seen compared to unilateral (20.4%), and the most prevalent CT patterns were GGO (69.9%), irregular or halo sign (54.4%), air bronchogram (51.3%), bronchovascular bundle thickening (39.5%), grid-form shadow (24.4%), and hydrothorax (18.5%); however, some of the used radiological terminology (e.g., grid-form shadows and bronchovascular bundle thickening) are not recommended by the Radiological Society of North America expert consensus statement in the reporting instructions for CT finding of COVID-19. According to another systematic review and meta-analysis, pure GGO is more prevalent in the early disease stage, which later progresses to consolidation, and 76% of patients had multilobar lung involvement, with the right lung being affected more frequently (Awulachew et al., 2020). Figure 5 shows chest CT findings of confirmed COVID-19 patients.

Some COVID-19 patients will also have atypical findings on chest CT. A study among 298 confirmed COVID-19 cases with pneumonia revealed 73.1% had typical CT features, while 21.1% presented with atypical and typical CT patterns. The most

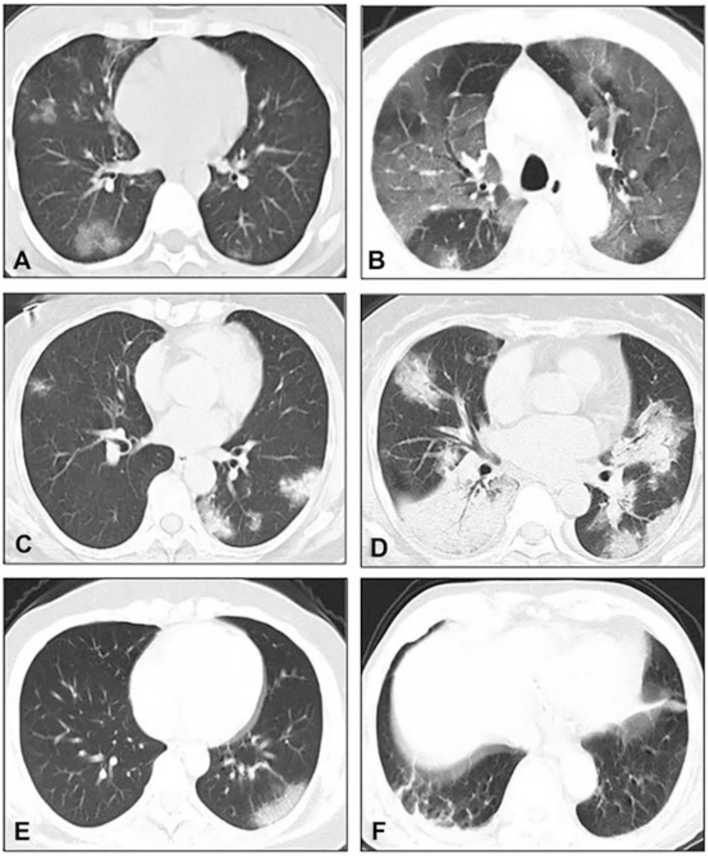

Fig. 5 Computed tomography (CT) findings of confirmed coronavirus disease 19 (COVID-19) patients. *Note*: (**a**) Pneumonia ground-glass opacity (GGO); (**b**) GGO and air bronchogram in a patient with severe pneumonia; (**c**) consolidation in patients with pneumonia; (**d**) consolidation and air bronchogram in a patient with severe pneumonia; (**e**) nodular opacities in patient with pneumonia; (**f**) pleural effusion on right side in a patient with severe pneumonia. (*Source*: Liu et al. (2020b))

prevalent atypical features were pulmonary cysts (9%), pleural effusion 5.7%, nodules 4.3%, bull's eye/target sign (1.3%), cavitation (1.0%), spontaneous pneumothorax (0.6%), hilar lymphadenopathy (0.6%), spontaneous pneumomediastinum with subcutaneous emphysema (0.3%), as well as halo sign, empyema, and necrotizing pneumonia with abscess (each 0.3% prevalent) (Gurumurthy et al., 2021). Studies have reported contradictory results regarding the CT findings in asymptomatic carriers, which ranged from normal to some GGO patterns (Zhang et al., 2020c).

COVID-19 Reporting and Data System (CO-RADS), a categorical system developed by The Dutch Radiological Society (NVvR), is a useful tool to assess the level of suspicion of pulmonary involvement in COVID-19 patients based on CT findings (Özel et al., 2021). It is revealed that patients with CO-RADS5 had a positive

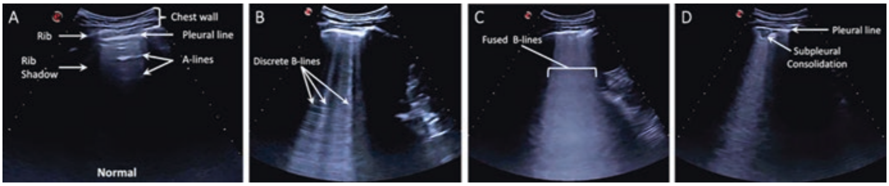

Fig. 6 Lung ultrasound patterns of coronavirus disease-2019 (COVID-19). *Notes*: (**a**) Normal lung with pleural sliding and A-lines; (**b**) discrete hyperechoic individual B-lines which are usually the first signs of COVID-19 and are due to increased interstitial fluid in the acute disease stage; (**c**) confluent B-lines are formed by coalescence of many individual B-lines as the disease progress and more interstitial fluid is accumulated; (**d**) subpleural consolidations (usually are small and <3 cm). (*Source*: Mateos González et al. (2021))

RT-PCR test which was statistically significant, while all cases in the CO-RADS2 category had negative RT-PCR; thus, they concluded that in the presence of a negative RT-PCR, CO-RADS is able to diagnose COVID-19 (Özel et al., 2021). Several other radiological systems were developed to standardize chest CT reporting in suspected COVID-19 cases, each having different sensitivity,[16] specificity,[17] positive predictive value (PPV),[18] and negative predictive value (NPV),[19] as well as different RT-PCR results. These systems included COVID-19 imaging reporting and data system (COVID-RADS), the RSNA expert consensus statement, and the British Society of Thoracic Imaging (BSTI), all with good performance and interobserver agreements in reporting CT features (Inui et al., 2020).

Lung ultrasound (LUS), such as point-of-care ultrasound (POCUS), has also been used to manage COVID-19 patients either at triage, ED, or ICU (Bhoi et al., 2020). The most common LUS findings are discrete B-lines (in 81.3% of cases), confluent B-lines (in 50%), small subpleural consolidations (usually <3 cm) (in 42.7%), and normal LUS (in 18.8%). The discrete hyperechoic B-lines, which are usually the first signs of COVID-19, are due to increased interstitial fluid in the acute disease stage, while the confluent lines are formed by coalescence of many individual B-lines as the disease progress, and more interstitial fluid is accumulated (Mateos González et al., 2021). Figure 6 shows LUS patterns of COVID-19. LUS was found to be able to detect pulmonary infiltrates more than CXR and with more sensitivity (81% vs. 63%) (Mateos González et al., 2021). The B-lines found on LUS correspond to the GGO on chest CT (Hussain et al., 2020), and the "light

[16] The ability of a screening test to accurately detect all individuals who have the disease (true positive) is referred to as its sensitivity (Trevethan, 2017).

[17] The ability of a screening test to accurately detect all individuals who do not have the disease (true negative) is referred to as its specificity (Trevethan, 2017).

[18] The positive predictive value (PPV) is the probability that those individuals who have tested positive for the disease in the screening test, truly have the disease in question (Trevethan, 2017).

[19] The negative predictive value (NPV) is the probability that those individuals who have tested negative for the disease in the screening test, truly do not have the disease in question (Trevethan, 2017).

beam" artifact ("waterfall" sign) is specific for COVID-19 pneumonia and represents the early GGO appearance on CT (Yau et al., 2020). Other LUS features of COVID-19 are thick irregular pleural lines, mobile air bronchograms (at live scan) with large consolidation, especially in those on mechanical ventilation, indicating ARDS progression or secondary bacterial infection (Hussain et al., 2020). Furthermore, in cases where vital signs are normal, LUS can still identify COVID-19 pneumonia and differentiate viral and bacterial pneumonia (Hussain et al., 2020). If pleural effusion is detected, other differential diagnoses must be considered (e.g., bacterial pneumonia, secondary bacterial infection, or congestive heart failure) (Campagnano et al., 2021). LUS is found to have comparable sensitivity and specificity to CT scans, with the advantage of avoiding radiation exposure (i.e., safe for pregnant patients and children), lowering costs, and decreasing the chance of spreading the virus (due to increased portability) (Schmid et al., 2020).

Musculoskeletal and Soft Tissue Findings

Electromyography (EMG) and nerve conduction studies can confirm and differentiate between SARS-CoV-2 myopathy and other diseases mimicking myopathy (e.g., motor neuron diseases); however, magnetic resonance imaging (MRI) is the gold standard to identify soft tissue necrosis and to localize pathology site (Ramani et al., 2021). Moreover, diaphragm involvement can be diagnosed and monitored using a fluoroscopy sniff test for real-time diaphragmatic movement and ultrasound to detect muscular atrophy and determine diaphragmatic thickening during inspiration (Ramani et al., 2021).

The MRI findings of acute GBS and MFS are enlargement, with signal hyperintensity, and contrast enhancement of spinal nerve roots, nerve plexus, and cauda equina, while COVID-19 peripheral neuropathy presents as nonspecific hypoechogenicity and hyperintensity on ultrasound and MR neurography, respectively (Ramani et al., 2021). Moreover, SARS-CoV-2-induced or vasopressor-induced (given for hemodynamically unstable patients) gangrene can present with MRI hyperintense signals and absence of enhancement of necrotic tissue, while arthritis and synovitis present as MRI synovial enhancement and ultrasound power Doppler signals (Ramani et al., 2021).

Histopathological Findings in Autopsy or Endoscopic Specimens

Several histopathological, immunohistochemical, and EM findings were reported in autopsy or endoscopic specimens of various tissues from COVID-19 patients, including pulmonary, GI, cardiovascular (CV), endocrine, and genitourinary, among others (Table 5).

Table 5 Histopathological, electron microscopic (EM), and immunohistochemical (IHC) findings in autopsy or endoscopic specimens of coronavirus disease 2019 (COVID-19) patients

Body systems	Histopathological and IHC findings	Source
Pulmonary system	Alveolar epithelial desquamation and squamous metaplasia Alveolar capillaries thrombosis Diffuse alveolar damage and hyaline membrane formation Intracytoplasmic viral inclusion Congestion and patchy hemorrhagic necrosis Mononuclear inflammatory cells infiltrate +/− multinucleate giant cells Massive fibrinous exudate Pyroptotic cell death features: cytoplasmic vacuoles, membranous blebs IHC: viral nucleocapsid protein along epithelial cells and CD8+ cytotoxic T-cell infiltration	Deshmukh et al. (2021) Nardacci et al. (2021)
Genitourinary system	Proximal tubules loss of brush borders Tubular cells vacuolar degeneration edema or necrosis Glomerular swelling and intracapillary thrombosis Subcapsular lymphocytic infiltrate Nonspecific fibrosis Interstitial space swelling in distal tubules and collecting ducts EM: viral spike-like particles along podocytes and TC IHC: viral nucleocapsid protein in tubular cells	Deshmukh et al. (2021)
Hepatobiliary system	Hepatocytes degeneration and focal necrosis Periportal and centrilobular necrosis Dense portal triad atypical lymphocyte infiltration Dilated sinusoids Fibrotic nodules (cirrhosis) Small bile ducts biliary plugs	Deshmukh et al. (2021)
Gastrointestinal and endocrine systems	GI mucosal degeneration and necrosis Gastric lamina propria and submucosal congestion with monocyte and lymphoplasmocytic cells infiltrate Pancreatic endocrine degradation Suprarenal cortical necrosis, cortical lipid degeneration, focal inflammation, hemorrhage, and vascular thrombosis	Deshmukh et al. (2021) Alzahrani et al. (2021)
Cardiovascular system	Endocarditis and interstitial tissue inflammation Lymphocytic myocarditis Focal edema and necrosis Interstitial hyperplasia Fibrosis	Deshmukh et al. (2021)

(continued)

Table 5 (continued)

Body systems	Histopathological and IHC findings	Source
Central nervous system	Hyperemia, edema Neuronal degeneration/demyelination Infarction or hemorrhage Congestion and patchy hemorrhagic necrosis Diffuse astrogliosis Cerebellar and frontal lobe microglia activation and CD8+ cytotoxic T-cell infiltration IHC: viral proteins in medulla oblongata, CN-IX and CN-X; HLA-DR+[a] in subpial and subependymal; GFAP+[b]; CD8+ cells in parenchyma and perivascular area; viral spike protein on NRP1 in olfactory epithelial cells	Deshmukh et al. (2021) Matschke et al. (2020) Cantuti-Castelvetri et al. (2020)
Musculoskeletal system	Pale/scattered degenerative myofibers surrounded by macrophage Atypical ring-like myofibrillar architecture (NADH stain)	Ramani et al. (2021)
Integumentary system	Intraepidermal Langerhans cells infiltrates Parakeratosis, acanthosis, dyskeratotic and necrotic keratinocytes Superficial dermal perivascular lymphoplasmocytic infiltrates Capillary thrombosis	Deshmukh et al. (2021)

Authors' Own Table

Abbreviations: *CN-IX* cranial nerve IX (i.e., glossopharyngeal nerve), *CN-X* cranial nerve X (i.e., vagus nerve), *HLA-DR* human leukocyte antigen—DR isotype, *GFAP* glial fibrillary acidic protein, *NRP1* neuropilin-1, *NADH* nicotinamide adenine dinucleotide reductase

[a] Activated microglia marker

[b]Activated astrocytic marker

Prognostic Value of Clinical and Laboratory Parameters

Fever combined with dyspnea and smoking is the most important prognostic factor for disease progression, while acute cardiac injury, preexisting cardiovascular disease (CVD), DM, respiratory disease, and HTN are reported to be the most significant prognostic factors for mortality rate (Hatmi, 2021). Moreover, CVD and HTN are prognostic factors for disease severity (Hatmi, 2021). It is reported that 52 (27.8%) out of 187 COVID-19 patients in China developed a myocardial injury, confirmed by an increased level of troponin (Guo et al., 2020). Heart failure (HF) was reported in 24.4% of 176 COVID-19 patients confirmed with HF marker, N-terminal pro-b-type natriuretic peptide (NTproBNP), with non-survivors having a higher prevalence compared to survivors (49.4% vs. 3.2%) (Gavriatopoulou et al., 2020).

Several laboratory parameters have been found to have prognostic value in COVID-19 patients. For instance, elevated NLR is associated with severe disease, whereas lymphopenia is correlated with a higher need for mechanical ventilation and death in severe cases (Lee et al., 2020). Similarly, reduced platelet to lymphocyte ratio is predictive of COVID-19 severity and worse outcome, and low platelets also increase hospitalization risk and inpatient mortality (Lee et al., 2020). In another meta-analysis and systematic review, platelet count was reported to be lower in severe patients (177.38 × 109 L^{-1}) than that of critical cases (205.96 × 109 L^{-1}) (Kazemi et al., 2021). Kazemi et al. (2021) also found the mean CRP level to be significantly higher in dead patients vs. recovered ones (85.82 vs. 32.99 mg/L), while the mean values among the invasive-ventilated, no-oxygen therapy, and noninvasive-ventilated groups were reported to be 48.89, 44.03, and 40.58 mg/L, respectively. Moreover, a significant correlation between Hb, platelets, and creatinine levels, and COVID-19 severity, with mean Hb and platelets being higher among critical patients is compared to other patients (Kazemi et al., 2021).

Moreover, the development of ARDS and mortality is associated with elevated ferritin (Lee et al., 2020). High levels of CRP, ferritin, procalcitonin, D-dimer, and neutrophils imply severe pneumonia, and a decrease in these parameters indicates therapy effectiveness; an increase in lymphocyte count is also correlated with a better outcome (Yu et al., 2020).

Furthermore, high admission levels of markers such as cardiac troponin-I ≥21 ng/L, D-dimer ≥1112 ng/mL, CRP ≥10 mg/dL, and LDH ≥334 U/L are directly correlated with short-term mortality (Peiró et al., 2021), while elevated bilirubin is linked to disease severity and progression (Gupta et al., 2020). This was in agreement with another study that reported total bilirubin level and LDH to be significantly elevated in deceased patients compared to survivors (Danwang et al., 2020).

Lung cancer tumor markers, such as CEA, NSE, CYFRA21-1, and SCCA, can predict clinical outcomes and increased mortality (He et al., 2020), and viral load, abnormal ALT/AST, CK, and CXR are also prognostic factors (Yi et al., 2020). In an investigation, it was demonstrated that, compared to mild COVID-19 respiratory samples, those with severe COVID-19 have significantly higher SARS-CoV-2 viral load (Zheng et al., 2020a). Elevated IL-1 (IL-1α) is correlated with high viral load and mortality and is found in severely ill cases, whereas high levels of IFN-γ are reported in COVID-19 patients compared to healthy individuals, which are correlated with higher viral load and lung injury (Costela-Ruiz et al., 2020). Moreover, it is reported that viral load is directly associated with elevated M-CSF, IFN-α2, IL-IL-1α/1β, IL-2, 4, 7, 10, 13, 17, IP-10, G-CSF, IL-12, IFNγ, and HGF but indirectly correlated to PDGF, while scores of lung injury are associated with IL-1α, IL-2, 4, 7, 10, 17 IFNγ, HGF, IFN-α2, IP-10, G-CSF, and M-CSF (Liu et al., 2020c).

Moreover, IL-6 was found in higher levels in those who died than in the recovered cases (Costela-Ruiz et al., 2020), and low CD4+ and CD8+ T cells are seen in severe diseases (Gupta et al., 2020). It is reported that even a moderate elevation in IL-6 (i.e., above 80 pg/mL) implies that the COVID-19 patient is at high risk of respiratory failure, and hence serial laboratory tests to measure IL-6 level might be critical in recognizing disease progression (Gubernatorova et al., 2020). It is reported that the plasma of both ICU and non-ICU patients contained high levels of several cytokines, such as IL-1β, IL-7, IL-8, IL-9, IL-10, G-CSF, GM-CSF, IFNγ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, TNFα, and VEGF, while patients who required both ICU admission and oxygen therapy due to severe pneumonia-induced

ARDS had higher levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α, and TNFα (Kircheis et al., 2020). The result of a study on laboratory diagnosed symptomatic or asymptomatic patients, as well as healthy individuals, demonstrated plasma level of 18 cytokines to be lower in asymptomatic patients, compared to symptomatic patients, while the same level of 32 cytokines was detected in both asymptomatic and healthy individuals (Long et al., 2020).

COVID-19 Complications and Long-Term Effects

For unknown pathomechanisms, some COVID-19 patients, referred to as long hauler COVID, long COVID, or long-term COVID by various sources, will still experience residual and long-term persistence and recurrence of symptoms after the initial 4-week period of the acute phase and during the last phase of COVID-19 that starts at T_T (time of the tail onset) in the post-acute tail phase (Griffin et al., 2021). A systematic review and meta-analysis (Lopez-Leon et al., 2021) on 47,910 patients revealed that 80% of patients continue to experience one or more symptoms in long term, with the most prevalent symptoms being fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), dyspnea (24%), ageusia (23%), anosmia (21%), postexercise polypnoea (21%), arthralgia (19%), cough (19%), sweat (17%), as well as nausea/vomiting, chest pain, memory loss (each 16%), and hearing loss/tinnitus (15%). It is estimated that 6 months after the onset of symptoms, 76% of patients will continue to have a minimum of one adverse symptom, with tiredness or muscular weakness being the most frequent complaint (63%), followed by sleeping difficulties (26%) (Wang et al., 2021a). It has been reported that D614G and possibly N501Y mutation are responsible for such neurological symptoms, as well as anosmia and ageusia (Wang et al., 2021a). Other chronic signs and symptoms such as anxiety, depression, digestive problems, weight loss, skin lesions, pain, sleep disorders, intermittent fever, and high heart rate at rest were also reported (Lopez-Leon et al., 2021). Moreover, the most common persistent abnormal laboratory results in long-term COVID-19 cases were abnormal CXR/CT (34%), D-dimer (20%), as well as elevated CRP (8%), ferritin (8%), procalcitonin (4%), and IL-6 (3%) (Lopez-Leon et al., 2021).

Furthermore, peripheral neuropathy due to prone positioning is a very rare complication in both the perioperative care (in 0.14% patients) and ARDS patients, to a point where the landmark PROne positioning in SEvere Acute respiratory distress syndrome (PROSEVA) trial does not even include it as a complication (Malik et al., 2020). Prone positioning is included in The Surviving Sepsis Campaign COVID-19 guidelines as the mainstay of treatment for moderate to severe ARDS cases and has been reported to significantly lower mortality and improve oxygenation (Coppo et al., 2020). However, a significantly high prevalence of possibly prone positioning-induced peripheral neuropathy has been reported in these patients. Malik et al. (2020) reported peripheral neuropathy diagnosis among 14.5% of COVID-19 patients with ARDS ($n = 83$), with 91.7% of them having prone positioning in their histories. Upper extremities were most frequently involved in these patients (76.2%), as well as ulnar nerve (28.6%), radial nerve (14.3%), sciatic nerve (14.3%), brachial plexus (9.5%), and median nerve (9.5%). The etiology behind such neural injuries seen in SARS-CoV-2 and other viral infections (e.g., HCV, HIV, and VZV) is still not known and might be the result of prone positioning-induced nerve compression or stretch, as well as postinfectious inflammatory neuropathy, systemic neuropathy, or hematoma-induced nerve entrapment (secondary to anticoagulant therapy) (Fernandez et al., 2021). Osteoporosis and osteonecrosis can be the complication of COVID-19 coagulopathy or corticosteroid treatment (Ramani et al., 2021). Similar to myositis seen in other viral infections (e.g., hepatitis, influenza, or HIV), myositis and its complication, rhabdomyolysis, have been reported in SARS-CoV-2-infected patients (Ramani et al., 2021). Myalgia and weakness in some COVID-19 patients can be due to myositis and/or rhabdomyolysis, which might result in compartment syndrome, and intravascular coagulation, and myoglobinuria-induced acute kidney injury (Ramani et al., 2021).

COVID-19 Clinical Trials

Since the start of the pandemic, approximately 500 randomized controlled trials (RCTs) have been registered globally for therapeutics or postexposure prophylaxes of COVID-19 (Davis et al., 2020). The most common drugs used for the treatment or prophylaxis purposes in decreasing order were HCQ, immunomodulatory drugs, antivirals, angiotensin system antagonists, colchicine, NSAIDs, and tranenxamic acid (Babaei et al., 2020).

HCQ and chloroquine (CQ), two antimalarial and anti-inflammatory medications, were among the earliest drugs used alone or in combination of several trials (Gao et al., 2020) for either prophylaxis or treatment of mild, severe, or critical COVID-19 patients (Babaei et al., 2020). It was found that neither CQ nor HCQ improve outpatient or inpatient outcomes, nor do they reduce infection rates when used as postexposure prophylaxes (Fang et al., 2020). The second category of widely used agents was immunomodulatory, such as mAb (e.g., tocilizumab, which is an IL-6 receptor antagonist), glucocorticoids, immunoglobulins, and IFNs (such as IFNα2b) (Babaei et al., 2020). Glucocorticoids (dexamethasone), alone or with other drugs, were found to decrease mortality (by one-third in those on ventilation and by one-fifth in on oxygen therapy) in critically ill patients; however, it might be dangerous if administered at early disease stage as it disrupts antiviral immune response (Babaei et al., 2020). A retrospective study on the effect of dexamethasone on COVID-19 pneumonia patients demonstrated no significant impact on clinical course, adverse events, or outcome (Hu et al., 2020). It is reported that immunomodulatory agents could increase the risk of bacterial and fungal superinfections, such as secondary invasive pulmonary aspergillosis (Fang et al., 2020). Additionally, combining inhaled IFN-α2b and angiotensin receptor blockers (ARB) was shown to increase inflammatory process resolution (by lowering IL-6) and viral clearance

(Zhou et al., 2020a). In a multicenter, open nonrandomized observational study (Pereda et al., 2020) in Cuba, where all laboratory-confirmed COVID-19 cases were treated with intramuscular IFN-α2b (Heberon Alpha R) combined with lopinavir-ritonavir (LPV/RTV) (except those with contraindications), it was concluded that those who received these agents had almost 60 times greater chance of recovery. Other clinical trials that tested the efficacy of antiviral therapy, including LPV/RTV, remdesivir, and umifenovir, found LPV/RTV to have therapeutic potential; however, they found no efficacy when antivirals (or HCQ) were combined with azithromycin (Babaei et al., 2020). Moreover, Babaei et al. (2020) reported umifenovir to be safe, with a higher rate of negative PCR on day 14 of infection, nonetheless, with no evidence of improved outcomes. The "Adaptive COVID-19 Treatment Trial" (ACTT), a double-blind placebo RCT, found that remdesivir decreased recovery time compared to a placebo, prevented disease progression and resulted in a shorter hospital stay and faster discharge (Beigel et al., 2020). A randomized trial of convalescent plasma (that contains Abs of recovered patients) and placebo in severe COVID-19 patients with pneumonia did not find any significant differences in overall mortality or clinical outcome (Simonovich et al., 2021). However, in an uncontrolled case series of five critical COVID-19 patients with ARDS, the administration of convalescent plasma improved clinical outcomes, reduced fever, viral load, pulmonary lesions on CT, and the need for mechanical ventilation (Shen et al., 2020).

Moreover, a double-blind RCT on hospitalized non-intubated COVID-19 patients indicated that tocilizumab has no impact on intubation or death prevention, although it decreased the risk of developing serious secondary infections (Stone et al., 2020). In an ongoing phase 2 trial (BLAZE-1 trial), the efficacy of placebo and intravenous infusion of neutralizing mAb bamlanivimab (LY-CoV555) in either 700, 2800, or 7000 mg in treating mild or moderate COVID-19 was compared. It was demonstrated that compared to placebo, those treated with bamlanivimab had lower symptom severity and lower hospitalization rate, and the patients who received the highest dose had lower viral load at day 11. Since this viral load reduction was found in most patients, it was considered to be the result of natural disease course and not having a clinical significance (Chen et al., 2021). Three other clinical trials in more than 300 hospitals across 5 continents are investigating the benefit of therapeutic (high dose) and prophylactic (low dose) anticoagulants such as heparin in moderately ill-hospitalized patients who are not in the ICU and not on any organs support (e.g., mechanical ventilation). It demonstrated that high-dose heparin is safe and effective in preventing thromboembolism in these patients (National Heart, Lung, and Blood Institute (NHLBI), 2021).

In addition, some studies have found that vitamin D supplementation decreases mortality rate and viral load in COVID-19 patients; thus, currently, a nationwide RCT is being conducted in the USA and is to be completed by March 2021 (Sengupta et al., 2021). In fact, the deficiency in vitamin D (25-OH-D) has been reported to increase the risk of SARS-CoV-2 infection and hospitalization due to COVID-19 (Babaei et al., 2020), as it prevents CRS by inhibiting the proliferation of inflammatory cells, decreases the AT-II level by upregulating ACE2 level, and decreases the hypercoagulability by increasing antithrombotic factors (Sengupta et al., 2021). The effectiveness of NK cells, as well as stem cells (SC) such as umbilical cord (UC)/Wharton's Jelly (WG) mesenchymal SC (MSCs), dental pulp SC, and human embryonic SC, are being investigated (Babaei et al., 2020). MSCs decrease inflammation by antagonizing the pro-inflammatory cytokines, such as IL-1α and TNF-α (Costela-Ruiz et al., 2020). It is reported that the injection of placental and UC/WG MSCs is well tolerated and can alleviate respiratory symptoms (Saleh et al., 2021).

It is noteworthy to mention that the stage at which these medications are administered plays a key role in the achieved outcome. For example, IFNs (that increase innate immune response), mAbs, and antivirals are most likely beneficial if given during the viral replication period at T_{DVR}, while immunomodulatory drugs affecting innate immunity and anticoagulants are more effective if administered during the early inflammatory period at T_{EI} (Griffin et al., 2021). Similarly, the unnecessary antibiotics given early in the course of the disease will not only be helpful but will increase antimicrobial resistance; hence, in order to be more effective and beneficial, they must be administered at the appropriate secondary infection phase at T_{SI} (Griffin et al., 2021).

Isolation, Quarantine, and Social Distancing

One of the primary reactions against new contagious diseases is quarantine (Parmet & Sinha, 2020) that restricts and confines the movements of individuals who have been in contact with infectious agents in order to confirm whether or not they were infected (CDC, 2017). Two weeks of quarantine at home or in an assigned facility has been suggested for those who have come into contact with a confirmed or probable case of COVID-19, as well as travelers from an endemic area (WHO, 2021d). It is reported that quarantine is recommended in case of continuous or cumulative unprotected exposure of more than 15 min within a distance of 6 feet (≈1.83 m) or less (Griffin et al., 2021). Quarantine is distinct from isolation, which segregates infected individuals from healthy ones (CDC, 2017).

In China, the government used a "mass quarantine" strategy, imposing quarantines on almost 60 million people, which drastically reduced disease incidence (Roper, 2020). The speedy Chinese response to the pandemic was reported by Gregory Poland—the director of the Mayo Clinic's Vaccine Research Group in Rochester, Minnesota, USA—as the critical factor that curtailed the spread of the virus, as compared to other countries, whose reactions were delayed despite a longer preparation time (Burki, 2020). It is worth mentioning that after the implementation of these preventative measures in Wuhan on January 23, 2020, R0 began to decline from a value of approximately four to below one by March 2020 (Rahman et al., 2020a). In other countries across the globe, such as the USA, quarantine measures have also been implemented; however, inadequate quarantines resulted in the USA, which has only 4% of the world's population, having almost 26% of world cases and 24% of world deaths as of July 16, 2020 (Blumenthal et al., 2020).

Surprisingly, it was also reported that, compared to those under the age of 42, people with confirmed COVID-19 who are above the age of 42 experience longer incubation periods, suggesting that effective quarantine policies could be targeted at specific age groups as opposed to the existing "unified" policies (Pak et al., 2020). Girum et al. (2020) systematically reviewed studies on some COVID-19 prevention strategies, such as quarantine and isolation. They concluded that isolation combined with a 3-month self-quarantine could prevent 31% of COVID-19-related deaths, but that isolation by itself is not very effective since, without high levels of contact tracing and screening, this strategy will miss 75% of cases. In contrast, if SARS-CoV-2 completely adapts to humans, it would be difficult to contain the pandemic through quarantine or other public health measures (Ye et al., 2020).

In the pre-exposure period, vulnerable individuals should employ a range of steps, including social distancing and minimizing contact with suspected cases, in order to reduce their risk of SARS-CoV-2 infection (Griffin et al., 2021). Social distancing is defined as "keeping a safe space between yourself and other people who are not from your household" (CDC, 2020, para.1). It is worth noting that several weeks into the pandemic, many scholars have emphasized that the term "social distancing" is misleading and, in fact, counterproductive (Sørensen et al., 2021). It has been argued that "distant socialization" must be encouraged instead, and in order to prevent the spread of SARS-CoV-2, efforts should be made to establish social connections while also keeping physical distancing (Sørensen et al., 2021). Thus, the WHO Secretary-General, Dr. Tedros Adhanom Ghebreyesus, started using the term "physical distance" in his announcements and speeches (Sørensen et al., 2021).

The WHO (2021b) advises people to keep an interpersonal distance of at least 1 m in indoor spaces and when they talk, cough, and sneeze in order to decrease infection by SARS-CoV-2 droplets. However, as previously mentioned, the virus can be airborne in certain conditions, and computational fluid-particle dynamics (CFPD) models show that wind and relative humidity can lead to further movement of virus-laden droplets in the air, which would make the implemented social distancing rule inadequate (Feng et al., 2020). It is, however, important to note that without any specific pharmaceutical therapy or prophylaxis, strict social distancing (i.e., such as in China, where movement and contact of more than 500 million individuals across 80 cities were banned) is the primary means to control the pandemic (Du et al., 2020) and to prevent asymptomatic carriers—who are usually not identified and diagnosed—from transmitting the virus (Zhang et al., 2020c). It is reported that presymptomatic and asymptomatic individuals are responsible for at least 50% of community transmission (Subramanian et al., 2021). The median duration of virus shedding by asymptomatic cases has been varied significantly among different studies and ranged between 4.5 and 19 days, with one analysis reported positive RNA for up to 2 months in a few cases (Zhang et al., 2020c). Moreover, viral shedding occurs 2–3 days prior to the onset of symptoms (Peng et al., 2021).

A study among 149 countries concluded that using any of 5 different social and physical distancing techniques (closing schools, closing workplaces, limiting social gatherings, restricting movement, and implementing lockdowns) will result in a

13% reduction in disease incidence (Islam et al., 2020b), while the addition of 4 months of social distancing to isolation and quarantine interventions for those over 70 years old will decrease virus reproduction and decrease the number of deaths by almost half (Girum et al., 2020). It is reported that some countries, including France, Italy, Spain, Switzerland, and the UK, have been unable to contain the pandemic due to failure to implement and maintain adequate social distancing measures (Islam et al., 2020a). Moreover, with the exception of Switzerland and the UK, the other aforementioned countries failed to control the pandemic owing to a lack of prompt lockdown enforcement (Islam et al., 2020a).

In contrary to the aforementioned preventative measures, it has been argued that several other new and novel viruses have emerged throughout history (e.g., H2N2 influenza viruses (H2N2 in 1957, H3N2 in 1968, H5N1 in 2004, H1N1 in 2009, and seasonal influenza), SARS-CoV (2003), and MERS-CoV (2012)), yet, no social distancing, face masks, lockdown, and school closures or other extreme preventative measures were introduced (United Health Professionals, 2021), even though no vaccines were available at the time of outbreak onset. They further explain the unscientific logic behind the mandatory use of face masks by asymptomatic and healthy individuals by giving reasons such as 77% of influenza cases are asymptomatic (yet they are not being asked to no wear masks or practice social distancing), prolonged use of face masks increases mouth breathing, thus decreasing saliva and drying the mouth, leading to oral inflammation, cavities, and periodontal diseases. They also point out to the hygiene hypothesis, stating that strict hygiene measures can increase the risk of developing inflammatory, atopic, and autoimmune diseases, as well as some types of cancers (United Health Professionals, 2021). According to the 1989 hygiene hypothesis by an epidemiologist, Dr. David Strachan, lower incidence of unhygienic-induced childhood infections, such as viral respiratory infections (RSV, rhinoviruses, etc.) as a result of contact with other children (e.g., in daycare settings) can increase the risk of adulthood atopic diseases, such as asthma (Schaub et al., 2006), which is exacerbated in 85% of children by most viral respiratory tract infections (Morais-Almeida et al., 2020).

COVID-19 Risk Factors and Vulnerable Populations

People with Preexisting Conditions, the Elderly, and Others

According to CDC (2021b), regardless of age, any adults who have cancer, DM type-2, chronic kidney disease, immunocompromised status (e.g., solid organ transplant patients), obesity (i.e., body mass index [BMI] $\geq$ 40 kg/m^2), or who are smokers are at increased risk of severe COVID-19. Adults with asthma, HTN, liver disease, a BMI of 25–30 kg/m^2, pulmonary fibrosis, DM type-1, or immunocompromised status (e.g., blood or bone marrow transplants, HIV, or corticosteroid medication), among others, might be at increased risk (CDC, 2021b). It is reported that approximately 0.9% of all deaths were not linked with any preexisting medical conditions (Islam et al., 2020a). A systematic review and meta-analysis (Cao et al., 2020) reported 35.6% of COVID-19 patients had comorbidities. Another systematic review documented the most common comorbidities and conditions to be HTN (20.7%), CVD (9.6%), DM (9.55%), respiratory diseases (7%), and smoking (9%) (Hatmi, 2021). Abdi et al. (2020) reported DM as a risk factor for COVID-19, with diabetes being 14.5% prevalent in patients. While the signs and symptoms of COVID-19 are the same for both diabetics and nondiabetics, the former experience higher severity and mortality (Abdi et al., 2020). On the other hand, COVID-19 not only can exacerbate and complicate preexisting diabetes but can also result in the development of new-onset DM (due to endocrine pancreas involvement) (Rubino et al., 2020). Furthermore, the high levels of glucose, free fatty acids, and AT-II in those diabetic, obese, and hypertensive patients, respectively, are found to create a chronic inflammatory state leading to the hyperactivation of the NF-κB pathway, resulting in severe COVID-19 with the worst prognosis (Hariharan et al., 2020). Additionally, it is reported that individuals with DM type-2, hypertension, chronic pulmonary disease, as well as elderly, have greater expression of ACE2-R, thus making them more susceptible to SARS-CoV-2 infection (Solis & Nunn, 2021).

Moreover, age is clearly correlated with poor COVID-19 outcomes, evidenced by high mortality rates among nursing home residents (Fang et al., 2020), which account for 42%, 54%, and 44.6% of the total deaths reported in the USA, Ireland, and France, respectively (Thompson et al., 2020). Similarly, the mean age of death in both the UK and Italy was around 80, and in the UK, those above 65 years of age accounted for 87% of all deaths (Sornette et al., 2020). It is reported that the percentage of men aged 70–84 who may die from COVID-19 rises from about 5% for the original SARS-CoV-2 strain to more than 6% for B.1.1.7 variant. Furthermore, for males 85 years old or older, the risk of death increases from 17% for the original virus to almost 22% for the Alpha variant (Mallapaty, 2021). Elderly men are at higher risk of COVID-19 and death than elderly women, as the immune system reacts less robustly in older men, besides aging by itself in males substantially decreases the total numbers of lymphocytes (Perrotta et al., 2020). In addition, elderly men and postmenopausal women have reduced level of testosterone and estradiol, respectively, leading to the disinhibition of NF-κB pathway and hence increased level of TNFα and IL-6 and subsequent cytokine storm and resultant lung injury, since estrogen attenuates NF-κB signaling cascade and lower cytokine (e.g., IL-6, IL-8, and TNF-α) production (Hariharan et al., 2020).

Moreover, younger COVID-19 males have a better outcome than older men due to their higher levels of testosterone, as well as the peripheral conversion of testosterone to estrogen, which will double the anti-inflammatory effects; testosterone deficiency is also associated with higher levels of the inflammatory marker, such as CRP (Al-Lami et al., 2020). In fact, the therapeutic role of hormone replacement therapy (HRT) has been supported by a reduction in IL-1, IL-6, and TNF-α levels in postmenopausal COVID-19 patients, and the exogenous estrogen and testosterone are believed to act similar to corticosteroid in reducing SARS-CoV-2-induced multi-organ inflammatory damage without hindering the host antiviral immune response, while the anticatabolic effects of testosterone on respiratory muscles are believed to decrease the need for mechanical ventilation (Al-Lami et al., 2020). Furthermore, the lower COVID-19 incidence and mortality in young and middle-aged females compared to the male counterparts are due to their extra X chromosome which carries the majority of the genes responsible for controlling and regulating immune responses, thus providing women with a more effective innate immune response against viral infections while preventing cytokine storm development (Hariharan et al., 2020).

Preexisting mental distress can also have an impact on the likelihood of having COVID-19. For instance, in a cohort study performed in the USA, Nemani et al. (2021) reported the probability of having positive COVID-19 test for schizophrenia spectrum, mood, and anxiety disorders was reported to be 22.3%, 25.4%, and 24.1%, respectively, which could be attributed to SES, as well as high viral exposure due to environmental factors, including crowded living space, institutional settings, and lack of personal protective equipments. Additionally, schizophrenia is reported to be associated with abnormalities in cytokine signaling pathways, which result in severe COVID-19 and increased mortality (Nemani et al., 2021). Moreover, lower SES, and low social integration, will increase the risk of the development of chronic diseases, including heart, liver, and kidney disease, as well as DM, asthma, and stroke, resulting in higher susceptibility to SARS-CoV-2 infection (Solis & Nunn, 2021). Similarly, air pollution which affects 90% of people living in urban area globally increases the risk of chronic obstructive pulmonary disease (COPD), lung cancer, asthma, and respiratory infections. In fact, according to recent findings, air pollution is responsible for approximately 15% of worldwide COVID-19 mortality (Solis & Nunn, 2021).

Besides these non-modifiable factors, women are less likely to smoke and have other bad lifestyle habits and chronic conditions (e.g., HTN, diabetes, etc.), which lower their risk of infection (Zheng et al., 2020b). Moreover, even though men were shown to be more susceptible to SARS-CoV-2 infection, women account for a disproportionate percentage of healthcare workers, thus having a higher risk of hospital-acquired infection (Jensen et al., 2021). The prevalence of being a current smoker was reported to be significantly higher in critical or fatal COVID-19 patients compared to noncritical individuals (Zheng et al., 2020b). Furthermore, the percentage of blood type “A” was considerably greater in COVID-19 cases than that of healthy individuals (37.75% vs. 32.16%), whereas this value was significantly lower for type “O” (Zhao et al., 2020). This is explained by the presence of anti-A Abs (inhibitors of virus-ACE2-R interactions) in people with blood type “O,” which prevents viral binding to ACE2-R and makes them less susceptible to COVID-19 (Zhao et al., 2020). The aforementioned risk factors still do not explain the development of critical COVID-19, need for ICU admission, and eventually death in healthy young individuals; although a recent report suggests that previously formed undetected auto-Abs in some people may be the reason behind this (New Findings on the Pathophysiology of Severe COVID-19 Infections, 2021).

Pregnant and Breastfeeding Women and Neonates

The global incidence of COVID-19 in pregnant women is not known; however, a screening of all pregnant women admitted for delivery at a New York hospital revealed that 15.4% tested positive for SARS-CoV-2, and 87.9% of these cases were asymptomatic (Rodrigues et al., 2020). In general, pregnancy-induced immunosuppression is a risk factor for symptomatic infection which increases the risk of maternal (i.e., endotracheal intubation, MOF and ICU admission, DIC, etc.) and neonatal complications (i.e., vertical transmission, intrauterine growth retardation, spontaneous abortion), and thus prenatal screening for COVID-19 must be performed (Lopes de Sousa et al., 2020). A systematic review (Rodrigues et al., 2020) reported that pregnant women do not seem to be at higher risk of severe COVID-19 compared to nonpregnant women. Another systematic review and meta-analysis of pregnant women with COVID-19 reported that 50% needed C-sections (indications not reported) and 13% were admitted to the ICU, while 45% experienced complications such as placenta previa, premature rupture of membrane, or non-reassuring fetal status (Capobianco et al., 2020). According to Capobianco et al. (2020), 6% of neonates were infected—with unknown infection time (i.e., intrauterine, during vaginal delivery, or postnatal period)—and 39% of cases presented with neonatal complications, including fever, pneumonia, respiratory distress syndrome, and preterm birth (weight < 3.0 kg); however, no SARS-CoV-2-induced congenital malformations are yet reported (Rodrigues et al., 2020). In another systematic review, 68% of neonatal COVID-19 cases presented with symptoms, such as fever, GI symptoms, hypoxia, or cough, but even so, 75% breathed spontaneously (no intubation needed), and all patients were discharged after 10 days (Trevisanuto et al., 2020). Interestingly, vaginal delivery is not a contraindication in infected women due to negative vaginal screenings for the virus (Qiu et al., 2020) and of rare and mild cases of neonatal infection; thus, mother-infant separation is also not recommended by the WHO and UK guidelines (Gale et al., 2021), though a few countries (viz., China, Singapore, and South Korea) still recommended separation immediately after birth (Yeo et al., 2020). Except for Singapore and South Korea, most countries recommended that COVID-19-positive mothers breastfeed their neonates, while China recommends using pasteurized expressed breastmilk (Yeo et al., 2020).

Children and Adolescents

Children can still experience the same typical symptoms of fever, dry cough, fatigue, and so forth; however, they usually present with mild or asymptomatic disease, and unlike adults, age and gender are not risk factors (Castagnoli et al., 2020). The mild clinical symptoms in children are attributed to the lower expression of ACE2-R in their nasal epithelial compared to that of adults (Lee et al., 2020). However, childhood COVID-19 cases with complications were first observed and reported in the

UK, where eight previously healthy children presented with symptoms of systemic hyper-inflammatory shock, called multisystem inflammatory syndrome in children (MIS-C) (Feldstein et al., 2020). MIS-C presented with CV (in 80%), hematologic (in 76%), mucocutaneous (in 74%), and respiratory (in 70%) symptoms, which were similar to those of KD—a rare pediatric vasculitis of unknown origin or possible abnormal immunological response to an infectious agent—yet, unlike KD, MIS-C predominantly affects children over the age of 5 and adolescents (Shaigany et al., 2020; Feldstein et al., 2020). This can result in coronary artery aneurysm in 25% of cases if left untreated (Gupta et al., 2020). Interestingly, cardiovascular manifestations have been reported in adults, including Kawasaki-like multisystem inflammatory syndrome, similar to the findings of complicated SARS-CoV-2 infection in children. For example, a 45-year-old male with no past medical history presented to the emergency department (ED) with fever, sore throat, diarrhea, bilateral pain in lower limbs, bilateral non-purulent conjunctivitis, periorbital erythema and edema, unilateral neck lymphadenopathy, diffuse skin rash, etc., meeting criteria for Kawasaki disease (KD) (Shaigany et al., 2020).

Severe COVID-19 GI complaints (e.g., diarrhea, vomit, or abdominal pain) were predominantly seen in children with COVID-19-related cardiac impairment (Giacomet et al., 2020). Among those hospitalized with MIS-C, 84.1% presented with GI symptoms (Miller et al., 2020). MIS-C was designated a reportable disease on May 14, 2020, by the CDC, which advises clinicians to report any cases meeting the criteria (Kest et al., 2020). However, according to Griffin et al. (2021), the MIS-C in children is similar to adult multisystem inflammatory syndrome (MIS-A).

Lower Socioeconomic Status (SES) and Ethnic Minorities

The pandemic has been found to disproportionately affect marginalized populations, people with lower SES, and racial and ethnic minorities (Fang et al., 2020). For instance, Black people (13% of the US population) account for 20% of COVID-19 cases and 22% of deaths, while Hispanics (18% of the US population) account for 33% of COVID-19 new cases (Blumenthal et al., 2020). A similar situation was reported in the UK, where COVID-19 mortality has been high among Black and Asian populations, as well as other ethnic minorities and those with lower SES (Han et al., 2020). In addition, compared to non-Hispanics, COVID-19 cases were more prevalent in American Indian/Native Alaskan and Hispanic/Latino people (CDC, 2021c). Furthermore, compared to white individuals, the American Indian/Native Alaskan group was 3.4 times more likely to be hospitalized, while this value was 2.8 times for Hispanic/Latino and Black/African American people. Moreover, the risk of COVID-19 death in these ethnicities was increased and ranged from 2.0 to 2.4 times (CDC, 2021c).

Moreover, exposure to SARS-CoV-2 is higher in those unable to social distance, including some of the world's most vulnerable groups (e.g., prisoners, homeless, and refugees), and those who cannot work remotely from home (e.g., healthcare workers, cashiers, food preparation and waitresses/waiters, retail associates, and janitors) (Solis & Nunn, 2021). Moreover, low SES and unemployment create food insecurity, which force affected individuals to rely on food banks and/or work in hazardous settings, thus being at higher risk of SARS-CoV-2 exposure (Solis & Nunn, 2021). According to the US Bureau of Labor Statistics, in 2019, 29% of the population was able to work from home, while 25% could only occasionally do so; however, this value was lower in Hispanic (13%) and Black (18%) wage workers (Solis & Nunn, 2021). In addition, many of those able to work remotely had higher education level (at least a bachelor's degree) and greater income (above the 75th percentile) (Solis & Nunn, 2021).

Another factor influencing access to health care is proximity to metropolitan areas, which have bigger hospitals with more advanced technology. For instance, people living in rural areas of the USA or sub-Saharan Africa have lower access to healthcare facilities and physicians for the treatment of severe COVID-19. Moreover, in the USA, other obstacles limiting equal healthcare access include race and gender discrimination, lack of health insurance, as well as disability status and SES (Solis & Nunn, 2021). Additionally, the imposed social distancing measures worsened healthcare access in some communities in the USA. A notable example is the Hualapai tribe that relies heavily on the revenue generated by tourists visiting the region; however, the social distancing measures compelled them to close down their tourist attraction site, which caused a scarcity of funds to sustain the healthcare facilities and clinics in the community (Solis & Nunn, 2021).

Hou et al. (2020) observed that the prevalence of ACE2 polymorphism was 54% and 39% among Non-Finnish European and African/African-American, respectively. This may explain the higher susceptibility to SARS-CoV-2 and even disease outcome in certain ethnic groups (Hou et al., 2020). In addition, the acquired genetic variants[20] such as chromosome 3 (SLC6A20) and chromosome 9 (9q34), which interact with ACE2-R and ABO blood group locus, respectively, are also more prevalent in European ancestry and increase their risk of COVID-19 (Solis & Nunn, 2021). However mortality is still higher among Black, Native American, and Latinx communities, implying social and environmental parameters are particularly significant in determining COVID-19 outcome (Solis & Nunn, 2021).

In addition, comorbidities, such as obesity, DM, and vitamin D deficiency, show health disparities affecting COVID-19 outcomes. For example, in 2011–2012 in the USA, the rate of DM type-2 was higher among Black and Latinx communities, and American Indian/Alaskan native, Latinx, and Black communities (Solis & Nunn, 2021). Similarly, vitamin D deficiency is found disproportionately in 84.2% of non-Hispanic Black communities, compared to Hispanics (56.3%) and of non-Hispanic White American (34.8%) (Solis & Nunn, 2021).

[20] This is the result of thorough introgression of Neanderthal DNA to the human lineage (Solis & Nunn, 2021), defined as infiltration of genetic materials from one species to another genetically differentiated species (Arnold & Martin, 2009).

Medical Insurance

"In an insurance-based health system, it's insurers who foot the bill for pandemic care […] The pandemic is further complicating an already complicated system" (Roehr, 2020, p. 1). The US healthcare delivery and funding are based on a private for-profit insurance system (Ridic et al., 2012), and unlike most developed countries, where health insurance is provided to everyone regardless of their employment status (Santhanam, 2020), in the USA, health insurance is predominantly provided by the employer-sponsored health insurance (ESI) (Fronstin & Woodbury, 2020). Prior to the COVID-19 pandemic, more than 160 million Americans relied on ESI, and 30 million Americans had no health insurance (Santhanam, 2020). Analysis has already shown that if the unemployment rate reaches 20%, a maximum of 43 million people could lose their health insurance, which is fatal for those with serious diseases (The Lancet Oncology, 2020). The US pandemic-related unemployment reached its peak of 14.7% in April 2020 (Fronstin & Woodbury, 2020), and from March 2020 to September–October 2020, 60 million unemployment insurance (UI) claims have been filed, compared to the previous highest rate of 695,000 per week, which occurred the week of October 2, 1982, and for 20 weeks (from late March 2020), new unemployment claims surpassed 1 million per week (Cutler & Summers, 2020). Furthermore, minorities such as Black and Hispanic Americans, who are already affected by the pandemic as well as poverty and riskier jobs, disproportionately lack health insurance coverage, which further affects their health (Blumenthal et al., 2020). The US 2017 census has reported that the insurance coverage rate was higher for those above 400% of poverty (95.7%), as opposed to those under the 100% of poverty (83%); the uninsured rate of the US population was 8.7%, and of children (<19 years) was 5.4%, with the pediatric population (<19 years) living in poverty was to have the uninsured rate of 7.8%, compared to the uninsured rate of 4.9% for those children not in poverty (Berchick et al., 2018). Moreover, for those who are still able to work during the pandemic, employers have decreased insurance coverage, leaving many employees underinsured (Blumenthal et al., 2020). The 1985 Consolidated Omnibus Budget Reconciliation Act (COBRA) gives laid-off workers the option to still have health insurance even after unemployment; however, if not qualified for the government subsidy, the employees must pay $600 (for individual coverage) to $1800 (for family coverage) at maximum. In other words, the employee must pay 102% of the total premium (i.e., both the employee's and the employer's share), as well as a 2% administrative fee, leading to low COBRA demand (Agarwal & Sommers, 2020; Roehr, 2020).

Moreover, the 2014 Affordable Care Act (ACA) forbids private insurers to exclude, deny coverage, or charge a higher premium based on individual preexisting medical conditions (i.e., "declinable" medical conditions, such as pulmonary or heart diseases), jobs (i.e., "ineligible occupations" with a higher risk of infection), or serious psychological conditions (depression after losing a loved one); however, in June 2020, the Trump administration has asked the US Supreme Court to invalidate the ACA. If this happens, it will be catastrophic for patients, physicians, hospitals, etc., as insurers can even discriminate against individuals with acute or long-lasting COVID-19 (Pollitz & Michaud, 2020).

The need for health insurance has grown due to the need for the COVID-19 diagnosis and treatment (Agarwal & Sommers, 2020). The cost of COVID-19 diagnostic tests among the top two largest hospitals in each state was reported to range from $20 to $850 in the USA (Wapner, 2020), and the cost of severe COVID-19 treatments is up to $20,000 for hospitalization (or as high as $90,000 if ventilator support is indicated) and $3000 for 5-day remdesivir (Pollitz & Michaud, 2020). As a result, many Americans are not willing to be tested or to go to hospitals due to high costs and lack of insurance (Wapner, 2020). Even though The Families First Coronavirus Response Act (FFCRA) that was passed on March 18, 2020, ensures all persons, whether insured or not, have access to free testing, and The Coronavirus Aid, Relief, and Economic Security Act (CARES) also requires insurers to cover "out-network" testing claim, yet, due to legislation loopholes, many individuals still have to pay substantial amounts out of their pocket when visiting the emergency room (ER) or private healthcare facilities. For instance, if a healthcare facility is in the network of the patient insurer, but the ER physician is employed by another agency (i.e., out of the network of patient insurance plan), the patient may not be covered for the cost; or when asymptomatic or mild COVID-19 patients are asked to return for a follow-up (if their status worsens), they may be charged in case no testing is required; or in case a doctor requests for influenza (not COVID-19) to be ruled, CARES and FFCRA don't mandate insurers to cover such costs (Wapner, 2020). Furthermore, as previously mentioned, COVID-19 affects older individuals more frequently, yet, several of the large insurance companies, such as Prudential, Lincoln National, and Protective Life, are imposing restrictions on new life insurance policies sold to those older than 80 by either suspending or delaying policy applications, and Securian does not take any applications from those who are 76 or older (Markowitz, 2021).

The failure of these health policies highlights the need to switch to a nonprofit social insurance model (Himmelstein & Woolhandler, 2020). For example, in the US neighbor, Canada, all the provincial healthcare systems must meet each and every principle of the Canada Health Act (CHA), including public administration, comprehensiveness, universality, and accessibility. The public administration refers to the provincial healthcare insurance being publicly administered and on a nonprofit basis; the comprehensiveness means that it is mandatory for provincial healthcare insurance to cover all the required and necessary healthcare services; by universality and accessibility, all Canadians must be provided with public healthcare insurance, and at no cost, respectively (Martin et al., 2018). Similarly, in order to promote a better healthcare system, the payments of health insurance benefits, off-site settlement, and financial compensation were all been established in China during the third phase of the pandemic (Islam et al., 2020a). Moreover, in China, everyone is covered for the cost of complex medical procedures through the established universal health coverage; hospitals are provided with additional funds and emergency equipment; and pharmaceutical companies are granted reimbursements to cover the cost of medications (Shadmi et al., 2020).

Death Tolls Among Different Nations

COVID-19 Infection Fatality Rate (IFR = COVID-19 deaths/total number of cases) varies significantly across different countries but is estimated to be 0.68% (Meyerowitz-Katz & Merone, 2020), while the mortality rate (MR) is reported to be 6.76% (Lu et al., 2020). Currently, the mortality rate associated with COVID-19 pandemics is markedly lower than that of SARS (9.6%) and notably lower than the mortality rate of MERS (34%) (Islam et al., 2020a). Sornette et al. (2020) have compared the number of deaths per million inhabitants among Western and Eastern block, developed Southeast Asian, Northern Hemisphere developing, and Southern Hemisphere countries (Fig. 7). Interestingly, the mortality patterns revealed that COVID-19 is responsible for more deaths in Western nations, which are most likely due to their higher proportion of elderly people (Sornette et al., 2020). For instance, high MR in Italy, where almost 60% of people are over the age of 40, is thought to be caused by population age (Triggle et al., 2020), and the high MR among developed countries (except Norway and Japan) that have "lavish healthcare systems" compared to developed Southeast Asian countries is also attributed to the higher age of their populations (Sornette et al., 2020). Even with the same public health measures, those countries with an older population still experienced higher IFR (e.g., Italy vs. Israel with a median age of 45.4 and 30 years, respectively) (Meyerowitz-Katz & Merone, 2020). It is estimated that IFR exponentially increases with age,

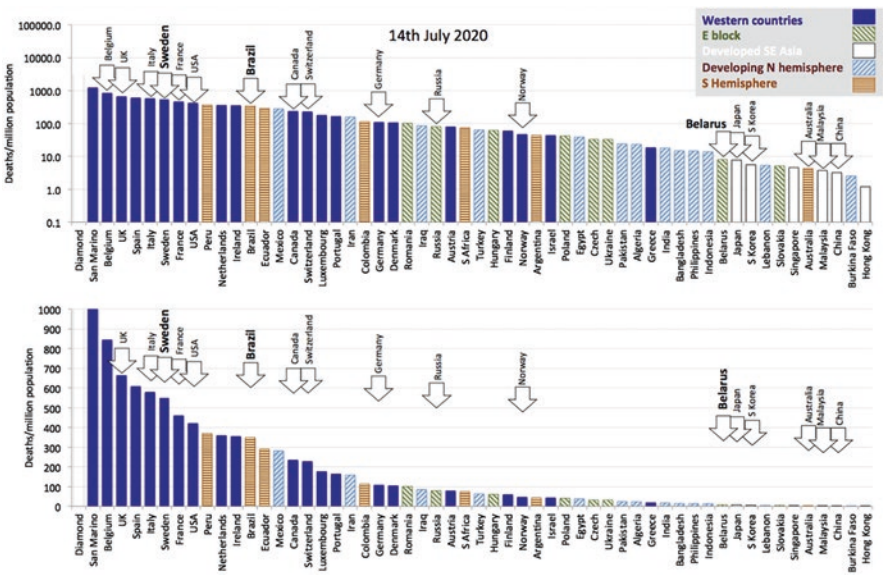

Fig. 7 Population-normalized deaths per million among 55 countries. *Notes*: Logarithmic (top) and linear (bottom) population-normalized deaths per million among 55 countries as of July 14, 2020. Countries with no lockdown policy (Sweden, Brazil, and Belarus) are in bold. (*Source*: Sornette et al. (2020))

from 0.005% for pediatric age groups to 0.2% for 50, 0.75% for 60, and 27% for those 85 years of age or older (Meyerowitz-Katz & Merone, 2020). It must be noted that depending on countries' testing and screening strategies, as well as an official report, IFR can be overestimated or underestimated (Subramanian et al., 2021).

Moreover, the difference in higher infection and MR of various geographic regions can be attributed to disparities in SARS-CoV-2 mutations distribution. For instance, ORF3a mutation is found to be associated with higher MR, and it is reported to be more prevalent in countries with higher rates of infection and mortality (e.g., Brazil, Mexico, Spain, and the UK) (Majumdar & Niyogi, 2020). Furthermore, a preliminary study conducted in Italy on COVID-19 patients demonstrated a higher rate of SARS-CoV-2 infection and death in individuals carrying HLA-DRB1*08 since this allele and its subtypes are not capable of viral peptides recognition. Interestingly, the higher frequency of HLA-DRB1*08 allele was detected in most of Northern Italy, where a more cumulative incidence of COVID-19 was reported. On the other hand, the two provinces with low incidence showed a low level of this allele in their population (Amoroso et al., 2020).

In an evidence-based review, healthcare policies, access to resources, demographics, population characteristics (comorbidity, genetics [e.g., blood group], etc., discussed earlier), and viral variants, among other factors, were found to influence MR (Abu Hammad et al., 2020). As the COVID-19 death toll is on the rise globally, it is being recognized that disease mortality is distributed disproportionately among vulnerable groups, including the elderly, those with lower SES, residents of crowded places (e.g., prisons), migrants, refugees, and other minorities; the pandemic has also increased all-cause mortality, as a result of people losing their jobs, homes, and health insurance (Shadmi et al., 2020). For example, in Iran, the lack of medical supplies due to US-imposed sanctions and the government's failure to implement COVID-19 measures is thought to have attributed to high MR (Triggle et al., 2020), while in other countries, the lack of ventilators could have increased the death rate among the elderly and other vulnerable groups, since medical staffs have been forced to choose some patients over others (Abu Hammad et al., 2020). Moreover, in India, a low-middle-income country with a high proportion of the low-income population and limited healthcare access, the implemented preventative measures (e.g., limiting gatherings and events, hand hygiene, etc.) by The Indian Ministry of Health and Welfare were most effective among the high-income population; this, combined with other sociocultural factors, such as congested living, religious gatherings, public transportation use, and so on, exacerbated the health disparity (Solis & Nunn, 2021).

The higher death rates in the USA and the UK compared to China and South Korea were due to the lack of screening of those with travel histories or contacts with suspected or confirmed cases (Yoo et al., 2020). Early detection can reduce MR (Das et al., 2020), and according to the chief executive of WHO:

"The most effective way to prevent infections and save lives is breaking the chains of transmission. You cannot fight a fire blindfolded, and we cannot stop this pandemic if we don't know who is infected. We have a simple message for all countries: test, test, test, test" (Yoo et al., 2020, p. 10). According to reports, one of the reasons for the inability to control the pandemic in countries such as Turkey, the UK, and the USA was their failure to implement nationwide testing and contact tracing (Islam et al., 2020a).

Between May 10, 2020, and September 19, 2020, the top 6 countries with the highest COVID-19 MR still had lower deaths per 100,000 population than the USA (e.g., Italy 9.1/100000 vs. US's 36.9/100000) (Bilinski & Emanuel, 2020). A lack of adequate measures by public health officials has made COVID-19 the leading cause of death in the USA (Woolf et al., 2020).

Biomedical Waste (BMW) Management

The composition of the generated BMW is 85% general nonhazardous and 15% hazardous infectious, and the sudden global surge in the volume of COVID-19-related hazardous infectious waste has created an additional burden for most governments, as they already did not own adequate capacities for the management of BMW generated even during regular times (United Nations Environment Programme, 2020). At the peak of the pandemic, 247 tons/day of BMW were produced in Wuhan, six times more than pre-pandemic levels (Singh et al., 2020). The daily amount of BMW (tons/day) during the COVID-19 pandemic has also increased in other countries, including the USA (8055.03), Brazil (2774.35), India (2160.34), Iran (81.31), and Italy (45.09) (Behera, 2021). According to the report, on average, 2.5 kg/bed/day of COVID-19-related BMW is produced in developed countries (United Nations Environment Programme, 2020). This pandemic-generated waste must be handled properly, as it will act as vectors not only for SARS-CoV-2 transmission and spread (Shammi et al., 2021) but will also contribute to the spread of other communicable diseases such as hepatitis, HIV, cholera, and typhoid (Singh et al., 2020). It is estimated that BMW-related diseases are responsible for killing 5.2 million people, including 4 million children, worldwide (Rahman et al., 2020b). It is still not known precisely how long SARS-CoV-2 survives on various fomites (WHO & UNICEF, 2020), but it is stated that it can remain viable on various fomites for 2–9 days, depending on the surface, temperature, relative humidity, and viral strain, as well as in serum, stool, and respiratory samples, for 11–21 days, 17–31 days, and 13–29 days, respectively (Behera, 2021). It is reported that when compared to aerosols, copper, and cardboard, the virus survives for a longer period of time (up to 72 h) on both stainless steel and plastic, and even for up to 96 h on glass surfaces (Islam et al., 2020a).

All the generated BMW during patient care, including those of COVID-19 patients, are considered infectious (Behera, 2021), and for proper handling, the 3Rs-based (reduce, reuse, and recycle) waste management hierarchy model must be followed to reduce waste generation and disposal in the first place and recover and recycle as many wastes as possible. This process starts from source segregation, storage, collection/transport, and treatment to the eventual disposal. The source segregation uses a double-layered bag, leak-proof and puncture-resistant (for sharp objects), color-coded and labeled bins, and separating reusable/recyclable items; on-site and off-site collection and transport of BMW must be done at regular times and routes, respectively, and utilize separate trollies for infectious/hazardous and general wastes and minimize contact with patients and other people; the storage site must be well-ventilated and secure to prevent human and animal pests access (United Nations Environment Programme, 2020). It is recommended that all trollies and transport vehicles be disinfected with 1% sodium hypochlorite, and the temporary storage of COVID-19 waste must not exceed 12 h (Behera, 2021). All BMW, especially COVID-19-generated waste, must be treated according to the local guidelines before their final disposal, and the most common ways for the treatment and dispose of these BMWs are chemical treatment, autoclaving, or incineration (Behera, 2021), with incineration being the most effective method (Peng et al., 2020). In China, to address this waste, an emergency incineration plant with a capacity of 30 tons/day was built, the national capacity for BMW management was also increased, and mobile incinerators were used to dispose the huge amount of BMW that accumulated during the lockdown and social distancing period (Singh et al., 2020). Even though incineration can be utilized for treatment and disposal, it produces toxic gases, such as furans and dioxins that increase the risk of developing cancer, diabetes, neurotoxicity, immunotoxicity, etc.; thus, many countries have used other alternative methods, including high-temperature pyrolysis and medium-temperature microwave (especially for on-site treatment), that completely eliminate digoxin (Behera, 2021). In situations where the number of incinerators does not meet the pandemic-generated waste volume, the final disposal can be done in a designated standard small landfill pit or in engineered sanitary landfills built far from residential and public areas (Behera, 2021).

The bodies of deceased suspected or confirmed COVID-19 individuals must be placed in fabric or cloth and sent to the mortuary as soon as possible (Hossain, 2020). However, before transferring them, all catheters and tubes must be removed, and their insertion sites must be disinfected with 1% hypochlorite, then sutured or covered with proper dressings; oral opening and nostrils must be packed completely; finally, the body must be put in a leak-proof plastic bag, and the outside must be disinfected using 1% hypochlorite and transported by a separate vehicle for cremation or burial (Behera, 2021).

In spite of all these rules and regulations, as a result of inadequate funding, shortage of equipment, poor knowledge of the dangers of hazardous wastes, and lack of qualified personnel, many countries (e.g., Bangladesh, India, etc.) still do not manage BMW properly (Shammi et al., 2021). According to reports, there are great disparities between rural and urban BMW handling, with rural regions lacking the practical knowledge of proper waste segregation and management. For instance, it is reported that in India, 82%, 60%, and 54% of primary, secondary, and tertiary healthcare institutes, respectively, do not own a proper BMW management facility (Shammi et al., 2021). Hence training healthcare staff and encouraging them to use PPE are recommended (United Nations Environment Programme, 2020). Table 6 summarizes COVID-19-related BMW types, with their segregation, treatment, and final disposal.

Table 6 COVID-19-related BMW types, segregation, treatment, and final disposal

BMW types	Color coding	Pretreatment requirement	Final disposal	Reference
Items contaminated with blood[a] and body fluids (e.g., dressings, plaster casts, cotton swabs, etc.)	Yellow	None	Incineration[b]	Behera (2021)
Liquid wastes, including infected secretions, aspirated body fluids, laboratories, and housekeeping liquids	Yellow	Separate collection	Pretreat chemical liquid waste shall be pretreated prior to mixing with other wastewater	
PPE made of fiber, such as face masks, gown, cap, etc.	Yellow	None	Incineration	
Contaminated linen, mattresses, beddings with blood, or body fluids	Yellow	None	Disinfection with non- chlorinated chemicals, then incineration	
Microbiology laboratory wastes, such as cultures, specimen, vaccine, petri dishes, blood bag, etc.	Yellow	On-site sterilization in safe plastic bags and container using autoclave, non-chlorinated chemicals microwave, hydoclave	Incineration of pretreated wastes	
Items such as catheters, tubes, bottles, urine bags, syringes (without needles), goggles, face shield, plastic apron, gloves, etc.	Red, non-chlorinated plastic bags	None	Autoclave and shred then recycle	
Sharp objects, such as needles, cutter or burner, scalpels, etc.	Translucent white puncture and leak-proof, sharp boxes	None	Autoclave or use dry heat sterilize and then followed by shredding or mutilation or encapsulation in metal container or cement concrete or sent for final disposal to iron foundries or sanitary landfill or designated concrete waste sharp pit	
Contaminated glass (e.g., medicine vials and ampoules[c])	Blue puncture proof container	None	Disinfect with 1% sodium hypochlorite[d] and then recycle	

Authors' Own Table

Abbreviations: *COVID-19* coronavirus disease 2019, *BMW* biomedical waste, *PPE* personal protective equipments

[a]Except blood bags

[b]Deep burial method for rural or remote areas, where BMW management facilities do not exist

[c]Except cytotoxic-contaminated wastes

[d]Chlorine present in hypochlorite inactivates SARS-CoV-2 by denaturing its proteins

Artificial Intelligence and Other Technology Applications

Artificial intelligence (AI) techniques have the potential to be used for COVID-19 diagnosis, treatment, vaccine discovery, prognosis, epidemiology, and awareness-raising (Abd-Alrazaq et al., 2020) or reportedly even predicting pandemics before they erupt. The most common techniques are deep learning (DL) models (e.g., convolutional neural network [CNN], recurrent neural network [RNN]), machine learning (ML) models, and natural language processing (NLP) (Abd-Alrazaq et al., 2020). Having extracted data from various sources (e.g., global traveler movement, online papers, local healthcare workers reports, climate, animal data, etc.), the Toronto-based company, BlueDot, utilizes AI, ML, big data, and NLP to predict and track communicable disease outbreaks and claims to have warned officials in the private sectors of the novel coronavirus days before its detection in China (Bowles, 2020). CNN could be used as diagnostic and prognostic tools to detect and interpret changes seen in patients' CXR and CT scans (Asraf et al., 2020). Furthermore, DL models (e.g., AlphaFold) can rapidly predict viral protein structures and help develop vaccines (Khemasuwan et al., 2020). Moreover, RNN and CNN algorithms are used in the laboratory for the rapid and accurate diagnosis of SARS-CoV-2 (Poongodi et al., 2021), and a hybrid of CNN and RNN (called pretrained molecule transformer-drug target interactions [MT-DTI]) can identify and predict the effect of existing antiviral drugs on SARS-CoV-2 life cycle (Beck et al., 2020). BenevolentAI was able to predict the potential efficacy of baricitinib, a drug used in rheumatoid arthritis patients, against COVID-19 (Zhou et al., 2020b). ML combined with bioinformatics and supercomputing can determine the Abs that are able to target RBD (Dey et al., 2020). Moreover, to better protect the public and to develop future preventative measures, big data technology is used to collect a huge amount of information from COVID-19 patients (Haleem et al., 2020), pretrained DL is used to classify cases according to all CXR and CT findings, and computer vision can be used to interpret and detect these findings (Ulhaq et al., 2020). Moreover, POCUS is an incredibly useful imaging option in remote locations since it is low in cost, can be connected to smartphones and tablets, and uses AI to assist in diagnosis (Yau et al., 2020).

Furthermore, IoT-based devices such as wearables, drones, robots, buttons, and smartphone applications are utilized for different purposes (Table 7) (Nasajpour et al., 2020). For example, Khan et al. (2020) reported that China and South Korea have successfully controlled the pandemic by using advanced technologies that reduced human interactions through various robots such as robot receptionists, doctors, and nurses; sampling robots; surgical robots for biopsies; CXR and LUS robots; sanitizer-dispensing robots; self-driving cars to transfer patients and collect lab samples; disinfectant robots (outdoor spraying robots and indoor UV robots); medicine-dispensing robots; and telemedicine robots, among others. Automated technology such as the Internet of Things (IoT) devices was also used in Wuhan to better control and dispose BMW (Singh et al., 2020).

Table 7 Some internet of things (IoT) technologies used during the coronavirus disease 2019 (COVID-19) pandemic

IoT-based devices	Examples	Applications	References
Wearables	1. Smart thermometers 2. Smart helmets 3. IoT-Q-Band 4. EasyBand and Proximity Trace	1. Detect fever 2. Detect fever, location, and face image 3. Track quarantine cases 4. Track social distancing (SD)	Nasajpour et al. (2020)
Drones	1. Thermal imaging drone 2. Disinfectant drone 3. Surveillance drone	1. Detect symptoms, check patients' respiratory signs, collect swabs, deliver treatments, and so forth 2. Prevent medical staff fatigue 3. Prevent mental strain	
Robots	1. Autonomous robots 2. Collaborative robots 3. Social robots	1. Detect symptoms, check patients' respiratory signs, collect swabs, deliver treatments, and so forth 2. Prevent medical staff fatigue 3. Prevent mental strain	
Smartphone applications	1. nCapp (China) 2. DetectaChem (USA) 3. Coalition (USA)	1. Keep data up to date, provide consulting, and follow up with patients 2. Provide low-cost tests 3. Conduct contact tracing	

Authors' Own Table

In order to inform public health officials, several IoT technologies, such as "Worldometer," monitor COVID-19 prevalence, incidence, and outcomes across countries (Ting et al., 2020), and Johns Hopkins University's Center for Systems Science and Engineering used all the data from the US CDC, WHO, the European CDC, the Chinese CDC, and China's National Health Commission to create a real-time tracking map that follows cases globally (Ting et al., 2020). Using the NLP algorithm, the Canadian Stallion company built Chatbots, a virtual healthcare assistant, to provide SARS-CoV-2-related information, answer any questions regarding coronavirus, monitor symptoms of infected cases, and give them appropriate recommendations whether they must take rest at home or visit hospitals for screening (Poongodi et al., 2021). Moreover, in order to monitor people's maintenance of the 6-feet social distancing rule, Andrew Ng's startup Landing AI developed a detector that transfers the result to a video screen in red and green color modes, indicating inadequate and adequate social distancing, respectively (Poongodi et al., 2021) Furthermore, once a likely infected person has been detected, Google Location History (GLH) can follow individuals' movements and identify the places they have visited (Mohammed et al., 2020).

Research, Education, and Clinical Lessons Learned

The pandemic has had a dramatic long-term impact on scientific research, either by curtailing or closing in-progress clinical research or by redirecting it toward COVID-19 (Weiner et al., 2020). Almost a year into the pandemic, more than 64,000 related papers have been published (Fang et al., 2020), some without undergoing peer review (Weiner et al., 2020). More than 4500 COVID-19-related papers have been submitted to The Journal of Clinical Infectious Diseases, more than the usual number of yearly submissions, and browsing this tsunami of literature is very challenging for researchers and clinicians (Fang et al., 2020). In addition, the COVID-19 pandemic has drawn more attention to the already existing academic gender inequality by disproportionately impacting females more than males in regards to academic research productivity. For example, in the USA, since the implementation of the lockdown, women have approximately written 14% fewer social science research papers than men, and this decrease in research productivity was observed in many other countries, including Japan, China, Australia, Italy, the Netherlands, Switzerland, and the UK (Cui et al., 2020). This is attributed to the more and more countries having implemented social distancing and lockdowns of restaurants, schools, and daycares, resulting in a higher number of females, including women researchers have to unequally perform the majority of childcare and household works, which has been the case even for those gender-egalitarian northern European countries (Cui et al., 2020). Similarly, the pandemic lockdown has further increased the gap in academic gender inequality by preventing women from contributing less to COVID-19-related research papers, with women making up only 34%, 29%, and 26% of all authors, first authors, last authors, respectively (Pinho-Gomes et al., 2020). The percentage of women authors for 2020 pandemic-related studies has decreased by 16% relative to the percentage of women authors for all 37,531 papers published in 13 US medical journals in 2019; women have also registered fewer clinical trials and research projects in March–April 2020, compared to the same month in the previous year (Viglione, 2020).

The pandemic has also affected clinical trials. Weiner et al. (2020) reported the majority of ongoing and recruitment stage trials were either paused or switched to home administration, which highly impacted patients and researchers. Due to the rush to find an effective treatment for COVID-19, thousands of trials and studies have been published that contain misinformation and that do not meet clinical trial or FDA standards, endangering lives and causing resources to be diverted from more promising therapeutic agents (Weiner et al., 2020). Hopefully, the pandemic will lead to the emergence of better research models and sustained research infrastructure for public health emergencies and disasters (Weiner et al., 2020). The outbreak has also drawn attention to the shortage of critical care resources in low- and middle-income countries and to the need for preparation, education of healthcare staff, and modification of medical guidelines to better match and manage the needs of the local populations (The Lancet Respiratory Medicine, 2020).

The most important clinical lesson learned is the inaccuracy of the conventional airborne-droplet classification, as previously mentioned (Fang et al., 2020). The successful control of the pandemic in China, South Korea, Taiwan, and Vietnam due to aggressive and early action is also a valuable clinical lesson (Triggle et al., 2020), as is the value of increasing test availability in order to identify patients in the early stages of the disease since patients are contagious 1–2 days before becoming symptomatic (Fang et al., 2020). Further, the use of telemedicine for healthcare delivery and artificial intelligence for clinical decision-making could be beneficial (Gunasekeran et al., 2021), with the potential of expansion for future use (Kichloo et al., 2020). It is also worth mentioning other clinical lessons learned, such as IFN's important role in the early phase of infection, remdesivir's effect of shortening symptom duration, the usefulness of corticosteroids in critical cases on mechanical ventilation, and HCQ's ineffectiveness (Fang et al., 2020). Moreover, the failure of many RCTs is likely due to the inappropriate timing of the administration of pharmaceutical agents. For example, the best time to administer prophylactic agents, active immunization (vaccines), or passive immunization (mAbs) is during the pre-exposure period (Griffin et al., 2021). Similarly, IFN-I therapy is beneficial in the preinfection or early infection period, while it is not effective or detrimental if administered at the late disease stage (Sa Ribero et al., 2020).

Following the COVID-19 pandemic, which has left governments and public health agencies in a state of shock and confusion, a call has been made for the adoption of "One Health" (OH) approaches in order to address the failure to predict and prevent the emergence of COVID-19 (de Garine-Wichatitsky et al., 2020). The WHO defines OH as "an approach to designing and implementing programs, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes" (WHO, 2017). Adopted more than a decade ago and with the goal of creating a more widespread societal responsibility for human and environmental health (de Garine-Wichatitsky et al., 2020), OH approach acknowledges that the health of people, animals, and the environment are all intertwined and interdependent (Ruckert et al., 2020). This implies that those form a variety of sectors (e.g., human, animal, and plant health, as well as the environment) must collaborate to develop a response infrastructure that places an emphasis on information sharing and action coordination among various sectors (Ruckert et al., 2020). Solis and Nunn (2021) have coined the term *OH disparities* to argue that social environment is equally important to OH and may aid in illuminating disparities in the COVID-19 pandemic, such as viral origin, transmission, exposure, and interindividual susceptibility. Health disparities, according to The National Institute of Minority Health and Health Disparities, are the preventable diseases that emerge as a result of underlying systemic social issues, such as combination of lower SES, unemployment, education level, and social systemic racism (Solis & Nunn, 2021).

The term "spillover" refers to the transmission of a pathogen from nonhuman animals to human host, while the word "pillback" is commonly used to describe the transfer from humans to animals (Solis & Nunn, 2021). Therefore, identifying which animals may serve as new reservoirs is essential in the public health setting, while determining which human hosts will have the greatest interaction with those animals and become infected is necessary in the context of One Health Disparities (Solis & Nunn, 2021). For instance, the agricultural sector would be particularly vulnerable if SARS-CoV-2 were to establish itself in farm animals, leading to an increased demand for animal vaccinations and greater strain on financial and scientific resources, as well as the potential of emerging a new viral variant that would evade such vaccines (Solis & Nunn, 2021). In order for an animal species to be an effective reservoir host, SARS-CoV-2 must initially be transferred from humans to the specific species and further get established in the species population through intraspecies spread and eventually be reintroduced to humans (Sharun et al., 2021). Thus, it is reasonable to hypothesize about the potential presence of animal host reservoir, which as a result necessitates animal surveillance to monitor viral frequency in animal populations and the risk of spillover into human populations (Sharun et al., 2021).

Moreover, geographic information systems (GIS) and methods are increasingly being regarded by health professionals as important tools in monitoring and controlling infectious diseases, especially when a disease spread so rapidly; it is essential for knowledge and information to disseminate at an even faster pace (Kamel Boulos & Geraghty, 2020). In such circumstances, several SARS-CoV-2 map-based dashboards (e.g., WHO dashboard and Johns Hopkins University's Center for Systems Science and Engineering (JHU CSSE) dashboard) become an essential tools in making information easily available, enhancing data transparency, while also assisting health official in the dissemination of information (Kamel Boulos & Geraghty, 2020). Developed by an epidemiologist (Lauren Gardner), JHU CSSE dashboard presents an interactive map that displays the number of confirmed cases, deaths, and recoveries, while graphs offer a visual representation of the progression of the virus over time; however, it lacks complete retrospective data visualization (Kamel Boulos & Geraghty, 2020). It relies on five reliable data sources, including WHO, the US-CDC, National Health Commission of the People's Republic of China, European Centre for Disease Prevention and Control, and the Chinese online medical resource DXY.cn (Kamel Boulos & Geraghty, 2020). Moreover, the WHO dashboard only showed laboratory-confirmed cases, the JHU CSSE dashboard included cases that were diagnosed based on a combination of symptoms and chest imaging, resulting in approximately 18,000 additional reports. However, as of February 19, 2020, both dashboards display similar total case counts, and their numbers are consistent (Kamel Boulos & Geraghty, 2020). Even with GIS technology, it is difficult to track the pandemic, and according to Lauren Gardner, "it is especially challenging to collect good data at a fine spatial resolution, which is what most people want to know, and without having travel data in real-time that captures these altered mobility patterns, it is hard to assess what the geographic risk profile will look like moving forward" (Kamel Boulos & Geraghty, 2020).

Discussion and Conclusion

This chapter reviewed some of the most recent literature (from 2019 to 2021) on SARS-CoV-2 and the COVID-19 and various medical aspects of the virus and disease itself. There are still enormous unknown issues that are yet to be elucidated, and it would be difficult to reach a conclusion regarding SARS-CoV-2 evolutionary origin since the related viruses in bats are still poorly analyzed. The finding that pangolin SARS-CoV-2-related viruses and SARS-CoV-2 have nearly identical S-RBD does not make pangolin a definite intermediate host (Han, 2020). There are still several possible pathways for SARS-CoV-2 interspecies transmission, and hence future studies are warranted in order to find the exact origin (Ye et al., 2020). Moreover, it will not be known where and under what circumstances the recombination occurred that resulted in the emergence of SARS-CoV-2. Did the recombination take place between wild viral strains of bats, pangolins, or another species? Did it adapt to humans in a farm or laboratory animals and accidentally escaped from these places? Or was it the result of an intentional bioterrorism act of the viral genome modification by molecular engineering (Sallard et al., 2021)? In order to prevent other future outbreaks, regardless of the origin, it is essential to know how the virus breached the species boundary and acquired high transmissibility from human to human (Sallard et al., 2021). On the other hand, relying on R0 to measure transmissibility is not reliable, as the value of R0 and the transmission rate of the virus vary among various cohorts (e.g., low vs. high SES or refugees vs. non-refugees); hence, it is still challenging to measure SARS-CoV-2 transmissibility using R0 (Shaw & Kennedy, 2021). However, it has been reported that the reliability of R0 will increase as more information become available about this novel virus (Liu, Gayle, et al., 2020).

Moreover, the immune cells response to SARS-CoV-2 infections is still not well understood. Several studies attribute COVID-19 to the overactivity of the immune response, while others believe the T-cell dysfunction and exhaustion are responsible (Mathew et al., 2020). The underlying mechanisms behind the defective and dichotomous humoral and cellular responses in asymptomatic/mild or moderate/severe cases (Gao et al., 2021a), or the three different identified phenotypes among critically ill patients, remain unknown. As a result, various responses to pharmacotherapies, such as anti-inflammatory or immunomodulatory medications, are expected among different COVID-19 immunophenotypes (Dupont et al., 2020). The emerging mutations and variants of SARS-CoV-2 that allow the virus to evade host defense mechanisms, vaccines, or neutralizing Abs are the ones that raise public health concerns (Callaway, 2020). Thus, it is critical to understand SARS-CoV-2 genomic variants to better understand the pathogenesis and disease progression, implementation of therapeutic and preventative measures, and vaccine or drug developments (Laamarti et al., 2020).

Furthermore, Jaber et al. (2021) performed a study among 3167 participants from Jordan and Iraq to determine their level of knowledge and perception of COVID-19. They have reported that in both populations, the most common sources to obtain pandemic-related information in decreasing order were doctors/healthcare professionals, social media, and newspapers. On the other hand, citizens of Australia and other European countries (e.g., Italy, Germany, and the Netherlands) have used traditional media, including the television, to obtain such information, which might be due to the differences in the way their government officials reported pandemic news (Jaber et al., 2021). Moreover, their study explained that social media, which is flooded with misleading and inaccurate information, may explain why only 80% of the participants were aware of the already-established droplet route of transmission of SARS-CoV-2. Furthermore, those who are not aware of the route of transmission are less likely to adhere to the recommended preventative measures, which highlight the significance of healthcare authorities and other sectors using such platforms to raise public awareness to prevent the spread of the virus (Jaber et al., 2021).

In addition, in regards to the implemented preventative measures by governments, it should be noted that social distancing alone is not a "magic bullet," and other factors, such as environmental setting, air ventilation, time spent indoors with others, viral loads, face mask use, and host factors play a role (Qureshi et al., 2020). Moreover, more stringent preventative measures by public health officials are warranted to reduce transmission of the VOCs and control the pandemic (Grubaugh et al., 2021). Furthermore, identifying the factors that contribute to the health disparities among various populations will enable the government, policymakers, and public health officials to distribute resources more effectively in order to achieve more equal health outcomes (Solis & Nunn, 2021). Additionally, modern-GIS technologies such as map-based dashboards have played a significant role in increasing awareness, as well as facilitating the surveillance, preparedness, and response to the COVID-19 outbreak (Kamel Boulos & Geraghty, 2020). Given the fact that viruses such as SARS-CoV-2 have little regard for national or continental borders, and the likelihood of similar pandemics occurring more frequently in the future, (i.e., it is not a matter of *if* but *when* and *where* the next outbreak will happen), it is important to consider the potential benefits of a such comprehensive GIS platforms in supporting the surveillance, preparedness, and response of another future outbreak (Kamel Boulos & Geraghty, 2020).

In addition, even though the use of technologies, such as AI, is fast compared to the conventional methods (e.g., an almost 30-min diagnosis with RT-PCR vs. few seconds with AI-inspected CT) (Abd-Alrazaq et al., 2020), choosing the appropriate technique to get the most accurate results could be challenging (Albahri et al., 2020). Additionally, even if accurate results are achieved, AI by itself is not the only solution to the pandemic; nevertheless, in the absence of AI, we will not be able to handle the next pandemic efficiently, and thus, in the future, AI-driven automation will play an important role (Poongodi et al., 2021). The COVID-19 pandemic has also resulted in unemployment and loss of medical insurance, further exacerbating the already complicated healthcare system. Thus more efficient health insurance policies are required to cover everyone, especially the underprivileged individuals of lower SES. Furthermore, the pandemic has resulted in an exponential increase in the amount of BMWs produced. For this reason, in order to better control future pandemics and decrease further spread of the virus, there is an urgent need to increase the capacity for BMW treatment and disposal facilities; to identify shortcomings in rural and urban places; to supply adequate equipment (e.g., bins, bags, transportation trollies, PPEs); and to train all the healthcare professionals involved in COVID-19-related issues (United Nations Environment Programme, 2020).

In conclusion, there are still a plethora of unanswered questions and concerns that must be addressed in regards to SARS-CoV-2 and COVID-19. More research is required to elucidate and fully understand the origin and pathogenesis of SARS-CoV-2, the types of immunologic response, risk factors, interindividual variabilities in clinical findings, and most promising treatments for each specific case, and the duration of vaccine-induced immunity. Finally, what could have been done differently, and more effectively in the first place, and when the pandemic will resolve we will return to the pre-pandemic state, are all crucial issues to consider.

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Advances in the Application of Geospatial Technology in the Mitigation of COVID-19 Pandemic

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Introduction

Coronavirus disease (COVID-19), caused by the novel coronavirus SARS-COV2, has been reported as a highly virulent virus. The disease usually targets the human respiratory system. The epidemic was first reported in Wuhan, China, in December 2019, and announced on January 30, 2020, by the World Health Organization (WHO) to be a public health emergency of international concern (WHO, 2020g). The pandemic led to the closure of universities and schools in about 193 countries of the world affecting more than 99.4% of student population globally (UNESCO, 2020). The COVID-19 pandemic has evolved rapidly into one of the most shocking and devastating public health crises in recent history. It was reported by mid-July 2020, an estimated 13 million worldwide cases, with at least 575,000 deaths and 7.33 million recoveries (Mansour et al., 2020).

Globally, the battle for containment of coronavirus disease outbreaks is taking a new dimension. Gross et al. (2020) reported that one of the most significant characteristics of epidemics is their spatial spread, a property that mainly depends on the epidemic mechanism, and human mobility and therefore offers control strategy.

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Geospatial technology is an evolving technique used to study real earth geographic information using geographic information system (GIS), remote sensing (RS), and other ground information from various devices and instruments (Singh et al., 2021). GIS is a system for capturing, storing, checking, integrating, analysing, and displaying data about the earth that is spatially referenced. GIS can play a critical role in the containment of the COVID-19 pandemic through mapping of the disease outbreak and tracking its spread. Disease outbreaks generally can be simulated by the degree of spatial diffusion of confirmed cases through spatio-temporal surveillance algorithm developed through GIS capability; thus, early detection and mitigation of disease outbreak can be facilitated (Meng, 2017). Collaboration between GIS expert team and health workers can play an active role in geospatial analysis of the diffusion of disease outbreak such as COVID-19 and provide workable field strategies for containment of the disease (Vynnycky et al., 2019). Comprehensive assessment of the spatio-temporal dynamics of COVID-19 is important for its mitigation, as it assists to illuminate the extent and impact of the disease and can aid decision-making, planning, and community action (Franch-Pardo et al., 2020).

Geographical information science (GIScience or GISc) is essentially the "science behind GIS". Adopting GIScience or GISc approach and, in particular, making use of location-based intelligence tools can improve the shortcomings in data reporting and more accurately reveal how COVID-19 will have a long-term impact on global health (Rosenkrantz et al., 2020). Geospatial technology is critical in the fight against pandemics including the COVID-19 pandemic. Numerous research works have been conducted geared towards providing solutions to the emergence of the COVID-19 pandemic using geospatial system. Some recent research on the relevance of GIS as a mitigation tool for the pandemic is further discussed here. Several studies have been done recently on the use of GIS in spatial analysis of COVID-19; early and prominent studies include the study of Guan et al. (2020), Huang et al. (2020a), and Chen et al. (2020a), all conducted in China during the emergence of the disease. Guan et al. (2020) used the data of laboratory-confirmed cases of 1099 patients from hospitals in China until 29th January 2020. The authors characterized the profile of the average patient and provided information on the spatio-temporal characteristics of the patients through identification and distribution of patients by province, thus providing spatial characteristics of those confirmed to be infected with the virus in the study area. Similarly, Chen et al. (2020b) applied the Bayesian spatial-temporal model in the determination of the spatial distribution of COVID-19 cases and correlated the mobility of the Wuhan population during the initial stage of the pandemic. The study is essential in providing early cautionary data needed for mitigation of future outbreaks in other regions of China and globally. Huang et al. (2020b), in a similar study, focused on the epidemiological characteristics of COVID-19, the mitigation measures applied, their consequences considering the pandemic, and its spatio-temporal distribution. Franch-Pardo et al. (2020) asserted after a thorough review of about 63 scientific articles on geospatial and spatial-statistical analysis of the geographical dimension of the 2019 coronavirus disease (COVID-19) pandemic that data processed with GIS and spatial statistics are important in the study of COVID-19.

The beauty of digital technology as offered by geospatial technology is the ability of people to perform several essential duties at safe and isolated locations of their homes.

GIS and geospatial techniques have been asserted to play important roles in analysing big data of the pandemic outbreak globally (Zhou et al., 2020). GIS has been established as a vital tool in the fight against pandemics. Several researchers have considered geospatial analysis in their studies and have equally attempted to model the outcome of various explanatory variables on COVID-19 incidence rates (e.g. Mollalo et al., 2020; Sannigrahi et al., 2020; DiMaggio et al., 2020; Scala et al., 2020). In Asia, precisely in India, researchers have used climatic, geographical, and topographical variables to simulate the number of persons infected by COVID-19 disease (Gupta et al., 2020). Further, on the importance of the use of geospatial technology in the mitigating pandemic, a study to model the impact of spatial factors of the pandemic in New York City has been conducted. The researchers applied global ordinary least squares and local geographically weighted regression (GWR) algorithms. The study established a correlation between specific factors such as mean travel distance, commuting method, etc. to higher rates of the pandemic (Chen et al., 2020a, b). To establish through geospatial technology the dynamics of the pandemic, spatio-temporal patterns of the pandemic were assessed at the early stages of the disease in China using Moran's I spatial statistics (Lee & Kang, 2015), and the spatial assessment established that from 22nd January, the pandemic spread from Wuhan to the various neighbouring cities through the transportation network. Consequent to the geospatial-based research work conducted by Ahmadi et al. (2020) in Iran, the spatial distribution and spreading patterns of the pandemic in the country were associated with environmental and spatial drivers, such as intra-provincial movement, precipitation, temperature, humidity, and average solar radiation.

GIS community is referred to as a community of users who are connected by the common interest in visualizing and analysing spatial information (Dempsey, 2011). The community consists of leaders in the production of geospatial tools and services, partners with the organizations, collaborators, innovators, and users. The unprecedented cooperation and collaborations within this community are largely responsible for major gains in the fight against the pandemic. The incredible work done by the GIS community has helped enormously in the fight against the pandemic; the community has provided the map resources to strengthen surveillance systems, etc. This study is aimed at exploring the various applications of geospatial technology in the mitigation of the COVID-19 pandemic.

GIS as an Integrated System for the Assessment and Response to the Pandemic

GIS is acclaimed and also reported as a complete system for understanding, assessing, and responding to the current pandemic (Franch-Pardo et al., 2020). GIS system consists of about seven subunits. It consists of GIS support team, disease surveillance, planning, logistics, field operations, executive awareness and management, and community engagement (Stouffer, 2020). The GIS support team maintains the crucial front line in solving GIS problems in innovative ways. Disease surveillance is an important aspect of the system. It provides live updates through various dashboards on the current state of the pandemic. The data from the surveillance unit is used in logistics operations, such as allocation of patients to hospitals (planning) and various field operations. Also, the data from the surveillance unit is often used in community awareness and engagement programmes (Berman et al., 2020). GIS helps to generate evidence for action; this consequentially leads to the low spread of the virus. GIS produces integrated spatial data and analytics needed to support a comprehensive and dynamic response to COVID-19 (Gao et al., 2020). It also provides near real-time information to countries and strengthens the healthcare surveillance system. GIS, as an integrated system, has been applied to support digital contact tracing and surveillance (Berman et al., 2020).

GIS Aided Regional/Community Risk Evaluation of COVID-19

There is a need to understand the risk of the spread of diseases during pandemic and endemic situations. Various communities are usually at various levels of risk; hence community assessment, as well as regional assessment, is a key to proper risk assessment. The goal of community risk assessment is to recognize and prioritize local risks; this is usually followed by a strategic investment of resources in the form of emergency response or prevention to reduce the impact, spread, or occurrence/reoccurrence of the outbreak. Proper assessment will reduce the workload of health workers in field operations. It will ensure that unnecessary visit to the community that does not need assistance is prevented, and reduction of workload on the frontline personnel. This will also ensure that critical situations or locations are given critical attention.

GIS plays a critical role in community risk assessment and in the deployment of resources to contain the spread of disease outbreaks. Figure 1 shows a typical flow chart of a community risk assessment programme. GIS plays a critical role at all phases of the programme. GIS helps to identify risk factors that enhance the spread of the COVID-19 pandemic in community such as the presence of airport(s) which aids in the mobility of infected persons. It also helps in identifying communities that have high confirmed cases as priority areas through near-real-time dashboards, and allocation of adequate resources based on the need of assessed communities is a known strategy for mitigation of risk. GIS plays a major role in doing this using network tools such as the allocation of resources as needed. Based on the community-prepared risk plan, GIS can help to monitor the effectiveness of the plan.

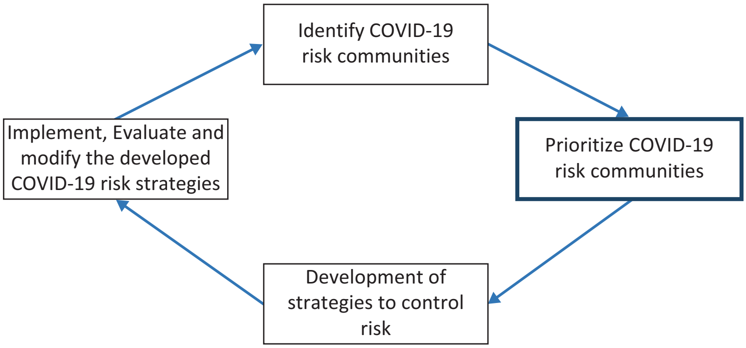

Fig. 1 A typical flow chart of community risk assessment programme. (Source: Authors' diagram, modified after Stouffer (2020))

Factors considered in risk evaluation include the age variation of the populace. It has been established that the population of age 60 and above is at greater risk. Other factors in community risk evaluation are population density, income level, tobacco per capita index, a reflection of tobacco spending, available healthcare resources, confirmed cases of COVID-19, etc. These factors are usually developed in the form of layers and geospatially overlaid in GIS environment. In the evaluation of the risk of the community, several forms of risk evaluation are recommended, and this includes transmission risk, susceptibility risk, socio-economic risk, exposure risk, and insufficient resource risk.

GIS Software-Based Risk Evaluation of COVID-19

A number of GIS software tools are used in risk evaluation of COVID-19: ArcGIS Pro a product of ESRI is among the top software used in the evaluation of the pandemic. ArcGIS Pro is the next generation of modern desktop GIS with the capability to perform advanced spatial analysis compared to ArcMap. It was released recently, and this has been used extensively for improving evaluation of the COVID-19 pandemic. To develop GIS-based risk evaluation of COVID-19, for instance, in ArcGIS Pro, several layers are created. Some of the layers include boundary layer, population data layer, age layer, income (purchasing power) layer, and household layer. COVID-19 studies utilizing spatial analysis are valuable tools for community response. Numerous studies to date have been done on COVID-19. Over 63 studies worldwide have examined COVID-19 using GIS, with some of the studies focusing on spatio-temporal analysis, environmental variables, health factors, and social geography (Franch-Pardo et al., 2020).

Geospatial Mapping Using Dashboards Across Continents and Countries

When disease has to travel so quickly, information has to travel even faster. This is where geospatial mapping becomes crucial (Boulos & Geraghty, 2020). As of mid-February 2020, it is reported that coronavirus dashboards were among the top ten requested applications in the Esri ArcGIS Online service. The use of the dashboard recently went viral with thousands of news articles and shares on social media (Boulos & Geraghty, 2020) (see Fig. 2). The John Hopkin dashboard gave the world a new view perspective on the use of dashboards in the COVID-19 pandemic. It probably sparks various institutions and organizations to adopt dashboards in integrating information systems across the globe. The dashboard provides basic spatial intelligence information on disease spread, the vulnerable location/population, information on areas for priority attention such as resources, etc. Spatial statistic of COVID-19 has been made easy through the use of COVID-19 dashboards. Boulos and Geraghty (2020) stated a number of prominent dashboards; they include John Hopkins University Centre for systems Science and Engineering dashboard (Fig. 2), the World Health Organization dashboard (Fig. 3), HealthMap for Wuhan Coronavirus (Fig. 4), HealthMap for the UK (Fig. 5), etc. The dashboard provides information on disease spread patterns, and it also furnishes information on spatial density of the affected regions, and these provide data for easy identification of vulnerable regions and populations. In addition, the dashboard serves as a platform to promote international coordination and state of affairs awareness report.

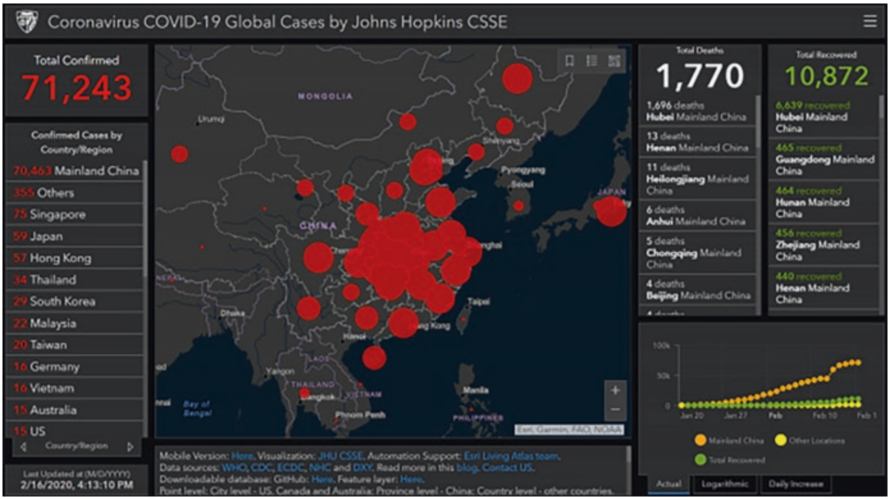

Fig. 2 Johns Hopkins University CSSE is tracking the spread of SARS-CoV-2 in near real-time with a map-centric dashboard. (Source: COVID-19 Map – Johns Hopkins Coronavirus Resource Center (jhu.edu))

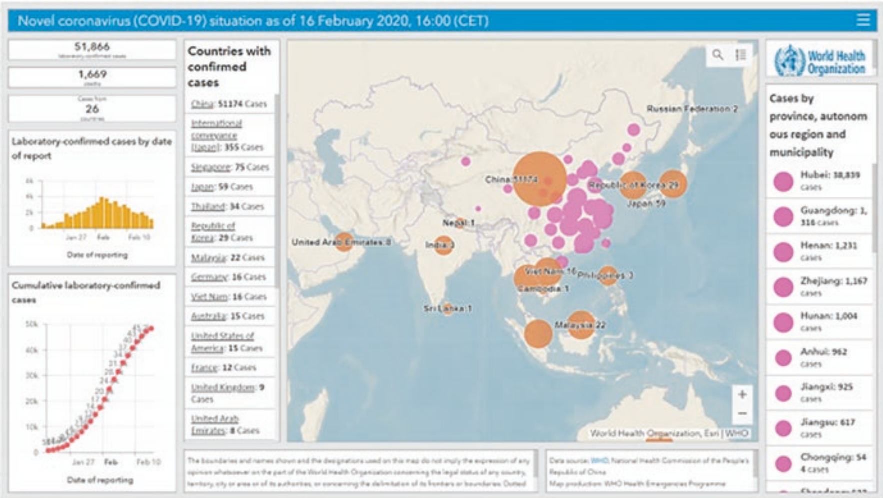

Fig. 3 The WHO COVID-19 situation dashboard. Screenshot date: 16 February 2020. (Source: WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data)

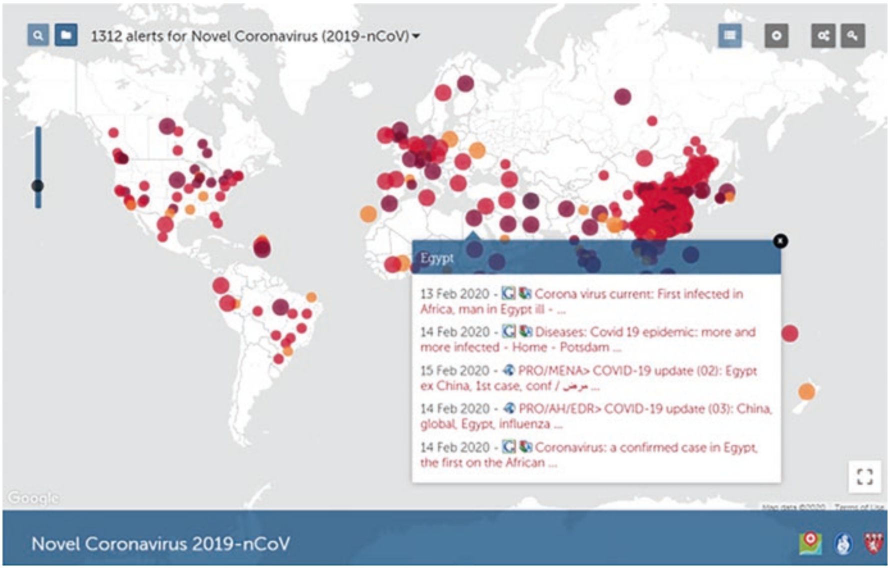

Fig. 4 Screenshot of HealthMap dashboard for Wuhan Coronavirus. Screenshot date: 17 February 2020. (Source: https://healthmap.org/en/)

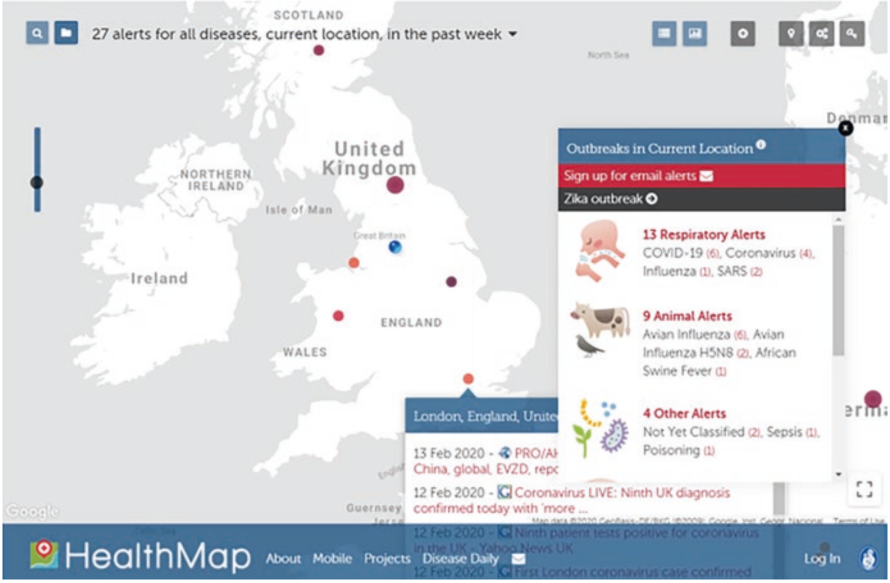

Fig. 5 Screenshot of HealthMap's outbreaks taken on 17 February 2020. (Source: https://healthmap.org/en/)

In Africa, the centres for disease control and prevention (CDC) adopted a dashboard that clearly indicates the impact of the pandemic on the various regions of the continent (Fig. 6). In South America, Columbia is paying close attention to the origin and importation of cases. In Hong Kong, they are showing hospitalization, mapping actual buildings, where there have been confirmed cases.

North America, Maryland to be precise, utilized enhanced features in her dashboard. Figure 7 shows the Maryland COVID-19 data dashboard with some unique features. The figure shows data at a zip code level. The number of cases in the affected ZIP codes is shown at the top right corner of the dashboard. For instance, ZIP code 20601 had 263 cases, while ZIP code 20603 had 315 cases. Such data create community awareness of the situation and encourage residents to keep watch in observing safety rules. Data on testing volume and the percentage of positive cases were also shown on the dashboard. The dashboard also shows the intensive care unit (ICU), hospital beds for acute cases, and total beds. This enhances knowledge on the hospital capacity and provides plans for the allocation of cases to available hospitals. The dashboard equally shows the gender, racial, and age distribution. Also essential in the use of the dashboard is the ventilator trends: the number of invasive ventilators and the reserved and the number of intubated and non-intubated persons were also displayed on the dashboard. The dashboard gives detailed information on the testing volume and the percentage of the positive test.

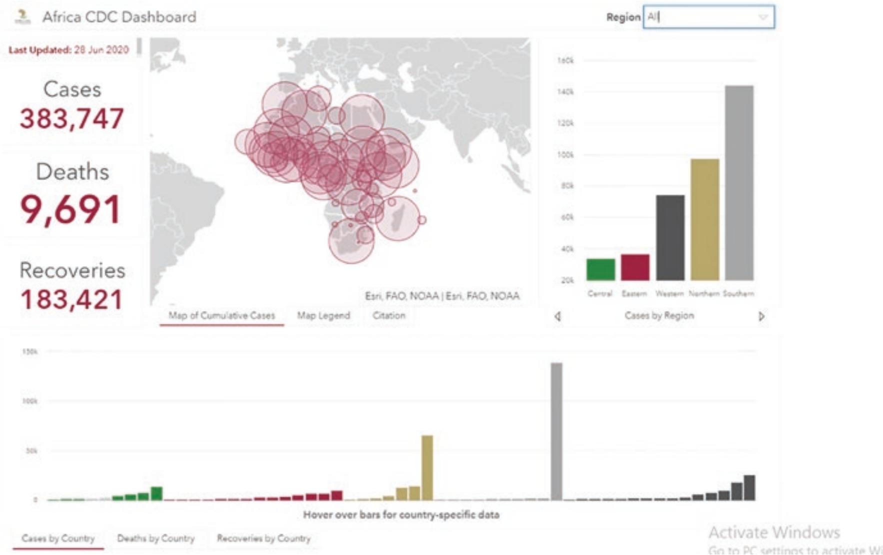

Fig. 6 Africa, CDC COVID-19 Data Dashboard. (Source: https://africacdc.org/covid-19/)

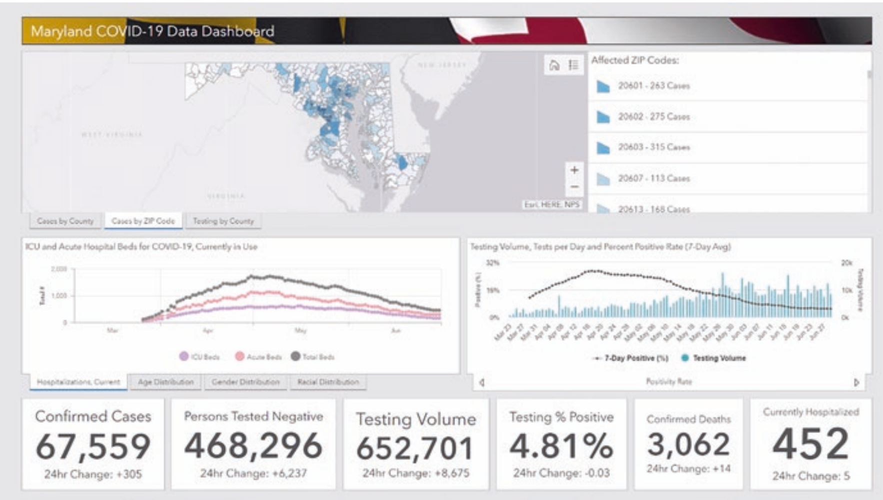

Fig. 7 Maryland COVID-19 data dashboard. (Source: https://coronavirus.maryland.gov/datasets/md-covid-19-data-dashboard)

Geospatial Modelling of the Spread of the Disease

A number of measures have been applied to model the resources needed to fight the pandemic and the spread of the disease.

Geospatial Time Series Forecast of the Pandemic

The dashboard to this present condition has served a useful purpose in providing data on the current state of the pandemic. However, this is not enough, since the pandemic demands a more strategic approach like the prediction of the trend to enable appropriation of resources and health agents timely. Hence, the projection of the current state into the future for useful information and subsequent planning has brought pandemic forecast in the frontline on the fight against the pandemic. Forecasting is a vital element in managing pandemics such as COVID-19, and it provides information on what could happen next. Forecasting as a tool helps to make the response to the pandemic to be more proactive rather than being reactive (Azarafza et al., 2020). One of the major ways leveraged by several authors and researchers in forecasting pandemics is the use of epidemiological models (Ahmadi et al., 2020). Secondly, the use of the time series approach has equally been used by several researchers. The new capability recently developed by the ESRI platform in the battle against the pandemic is based on the use of time series forecast by analysing patterns and trends of current pandemic data in the ArcGIS Pro platform. The tool utilizes data of the COVID-19 in the form of current map data to forecast, for instance, 1 week or more of new cases of the pandemic for a given location. The ArcGIS Pro uses both traditional learning and machine learning algorithm in the forecast. Few of the geoprocessing tools in the platform include exponential smooth forecast, curve fitting forecast, etc. The platform can predict complex time series trends using an algorithm based on exponential smoothing and a random forest-based approach. One of the outstanding features of this forecasting platform is the use of an auto-detect curve fitting tool in forecasting cases based on various algorithms for different locations. The application of various models as utilized in the ArcGIS Pro platform is essential owing to the fact that no single model is effective in modelling the pandemic for various locations. Data usually forecasted in the ArcGIS Pro platform could include new cases, the cumulative number of cases, energy usage, etc.

Geospatial Modelling of COVID-19 Medical Facilities

Apart from geospatial assistance provided through data collection/visualization and operational decisions from geospatial technology during the pandemic, modelling of COVID-19 logistics has also advanced beyond the infection rate. Provision of adequate healthcare facilities is critical in the containment of the pandemic. To proactively cater for medical supply needs, an increasing number of models have been established all over the world by research institutions, consulting firms, healthcare systems, etc., to model the quantities of medical facilities such as hospital beds, ventilators, intensive care unit (ICU) beds, the timing of patient surges, and more. Some of these models have been integrated into the ArcGIS platform; the spatial data is often used as input to these models; and the output is used in modelling the COVID-19 situation. A few examples of these modelling tools include Hospital Resource Calculator for COVID-19, produced by Rush University; the model projects at state level the number of confirmed COVID-19 cases; the resource needed for ICU beds and non-intensive care unit; and ventilators and personal protective equipment (PPE). Other modelling tools are Regional Hospital Capacity Calculator by Harvard University and a Localized COVID-19 Model and Scenario Planner; by Qventus to mention but a few, these model tools play a critical role in the operational decisions on utilization of medical facilities. Among these models and also integrated into ArcGIS software are the COVID-19 Hospital Impact Model for Epidemics (CHIME) and COVID-19 surge tool. The input to these geospatial tools varies and ranges from population data, the number of cases, infection rate, hospital resource and stay data, intervention plan(s), epidemiological data, etc., and the output of the model also varies such as daily hospital census projection and peak model demand for the various medical facilities. Figure 8 shows hospital resource projection using ESRI software.

The production of geospatial map of various medical facilities as achieved recently in modelling of medical facilities is critical in making informed decisions; it enhances optimization of medical facilities through informed resource allocation, based on variation in demand.

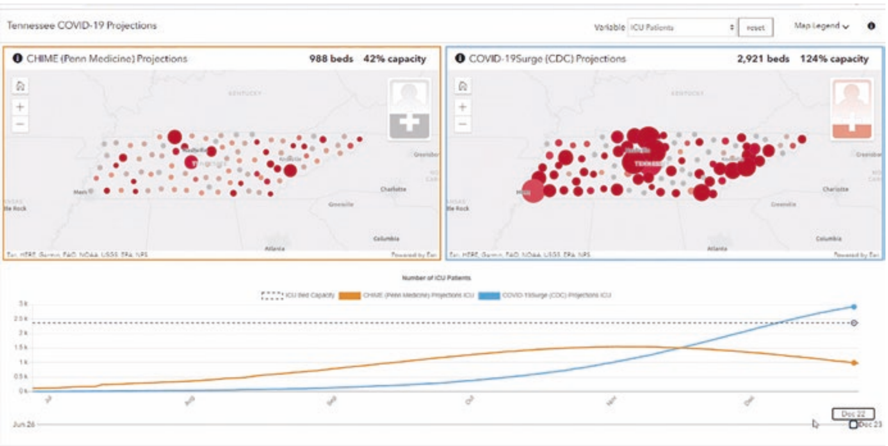

Fig. 8 Hospital resource projection using ArcGIS programme. (Source: https://www.youtube.com/watch?v=8AfVrB8Ig5E adapted from modelling Covid-19 in ArcGIS; ESRI)

Geospatial Location-Allocation of Resources

The pandemic has resulted in the building of more laboratories with increasing demand to meet certain testing targets. Testing laboratory has therefore been a major factor in the fight against the pandemic; however, proper siting of testing facilities weighs more as it reduces the transportation cost and saves time and would enhance recovery from the pandemic. GIS spatial analysis plays a critical role on this.

ArcGIS Indoors Building Level Assessment Tool

GIS traditionally is used in outdoor analysis and visualization; however, the COVID-19 pandemic has created the need to think of health safety, not just in the outdoor context but in the indoor context. As global economies start to reopen due to decline in the number of confirmed cases and containment of the virus, there is need to plan on the reopening conditions based on strategic geospatial mapping tools. ArcGIS indoors serve to provide such much-needed platform; this facility helps in managing the pandemic at building level; it is essential in decision-making in planning and operating activities at classrooms, offices, shops, conferences, business centres, etc., based on the new social distancing guidelines for safety. The ArcGIS indoors can be used to explore building attribute, such as capacity, name, floor level, type, address, locality, province, etc. Return-to-work analysis could be done in the platform to provide information on how social distancing guideline could impact workplace. A typical output of the ArcGIS indoor tool is shown in Fig. 9; Fig. 9a shows the 2D spatial map of a building in the ESRI campus; and the various buffer colours in Fig. 9b show the safety conditions within the building. The purple, green, and orange buffer colours indicate rooms with safe social distancing; the blue buffer colour however indicates areas that are unsafe; and in the above case study, it is the area in the building where staff is seating close to each other in cubicle.

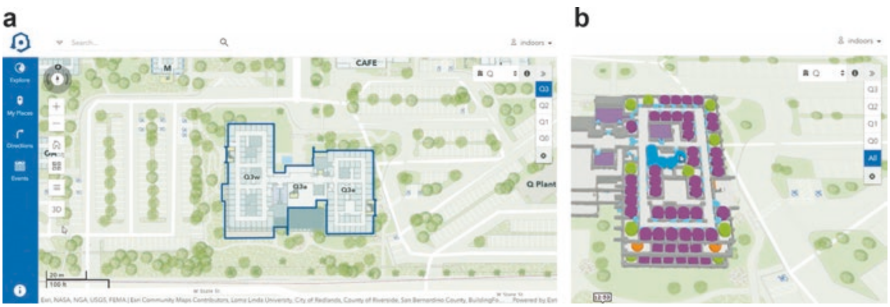

Fig. 9 (**a**) ArcGIS indoor 2D pictorial view of a building (**b**) buffers showing condition of safety or otherwise in a building. (Source: Adapted from https://www.youtube.com/watch?v=qBl01idKkmU, GIS and Airports response to COVID-19 webinar, ESRI)

The potential seating conflicts can be seen in the platform and various seating arrangements explored, and subsequently, new seating plans developed around safety requirement through, for instance, unassigning persons in a conflicting seating context to another safe area. The indoor space planner tool in the ArcGIS indoor is a perfect platform for creating such safe seating plan with multiple seating arrangements, such as alternating days, to minimize the number of staff at a given time. The ArcGIS indoor tool provides innovative approach on balancing the health of the people while targeting to reopen economies.

Smart Airport Geospatial Response Strategies

Airport industry is one of the major travel sectors worst hit by the pandemic, and the coronavirus has been widely distributed through travels. To stay ahead of the curve, it is important that this industry is renovated with technologies that will mitigate the impact on the virus. ESRI has played significant role in the process of recovery from the pandemic by introducing smart airport geospatial operation technologies in response to COVID-19 in aviation industry. Information on travelling and safety measures in airports is a necessity, and spatial map to access the availability of airport is one of the technological-based solutions provided by ESRI as coronavirus response support for airport operations during the response and recovery from the pandemic. This involves the use of apps that indicates various airports and can clearly indicate airports with travel restrictions. This will guide travellers in their choice of places to travel, and otherwise, it also indicates places (airport) that are experiencing delays. Another smart airport resource is airport terminal deep cleaning solution, and there is need to ensure safety of passengers through cleanliness of airport operations. Smart airport geospatial technology is very important in maintaining social distancing and in disinfecting the airport terminals against the spread of the virus; it gives the management of the airport access to geospatial map of the cleaning operations of the airport through a dashboard using digital device such as tablet in real time; and it indicates portions that have been cleaned, in progress, and inspected. Figure 10 shows airport terminal cleaning operations interface.

The application gives the manager control to inspect all areas including sensitive areas such as the restroom, the manager communicates with supervisors that are meant to inspect the cleaning operations, and areas that have passed inspection are uploaded at real time and automatically reflect in the dashboard. Smart airport geospatial operations technologies therefore provide airport authority with the technology that allows the tracking of cleaning operations in an easy and efficient way.

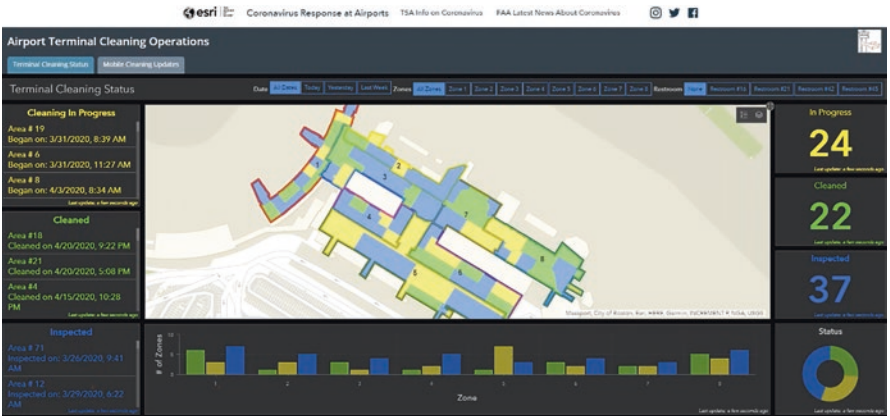

Fig. 10 Coronavirus response at airport. (Source: Adapted from https://www.youtube.com/watch?v=qBl01idKkmU, GIS and Airports response to COVID-19 webinar, ESRI)

Geospatial Mobile Contact Tracing Technologies

Bluetooth technology plays an important role in identifying if individuals have come into close contact with someone infected by COVID-19 (Rosenkrantz et al., 2020). Despite the progress made in the use of mobile contact tracing, a number of limitations have need reported by European Centre for Disease Prevention and Control (2020), these include:

(a) The possibility that not everyone has a smartphone, especially among the elderly persons, and having a smartphone without having the app downloaded.
(b) Some people with the app may choose not to carry their phone around or probably switched off their phones.
(c) The difficulty of some apps to work on older smartphones or operating systems.
(d) Limitation of mobile phones utility in investigating outbreaks in healthcare settings or long-term care facilities.

Limitations of Geospatial Technology

Despite the progress made in the fight against the pandemic using geospatial technology, several limitations or challenges have been identified by researchers and the GIS community. Few of the limitations are highlighted here considering data issues only. One of the limitations is based on inadequate data for geospatial analysis. A recent study acknowledged that the outcome of the study is rather an approximated predictive model of COVID-19 case distribution owing to the inadequacy of the dataset to account for important variables in the study (Quereshya et al., 2020). Still, on data issues, public health privacy policy adopted by countries and various agencies has also hindered the availability of datasets for research (Naudé, 2020). Therefore accessibility and accuracy of data for geospatial analysis remain a critical challenge. In addition, time constrain for the construction of big data management system for geospatial analysis has been identified as a major limitation in the application of geospatial technology during a pandemic. The development of large-scale pandemic control and prevention measure depends on data support. However, time constrain for adequate data collection and formulation of models to make a reliable decision has been reported as a limitation (Zhou et al., 2020). It is recommended that an interdisciplinary, multidimensional approach will be instrumental in the studies on the utilization of data in geospatial applications to mitigate the pandemic (Bontempia et al., 2020). In addition, collaboration among the GIS community and various stakeholders (especially in the health sector) in the fight against the pandemic should be intensified. This will enhance data accessibility and availability for geospatial analysis. Since the pandemic is dynamic and numerous data is generated on a daily basis, there is a need to constantly update existing models used in the assessment of the pandemic, in an open-source platform for easy applications and adaption to regional, national, and local peculiarities, where they exist.

Conclusion

Globally, the battle for containment of coronavirus disease outbreaks is taking new dimensions with various fields of study applying old and new techniques to combat the virus. Prominent in the fight against the virus in the application of geospatial technologies, this study explored a number of these innovative solutions currently applied by various stakeholders. GIS is seen as a complete system for understanding, assessing, and responding to the current pandemic. Geospatial mapping has taken a new dimension using various dashboards: the Johns Hopkins University's Center for Systems Science and Engineering (JHU CSSE); WHO COVID-19 situation dashboard; HealthMap dashboard; etc. The goal of the dashboards is to provide information on where and how quickly the disease can travel. Various communities were able to utilize the geospatial mapping tools to recognize and prioritize local risks; this is usually followed by strategic investment of resources in the form of emergency response or prevention to reduce the impact, spread, or occurrence/reoccurrence of the outbreak. Geospatial big data and Web map viewers as geospatial mapping tools have equally played critical role in the dissemination and provision of (official) information on COVID-19. Geospatial modelling of the spread of the disease has attempted to capture the dynamics of the transmission of the disease. Various statistical and epidemiological tools have been utilized as models to simulate the dynamics of the pandemic in the quest to stop the virus. Time series forecast played a major role in this. Modelling of medical facilities and location/allocation of resources was geospatially integrated to capture the trend and optimum utilization of facilities. Innovative tools have been invented by ESRI industry; in the context of indoor assessment of facilities for the new normal, this has been extended to airport smart strategies and mobile tracking technologies. It is imperative to note that geospatial technologies have played a critical role in the fight against the pandemic, and effort to maximize the technology should be encouraged.

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The Ontological Nature and Cause of COVID-19: A Philosophical Analysis

Cyril Emeka Ejike

Introduction

One attitude of philosophy, as a second-order activity, is to critically examine reality in order to understand its true nature and provide the whys and wherefores of it. The search for truth and the nature of things has been the main preoccupation of philosophers, especially metaphysicists, right from the ancient era. Metaphysics, a major branch of academic philosophy, is concerned with the fundamental nature of reality. In an attempt to comprehend and unravel the true nature of reality, a metaphysicist studies principles and causes of existents. Hence, Aristotle (1995) asserts that knowledge and understanding of an object of inquiry is attained when we are acquainted with its principles, causes and elements. We know a thing only when we have grasped the "why" of it, that is, its cause.

For Aristotle (1995), an investigation into the nature of reality consists in studying all causes, namely, material cause, formal cause, efficient cause, and final cause, that are ontological constitutions of things in the natural world. These four constituents or components of a natural thing embody responses to questions, respectively: What it is to be a thing? What makes a thing one particular kind of a thing rather than another? In other words, what are certain things that necessarily hold for an entity? What initiates the change of a thing? For what end or aim is a thing made?

THE COVID-19 pandemic, which first emerged from the central Chinese city of Wuhan late 2019, has killed off 2,721,891 people globally as of 25 March 2021 (ECDC, 2021). There is a conspiracy theory that the novel coronavirus (SARS-Cov-2) was produced in a laboratory at the Wuhan Institute of Virology (WIV) as a biological warfare used by the Chinese Communist Party to create panic in the West (Bertin et al., 2020). However, the director of the Institute, Wang Yanyi, has denied the claim, stating that the claims that the virus was manufactured in a Wuhan laboratory are a pure fabrication (Vanguard, 2020a). The World Health Organization (WHO) has equally denied the claim that the coronavirus was manipulated or

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constructed in a laboratory or somewhere else in Wuhan city of China (Vanguard, 2020b).

Many scientists have found that coronavirus is of animal origin, tracing its origin specifically to bats (Li et al., 2005; Ge et al., 2013; Yang et al., 2013; Hu et al., 2017). A study by Zhou et al. (2020, p. 270) shows that SARS-Cov-2 is “96% identical at the whole-genome level to a bat coronavirus”. International pulmonologists generally agree that the coronavirus originated from bats (Joseph, 2020, p. 2). According to the WHO, “all available evidence suggests that the novel coronavirus originated in bat in China” (as cited in Vanguard, 2020b, para. 2). Yanyi (2020) discloses that the WIV has “isolated and obtained some coronaviruses from bats” (as cited in Vanguard, 2020a, para. 4). Presently, there is no scientific evidence that the coronavirus is an artificial creation, and thus the claim that China manufactured the virus is uncorroborated.

This is not the first time the world has experienced a pandemic, and a natural viral infection is usually implicated in the development of a pandemic. The COVID-19 pandemic is a repetition of history. Some of deadly infectious diseases in human history include Antonine Plague (165–180 AD) that claimed an estimated five million lives; Plague of Justinian (541–542 AD) which exterminated an estimated 30–50 million people; Black Death (1347–1352) which decimated an estimated 75–200 million people; New World Smallpox (1520–unknown) that annihilated an estimated 25–55 million people; Third Plague (1885) that claimed an astonishing 12 million lives and the Spanish flu/influenza pandemic (1918–1920) that killed off an estimated 50 million people (Rosenwald, 2020). The AIDS pandemic has terminated an estimated 32 million lives by the end of 2018 since its outbreak in 1981 (UNAIDS, 2019).

Recent scientific studies of the previous pandemics like the 1918 Spanish flu/influenza pandemic as well as that of the COVID-19 pandemic show that viruses that cause the pandemics are predominantly of avian, swine and equine origins. For example, a recent scientific study published in 2014 in *Nature: International Weekly Journal of Science* reveals that the virus that caused the outbreak of the 1918 influenza pandemic (Spanish flu), which originated in US state of Kansas, sprang from birds and animals especially bats, pigs and horses (Hoag, 2014). Another recent research carried out by Tong et al. (2013), which was published in the *Proceedings of the National Academy of Sciences*, finds that fruit bats in Guatemala (Central America) harbour a novel strain of influenza A virus designated as H17N10. They observe that bats harbour “more influenza virus genetic diversity than all other mammalian and avian species combined, indicative of a long-standing host-virus association” (Tong et al., 2013, p. 1.). Epstein notes that bats, which are the second-largest mammal group with more than 1200 known species, carry a large diversity of viruses, including influenza, and they are responsible for viral spread to other mammals, including humans (Gewin, 2012). It has been scientifically established that the same fruit bats are linked to the emergency of Ebola virus, severe acute respiratory syndrome (SARS) and Nipah virus (Gewin, 2012).

A new study published on June 29, 2020, in the *Proceedings of the National Academy of Sciences* shows that pigs in China are increasingly becoming infected with a new strain of influenza virus identified as genotype 4 (GA) reassortant Eurasian avian-like (EA) H1N1 virus which poses a serious threat to human health (Sun et al., 2020). The GA EA H1N1 virus is a genetic mix of the H1N1 virus strain (A/H1N1 pdm 09) that triggered the 2009 swine flu pandemic and other flu viruses (Retner, 2020). The new swine influenza virus has the potential to mutate and jump to humans (Cohen, 2020). For instance, the H1N1 virus strain that caused the 2009 swine flu pandemic jumped from pigs to people, as first human infection with the virus was detected in April 15, 2009, in California in North America. In fact, the research by Sun et al. (2020) finds that the emergent G4 EA H1N1 viruses have acquired increased human inactivity, as workers on pig farms in China have been infected with the virus. The researchers are therefore perturbed that this potentially dangerous new virus could mutate further and spread easily from person to person, thus triggering a global pandemic (Robert, 2020).

The aim of this chapter is to investigate the ontological nature and cause of the COVID-19 pandemic. To do so, it will first explore an Aristotle's account of causality as a framework for examining the ontological nature and cause of COVID-19. It will thereafter draw heavily on the metaphysical works of Aristotle, Saint Augustine and Aquinas to show that privation is a corruption or lack of good in a being and argue that COVID-19 is not a being per se but rather a privation of being. It will conclude that humanity must live in harmony with nature and stop disrupting the natural order of things to heal the world and forestall further pandemics. Figure 1 provides the roadmap to chapter discussions:

Understanding the Causes of Things in the Natural World

Aristotle (1995) presents theory of causes as indispensable resources for a successful investigation of the natural world. They include the material cause, the formal cause, the efficient cause, and the final cause. For him, an inquiry into nature consists in a search for "the causes of each thing; why each thing comes into existence, why it goes out of existence, why it exists" (as cited in Falcon, 2019 "Introduction" section, para. 1). The search for causes of existing things did not begin with Aristotle, as his predecessors (Ionian or pre-Socratic philosophers) were preoccupied with fundamental causes and principles of existence in the natural world.

However, Aristotle's predecessors lacked a "complete understanding of the range of possible causes and their systematic interrelations" (Falcon, 2019, "Introduction" section para. 1), and thus their causal investigation of ultimate reality and their accounts of causation were incomplete and therefore not entirely successful. For instance, Aristotle (1995) contends that Ionian philosophers were too limited in their approach by emphasizing only one cause – the material constituents only. The Pythagoreans went to the other extreme by stressing the formal cause (number) at the expense of material cause. Aristotle acknowledges that Plato was the only philosopher before him that employed both material and formal causes in his (Plato's) cosmology.

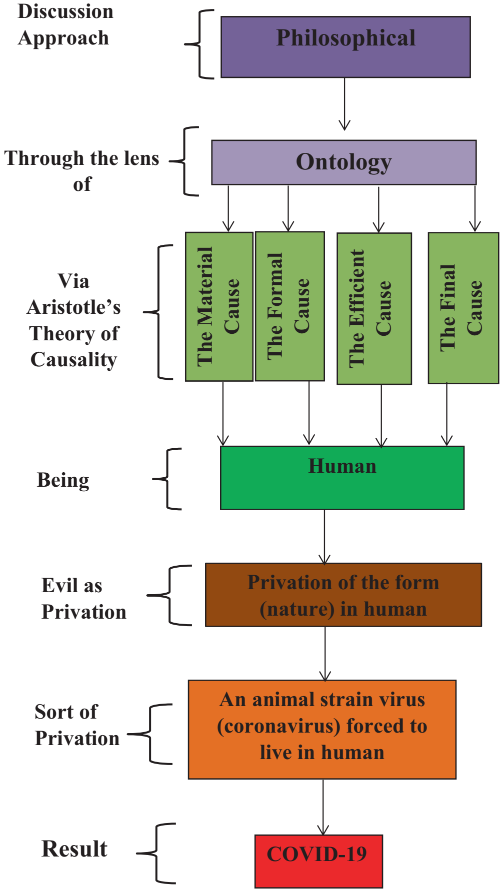

Fig. 1 The roadmap to chapter discussions. (Source: Author's own figure)

Aristotle (1995) sees his general account of the four causes as the culmination of the search for ultimate reality. He insists that we cannot have a proper knowledge of the whys and the wherefores of things without a full grasp of systematic interrelations between the four causes. The search for causes is the search for an answer to the question "why"? In the *Physics*, he states that we do not have knowledge of a thing until we have grasped the "why" of it – that is, its cause (Aristotle, 1995). In the *Posterior Analytics*, he reiterates that we think we have knowledge of a thing *simpliciter* only when we have grasped its cause or the explanation of why it *is* and not otherwise (Aristotle, 1995).

The Material Cause

This is the substratum – the stuff out of which a thing is made. It is "that out of which a thing comes to be and which persists" (Aristotle, 1995, p. 736). In other words, it is that from which a thing comes into being and which endures through the change. Illustrating the material cause, Aristotle states that further that it is "that from which (as immanent material) a thing comes into being, e.g. the bronze of the statue and the silver of the saucer, and the classes which include these" (1995, p. 3443). For instance, the material cause of a silver medal is silver and that of a table is wood. The material cause provides potentialities to be actualized. It is therefore an indispensable precondition for the realization of the form of an entity.

The Formal Cause

This is the structure, the essence (form) of a thing. As Aristotle (1995) puts it, formal cause is "the form or the archetype, i.e. the definition of the essence, and its genera" (p. 736). It constitutes the very nature of an object, that is, that which makes it a particular kind of an object and which marks it off from other objects. The formal cause is therefore the defining characteristics of a thing. The essence of a silver coin, for instance, is the form in which it exists, and it includes all the basic characteristics that are necessary to define it as a coin such as colour, metallic lustre, shape, weight, composition, inscription, specific gravity and so forth.

The formal cause of a table is its design or shape made by a carpenter. The formal cause directs the final cause (the end) since the end of an entity is shaped by its very essence. A being that is yet to fully realize its inherent form is said to be in potency, suggesting that it has the inherent potential to realize its form or essence (the formal cause). But a being that has fully realized its form is said to be in act (Aristotle, 2006). For example, an acorn has the potentiality to become an oak tree. Goodness (*bonum*) is an intrinsic nature of a being. It denotes the dispositional attribute which constitutes the forma cause.

The Efficient Cause

This is the source or initiator of change/movement. It is the agent that is responsible for bringing a thing into existence. Explaining with examples, Aristotle (1995) states that the efficient cause or the moving cause is "the primary source of the change or rest; e.g. the man who deliberated is a cause, the father is a cause of the child, and generally what makes of what is made and what changes of what is changed" (p. 736). The efficient cause is therefore that which produces an entity or makes it come to be. For example, a carpenter is the efficient cause of a table since it is constructed from a wood by him. The efficient cause is the actual force that brings something into being.

The transformation of an entity from one form to another requires an efficient cause. Illustrating the workings of the efficient cause as the initiator of change, Copleston (2003, p. 312) asserts: "Stone that is unhewn remains unhewn so far as the stone itself is concerned: it does not hew itself. No more does hewn stone build itself into a house. In both cases an external agent, source of the change or movement, is required". The wood upon which a carpenter works is in potency to receiving the new form – the form of the table. Things therefore receive new form under the action of some efficient cause. The efficient cause initiates processes and brings about their effects.

The Final Cause

This is the end or purpose for which a thing is made or done. It is the ultimate goal of a thing, a teleological explanation of why something exists. Nature makes everything for a purpose. Every being, art or action tends towards a certain end or a goal which is rooted in the nature of the very being that act or is acted upon. Aristotle (1995, pp. 2621-2622) explicates thus:

> Everything then exists for a final cause, and all those things which are included in the definition of each animal, or which either are for the sake of some end or are ends in themselves, come into being both through this cause and the rest. But when we come to those things which come into being without falling under the heads just mentioned, their cause must be sought in the movement or process of coming into being, on the view that the differences which mark them arise in the actual formation of the animal. An eye, for instance, the animal must have of necessity (for an animal is supposed to be of such a sort), but it will have an eye of a particular kind of necessity in another sense, not the sense mentioned just above, because it its nature to act or be acted on in this or that way.

The goal is the end product of an activity or a process of moving from the state of potentiality to that of actuality. The conviction that nature has a capacity for development and thus aims at a particular end (*telos*) in respect to both physical and moral phenomenon underlies Aristotle's natural law doctrine (Njoku, 2010). In *Nicomachean Ethics*, Aristotle (2004) defines good in terms of an end. For him, "the good has been aptly described as that at which everything aims" (p. 3). The end coincides with the good. Buttressing this assertion, Aquinas (I–II, q. 1. a. 2) states that "every agent of necessity acts for an end". An agent acting for an end can be intelligent or non-intelligent. An intelligent being is intrinsically directed towards the attainment of its definite goal if the tendency towards a particular goal is built in the very nature of the being.

However, a non-intelligent entity has an extrinsic orientation since its natural tendency towards a specific goal is directed by an extrinsic agent that acts within its particular nature. For instance, a rational human being leads himself to an end which he tends towards, but a car (irrational entity) tends to an end as directed or led by a rational human being. It is in the nature of an entity to tend towards that which defines its essence (nature). Every entity has the inherent potential to become what its form (essence) has set as its end. Therefore, "there is in all things a dynamic power of striving toward their end" (Stumpf & Fieser, 2003, part 1, p. 85). It is the essence of a being (forma cause) that determines its end/goal (the final cause). To this extent, the end is built into the very nature (essence) of a being that acts.

The final cause is the completion (end) of the development of the intrinsic nature (formal cause) of a being. A being attains its final cause (end) when it its formal cause is actualized. An acorn, for instance, attains its purpose or end (final cause) when it reaches the perfection of development – a full-grown tree (an oak tree) – of which it is capable. The final cause offers a justification for bringing something into being. For instance, “there is no way to explain natural generation than by reference to what lies at the end of the process” (Falcon, 2019, “The Explanatory Priority of Final Cause” section, para. 2). Every being in the world therefore aims at the realization of its essence or immanent form as the end (the good). The realization of the end at which it aims is the final cause of becoming.

These four causes that constitute aspects of an existent in the natural world account for the change and process of continuity observed in all things (Iroegbu, 1995). They embody a framework for the total explanation of things in the natural world. Aristotle’s theory of causality is elucidated to show that COVID-19 is not a being per se; it can only exist through a human person, and its effect is produced in him. As it will be argued, COVID-19 has no formal cause; it results originally from a privation of the form (good nature) of a human being.

Privation as a Factor in Change

Generally, privation is seen merely as not being something. But in philosophy, privation, as a principle of coming to be, means more than just *not* since it is “not every instance of some matter’s not being something corresponds with what can come to be in that matter” (McGinnis, 2012, p. 551). For example, I am not 20 feet tall but I do not have the potentiality to be it. Aristotle’s account of a privation refers in some way to an absence or loss of some natural attribute of a being. A privation is a lack of something. It occurs when a matter is deprived of its form. For example, we can speak of a privation as it relates to the mind and to the body. A privation of perception is to fail to perceive because something is lacking. As it relates to the body, a privation of perception is blindness. But as it relates to the mind, we cannot speak of the mind as being blind except metaphorically. Instead we speak of the person as being slow, or stupid. Privation is therefore the deprivation of the form (nature) of something.

A form is a positive property of a thing, while privation is a lack of that form. For Aristotle (1995), there are three principles that underlie change or are required for anything coming to be (genesis), namely, subject (*hupokeimenon* – an underlying thing – the primary substratum of a thing, which has been traditionally associated with matter); form that will come to be; and privation, the initial contrary or opposite of that form in the subject. For example, in the statement, “some silver which was shapeless becomes a medal”, the silver is the subject, and the medal is the form, while shapelessness is the privation.

Change is the development of something that has the inherent potential to become something else which it is not yet. It is the process of realizing the potentiality of becoming something that is in the very nature of a being. Change "includes every passage from a *terminus a quo* to a *terminus ad quem*" (Copleston, 2003, p. 306). The subject persists through the change, but the form or the privation can cease to exist when there is change, a thing can change either by generation (coming-to-be) or destruction (ceasing-to-be). Generation occurs when a privation is replaced by a form. But destruction occurs when a form is supplanted by a privation. For Aristotle, matter, form and privation therefore traditionally account for paradigmatic substantial changes (Krizan, 2013).

Privation is not a principle per se, unlike matter and form, but per accidens principle, that is, a principle by coincidence in that it coincides with matter (Aquinas, 2007). Its accident is necessary since it does not exist in isolation from its subject. The term *accidens* in relation to privation is used in the sense of "through matter". Privation exists through a subject in an incidental way when the subject is deprived of its form. Although it may be contingent that a subject has a particular form or deprived of it, it is still necessary that the subject is in that state or the other. Both Aristotle and Aquinas maintain that privation is an incidental (per accidens) principle of change, while matter (the substrate or the subject of the motion) and its determination (form) are essential principles of change (Muhoney, 2003). For Copleston (2003), privation is not a positive element of change, unlike matter and form, albeit it is necessarily a presupposition of change.

Accordingly, in one respect, privation is related to matter in that privation exists through matter. The causality of privation is exercised in matter, and its effect is produced in matter since privation exists through matter. Every subject that has the potentiality for a particular form, say good, also has the potentiality or possibility for the opposite, say evil. Aristotle (1995) therefore views privation as potentiality of matter:

> Every potentiality is at one and the same time a potentiality for the opposite; for while that which is not capable of being present in a subject cannot be present, everything that is capable of being may possibly not be actual. That, then, which is capable of being may either be or not be; the same thing, then is capable of both being and of not being. And that which is capable of not being may possibly not be; and that which may possibly not be is perishable, either without qualification, or in the precise sense in which it is said that it possibly may not be, i.e. either in respect of place or quantity or quality…. (pp. 3566–3567).

Every perishable substance that has the potentiality to do something or be something therefore has the potentiality for the opposite. It is this potentiality for contraries that opens up the possibility of evil. Concerning perishable substances, Aristotle (1995, pp. 3568–3569) writes thus:

> Everything of which we say that it can do something, is alike capable of contraries, e.g. that of which we say that it can be healthy is the same as that which can be ill, and has both potentialities at once; for one and the same potentiality is a potentiality for health and illness, for rest and motion, for building and throwing down, for being built and being thrown down. The capacity for contraries is present at the same time but contraries cannot be present at the same time, and the actualities also cannot be present at the same time, e.g. health and illness. Therefore one of them must be good, but the capacity is both the contraries, or neither; the actuality then is better. And in the case of bad things, the end or actuality must be worse than the potentiality; for that which can is both contraries alike.

In another respect, privation is related to form in that it is the opposite or contrary of some form that will come to be. Privation is always a privation of form (nature) of something; there is no bare privation. Privation is contained within an entity. When an entity contains the privation, it ceases to be in its own nature (Aristotle, 1995, p. 727) – which is a deprivation of its form.

Evil as Privation

Aquinas defines privation (*privatio*) as neither an aptitude for form nor an inchoate form, nor some imperfect active principle, but lack or contrary of form itself (Muhoney, 2003). For him, it is "the want of some property in a subject that ought naturally to possess that property" (Gartenberg, 2020, p. 306). Augustine denies the existence of evil as an independent entity but rather describes it as a privation of good in a being (Menn, 2002). He explicates thus:

> For what is that which we call evil but the absence of good? In the bodies of animals, disease and sounds mean nothing but the absence of health; for when a cure is effected, that does not mean that the evils which were present – namely, the diseases and wounds – go away from the body and dwell elsewhere: they altogether cease to exist; for the wound or disease is not a substance, but a defect in the fleshly substance – the flesh itself being a substance, and therefore something good, of which those evils – that is, privations of the good which we call health – are accidents. Just as in the same way, what we called vices in the soul are nothing but privations of natural god. And when they are not transferred elsewhere: when they cease to exist in the healthy soul, they cannot exist anywhere else (Augustine, 1974, p. 65).

Evil consists in the corruption of being or the defect of some principle of action which proceeds from the defective will that fails to subject itself to its proper principle. Aquinas (1947, part I–II, q. 49, a. 1) asserts thus:

> It must be said that every evil in some way has a cause for evil is the absence of the good, which is natural and due to a thing, but that anything fails from its natural and due disposition can come only from some cause drawing it out of its proper disposition. For a heavy thing is not moved upwards except by some impelling force; nor does an agent fail in its action except from some impediment. But only good can be a cause; because nothing can be a cause except in as much as it is a being, and every being, as such, is good.

Evil is therefore a privation of form that corresponds with a possibility or potentiality in the matter for that form. It signifies the absence of good or form (Aquinas, 1947, part I–II, q. 48, a. 1). It lacks form or nature; it has no formal cause, for it is not a property of thing. Evil is caused in the action by reason of defect of an agent or the matter. In the words of Aquinas (1947, part I–II, q. 49, a. 1): "Evil has no formal cause, rather is it a privation of form; likewise, neither has it a final cause, but rather is it a privation of order to the proper end; since not only the end has the nature of good, but also the useful, which is ordered to the end. Evil, however, has a cause by way of an agent, not directly, but accidentally".

According to Sanford (2017, p. 201), "what makes an actuality good is precisely its degree of achievement of the *telos* that is definitive of a given substance, and what makes a bad actuality bad is the degree to which it thwarts the achievement of the *telos* definitive of a given substance". Evil is the result of failure of a given substance/being to realize the end (*telos*) that is definitive of its nature. Evil is therefore a defect, corruption or perversion of a good in a being or being that ought to be good rather than being a substance that exists on its own. In this regard, Aristotle (1995, p. 3569) writes: "Clearly then, the bad does not exist apart from bad things; for the bad is in its nature posterior to the potentiality. And therefore we may also say that in the things which are from the beginning, i.e. in eternal things, there is nothing bad, nothing defective, nothing perverted (for perversion is something bad)".

The absence of good, taken in a privative sense, rather than in a negative sense, is an evil (Aquinas, 1947, part I–II, q. 48, a. 3). Given that evil is not a mere negation, but the privation of good, every defect of good is not an evil but only the defect of naturally due good. Aquinas (1947, part I–II, q. 48, a. 5) explicates with illustrations thus: "For the want of sight is not an evil in a stone, but it is an evil in an animal; since it is against the nature of a creature to be preserved in existence by itself, because existence and conversation come from one and the same source. Hence, this kind of defect is not an evil as regards a creature". So, the inability of a stone to see is not evil, by nature, since a stone cannot see. But it is evil for an animal, say cat, not to see since, by nature, it should not be blind.

The object of the will is good in itself and so evil, which is the privation is found in rational creatures that have a will (Aquinas, 1947, part I–II, q. 48, a. 5). Free will makes evil possible.

COVID-19 as a Privation of Some Good in a Being or Nature of a Being

Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) – a new strain of coronavirus that had not previously been identified in humans. There is a consensus among the international pulmonologists that the virus originates from animals and it is traced to a seafood market in China where animals like bats, snakes, rabbits and so forth are sold (Joseph, 2020, p. 2). The virus is traced to snakes at initial outbreak of the COVID-19 pandemic, but later studies show that it has more similarities with bats (Joseph, 2020, 2). Since the outbreak of severe acute respiratory syndrome (SARS) 18 years ago (2002), a large number of SARS-related coronaviruses (SARSr-CoVs) have been discovered in their natural reservoir host, bats (Li et al., 2005; Ge et al., 2013; Yang et al., 2013; Hu et al., 2017), and previous studies have shown that some bat SARSr-CoVs have the potential to infect humans (Menachery et al., 2015, 2016; Wang et al., 2018).

The first human cases of SARSr-CoVs were reported officially to the WHO on December 31, 2019, in Wuhan city of China. It is a zoonotic virus that can be transmitted from animals to humans and from human to human. The virulent virus spreads from human to human primarily through close contact from person to person, droplets and surface contact. For instance, when an infected person coughs or sneezes, droplets may enter another person's mouth or nose and be inhaled into the lungs. A person can also get COVID-19 by touching a surface or an object that is infected with the virus and then his mouth, nose or eyes. Some common symptoms of COVID-19 are fever, dry cough, sneeze, breathing difficulties (dyspnoea) or shortness of breath, dry and itchy throat, persistent pain, headache and pneumonia.

The COVID-19 pandemic is a force of nature and so is natural evil. Though natural evil is seen as natural, non-moral catastrophe, some natural evil like COVID-19 is precipitated indirectly by the misuse of freewill of a moral agent, and thus COVID-19, as natural evil, correlates indirectly with a wrong free moral choice. It comes about as a result of corruption of natural order or form in animals and humans by humans themselves out of their own volition. Viruses implicated as the causes of the COVID-19 pandemic and some previous pandemics originate from bats, pigs and horses, as research indicates. These birds and animals are unfit for human consumption due to what they feed on. Bats are scavengers or carrion eaters that feed on carcasses or decaying flesh of dead animals which are diseased. Pigs, especially wild pigs, are scavengers and/or predators that eat carcasses and/or kill and eat disease-prone animals, while horses are predators that hunt, kill and eat disease-prone animals. So, ultimately, these birds and animals feed on disease-prone animals (dead or alive) which could sicken or kill humans. No wonder the Bible (Leviticus 11: 4–8, 13–19, 27, 29–30, 41–42; Deuteronomy 14: 7, 12–19) considers these birds and animals, among others, unclean and thus not fit for human consumption.

Prior to the COVID-19 outbreak, bats had been implicated as an original cause of previous outbreak of viral infections like 1918–1919 Spanish flu/influenza pandemic and Ebola virus. Yet, people continued to eat bats in exercise of their free will. There are naturally animal strain viruses (viruses that are made to live in animals by nature) and naturally human strain viruses (viruses that are made to reside in humans by nature). Humans disrupt an idyllic state and natural order of viruses in the scavengers and predators by forcing the viruses to live in humans through consumption of the birds and animals that are unfit for human consumption or eating foods contaminated by them. By forcing the animal strain viruses to live in humans, the natural order or idyllic state of the viruses is upset and corrupted. Humans too corrupt their own good nature and harm themselves in doing so. Therefore, COVID-19 as a corruption of natural order or privation of some good in a being is anthropogenic (human-induced). COVID-19 is not a property of a thing. It lacks a formal cause since it is not a being per se. It cannot exist in isolation from a being that has a formal cause. It comes about originally when a being is deprived of its good nature or form. Humans are robbed of their good nature by forcing an animal-strain virus (SARS-CoV-2) by nature to live in humans where it is not naturally created to be through the consumption of bats that are unfit for human consumption or eating foods contaminated by bats. The COVID-19 pandemic resulting from SARS-CoV-2 becomes a privation or corruption of good nature of human beings.

Conclusion

The ontological nature and cause of the COVID-19 pandemic has been examined in this chapter. It is showed that four types of cause, namely, material cause, formal cause, efficient cause and final cause, are ontological components of every being in the natural world and argued that COVID-19 has no formal cause and so is not a being per se. It cannot exist in isolation from a being (a human person) that has a formal cause. COVID-19 signifies the absence of form or privation of some form or good that should be present in a being by nature. COVID-19 and other pandemics break out originally when a being is corrupted or its good nature or form is deprived of.

Though COVID-19 is a natural evil, it is anthropogenic and an indirect product of human volition. It comes about indirectly as a result of misuse of human freedom. Its outbreak is a result of disruption of natural and idyllic state of viruses in certain birds and animals that are unfit for human consumption by eating the birds and animals, or eating foods contaminated by such birds and animals. Pandemics had occurred in the past, and so the COVID-19 pandemic is a repetition of history. But, regrettably, humanity hardly learns from history. Humanity will continue to experience a novel pandemic unless it abstains from eating certain birds and animals that are unfit for human consumption, as well as eating foods contaminated by such birds and animals. Humanity must live in harmony with nature and stop upsetting and disrupting the natural order of things to heal the world and forestall further pandemics.

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Part II
COVID-19 Shock and Socio-Economy

Digital Transformation: Prior to and Following the Pandemic

Farhad Khosrojerdi, Hamed Motaghi, and Stéphane Gagnon

Introduction

Transforming to digital solutions has been one of the main topics in the fourth industrial revolution (4IR). For almost a decade, digital transformation (DT) has been perceived as a way of business growth, expansion, quality, and sustainability (Shinde et al., 2014). Without any doubt, the COVID-19 pandemic has been one of the most unprecedented events mankind faced in the modern world. Both private businesses and public sectors have been drastically affected. Immediate lockdowns and interruptions, required by authorities and governments, changed the way many businesses and organizations perform. Thus, thinking of undergoing improvements and operating upgrading functionality of an organization or an entity are deemed as supplementary threats (Wuest et al., 2021). Known as the digital revolution, 4IR is more than a technology-driven aspect. It provides opportunities for everyone to use technologies for a human-centered future (Pombo et al., 2018). Thus, many businesses and organizations started transferring to digital solutions. However, the implementation of digital transformation (DT) has been quite slow in different sectors in most cases (Mahmood et al., 2019). Due to the required significant

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adjustments in the institutional model (Voronin et al., 2020), it is difficult to rapidly modify various processes of learning models.

There are many literature reviews about the effects of DT in different sectors before the pandemic hit the world at the end of 2019. The early studies tie up the concept of DT with utilizing digital technologies including Internet of Things (IoT), cloud computing, and data-analytics solutions (Majchrzak et al., 2016; Matt et al., 2015). Some of the papers elevate the concerns to business models, information technology (IT) perspectives consisting of methodologies, applications, and various impacts of digital transformation on businesses (Gebayew et al., 2018; Reis et al., 2018).

On the other hand, the literature reviews assessing the effect of COVID-19 on DT mainly provide an overview of the challenges, possible opportunities, and methodologies used (Shaughnessy, 2018; Van Veldhoven & Vanthienen, 2019). These papers were obviously published after the global lockdown in 2020 and 2021. Nevertheless, there exist some papers, published between 2020 and 2021, assessing the impact of DT in different sectors without mentioning the pandemic.

This chapter emphasizes two important factors for future literature reviews: (I) considering the pandemic timeline for choosing references and articles and (II) including the impact of COVID-19. Otherwise, the validity of the output results can be questionable because the business models, operations, and structures of many organizations have been changed. To accomplish our goals, a systematic literature review is performed about DT and its impacts in different sectors before and after the coronavirus pandemic. The challenges, opportunities, and implementation of DT are described as well.

This chapter is structured as follows: digital transformation and the implications in different sectors are reviewed in section "Systematic Review Approach", in which the systematic review approach used in this chapter is explained. In section "Effects of DT on Different Organizations", the effects of implementing DT in several sectors are presented. Addressing organizational challenges and opportunities caused by the immediate shutdown are discussed in section "Discussion". Finally, the conclusion is made in section "Conclusion".

Systematic Review Approach

This chapter follows the steps introduced by Keele (2007) for performing the systematic literature review. A systematic literature review is conducted to develop research questions on the topic of interest. Query keywords are used to search scholarly databases, browsing articles and papers in different journals and conference proceedings that address research questions. To increase the number of relevant articles, forward search (searches for literature that cited the identified articles) and backward search (searches within the bibliographies of the identified articles) are implemented (Keele, 2007). Finally, exclusion and inclusion criteria are defined to identify the articles that will be included in the review. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA), including identification, screening, eligibility, and inclusion (Moher et al., 2009). In the identification step, answers to the following research questions are considered:

- What are the impacts of DT on different organizations, industries, and business sectors?
- And what are the impacts after the pandemic?
- How important is the COVID-19 timeline in DT's future research?

In order to answer these questions, the applied queries were defined as: "impacts of digital transformation," "implementation" and "digital transformation," and "digital transformation" and "review." The selected scholarly databases included Google Scholar, IEEE Xplore, Web of Science, and ProQuest (PQ). The abstract of an article was navigated for the query keywords. At the end of this step, 172 papers were identified. Duplicated records and articles with unrelated content were removed, resulting in 122 full-text papers in the screening phase. An EndNote library was created with DT-linked subject matters consisting of COVID-19, the education sector, DT reviews, and DT in different sectors. After reviewing the screened articles, we assessed 93 full-text papers for eligibility. In this stage, we evaluated the contents of the papers for possible similarity in their results, applications, and conclusions. Furthermore, the impact of COVID-19 on digital transformation has been the key factor for a paper to be added to the eligible list. Thirty-four studies were excluded from the list because either the pandemic was neglected or the papers represented similar contents. Therefore, a total of 59 full-text papers were submitted for the literature review at the end. Figure 1 depicts the processes of collecting articles in each stage.

Herein, we focus on undergoing the implementation of DT in several domains, considering articles published prior to the pandemic. Papers studied DT before COVID-19 are evaluated, in addition to publications submitted before the pandemic but accepted later in 2020 and 2021. The collected papers were reviewed and classified into relative group sets in the EndNote library. Overviewing of the papers revealed that they were distributed over COVID-19-related papers, the literature review articles, and the application of DT in different sectors. Finally, we clustered the selected papers into four classes: (1) COVID-19, (2) DT and education, (3) DT in different sectors, and (4) DT reviews. Figure 2 presents the number of articles in each category.

Effects of DT on Different Organizations

Companies started investing millions of dollars in information and communication technologies (ICT) during the 1990s (Andal-Ancion et al., 2003). Digitalization of businesses and different organizations has been believed to be the main key toward the 4IR. Using advanced technologies and new equipment for operating businesses are unlike the idea of transforming business processes to digital. In fact, the concept

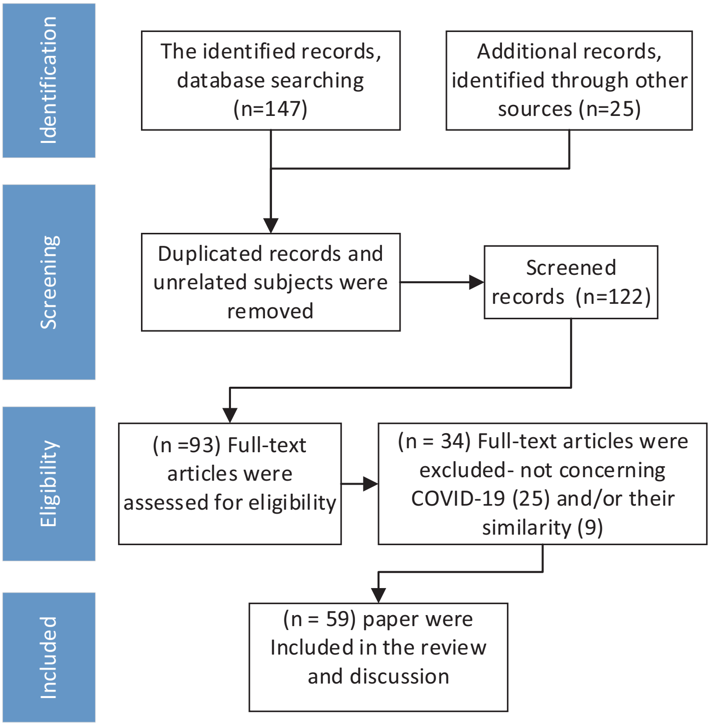
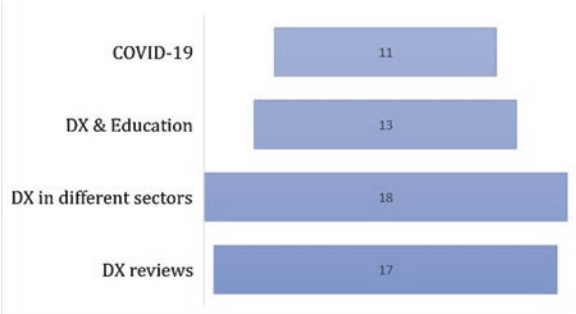


Fig. 1 The systematic literature review based on the PRISMA flow diagram. (Authors' own work)

Fig. 2 Breakdown of the papers based on their research interests. (Authors' own work)



of digital transformation means to use technology for the value added to end-users and increase the performance of the entity. Digital transformation is defined as "the profound transformation of business activities and organizations, processes, competencies and models, for the maximum transformation of the changes and opportunities of a technology mix and its accelerated impact on society, in a strategic and prioritized way" (Gobble, 2018). Digital transformation refers to implementing technological approaches to achieve organizational objectives and improve the performances of different processes. In fact, implementing digital-oriented solutions defines the most promising characteristic of digital transformation. It introduces innovative approaches to enhance traditional methods (Bogdanby et al., 2020). DT has been applied to various organizations in many businesses (Andal-Ancion et al., 2003), industries (Ustundag & Cevikcan, 2017), healthcare systems (Agrawal et al., 2010), and education institutes (García-Peñalvo, 2021). Therefore, the impacts of transferring from traditional to digital learning systems have been reviewed in numerous studies prior to and following the global pandemic.

Implementation of DT in Different Sectors Prior to the Pandemic

Transformation to the digital world has been utilized by financial institutes and banks for more than a decade. Related to e-banking, an integrative framework is developed and evaluated by Liu, Chen, and Chou (2011) to improve the performance of banking services. Despite challenges, it has been claimed that analysis of both resources/capability and external demands can be reduced by an understanding of the resource fit perspective. Concerning digital banking, Gouveia, Perun, and Daradkeh (2020) address the characteristics of the use of advanced technologies in customer service automation. In healthcare services, digital solutions can increase the quality of care, efficiency, financial performance, affordability, and accessibility (Agrawal et al., 2010). Named the digital economy, the application of drones in construction is perceived as a transformation to the digital world (Mottaeva et al., 2018); whereas, the major elements of the digital economy are reflected through modern consumers and cultural communications including personalized service model, direct interaction between producers and consumers, individual members' contributions, and financial activities focusing on the digital transformation platform. Exploring digital organizations, Shahiduzzaman and Kowalkiewicz (2018) present a "Digital Business Maturity Model." The proposed maturity model measures digital maturity throughout two broad categories, digital capabilities and digital impacts. In terms of organization and business changes, digital transformation offers value to customers and end-users so that new products and services can be developed and commercialized (Stief et al., 2016). The role of IT professionals managing digital transformation projects opens a new research agenda in the human resource management knowledge areas (Cabot & Gagnon, 2021). Garzoni, De Turi, Secundo, and Del Vecchio (2020) introduce a four-level approach to small- and medium-sized enterprises (SMEs) in the adoption of digital technologies including digital awareness, digital requirement, digital collaboration, and digital transformation. In the connection with entrepreneurship, Gavrila Gavrila and De Lucas Ancillo (2021) find that the pandemic has been a negative force for innovation. Businesses can use internal ideas for innovation by utilizing digital technologies and harnessing entrepreneurial approaches (Gunasilan, 2020). The impact of DT on technology entrepreneurship was also explored in a study (Jafari-Sadeghi et al., 2021) based on three classes: ICT investments, research and development, and patents and trademarks. It provides important implications for business management and practitioners. A survey reveals some concerns about technology that are linked relevant to digital transformation initiatives (Furjan et al., 2020). However, digital transformation needs to be viewed from a strategic perspective instead of a technology-related standpoint (Kane et al., 2015).

Investigating an enterprise's digitalization, Andriushchenko, Buriachenko, Rozhko, Lavruk, Skok, and Hlushchenko et al., (2020) recommend recognizing five main factors to understand the situation in which an enterprise involved in DT: (I) definition of the business strategy, (II) engaging insiders, (III) customer focus, (IV) recognition of workers' experiences before changes, and (V) implement the silicon valley management system at the enterprise. In another research (Bican & Brem, 2020) examining sustainability and DT, it is stated that digital transformation is affected by margin pressure, speed of change within respective business activities, customer focus, and proximity. As an example from the manufacturing industry (Sanchis et al., 2019), the virtual factory open operating system (vf-OS) platform is introduced, managing the overall network of a collaborative manufacturing and logistics environment. The paper claims that it helps IoT devices, humans, and software applications to communicate and interoperate without a glitch in the interconnected environment. The results of the study by Lombardi and Secundo (2020) introduce promising research domains in the context of corporate reporting including: digital technology for corporate information management and decision-making processes; digital technologies as a tool of stakeholder engagement and sustainable reporting practices; and digital technologies as a way to address earning management, corporate social responsibility, accountability, and transparency. Digitalization of entrepreneurial organizations, its opportunities, and challenges in the tourism sector experienced in the Republic of Serbia are described in Simic (2020). The paper presents prospects as well as avoiding or successfully handling potential challenges. In a literature review (Nadkarni & Prügl, 2020), it is stated that the pace of transformation, the culture and work environment, and the middle management perspective are substantially underdeveloped.

Compared to the private sector, public institutions have been practicing digitalization to improve the performance of their essential services to the public. The results of a study on digital government by Alvarenga, Matos, Godina, and C. O. Matias (2020) indicate a growing number of publications addressing DT in Public Administration. Lack of knowledge about the concept and untrained employees originate from unsuccessful knowledge management, which according to the paper is the critical key in DT. Among different organizations in the private sector, digital transformation has been practiced by higher education institutions the most. In the education sector, digital transformation means to establish a collaborative, active, self-directed, and engaging model from a knowledge-transfer model (Selinger et al., 2013). Performing DT in an educational system can improve the learning outcome of students alongside productivity in teaching and administrative works of faculty members (Castro Benavides et al., 2020). In another paper (Androutsos & Brinia, 2019), DT has been used to propose a pedagogy enhancing innovation, collaboration, and co-creation of students. In addition to this study, Demartini, Benussi, Gatteschi, and Renga (2020) state four major benefits of implementing DT in an educational system including access to information, availability of content, creativity and digital production, and collaboration and sharing. Still, there are studies focusing on the use of ICT in higher education (Santos et al., 2019), instead of transforming the business model. In connection with the latter, the application of digital technologies and social media is perceived as DT (Secundo et al., 2020). In an exploratory study at Qatar University (Younis et al., 2020), the potential growth related to digital entrepreneurship and the educational institute is examined. Likewise, there is a paper by Asmar and Badr (2020) that highlights the design of accessible and inclusive technologies that can be used for people with learning disabilities.

Post-Pandemic and Digital Transformation

The manufacturing industry and related companies have been influenced by the pandemic at different stages of manufacturing. Wuest et al., (2021) depict these stages including R&D, sourcing, manufacturing, assembly, logistics, sales, usage, after-sales services, repair and maintenance, remanufacturing, recycling, and disposal. Various clusters in manufacturing such as automotive, pharmaceutical, aircraft, defense, and household products experience distinct disruptions regarding those stages. Reviewing DT in the Russian economy, Kharlamov, Raskhodchikov, and Pilgun (2021) indicate that "...33% of the total number of Russian companies in the first half of 2020 suffered losses of more than 1.5 billion rubles, 46% of *representatives* of business structures announced a decrease in demand for their products or services." In the case of manufacturing, transforming to digital solutions means automation of processes in the production line and utilizing robotics, in order to comply with stay-at-home orders (Wuest et al., 2021). Installations of these advanced systems are time-consuming and require a huge amount of investment. In a study, digital entrepreneurial-based SMEs in the post-era of COVID-19 are investigated (Purbasari et al., 2021). Lack of accurate and specific policies regulating the content in the digital world may ascertain conflicts with social norms and consequently business operations.

Travel and relocation restrictions, social distancing, and governments' regulations to control the spread of the coronavirus have hammered private and public sectors to adopt DT, even more than before the outbreak. Due to the magnitude and vertiginous halt of operation, many organizations and businesses confronted unlike experiences, surely depending on where they were in implementing DT. Among different public sectors, the operation of educational systems and health institutions by far is the most crucial than other counterparts during the pandemic. While healthcare systems were obviously excluded from the lockdown, most education sectors had to close their doors to the public across the globe. Thus, the consequences of interrupting operations are occurred to the scholars, while hospitals experienced an overwhelming amount of work in their everyday business operations. In this environment, healthcare sectors cannot tolerate extra pressure by implementing new organizational development or any changes including digital transformation. However, educational institutes along with many organizations in the private sector need to undertake immediate actions to respond to the unforeseen event. Across the globe, private sectors also had to comply with governments' rules. It means that even if improving performance and added value throughout DT were not the private sectors' concerns, now, they may envision it as a solution to overcome their present hurdles.

The key factor regarding the pandemic is that various businesses and organizations in different sectors practically implemented digital transformation. Practicing the digital layout of usual business operations has helped them to accelerate the transition from traditional to digital processes. As presented in a study (Kharlamov et al., 2021), 57% of business representatives noticed the stimulation of DT within their companies, 38% experienced changes in management and corporate culture, and 29% noted a reduction and reorganization of ineffective components of their business processes. Intelligent systems are being applied to prevent the spread of coronavirus by using cell phones and drones to track and detect affected people. Furthermore, utilizing advanced technologies such as AI-based methodologies provides prospects to mitigate the negative effects of the pandemic on manufacturing and supply networks. The application of such technologies increases connectivity, transparency, and visibility (Wuest et al., 2021). In a paper, DT is perceived as having practical implications offering tools and techniques to adapt during the pandemic (Klein & Todesco, 2021).

When COVID-19 hit the world, about 1.8 billion students were affected due to institutional closures in reaction to the pandemic (Ngwacho, 2020). Its destructive impacts entailed all educational systems and academic organizations around the world to perform remote learning and consider digital transformation as the only option to continue schooling. Remote learning and online courses have been employed in many private and public education systems already (Bogdanby et al., 2020). Most of them have experienced numerous hardware-based and/or software-centered technologies to deliver remote schooling before, although they have never been forced to apply DT in a short period of time for the entire educational system. In fact, the digitalization of educational organizations started unwillingly without any initiatives and prior planning. In this case, a significant number of educational organizations and businesses started digital solutions immediately. Reviewed in Ngwacho (2020), educational challenges amid the pandemic for students in Kenya are described in 13 terms correlating educational and socioeconomic concerns about homeschooling.

In a comparable survey performed in higher education institutes in Saudi Arabia (Abdulrahim & Mabrouk, 2020), using digital technologies has been seen as a catalyst for improving productivity, learning outcomes, and a safe environment during the lockdown. The need for utilizing technologies to deliver online learning has compelled educational entities to accelerate digital transformation. The results of a paper, studying the education system in South Africa during the lockdown (Mhlanga & Moloi, 2020), present successful accomplishments toward digital transformation. Private institutions were involved in helping the government of South Africa create TV/radio/desktop platforms for offline schooling platforms. As a result, the solution motivated public schools and higher education institutes to practice other forms of digital technologies. The role of COVID-19 in applying DT and leading to establish a new norm in the scholarly journals and publication sector (Hayashi, 2021) highlights the benefits of digital applications in scholarly communication, preprint, peer-review, and open science transforming into online journals. In a framework proposal (Garcez et al., 2021), the intensified DT changes due to the pandemic are perceived as an opportunity for academic entrepreneurship. In another work, a survey was conducted in a Hungarian higher education institute among the Computer Science and Information Technologist students of Eszterhazy Karoly University (Bogdanby et al., 2020) to determine the impact of DT. The results indicated that shifting to digital education was preferred to the traditional approach. However, there have been technical difficulties for some students in this manner. In a survey conducted in Saudi Arabia's universities (Omar & Almaghthawi, 2020), it has been found that data governance is an effective tool in the implementation of digital transformation processes in higher education institutions. To create an innovative business model in a higher education system, Rof, Bikfalvi, and Marquès (2020) focus on the existence of tensions in the current business models.

Characteristics of Different Organizations Transferring to Digital

The impacts of digital transformation can be measured by considering several attributes involving (I) technology and data, (II) people and management, and (III) product and services interacted across an organization's environments (Shahiduzzaman & Kowalkiewicz, 2018). The criteria for the digital impacts are defined as eight indicators: vision, leadership, governance, innovation, culture, shared value, business agility, and revenue resilience. The indicators for digital capabilities measure the strength of the organization's digital foundation to derive value from technology. Using Internet domain registration analysis as an indicator for innovation and entrepreneurship initiatives, Gavrila Gavrila and De Lucas Ancillo (2021) present a parameter that can be deployed for measuring the success of the DT implementation. Studying multiple case studies in a paper, Priyono, Moin, and Putri (2020) show that transferring to digital solutions for SMEs depends on the level of digital maturity in which they are. Strive toward long-term achievable ICT integration strategies is suggested by Ngwacho (2020), adopting policy initiatives incorporating digitalization in education, training, and research.

Discussion

The main concern in implementing digital transformation is to provide an effective and efficient solution that can operate predefined technologies. As posited in different sections of this chapter, the definition of DT and one's perception, of what it really means, can change the deployment of DT in an entity. Evaluating the full text of the collected papers reveals the challenges and opportunities of implementing DT in different sectors before and after the pandemic. Moreover, it reveals the important timeline of announcing the global pandemic, January 2020 (WHO, 2020). Hence, we take into account this timeline as a criterion for measuring the validity of a research study in the research domain of digital transformation. Figure 3 emphasizes the papers, from the group sets, published prior to and following the global lockdown starting in 2020.

As depicted in the figure, 36 papers from the collected list were published prior to the pandemic from 2003 to the end of 2019; whereas 34 papers were published after the timeline.

Obviously, there is no correlation between DT and COVID-19 before 2020. However, there are still many articles and literature reviews published in 2020 and even 2021 focusing on digital transformation without mentioning the pandemic. The reason is that the process of publishing a paper for most journals, from the submission to and acceptance for publication, is very time-consuming. Nevertheless, COVID-19 has reshaped many organizations' environments, and previous strategies and provided solutions for implementing DT cannot be trusted. Although many challenges and opportunities remain valid, the approaches implemented prior to the pandemic should be validated.

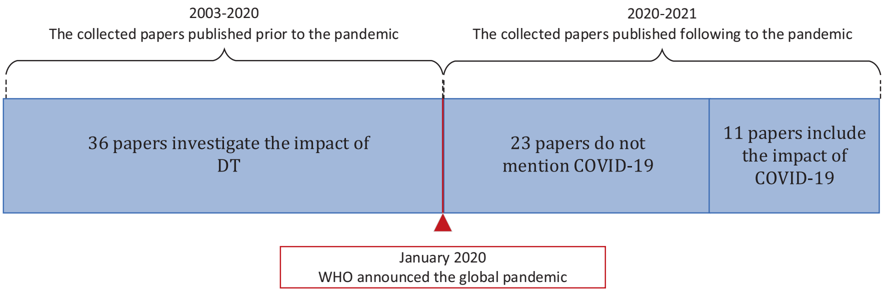


Fig. 3 Breakdown of the collected papers published pre- and post-pandemic, and including/excluding COVID-19. (Authors' own work)

Conclusion

We address the importance of the pandemic on DT-related studies, claiming that a great number of challenges, opportunities, and strategies, provided by researchers for implementing DT prior to the pandemic, must be modified and reevaluated. The epoch following COVID-19 would be ever-changing, and previously envisioned approaches require some adjustments. The organizational architectures of many businesses in different industries have been changed. So that solutions presented in pre-pandemic papers for implementing DT projects, or post-pandemic without noticing the event, cannot be applied. Employing digital technologies in several industries and businesses have already been performed during the pandemic. Unlike our counterparts, we deem opportunities linked to the DT implementation meanwhile.

Using papers before and after the event in the PRISMA, section "Systematic Review Approach", helped us to highlight studies that include COVID-19 in the papers. In addition, we described the characteristics of DT projects with regards to the post-COVID epoch. We recommend that decision makers in the public sector should reassess their pre-pandemic policies regarding DT implementation due to changes in the business model and organizational architecture. Now, managing DT projects requires using project management approaches which address organizational changes caused by the pandemic. However, in the private sector and especially small-size businesses, where organizational architectures are more flexible for alterations, they can benefit from the pandemic and accelerate the transition.

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The Sociocultural and Economic Barriers to Self-Care Culture for COVID-19 Control in Developing Societies: The Case of Iran

Asghar Mirfardi

Introduction

Human life, always, has been faced with natural and unnatural threats. Human history has seen many diseases, and some of them have caused great human losses (Mirfardi, 2020a) and even significant changes in the course of human civilization. Since December 2019, the COVID-19 virus, known as the coronavirus, was detected in China and rapidly spread to the rest of the world (United Nations Department of Economic and Social Affairs, 2020). The World Health Organization (WHO) introduced the prevalence of this disease as a pandemic while announcing its emergency status. This health crisis has had a wider impact on the everyday lives of people (Wang et al., 2021). Iran, as a third-world country, has also been involved in such a viral disease, and due to the rate of prevalence, speed of spread, and lost lives caused by the virus, it is considered a high-risk area in the world.

There are various measures ongoing at the national and regional levels. The world has experienced a rapid prevalence of this disease. According to World Meters (2020a) by August 30, 2020, more than 25 million cases of risk were detected, and about 850 thousand cases died regarding COVID-19 in the world. This data, by November 2, 2021, reached more than 248 million cases of risk and more than 5 million cases of death (World Meters, 2021). According to the latest report by November 2, 2021, the number of patients with coronavirus was close to 5,944,599 cases, and the number of victims was 126,616 cases in the whole country (World Meters, 2021). This requires multiple scientific, executive, and hygienic measures to inhibit and control such situations. Realistic recognition of the ways to confront this phenomenon is necessary, which can be done through scientific studies (Mirfardi, 2020b). Health experts believe that the most important way to prevent and stop the coronavirus is to interrupt the human cycle of its occurrence and perform health care. In other words, people should take care of themselves as well as

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others by following general self-care principles, especially with this disease. Recognizing the status of knowledge, attitudes, and beliefs of citizens about health care, especially self-care, may help in the planning process and actions in this field.

Pandemic diseases emerge some challenges, especially for poor, old, and disabled individuals. The capacity to cope with these challenges is dependent on access to quality advocacy, supportive family, friendships, productive occupational learning environments, and peer support, while these are not always available for mentioned people (Macpherson et al., 2021). At the micro-level, the COVID-19 disease has unpleasant consequences such as isolation, especially among old people. Lazzari and Rabottini (2022) in a meta-analysis showed that in older people, the risk of developing dementia because of the impact of prolonged loneliness and social isolation is about 49–60% higher than in those who are not lonely and socially isolated.

The theoretical and research literature on health had been expanded over the past decades, and interdisciplinary studies have been developed in this area. Self-care is one of the common mechanisms for combating illnesses, especially pandemic ones. WHO defines self-care as "the ability of individuals, families, and communities to promote health, prevent disease, maintain health, and cope with illness and disability with or without the support of a healthcare provider" (WHO, 2021). The studies related to self-care are part of this expansion. Recently, some studies regarding COVID-19 have been conducted (Shi et al., 2020; Paital et al., 2020; Yezli & Khan, 2020; Ali & Alharbi, 2020; Vieira et al., 2020). The mentioned studies indicated the socioeconomic dimension of the coronavirus spread. However, there was less attention to self-care culture in dealing with infectious diseases. Considering the changes in lifestyle and the spread of noncommunicable diseases, a large part of studies has focused on self-care in this area. According to the short interval of the COVID-19 virus appearance, studies in this field are in the early stages. Based on the prevalence of COVID-19 in the world, on the one side, and the lack of accurate treatment for risk cases, on the other side, health care especially self-care is so vital for the prevention of this communicable virus.

The public and private sectors are engaged in coronavirus challenges, and the private sectors offer some assistance in wide and coherent cooperation (Akbari et al., 2021). While medical education and services in Iran are in advance and accordingly life expectancy in Iran experienced considerable growth, like other third-world societies, it seems that the self-care culture is not as well as medical education and services. This chapter aims to review the main sociocultural barriers to health programs regarding COVID-19 with an emphasis on self-care culture. Specifically, this chapter aims to evaluate the sociocultural barriers to the health program in three phases: short-term, medium-term, and long-term barriers.

Concepts and Theories

According to Parsons and Krober (1958: 582–583), culture is a "transmitted and created content and patterns of values, ideas, and other symbolic-meaningful systems as factors in the shaping of human behavior and the artifacts produced through behavior." In their view, the social system is "the specifically relational system of interaction among individuals and collectives" (cited in Armour, 2003: 19). Thus, in the definition of culture and social system, the interaction between micro- and macro-levels of society is required, from family to big institution and organization. Culture in recent decades has been found important in social structure and formation, so Hechter (2004) declared that during the past century, the importance and function of the socioeconomic class were replaced by culture. In other words, during the past century, cultural policies have increased. However, the shift from class to cultural politics is neither universal nor permanent.

Culture plays a meaningful role in every society. According to Alexander (1996), every institution, no matter how technical, coercive, or seemingly impersonal, can only be effective if related to patterned sets of symbols that instruct it to become so, and to an audience that "reads" it in a technical, coercive, and impersonal way.

Determinants of Behavior

Human behaviors are determined via motivational and volitional factors (Brandstätter & Gollwitzer, 1994). These factors had been declared by the Theory of Reasoned Action that was introduced by Fishbein and Ajzen (1975) and Planned Behavior (Ajzen, 1985). In this theory, intention mediates the relation between motivation (attitude) and behavior. Harland et al. (1999) argued that personal norm was another determinant in the theory of Planned Behavior (Garling et al., 2003: 1). This theory can be used for explaining various behaviors.

Theories of Health Care and Illness

There are various social theories for explaining health care and illness, from which conflict, functional-structural, and symbolic interactionism theories are the most famous. According to the conflict theory, some factors such as wealth, economic status, and power influence illness and health care. This theory divides people into owners who have access to economic, welfare, and medical accessories and services and have-nots who have no access or have less access to medical insurance and quality medical care. The life expectancy of human beings is in line with their economic situation and medical services. This perspective also focuses on gender inequality in access to medical services and on the profit motive that influences health, illness, and health care (Mooney et al., 2021: 36–37).

According to the symbolic interactionist perspective, meanings, definitions, and labels influence health, illness, and health care. These meanings are learned via interaction with others, mass media, peer groups, and other socialization mechanisms and agents (Goldstein, 1999). The importance of meanings in the symbolic interactionism perspective is that there are various perceptions of health and illness in different societies: For instance, in some countries, obesity is a sign of health and wellness, but in other countries, it is a sign of mental illness or a lack of self-control (Mooney et al., 2021: 37). The family patterns of interaction and socialization contribute to illness and health care (Lauer & Lauer, 2010: 394). From the structural-functionalist perspective illness, health, and health care are analyzed according to changes in social, cultural, economic, and political structures. Parsons (1951) saw various aspects of society in the form of an integrated social system. The four sub-systems of the social system play different roles and have various functions for the survival of society.

Culture, Self-Care, and Other Care

There are various viewpoints regarding health-care systems. Self-care and other care are the most common perceptions about health-care mechanisms. Orem (1980: 35) defined self-care as "the practice of activities that individuals initiate and perform on their behalf in maintaining life, health, and well-being." The Self-Care Ideology and Practice theory offered by Orem (1980) is focused on the self-control, individuality, and autonomy that may encounter with cultural beliefs, ideology, and values of non-Western cultures. Orem differentiated the health culture between Western and non-Western cultures. He aimed to mobilize individuals to meet their self-care deficits, demands, or needs which have been on Western American values of individualism, self-reliance, self-sufficiency, independence, autonomy, self-control, self-management, self-directedness, and other related self-focused modalities.

Leininger believed that this theory is appropriate for Western societies in which individuality and individualism have been institutionalized in their cultural structure and values. In contrast, it may be not applicable to non-Western societies, because their worldview and cultural values are so different from Western societies. Referring to Papua New Guinea, Leininger and McFarland argued that nurses of such societies do not agree with the safe-care values proposed by Orem (1991).

Leininger argued that in non-Western cultures, and even in some ethnic groups in the United States such as Mexican-Americans, African-Americans, and Asian-Americans, the other care is respected. These groups value the other-care norms and practices because they believe in interdependence and close interfamily relationships (Leininger, 1990). These two theories (self-care and other-care theories) focused on the nursing practice, while in the pandemic diseases such as Covid-19, personal behaviors are important for encountering such diseases and their consequences.

Rational Thought and Behavior

Rationality, from the classic sociology era, has been one of the critical concepts in social science. Weber's view (1968) in his categorization of rationality is one of the main debates in this regard. According to McIntyre (1962), being rational in some societies is the first criterion for being rational. Peter Winch (1970) believes that there are various rationality criteria in different societies even "the possibilities of our grasping forms of rationality different from ours in an alien culture" are limited by certain formal requirements centering around the demand for consistency (Winch, 1970: 100). According to Sahlins' perception, the Western account of rationality includes some components: First, it has a series of dualisms; for instance, the dualism of logos and mythos, empirical reason and mental illusion, the practical and mythical, and the observable and the fictional one (Sahlins, 1995: 6). Second, an empiricist view of knowledge. Third, the native Western praxis theory of knowledge is not simply that we know things through their use but as their utilities. Fourth, there is the idea that the world is purely material and without a spiritual presence (Sahlins, 1995 cited in Lukes, 2000: 7).

Lifestyle and Social and Cultural Capitals

In contemporary sociology, lifestyle and everyday life are important for social thinkers. Bourdieu analyzed the social class and lifestyle regarding the habitus and the social field that contained different types of capital. Bourdieu's idea is emphasized on the subject of taste. On the one side, Bourdieu discusses classes, and types of economic, social, cultural, and symbolic capital, and, on the other side, he stresses the lifestyle, the taste, as well as the use of cultural goods, which expresses the individual's economic and social status. From the perspective of Bourdieu, four capitals form the class status of individuals. According to these four capitals, people have their own culture, tastes, lifestyles, and activities, and are distinguished from other groups (Bourdieu, 1984).

Tradition and Modernization

Many theories of modernization assumed that during the development process, traditional traits, attitudes, and behaviors are replaced by modernity (e.g., Lerner, 1958). In other words, tradition appeared as a defunctive part of society and was even considered an obstacle to modernization (Norbu, 1996). In a perception, modernization is a complete process of social changes, including growing urbanization, expansion of industry, technological innovation, scientific education, mechanization of agriculture, the spread of bureaucracy, prominence of science, and development of mass communications (Inkeles, 1977; Mathias, 1990). Accompanied by modernization, concepts of progress and development have been applied in modernization literature. Each of them has objective and subjective indices (Tzeng & Henderson, 1999).

The Consequences of Modernization for Human Life

Modernization has various consequences in sociocultural and economic contexts. In lifestyle and quality of life, we can notify some important consequences of modernization and development practices. For example, modernization can lead to poverty reduction, better medical treatment, and health services, "material goods, and an overall better quality of life for third-world populations" (Chafy, 1997: 635). Alongside with extension of modernization, the health-care system especially in developed societies engaged with this process (Newman & Kuhlmann, 2007). Meanwhile, in third-world societies, these promises have not been realized, completely. According to Florman et al., one of the positive aspects of progress is the advancement in medical sciences and technology. Advances in health care are seen as an indication of social progress (Chafy, 1997: 635). Thus, health care conveys the symbolic meanings of modernity (Gallagher, 1988). The eradication of diseases has not been worldwide, with the exception of some diseases "such as Small Pox, and vaccination has been sporadic in the third world. Polio, Tuberculosis, and Malaria are persisting, while some strands of these diseases are mutating and coming back stronger than ever" (Chafy, 1997: 636). Some studies showed that modernization process has important impact in changing the traditional context (Mirfardi, 2000), or the sociocultural values of Iranian residents (Jahangiri & Mirfardi, 2006).

Development and Health Condition

The relationship between development and quality of life can be traced in some indicators such as mortality, health-care services and programs, and life expectancy. Demographic transition is a consequence of economic, scientific, and technological development and innovation. Declining fertility and mortality rates are the consequences of structural changes that happened during the demographic transition. There are different viewpoints on mortality decline. John Coldwell believed that government investment in increasing education and health services is crucial for mortality declines (Caldwell, 1986: 179), but others believed that economic growth and social welfare are interdependent, and the economy cannot be sustained without social and institutional forces that are promoted by public health policies (Szreter, 1997: 719). Education and awareness are important factors in the relationship between development and public health. In summary, education in the form of new institutions has affected public health and mortality decline (Stroud et al., 2016: 225). Third-world societies had some common traits that differentiated them from developed societies: low level of life quality, unemployment or instability in jobs, inequality, weakness in the middle class, illiteracy, health problems, and poverty (Azkia, 1990). Life expectancy shows large differences in health across the world.

Human Development Index (HDI) The Human Development Index, which includes the indicators of education, per capita income, and education (literacy), indicates the level of biological, social, and economic development of societies. This index shows the convergence of health indicators with economic and social indicators of development (Jahangiri & Mirfardi, 2006) (Table 1).

Mortality, especially for those under 5 years, is a sign of health situation and health care, and for three decades mortality rate decreased in the world countries, according to their development degree (Table 2).

According to World Bank (2019), many of the richest countries have life expectancies of over 80 years. In 2019, the life expectancy in Spain, Switzerland, Italy, and Australia was over 83 years. In Japan, it was the highest with close to 85 years. On the other side, in the poorest countries that have the worst health conditions, the life expectancy is between 50 and 60 years. The population of the Central African Republic had the lowest life expectancy in 2019 at 53 years (Table 3).

Table 1 Life expectancy at birth in the United States, 1900–2020

Year	Total	Male	Female
1900	47.3	46.3	48.3
1920	54.1	53.6	54.6
1940	62.9	60.8	65.2
1960	69.7	66.6	73.1
1980	73.7	70.0	77.5
2005	77.8	75.2	80.4
2020	79.11	76.61	81.65

Source: U.S. Census Bureau (1975: 55) and U.S. Census Bureau (2009) cited in Lauer and Lauer (2010: 379); World Meters (2020b)

Table 2 Under-5 mortality rate for some selected countries, 1960 and 1996

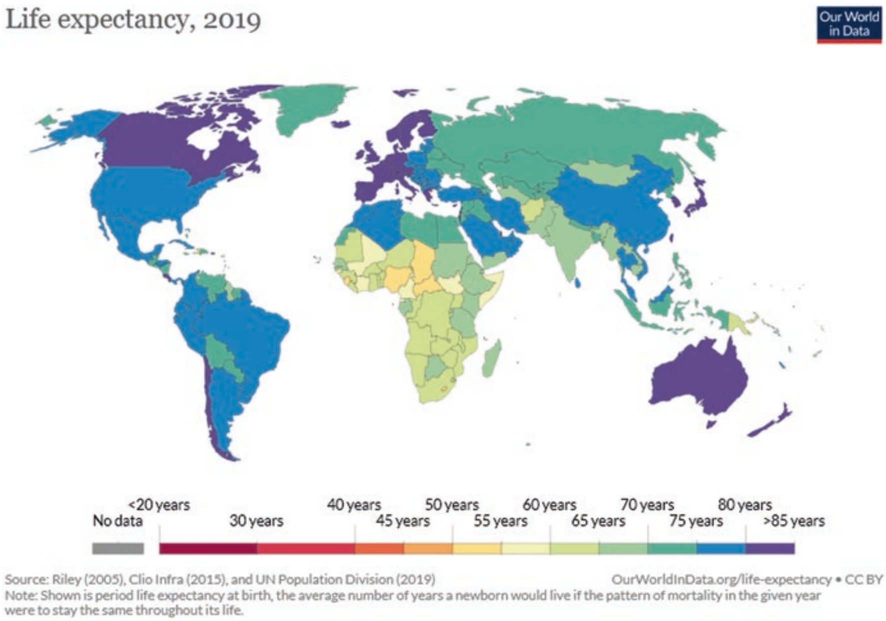
Country	1960	1996
China	209	47
Ethiopia	280	177
Iran	233	37
Japan	40	6
Mali	500	220
Sweden	20	4
United States	30	8

Source: UNICEF (1998) cited in Mooney et al. (2021: 34)

Table 3 Life expectancy at birth in Iran and the world, 2020

Country	Total	Male	Female
Iran	73.2	70.8	75.6
The world (mean)	77.33	76.22	78.54

Source: World Meters (2020b)



Method

This research has been done by the documentary method and various sources such as books, scientific journals, scientific databases, and valid organizational and specialized databases have been used. The most used databases were PubMed, Magiran, Noormags, Google Scholar, Sid, Iran Statistic Center, Trading Economics, and World Meters. Corresponding short-term, medium-term, and long-term periods were identified. In each time/subject period, two levels, micro and macro, are presented. According to data and text contents, barriers were identified and categorized.

The components of analysis of the self-care barriers in Iran.

Duration	Subject	Macro	Micro
Short term	Economic factors	1. Economic poverty 2. Economic recession and inflation	1. Malnutrition 2. Lack of financial ability to use health-care and self-care facilities 3. Lack of living facilities 4. The work time in epidemiological conditions
Medium term	Social factors	1. Social inequality 2. Lack of attention to prevention 3. Weakness of social organization 4. Family size in less developed areas	1. Weakness of education and socialization 2. Unstable job conditions

Duration	Subject	Macro	Micro
Long term	Cultural factors	1. Fate-orientation (fatalism) 2. The weakness of preventive insight 3. Application of common beliefs and common senses 4. Low social trust 5. Social traps 6. Traditional habitus in health care	1. Poverty of knowledge and living awareness 2. Self-medication belief 3. Self-healthy imagination and misunderstanding of disease risks 4. Social indifference and social irresponsibility

Administered by author

Barriers to Self-Care Culture

Since self-care is human behavior, it is affected by various fields. Human behavior depends on multiple factors and fields and cannot be considered dependent on one or a few factors. Factors affecting self-care culture may vary among communities and even between different classes and strata. The cultural and social context can determine various markers for the individual and social behaviors of human beings. Cultural and social barriers to self-care culture can be divided into three periods: short-term, medium-term, and long-term. Specifically, economic barriers should be considered as a subset of short-term barriers. Social barriers are among the medium-term barriers. Cultural and historical barriers are a subset of the long-term barriers to self-care barriers. Each of the three periods has micro and macro factors that are barriers to health care.

The Short-Term Barriers: Economic Factors

The short-term barriers include the characteristics and economic, welfare, and livelihood status of individuals. Such barriers deprive people of access to adequate biological, livelihood, and health-care facilities and have adverse effects on their quality of life.

Micro-economic Barriers

The economic situation embedded in social class is one of the important factors in health care and health situation. There is a strong relationship between a higher rate of illness and membership in a lower economic class (Kornblum & Julian, 2010: 34). Socioeconomic status includes a set of job, educational, welfare indicators, and even cultural insight. Therefore, the economic status of the individual can be the grounds for various behaviors. These behaviors are influenced by economic status, whether in terms of consumption, leisure, and recreation, or social behaviors such as political and social participation. Factors related to the economic status that can be considered an obstacle to the institutionalization of self-care culture in developing countries are as follows:

Malnutrition

Malnutrition itself is the background for physical weakness, diseases, or exacerbation of previous diseases. The weakness of the immune system and resistance to diseases are the consequences of malnutrition. According to Boek et al. (2012), economic factors alongside other factors can affect nutrition and health situations. Mehrabian et al. (2014) showed the impact of nutritional behavior and the situation on iron deficiency among girls in Iran (Babol city).

Lack of Financial Ability to Use Health-Care and Self-Care Facilities

Self-care during the prevalence of communicable diseases requires the use of a set of equipment. Poor people and households cannot provide all or even part of this equipment. This situation increases their vulnerability to communicable diseases such as corona. According to Maher (2005), in Iran for achieving the Millennium Development Goals many activities were started 3 years ago to target health-care services for poor people. Although the quality of primary health-care services in some rural health centers in Iran is higher than average and correlated with the quality of life of the recipients (Bakhshi et al., 2019), spatial inequality in health-care services and facilities affects health-care behavior. This inequity can be eradicated or at least reduced through the adjustment of social determinants of health and primary health care (Torkaman Nejad & Nasiri Pour, 2016). The lack of personal protective equipment and disinfectants is one of the challenges in public health during the COVID-19 pandemic in Iran (Masoumbeigi & Ghanizadeh, 2020).

Lack of Living Facilities Such as Housing and Proper Clothing

Absolute poverty deprived people of vital facilities (Azkia, 1990). The results of a study in India showed that overall utilization of health-care services has declined and the odds of not seeking care due to financial inability have further increased among the poor and rural population during the period of reforms (Ghosh, 2014).

The Work Time in Epidemiological Conditions

The lack of financial support for reducing the work time in epidemiological conditions and implementing the physical and spatial distance to break the chain of disease transmission is one of the prevalent problems. The working hours have been reduced on average, it has been reduced for those who had incomplete employment before the pandemic, but unexpectedly increased for those who had worked completely (40 hours/week) before the pandemic (Pourmohammadi & Yousefi, 2021).

Macro-economic Factors

Economic Poverty and Lack of Welfare Facilities

Poverty includes absolute poverty and relative poverty (Azkia, 1990). Both types of poverty, especially absolute poverty, play a role in the expansion of communicable and noncommunicable diseases. Mirfardi et al. (2019) showed that poverty reduction is one of the most effective mechanisms for accessing welfare and well-being. Poverty and health had been considered by researchers and scholars for past decades (e.g., Kosa & Zola, 1975; Abbott & Hobby, 2005). Research findings show that "poverty affects the social determinants of health on multiple levels, compromising economic stability, education, social and community contact, lifestyle and healthcare access, and the physical environment" (Shahid, 2018). There are various poverty reduction programs proposed via these patterns and schools of thought in economics, but little success has been achieved yet (Ghasemian, 2005). Economic growth has had negative impacts on poverty reduction in Iran during the last decades (Shahiakitash & Alizadeh, 2021). In the year 2020, the Gini coefficient of households in the whole country was 0.4006, which shows an increase of 0.0014 compared to the previous year. Also, the Gini coefficient of urban and rural households is 0.3835 and 0.3590, respectively, which increased by 0.0008 and 0.0051, respectively, compared to the previous year (Iran Statistical Center, 2021). According to Trading Economics,[1] the national currency value in Iran decreased, rapidly. Iran's GDP per capita is as follows (Table 4):

Table 4 Iran GDP per capita, 2020

Related	Last	Previous	Unit	Reference
GDP	191.72	258.25	USD billion	Dec/20
GDP per capita	4802.05	4785.03	USD	Dec/20
GDP per capita PPP	12433.30	12389.20	USD	Dec/20

Source: Trading Economic (2021a). At: https://tradingeconomics.com/iran/gdp-per-capita

[1] Trading Economics provides data for 20 million economic indicators from 196 countries including actual values, consensus figures, forecasts, historical time series, and news. Iran Indicators was last updated on Wednesday, November 10, 2021.

Table 5 Iran: Economic indicators

Related	Last	Previous	Unit	Reference
Inflation rate	39.2	43.7	Percent	Oct/21
Consumer Price Index (CPI)	364	351	Points	Oct/21
Producer prices	190	181	Points	Mar/19
Food inflation	61.3	62.4	Percent	Oct/21
CPI housing utilities	255	220	Points	Oct/21
CPI transportation	452	394	Points	Oct/21
Inflation rate MoM	3.7	3.9	Percent	Oct/21
Producer prices change	62.28	56.83	Percent	Mar/19

Source: Trading Economic (2021c). At: https://tradingeconomics.com/iran/indicators

Poverty is a context for some problems and inappropriate behaviors in the field of health.

Economic Recession and Inflation

Economic recession and inflation along with the instability of economic indicators are the determining factors in the quality of life and health services. A developed society, As Parsons (1951) emphasized, has an even change in the economic, social, political, and cultural subsystems. In such a society, the economic subsystem has an important function in providing resources for other subsystems, thus a crisis in a society's economy will affect the quality of its other subsystems. Health care is directly and indirectly affected by the economic crisis.

Official statistics show that in the winter of 2020 and the spring of 2021, due to the intensification of sanctions, and the corona pandemic, economic growth in Iran reached a negative level (Donyayeh Eghtesadi Newspaper, 2021). The inflation ratio for Iran in this duration was high (Table 5).

The Medium-Term Barriers: Social Factors

In the medium-term period, we encounter social factors, which lead to a reduction in health-care behaviors. Social factors, to some extent, have an affinity with some economic factors, in a way that they are known as socioeconomic factors.

Micro-social Factors

Weakness of Education and Socialization

Socialization from childhood age is a critical base for determining individual and social behavior. Lack of education, including lack of proper and efficient education, by either family or formal education, is a characteristic of underdeveloped and less developed countries. Education in the form of the Human Development Index (HDI) correlates with health and quality of life. Education, per capita, and life expectancy are components of HDI (Jahangiri & Mirfardi, 2006). Being non-creative, old-oriented, ideological, and unequal distribution of facilities are associated traits of the education system of such countries. Rakhmani et al. (2020) declared the function of the family in prevention and health care. Salahmanesh et al. (2017) showed the role of education on family health and medical expenditure. Gage-Bouchard (2017) found that cultural dispositions and competencies shape parents' abilities to effectively navigate the health-care system. Health literacy is a critical factor in physical and mental health and well-being. For example, O'Meara et al. (2019) found that health literacy was associated with an increased risk of developing Type 2 Diabetes. According to Asadzandi et al. (2007), education focusing on changing health beliefs and increasing awareness may be effective in promoting self-care behaviors.

Education in third-world societies is not paying attention to a healthy lifestyle, sufficiently. Many people in third-world countries are far away from education due to their increasing poverty and family conditions. The weakness of education leads to the weakness of practical awareness in everyday life. Unequal distribution of educational facilities between urban areas, especially macro-urban areas, from one side, and rural areas and the margin of cities, from another side, is another characteristic of education in the third world that reproduces economic, social, and cultural inequality. A review of the data and analyses of COVID-19 showed social inequalities, and in multiple intersectional ways (Lynn Ee-Ho & Madrell, 2020). Women and girls in less developed areas have more educational deprivation than men do. Formal education along with informal education has an important role in the socialization of individuals, and it is very important to learn health standards and teachings. In this case, the formal education that offered by health experts and the formal education system is more efficient for health lifestyle.

Unstable Job Conditions

In the lower classes, job stability is not as high as in the medium classes of the society. Temporary or part-time, false, hidden, or informal housework jobs that do not have the necessary social security are mostly available among lower-class citizens. Lack of unemployment insurance, health insurance, and pension, low and unstable salary, and benefits are characteristics of some jobs in this class. Workers, who are working in jobs with such characteristics, while not having suitable living facilities, lose their jobs and income in the epidemiological conditions of communicable diseases or are obliged to meet their living needs under any bad health conditions. Research shows that the participation rate has decreased substantially for women and youth in Iran. This study also indicates that the job destruction rate is higher among low-medium size firms, as compared to micro-firms or large ones (Pourmohammadi & Yousefi, 2021). This disease has caused significant rises in unemployment and drops in Gross Domestic Product around the world (Ulen,

Table 6 Iran: Indicators in employment

Related	Last	Previous	Unit	Reference
Unemployment rate	9.6	8.8	Percent	Sep/21
Employed persons	23,675,894	23,134,913		Jun/21
Youth unemployment rate	22.1	23.6	Percent	Jun/21
Population	84	82.1	Million	Dec/20

Source: Trading Economic (2021b). At: https://tradingeconomics.com/iran/indicators

2021). As the data show, the unemployment rate, especially among the youth, is high in Iran. During the COVID-19 pandemic, many employees lost their job, temporarily or permanently (Table 6).

Macro-social Barriers

Among the macro-economic barriers to self-care culture are the following:

Social Inequality in the Distribution of Living and Health Facilities

Socioeconomic factors have a critical role in health care (Marmot, 2005). One of the characteristics of third-world countries is the uneven development of different regions and sectors. Health centers that can promote health and self-care patterns are mostly in urban areas, especially in large cities. In these countries, rural areas, marginal, informal settlements, and small cities do not have enough health facilities. Less developed areas depend on large urban centers, and residents of these areas are deemed to receive specialized health services from big cities. This situation makes health monitoring difficult for many residents of these areas. A study in Iran showed that income growth per capita affects the growth of the life expectancy index positively by 31%, but the growth of social-class differences or income inequality harms this index. Economic growth had a positive impact on life expectancy and infant mortality in Iran during 1981–2018 (Hosseinidoust et al., 2021). After the prevalence of the COVID-19 virus, even large cities faced a lack of care facilities, and in small cities, rural and marginal areas faced more challenges to receive health and care services. Faraji Sabokbar and Vazin (2013) showed that health services had an impact on the health indicators in Iran.

Lack of Attention to Prevention and Promoted Programs of Macro-health Policies

Despite the importance of prevention to treatment, even in macro policies, not enough attention is given to educational and preventive programs for empowering people in line with self-care. Horowitz et al. (2000) found that the lack of technical expertise, resources, and sensitive tools are all common barriers to evaluating health programs.

Less attention to prevention leads to a large volume of diseases, and this situation is leading to centralizing the socioeconomic credits and programs on treatment and control issues. Such a situation has little attention to prevention, from the viewpoint of human resources and budget. In this way, a vicious cycle is formed in which self-care is depleted.

Weakness of Social Organization

Promoting health programs, especially in the field of prevention, requires appropriate organization and coordination of various related institutions. To improve the culture of self-care, coherent and coordinated links between cultural, educational, health, and executive institutions are needed. The sectional view in the health activities causes failure in the determination of the goals and programs and thus the desired goals are not fulfilled. Parallel or even conflicting activities in the field of health make it difficult to achieve desirable indicators and make it even impossible. Rationalization is the main point for policy-making in the health-care system. In this regard. Vabø (2006) emphasized the consequences of new forms of governance such as rationalization in health-care occupations. Lupien et al. (2021) showed that decision-makers and bureaucracies in Latin American countries are influenced and constrained by their countries' institutions. This procedure exists even during a global pandemic so that the policy reflects path dependency and serves to protect established interests while neglecting the needs of marginalized populations.

Family Size in Less Developed Areas

In line with the relatively high rate of fertility in less developed areas, family size in these areas is more than in developed urban areas. The upper family size increases the dependency ratio for the head of the household and encounters the socioeconomic management of the household with problems. In such a situation, the share of health care costs from household costs—for health monitoring and follow-up of health affairs—is reduced. For example, during the corona prevalence period, which required the use of detergents and preventive equipment such as face masks, gloves, etc., people with high family sizes and high dependency ratio encountered problems in providing the cost of self-care equipment.

Najafi and Ashan (2007) indicated that poverty in rural areas was more than in urban areas. Household size and the number of employed persons in the households were among the most important determinants of poverty in Iran. Another study declared that the household size, wealth index, gender of household head, job status of household head, presence of household members less than 12 years, and the number of hospital services to be covered by compulsory insurance and supplemental insurance are the long-term determinants of catastrophic health expenditures (Fattahi & Naderi, 2015).

The Long-Term Barriers: Cultural Attitudes About Health

Micro-cultural Barriers

As Fishbein and Ajzen (1975) have shown, behaviors depend on individuals' attitudes, and attitudes are formed in light of the education and socialization system (learning). Cultural beliefs that exist in undeveloped countries, such as Iran, can be noted as follows:

The Poverty of Knowledge and Living Awareness

Knowledge and awareness are useful elements for managing problems and crises in individual and social life. They are also useful for the treatment of diseases (Rashidi et al., 2012) and nutrition (Hoque et al., 2016). Lack of health information leads to various problems in individual health (Lecerof et al., 2011). Rationality is a useful outcome of knowledge and wisdom. In the lack of such elements, various problems in daily life become continuous crises. In third-world countries, although the education level has improved in the past decades, practical knowledge and awareness have not increased in line with the education level. The sect, religious, and political conflicts; communicable and noncommunicable diseases; and relatively high mortality can be due to poor knowledge and living awareness. Orupabo (2021) addressed the importance of rationality in self-care.

Self-Medication Belief

Self-medication is defined as "the taking of drugs, herbs or home remedies on one's initiative, or on the advice of another person, without consulting a doctor" (Hernandez-Juyol & Job-Quesada, 2002). It is a global phenomenon (Bennadi, 2013/2014). This treatment is considered unhealthy since the 1960s in Western societies (Hughes et al., 2001). Self-medication is an unhealthy and abnormal feature in the field of living behaviors that has unpleasant consequences for individuals, families, and societies. Such belief leads to the self-willed use of drugs for the treatment or prevention of diseases. Self-diagnosis of illness and treatment is the context for self-medication and causes multiple harms.

Self-Healthy Imagination and Misunderstanding of Disease Risks

Scientific studies showed the contribution of imagination to well-being and health care (Alma & Smaling, 2009; Gamble et al., 2021). This image may have various perceptions and thus either lead to modern health care or be in contrast with it. Another cultural belief in health and disease in undeveloped areas is that some people think that people who are affected by a communicable disease are physically ill and weak and healthy people are not at risk of such diseases. This belief is especially common among young people and adolescents and they find themselves safe against various diseases, especially communicable ones. Even if they have a high physical ability to deal with the disease, they play the role of vectors of the disease in society with their reckless behaviors.

Social Indifference and Social Irresponsibility

Besides the weakness of awareness and false cultural beliefs about disease and health, social indifference and social irresponsibility are other barriers to the institutionalization of self-care culture. As a citizen, everyone has a set of social duties and responsibilities, on the one hand, and citizenship rights, on the other hand, to have a good life and a developed society; it is necessary to perform such responsibilities and benefit from the mentioned rights. Corporate social responsibility (CSR) is an effective factor for social management and organization. According to the European Commission (2017), corporate social responsibility (CSR) refers to the social responsibility of corporations and their impact on society. Carroll (1991) divided CSR into four components of economic, legal, moral, and charitable responsibilities. The charitable responsibilities are at the top of the pyramid (Akbari et al., 2021).

Macro-cultural Barriers

Fate-Orientation (Fatalism)

Fate-orientation is one of the traditional beliefs that are found in many behavioral fields, especially when fatalism is infused with some kind of religious beliefs and interpretations; it has a high determinant in people's behaviors and attitudes.

Fatalism, the belief that an individual's health outcome is predetermined or purposed by a higher power and not within the individual's control, has been examined as an inhibitor to participation in health promotion programs and health-care utilization (Plante & Sherman, 2001). People who have fatalistic beliefs see health as being beyond one's control and instead dependent on chance, luck, fate, or God (Straughan & Seow, 2000). Attributing health, disease, and death to a fate outside human control has a kind of disappointing passivity and a kind of social indifference and irresponsibility toward oneself and others. In my field observations at the time of corona prevalence, I observed that some people in the lower class and even some people in the middle class in Iran had such beliefs about corona. In one of the bakeries in Shiraz, the seller's hand wrote on a paperboard: "Only God can destroy the Corona, it is not made by man." Alternatively, about the corona, some who do not follow health practices say that "whatever the part, it is the same, everything related to fate." Such beliefs are not compatible with the characteristics and requirements of self-care against communicable diseases, especially COVID-19, and are caused by the development of passive behaviors, less attention to the risks of these diseases, and therefore the prevalence of them more than before.

The Weakness of Preventive Insight and Having a Post-Occurrence Therapeutic View

Despite the importance and effectiveness of the preventive approach to preventing the prevalence of diseases (Albee, 1983; Chehimi et al., 2011), especially, in third-world countries, this approach is less considered. In the field of communicable diseases that demand a lot of preventive care and prevention, lack of preventive insight causes less attention to self-care, thus the fundamental assumption of human beings with this view is that they are always healthy. With this approach, humans live healthily without any need for action and if he/she gets sick, he/she will treat and control the disease or physical and mental syndrome and damage.

Application of Common Senses and Vulgar Medicine

The application of common-sense beliefs in various fields, especially everyday life, is one of the depredations for the institutionalization of rational living methods. These beliefs, which are based on informal and traditional socialization in society, play an inevitable role in the formation of attitudes, values, and behaviors of human beings. Such beliefs are more based on heard than valid texts and writing resources. Sometimes such beliefs are combined with superstition beliefs and show features of luck and unlucky. Considering these beliefs as a postulate by people who do not have enough education and knowledge can affect the behaviors of such individuals. In the field of health and prevention of diseases, such common senses can harm the acceptance of medical and health recommendations. The stronger the common senses, the less acceptance, and application of scientific recommendations.

Reviewing the historical data showed that vulgar medicine was prevalent from the past centuries in Iran. For example, the health system in the Qajar era was fused with fatalism accompanied by the lack and shortage of governmental care services. In this situation, the belief of people greatly affected the health-care system, which was classified into three subgroups consisting of: physicians, magicians and charlatans, and lastly old females (Nayebian et al., 2015). Azadbakht et al. (2014) found that perceived barriers, self-efficacy, and perceived severity are determinants of health behavior.

Low Social Trust

Social trust is one of the components of social capital (Mirfardi & Valinezhad, 2016). Trust is a vital part of society and forms the basis of a universal relationship (CIPD, 2012). Social capital is associated with general health (Khajedadi et al., 2008; Naderifar et al., 2018). Low trust in public institutions is one of the social-cultural barriers to self-care programs in third-world countries. Reducing social capital, especially institutional trust, causes carelessness toward health principles and teachings that are promoted by public institutions.

In the health-care services, the value of trust could be considered one of the most important (Layland, 2018). Næss (2019) declared the importance of trust to cultural health capital among Norwegians and immigrants in Norway. According to Lynn-sMcHale and Deatrick (2000), trust between the family and health-care provider is a process, "consisting of varying levels, that evolves and is based on mutual intention, reciprocity, and expectations." Trust between the family and health-care provider is important as it has significant effects on the family involvement and support of treatment recommendations, family and health-care provider communication, family and health-care provider relationship, and patient and family benefits. Zhu (2017) found that social capital reduces health-care inequality.

Social Traps

One of the characteristics of undeveloped countries is the people's entrance into social traps (Rothstein, 2010). A social dilemma is where a person maximizes their goals over the goal of the community or society as a whole (Sam, 2013). In light of such a trap, each individual believes that his/her caring behavior will not affect because of other citizens' carelessness and that it will be accompanied by norm breakers and carelessness toward health principles.

The social trap may affect the various divisions of social and personal life. The health-care system must be far away from such traps. Healthy self-care is an efficient behavior and is not a solipsistic trap (Katz & Levin, 1980).

Traditional Habitus in Health Care

The traditional habitus, which is the historical heritage of human behavior that originated from past times, is one of the barriers to a self-care culture that requires the use of new health principles. With traditional approaches, past habitus is reproduced. Habitation of living approaches that have been so far and resistance to necessary changes is the outcome of reproducing this habitus, especially in the health-care fields. According to Bourdieu (1984), the habitus is the result of interaction between social structure and characteristics of actors in a way that values and structural criteria are reproduced in society. The traditional habitus in the field of health leads to the institutionalization of self-care culture. Some traditional beliefs are present in the form of local or religious medicine. Nayebian et al. (2015) declared the traditional procedures in the health-care system in the Qajar era in Iran. Almost all actors of that system were uneducated people.

What has been offered as Islamic medicine cannot satisfy the principle of distributive justice. It also makes unfair judgments and fears about modern medicine and harms clients by refusing scientific evaluation of medicines and therapies (Eslami & Boosaliki, 2019).

Conclusion and Discussion

Well-being is one of the most important indicators of human development. Prevention and control of communicable and noncommunicable diseases are the most important policies for achieving health indicators. Regarding the prevalence of COVID-19 communicable disease in the world, prevention and self-care programs are of great necessity. The activation of such programs requires the institutionalization of self-care culture. In third-world countries, which are not faced with the harmonious development of different sectors, the culture of health and self-care is not well institutionalized for structural reasons. In this chapter, economic, cultural, and social barriers to self-care culture against communicable diseases were reviewed.

In less developed societies such as Iran, a set of characteristics such as inconsistency in economic, social, and cultural developments has created problems that are in contrast to self-care culture. Most of the barriers to self-care culture in a less developed society such as Iran can be divided into three times and accordingly three subjects: short-term barriers (economic factors), medium-term barriers (social factors), and long-term barriers (cultural factors). Each of these time-based barriers is divided into two parts: micro and macro factors. Differences in socioeconomic status are the background for the differences in individuals' capabilities and tendencies to apply self-care principles.

Traditional beliefs and tendencies in a less developed country such as Iran are common among some people and play a role in their health behaviors. Common sense, fate-orientation, and self-healthy imagination are the characteristics that reduce the importance and necessity of prevention with self-care principles. By referring to structural functionalism theories, we found the importance of organization, coordination, and coherent transformation of all parts of society to achieve the general goals of society. Considering the health of the people of the society as a general goal, the role of various institutions in achieving this goal is shown.

According to the training that is transferred from generation to generation and the role of a new family and mass media in producing traditional beliefs or promoting new beliefs and teachings in the field of health and disease prevention, using symbolic interactionism, it can consider the role of cultural and educational interactions in self-care. As Bourdieu (1984) showed, the training derived from society is appearing in habitus formation in everyday behaviors and lifestyles. The self-care culture is also largely affected by the habitus in society.

Some factors such as poverty and its consequences, traditional beliefs, and habitus about health and disease are the main barriers to the institutionalization of self-care culture in third-world societies.

This study shows that self-care practices in developing societies, especially in Iran, depend on a set of structural, macro, and micro factors that are formed in three categories: short-term, medium-term, and long-term, and according to the period of their formation have a various effect on the self-care behaviors of people against communicable diseases.

Cultural attitudes, which are derived from the historical and cultural traditions of society, appear in people's beliefs and attitudes and have a strong and relatively lasting effect on people's behavior. Cultural characteristics and barriers became the most prominent barriers to self-care. As Bourdieu (1984) stated, cultural habitus determines social and individual behavior.

Social characteristics and factors, which in some cases interfere with cultural and economic factors, play a prominent role in health behaviors in the medium term. A wide range of social factors contributes to self-care.

The set of economic, social, and cultural subsystems together with political factors in every society form a macro-social system, and according to Parsons (1951), these subsystems have functional coordination despite the structural differentiation. The mentioned subsystems also have the characteristic of change, and their even change contributes to the dynamics of society and their uneven change causes disorder and functional disorder in various subsystems. The health-care system and health behaviors that are a subset of the social system are affected by the status of other subsystems.

In a society with traditional beliefs and attitudes in its cultural subsystem, self-care behavior appropriate to the new health principles is not accepted. In a society where economic and livelihood problems are widespread, there are no facilities and resources needed to manage health care. In a society with inefficient education and socialization and social disorganization, institutional and individual behaviors in the field of health care do not have the necessary efficiency. Totally, according to various barriers, self-care behavior in developing societies such as Iran is not sufficient for disease prevention. According to Leininger, self-care behavior in non-Western societies is less accepted than in Western societies (Leininger & McFarland, 1991).

To overcome these barriers, a set of economic, social, and cultural practices is needed. Economically, providing the grounds for using health and safety facilities and reducing poverty is one of the strategies for strengthening self-care. Socially and culturally, it is necessary to correct inappropriate beliefs and perceptions about disease and well-being through education and expert extension of self-care principles.

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The COVID-19-Induced Transaction Cost Suggests Considerable Cost Effectiveness Resulting from the Prevalence of Universal Health Care in the United States

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Introduction

This study analyzes the COVID-19 pandemic from an economic transaction cost perspective with the aim of economizing health-care costs. Transaction cost economic theory (TCE) developed by Tadelis and Williamson (2010) incorporates the "make-or-buy" decision into the institutional setting, where they established that a relationship exists between transaction costs, asset specificity, and institutional choice. TCE frames the make-or-buy choice as a role of governance; in the public policy space, the make-or-buy decision is a choice between two forms of governance, defined as market or hierarchy. This study finds that a transaction cost (TC) analysis promotes collaborative relationships between organizations and reveals economic efficiencies that might not be observed without the consideration of transaction costs. According to the theory of transaction cost economics, the transaction costs of adaptation and incomplete contracts can indicate the most economizing choice of governance, market, or hierarchy, for the delivery of universal health care.

This study is guided by the following research question: Do COVID-19-induced transaction cost effects suggest that the implementation of universal health care would be economizing? The real-world application of a transaction cost model is used to consider this question. The goal of the chapter is to determine in theory and with real-world evidentiary support whether a transaction cost approach can increase the efficiency of the US health-care system. We study the COVID-19-induced transaction cost effects on registered nurse (RN) and travel nurse (TN) staff. Registered nurses are employed through the nationwide private insurance health care and hospital system, while travel nurses are employed directly through the market created

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by travel nurse[1] staffing systems. This study collected data from the U.S. Bureau of Labor Statistics (BLS) and proprietary industry data.[2] The aim of this study is to make a compelling theoretical argument with evidentiary examples. The study proposes that in not considering TCs, the government is operating with incomplete knowledge of observable efficiencies.

In the United States, the debate between continuing the private health-care system or establishing a universal health-care system is a partisan issue for Congress, society, and the media. This debate has been divisive for decades of political activity, not only dividing the Democrat and Republican political parties but also creating ideological divides within these political parties.

Background of COVID-19 in New York State

In New York State, the New York State Government and the federally controlled Centers for Disease Control and Prevention (CDC) were primary actors engaged in the fight against COVID-19. New York State Governor Cuomo (2020) opined in televised public conferences that what happened with regard to the transmission and infection rate of COVID-19 would be a direct result of what organizations and people did to "flatten the curve." This first widely promoted and organized public response to COVID-19 in New York State was premised on the principle of flattening the infection curve. In New York State, the "flattening the curve" message became a central focus of the state's response to COVID-19 from early March 2020 through July 2020. This message was promoted widely by the New York State government and the CDC. The relationship between the CDC and New York State was sometimes contentious, although they often promoted the same public message. While the state government may have had the immediate safety of the public as a first priority, the CDC had a primary fiduciary role.

The CDC is a federal department of the US government, and the CDC website states that it "works 24/7 to protect America from health, safety and security threats, both foreign and in the U.S.". The CDC's mission includes the pledge to the American people that the CDC should be a "diligent steward of the funds." This pledge of fiduciary responsibility is the first of five CDC pledges, and it notes the central importance of the efficient use of public money. The CDC is administered at the federal level, and the decision of how and when state and local governments were to respond to the pandemic was left largely to the state and local governments, although the CDC did determine and promulgate technical and safety guidance that the states incorporated.

[1] TNs are not employed permanently by a hospital or regional health-care system or facility but are engaged by health-care providers in times of increased need for RN services. The employment of TNs is a market place operation, with several large companies connecting nurses with organizations that require additional short-term nursing staff.

[2] The North American Industry Classification Association (NAISC) code for RNs is 29–114. TNs are not industrially coded and cannot be identified by a NAISC code.

The Transaction Cost of Health-Care Systems in the Current Literature

Studies that apply TCE to universal health care set out to define the association between transaction-specific assets and how these assets are used most economically by a health-care system. The following review of international studies is selective, with the aim of revealing the general consensus among scholars that engaging in a TC framework requires associating transaction cost concepts with real-world variables.

Taiwan operates a nationalized single-payer social insurance health system that is compulsory for all citizens and is documented by Wu et al. (2010). Lu and Hsiao (2003) suggest that the administrative costs of reporting and claims associated with health care were greatly reduced when centralized with one administrator. Note that these costs currently represent 2% of the budget in Taiwan, while in the United States, these costs represent 20% of revenues. In the Lu and Hsiao study, transaction costs are considered to be directly associated with administrative functions.

Lu and Hsiao's study provides an interesting perspective on the US system. Taiwan implemented universal health care, known as the NHI, in 1995. Taiwan, a market-driven capitalist society, chose to implement a single-payer insurance system. Lu and Hsiao study the effects on the health-care costs of the implementation of the NHI, and they do so by measuring a cost "residual." The residual is a measure of the cost growth in health care after normal and predictable cost increases (aging, demographic, and income changes) are accounted for. The Taiwan case is relevant to our study. Lu and Hsiao found that the growth in the cost "residual" initially increased when the NHI was enacted but then decreased to levels below those measured prior to the implementation of the NHI. They account for this difference in cost residual as attributable only to the NHI. The evidence for Taiwan is clear; the implementation of the NHI has increased efficiency and lowered the residual growth in cost while providing universal health insurance coverage.

Our study of TCs also uses the calculation of a cost residual associated with the change in the transaction costs of adaption and complexity induced by COVID-19 on registered nurse compensation. Similar to Lu and Hsiao's study, the "residual" in our study is an index of that remaining cost residual, which is attributable to the economic effects induced by COVID-19. In the case studied by Lu and Hsiao, the event was the implementation of the NHI in 1995, and for our study, it is the TC effects induced by COVID-19 during 2020.

The vertical integration of resources can be an economizing organizational structure. Mick and Shay (2016) consider the transaction costs faced by health-care providers to be the "nonproduction" costs of care. Mick and Shay focus primarily on vertical integration as an economizing choice between market or hierarchy. They make the point, differing from Williamson, that TCs internal to the organization are generally lower than those in the market even when specificity is high. This might be considered an aspect of incomplete contracts; as the complexity of the project becomes greater, contracts become less complete "ex ante," leading to greater inefficiency. Mick and Shay determine that there is an economizing result using a TC approach. TC analysis “may remedy transaction costs stemming from diverse sources of uncertainty, providing ACOs [accountable care organizations] with a means to limit opportunistic behavior, defend competitive advantages, [and] adeptly pursue adaptive strategies in the face of unforeseen contingencies….” Mick and Shay’s study is methodologically relevant to our study. Mick and Shay consider the benefits of a TC approach from within the totality of the private US health-care system. They achieve this by using economic TC analysis to compare “internal” and “external” costs. These costs are a measure of the efficiency of accountable care organizations (ACOs). They use a TC model to consider the most efficient “form” of governance, which is internal or external, of the ACO. Our study utilizes a similar approach, comparing two systems operating within the overall US health-care environment. Mick and Shay’s study operationalizes variables from within the ACO system on the premise that the dichotomy between the internal and external forms of governance creates a mutually exclusive variable for analysis. Our approach is similar; our study uses an economic TC analysis to consider the COVID-19-induced change in the TCs of travel nurses in the private market (external) to the TCs of RNs operating in the private insurance and hospital health-care system (internal).

International studies offer insights into the prevailing universal single-payer health-care systems. One of the difficulties encountered in the United States is the lack of discernment between a public need and a market demand. Fiani (2013) notes that without transaction costs, analysis efficiency in the system is limited to “productivity differentials” and that the problem of cost in health care is seen as one of “excessive demand.” Fiani reveals this to be the classical economic approach to accounting health-care costs. Fiani studies TCs in the Brazilian national health system, specifically the TCs that affect the efficiencies “between the supply chain of health services and health insurers.” Fiani’s study supports the approach of utilizing TCE to further the most efficient collaborative and vertically integrated relationships between organizations and institutions. In the United States, there exists an ideological divide between those who support universal health care and those who support the private insurance model of health care. A significant number of Democrats and Republicans support the private market model, and the support of these centrist politicians helps maintain the private insurance health-care system in the United States, although public opinion polls regularly show greater public support for universal health care. In comparison to similar nations, the United States ranks low in health-care outcomes but highest in health-care costs; one might consider that the United States is paying high transaction costs to sustain the argument of a private and demand-driven free choice health-care system.

Economic Transaction Costs

The study of transaction cost theory starts with the contribution of economist Ronald Coase. Coase promotes the transaction rather than the commodity as the primary unit of economic activity and posits that as transaction costs are never zero, the market is to some degree always imperfect. Building on Coase, Oliver Williamson developed transaction cost economic theory, and this theory was further developed with collaboration between Williamson and Steven Tadelis. Studies that incorporate a transaction cost approach usually outline the development of important paradigms of the theory, and they generally make a case justifying the validity of a transaction cost approach. This chapter applies the same strategy and builds on several past studies. The first step is to show that the subject can be identified as having characteristics that fit the concepts of TCE.

Coase (1937) draws attention to what is known as the "make-or-buy" decision. For Coase, this question, of whether production should be undertaken by the firm or the market, highlights a primary question in the production of goods and services. Coase suggests that the transaction is the primary economic unit and that transaction costs are associated with the transaction. Oliver Williamson makes the case that the make-or-buy decision can be applied to the process of government, specifically if the government can make more efficient economizing decisions by understanding the transaction costs involved in the process of supplying goods and services to the public. The firm in this case becomes the government, which Williamson calls the hierarchy. The make-or-buy decision is a choice between the hierarchy and the market.

In transaction cost theory, the transaction is the primary economic unit, economizing is a primary goal, and a transaction occurs when there is an exchange of goods and services between separate entities. Assets, which can be considered specific or nonspecific, have differing transaction costs according to their ability to adapt to change, which Williamson refers to as asset specificity. Assets and investments can be considered specialized by their association with transactions. If a transaction relies heavily on particular assets and to some degree is dependent on these specialized assets, the transaction is said to have high asset specificity. The cost of adapting these assets is high, and these transactions are understood to be more economizing when provided by hierarchy rather than the market. Conversely, if the transaction engages nonspecific assets, the market is the more efficient choice for the provision of these goods and services. An asset vulnerable to the effects of uncertainty and risk has higher asset specificity and greater transaction costs. When considering a transaction cost model, uncertainty is generally held as a constant value. For Williamson transaction costs can be defined as the "comparative costs of planning, adapting, and monitoring task completion under alternative governance structures" (Williamson, 1989, p. 149). Coase delineates between the firm and the market when considering the make-or-buy decision. The firm can make internal choices that promote efficiencies, such as vertical integration, while in the market, the benefits of competition lead to lower costs. Williamson theorizes the platform of economic TC as an institutional application that takes the make-or-buy decision as a choice between the market or the hierarchy. Asset specificity is a variable that can inform the most economizing choice between the market and hierarchy, and understanding organizational transaction costs can lead to economizing through organizational collaboration.

Krueger and McGuire (2005) note the difficulties that might be associated with collaboration agreements due to the differing transaction costs (between organizations) of providing the service. Transaction costs might differ from one government locality to the next, and different transaction costs lead to variation in the success of governments forming collaborative agreements through choice. For this reason, the control of transaction costs, or the underwriting of transaction costs by the hierarchy, promotes organizational collaboration.

In the next section, the proposition of universal health care in the United States is modeled using TCs. TC theory suggests that the implementation of universal health care is economizing due to the low transaction costs associated with the administrative control of transaction-specific assets, incomplete contracts, and the advancement of collaboration between organizations.

Transaction Cost Theoretical Framework

Williamson (2010) applies transaction cost theory to institutions and the prospect of the government choosing between the hierarchy or the market in the provision of public goods and services, which he refers to as institutional TCE.[3] Characteristics of the transaction costs of institutional transactions are the amount of uncertainty/risk as displayed in incomplete contracts, the frequency of transaction occurrence, and the degree to which assets are "transaction specific." The best form of governance (market or hierarchy) is selected through the analysis of transaction costs, rather than the neoclassical approach of the mode of production, commodity price, and resource allocation. Institutional TCE is a substantive theory that pays particular attention to transactions in which an incomplete contract (a breakdown of relationship) is of special importance. With the knowledge of transaction-specific assets, it is possible to compare how transactions are different between organizations. Transaction costs and the measure of asset specificity can be implicated in outcomes regarding the choice of the delivery system for publicly needed goods and services, in this case, universal health care. Williamson defines the choice as selecting the market when there is "strong incentive intensity" with firm legal contracts and limited administrative control, while the hierarchy is selected when there exists "weak incentive intensity," strong administrative control, and incomplete contracts. Williamson outlines the concept, operation, and application with regard to TC analysis.

Concept: Human actors as assets are assumed to function within bounded rationality theory; changes in price incur a transaction cost of adaptation, and incomplete contracts incur greater transaction costs than less complex and more complete contracts.

[3] Williamson (1971, 1975, 1985) notes the stages of development of TC theory and the importance of each development in his own papers.

Operation: The unit of analysis is the transaction and the mode of governance is the market or the hierarchy. The market is selected for generic transactions where asset specificity approaches zero and adaptation is autonomous, as these are ideal transactions. Hierarchy and administrative control are selected for transaction-specific assets facing the burden of disturbances from risk and uncertainty.

Application: TC analysis addresses the relevance of the political environment while still maintaining that the goal of economizing is central. Williamson accounts for the problem of better efficiency being "scanted" due to the politicization of the design of public bureaus. He suggests that the outcome can be considered efficient if it provides the most efficient and feasible alternative.

The make-or-buy decision and the transaction costs associated with adaptation are central to selecting efficient governance.[4] In the case of health care, there are large amounts of specialized human labor, learned procedures and knowledge, dedicated equipment and personnel, site-specific assets, and investment specificity, and when considering pharmaceutical companies, even brand name capital and intellectual property rights. Health care has high transaction costs of adaptation. These assets cannot be redeployed without a loss in productivity. The complexity of the project and contract are a source of ex post transaction costs.[5] In the hierarchy, administrative control endogenously promotes the vertical integration of production and supply, and contracts are authoritative based on ex post outcomes and the need to be economizing.[6] Williamson defines the market versus hierarchy in a single attribute, the administrative control of production and the adaption of assets. Zero transaction cost reasoning in the public policy sector allows the private health-care market to function with sustained inefficiency in the delivery of public products and services with complex assets and high adaption costs; this is not an economizing platform. High asset specificity induces high transaction costs, which are not reflected in the output value of production, as noted by Mick and Shay (2016).

[4] The Tadelis and Williamson (2010) chart of "efficient governance" suggests that "When asset specificity increases… or when contracts are more incomplete… the relative benefits of hierarchy over markets increase."

[5] Tadelis and Williamson (2010) note that "Contractual completeness…[is] interpreted as the probability that the contract will adequately cover ex post needs."

[6] The hold-up problem suggests that contracts are incomplete between parties even when there is a strong incentive for firms/organizations to work together. Parties are cautious of losing some competitive advantage through disclosure due to cooperation with a competitor; thus, contracts remain incomplete as each party tries to protect its own interests. Vertical integration is efficient, and complete contracts lower TCs; however, both of these economizing conditions are lost when hold-up problems prevent cooperation.

Transaction Cost Model

This study uses the make-or-buy model developed by Tadelis (2002) and applies it to universal health care in the United States. The model is built on the premise that a buyer wants to "procure a project from a seller" (Tadelis, 2002, p. 434). The use of the Tadelis model and the make-or-buy choice needs clarification in its application to economic TCs. It is noted that the economic TC argument frames the institutional choice, the choice between the hierarchy and the market, as akin to the make-or-buy decision. The choice of the decision maker can be considered a function of the outcome: Is the policy to be implemented and influenced by an external entity, the market, or is the policy enacted in the hierarchy with the aim for the ex ante and ex post outcomes to be as similar as possible? TC analysis can inform this decision through the analysis of real-world TCs. In the case of universal health care, the policy maker first determines whether health care is delivered by demand or need.

The case against the use of the market to deliver a public need has been made in the academic discourse; in social and political discourse, universal single-payer health care is sometimes referred to as the Medicare For All (M4A) movement. The market is not the most efficient method for the delivery of a universal public need. If the public need is universal, when project complexity is high and contracts incomplete, and when assets have high TCs of adaptation, a TC cost analysis promotes hierarchy as the most economizing and efficient form of organization. In terms of TC analysis, the failure of the market to effectively provide a universal public need resides on the false assumption that TCs in the provision of public services by public entities are zero. Fiani (2013) reveals that even if health care were provided in a competitively perfect demand-driven market, the "effect of health insurance" would be to raise costs (according to Lu and Hsiao, the residual would increase) through an "excess of health care demand."

Tadelis's (2002) simple model is chosen for our study because Tadelis links the institutional "make-or-buy" choice to the complexity of the service or product being delivered. Tadelis establishes this interaction to be "associated transaction costs." This link is important, and Tadelis and Williamson utilize it in subsequent studies of institutional transaction cost economics, notably in which they state that "TCE [transaction cost economic theory] was transformed into an operational methodology by taking the 'make-or-buy' decision to be the focal transaction" (2010). The make-or-buy choice is an operation of the market, and Coase observes that it is fundamental to the establishment of the transaction as the primary "unit" of the market. The "make-or-buy" choice with regard to TCs does not define a public need as a market demand; it uses the "make-or-buy" choice as an instrument to study the transaction, and importantly, it uses the "make-or-buy" choice as a vehicle to "scale-up" the TC hypothesis in "real-world" scenarios. This "scale-up" role of the "make-or-buy" choice interests Tadelis and Williamson (2010). They suggest that through the repeated ("real world") application of the basic mechanism of the simple model, the transaction associated with each make-or-buy decision might reveal a result that fits the simple model. Tadelis and Williamson refer to this real-world test as "scaling up" the simple model. They consider that the "intermediate market transaction – [known as] the 'make-or-buy' decision" leads to an understanding of many other "phenomena" in the development of an institutional transaction cost economic theory. The make-or-buy decision is part of a preexisting "general theory," in which Williamson and Tadelis consider the "particulars" and operation as "real-world" and instrumentally elaborative to establishing an institutional TC theory. They state, "we focus our analysis on the two conventional polar modes of governance, markets ('buy') and hierarchies ('make')."

This study utilizes Tadelis's (2002) "make-or-buy" model because it incorporates the transaction cost of complexity. This model was further developed by Tadelis and Williamson (2010), establishing the "make-or-buy" choice as an institutional choice of the market ("buy") and hierarchy ("make"). In our case, the transaction cost of a project and contract complexity are relevant to the provision of universal health care in response to the public need.

Simple Transaction Cost Model

Buyer Outcomes = (Completeness of Contract × Buyer Payoff for Complete Contract) + (Complexity of Project × Buyer Payoff for Incomplete Contract) – Costs Incurred.[7]

In adapting the model, the following conditions apply:

"Buyer Outcomes" are considered a measure of the total benefit to the buyer, which is an indication of efficiency and is termed "health-care costs per unit."

"Completeness of Contract × Buyer Payoff for Complete Contract" are the transaction costs associated with the completeness of the contract (including the completeness of the product/project design) and are termed "Completeness Δ."

"Complexity × Buyer Payoff for Incomplete Contract" are the transaction costs associated with adaptation (including the transaction specificity of assets) and are termed "Complexity Δ."

"Costs Incurred" represent the costs outside of the transaction (risk and uncertainty), and these costs are comparable in the market or the hierarchy and are included as a constant "C."

The model is adapted as follows and displayed graphically in Fig. 1.

Health-Care Cost Per Unit = Completeness Δ + Complexity Δ – C.[8]

[7] Adapted from Tadelis (2002). Tadelis notes that the variables "Payoff for Complete Contract" and "Costs Incurred" are a function of the following additional variables: Z = share of costs on the seller, X = make-or-buy decision – hierarchy or market, and S = specificity.

[8] Author's own model adapted by the author and J. T. Parker from Tadelis (2002).

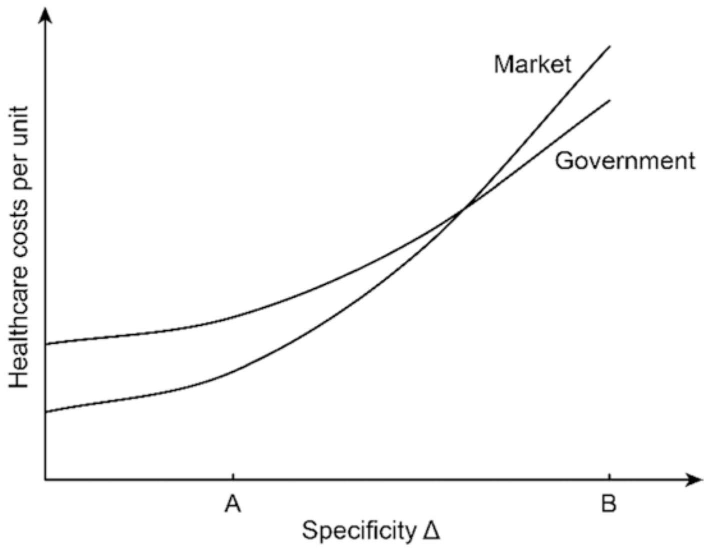

Fig. 1 Efficient health care. Health-care costs per unit are a function of transaction cost, and Complexity Delta and C are a function of Specificity Delta. Points A and B represent the change in Health-Care Costs Per Unit resulting from the change in asset specificity of health care during the COVID-19 pandemic. (Author's own figure is adapted from the original graph of "Efficient Government" developed by Tadelis and Williamson (2010), Transaction Cost Economics, University of California, Berkeley. Adapted from http://faculty.haas.berkeley.edu/stadelis/tce_org_handbook_111410.pdf)

There are two descriptive points on the horizontal axis: point A and point B. As transaction costs rise, the most efficient control of service delivery moves from the market to the hierarchy, and the most efficient method of governance moves from the market to the hierarchy. The change in the position of specificity Δ from point A to point B is caused by a change in the transaction costs of the adaptation of transaction-specific assets and the increasing public need for assets with high asset specificity. The cost of adapting health-care assets has become greater under COVID-19 conditions. This study investigates the high transaction cost asset of travel nurses. The notion that the COVID-19 pandemic transformed the characteristics of the asset is not contentious. It has been shown by Aurland-Bredesen (2020) that catastrophic events have an effect on the benefit-cost relationship. When projects are marginal and interdependent, benefit-cost analysis is biased due to catastrophe. Risk management is used as the comparative variable of the interaction between projects to determine marginality and the benefit-cost bias prevalence.

The institutional changes brought about by the COVID-19 pandemic also affect the transaction cost characteristics of health-care assets. In the United States, changes in institutional monetary policy led to the lowering of interest rates, instigated by the Federal Reserve Bank on March 15, 2020, and economic stimulus denoted by the passage of the S.3548-CARES Act introduced into the US Senate on March 19, 2020. These changes in economic and monetary policy introduce contract complexity, uncertainty, and risk (into the market), which have the effect of increasing asset specificity Δ.

Pandemic-specific assets with high transaction costs of adaptation and complexity, for example, intensive care unit (ICU) beds and staff, are required in greater numbers during the pandemic. The greater volume of assets with high specificity contributes to greater specificity. Figure 1 reveals that the adaptive capabilities of a governance structure or bureau can be aligned to transactions in a manner best suited to economizing the transaction costs for universal health care. The COVID-19 pandemic required the redeployment of specialized nursing staff across America. In March, the demand for travel nurses to deal with the growing coronavirus pandemic increased. This research commenced in May 2020 and COVID-19 was still at pandemic levels in parts of the United States. Institutionally published data on travel nurse conditions during the pandemic are not yet available, and for this reason, travel nurse data are sourced from industrial for-profit enterprises.

Travel Nurse Data, 2019 and 2020

Studying registered nurse compensation is meaningful for this study, as the travel nurse asset is a high transaction cost asset, and the economic costs induced by COVID-19 may be emphasized. Travel nurse data are not collected directly by any governmental bureau. RN employment data are collected by the U.S. Bureau of Labor Statistics (BLS); this study relies on the integrity of these data to offer a multiyear reference point of RN compensation. Our study is limited by the low availability of travel nurse data points. Our study relies on proprietary data collected from travel nurse staffing agencies. These data from travel nurse agencies are generally collected in surveys of the population of travel nurses or mined from their employment listings across multiple agencies. The available data on travel nurse compensation are limited, although our tests reveal their consistency with the BLS data, which we regard as a reference point for RN compensation in the United States.

In an article published on March 27, 2020, Pennic writes that the largest temporary health-care staffing platform in the United States, NurseFly, reported that the compensation for travel nurses nearly doubled, and the particular demand for emergency department specialists increased by more than 100%. Travel nurses serve hospitals that have short-term staffing shortages. NurseFly notes the greatest demand for ICU (intensive care unit) and ED (emergency department) staff with infection control experience. Brusie (2020) writes in Nurse.org, an online media source dealing with the lives of nurses and nursing students, reported on March 29, 2020, that recruiting nurses to meet the needs of COVID-19 required the modification and fast tracking of state institutional nursing licenses, the redeployment of

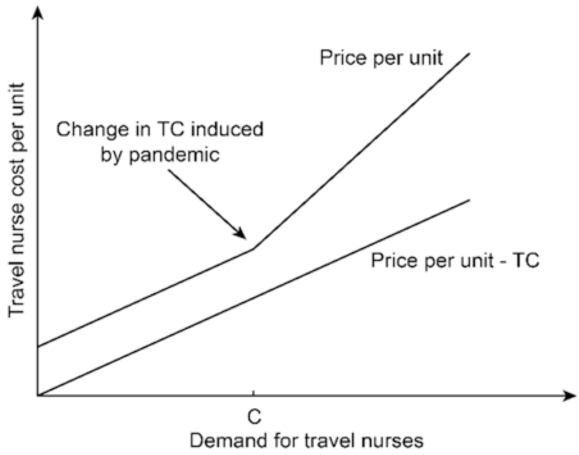

Fig. 2 Simple model of COVID-19-induced transaction costs (price per unit inclusive of transaction costs). Point C represents the change in demand for travel nurses in the United States induced by the COVID-19 pandemic. (Author's own figure)

retired nursing staff, increased quarantine pay rates, and the reengagement of retired army nurses.[9]

These market and institutional changes across the nursing sector brought changes to the TC characteristics of travel nursing. A greater need for travel nurses increases the transaction costs of adaptation and complexity for registered nurse staff, which increases the asset specificity of nurse staff. Our study finds that COVID-19-induced changes in travel nurse TCs might be indicative of similar changes in the asset specificity of other professions in the health-care system. The overall asset specificity of specialized staff within the health-care system can be expected to increase due to the changed TC of these assets induced by the COVID-19 pandemic.

Figure 2 presents the need for travel nurses as a function of the total cost per unit of travel nurse employment. In the market, the pandemic increased the demand for travel nurses, and the employment cost per unit rose. At Point C in Fig. 2, the asset specificity of travel nurses increases, which increases the transaction costs associated with travel nurses, resulting in a change in the slope of the price per unit.

After point "C" in Fig. 2, the asset specificity of travel nurses, which measures their transaction costs as a function of adaptation, contract completeness, and complexity, increases. Furthermore, in this study, the simple model presented in Fig. 2 is tested with real-world data in Fig. 3.

[9] It is important to note that higher TN compensation does not in itself constitute higher TCs. Compensation is indicative of the labor market and workplace conditions of demand, specialization, and complexity, which factor into the calculation of TCs. Changes in TN compensation correlate with changes in TCs, and the variation can be considered a function of the labor asset's specificity.

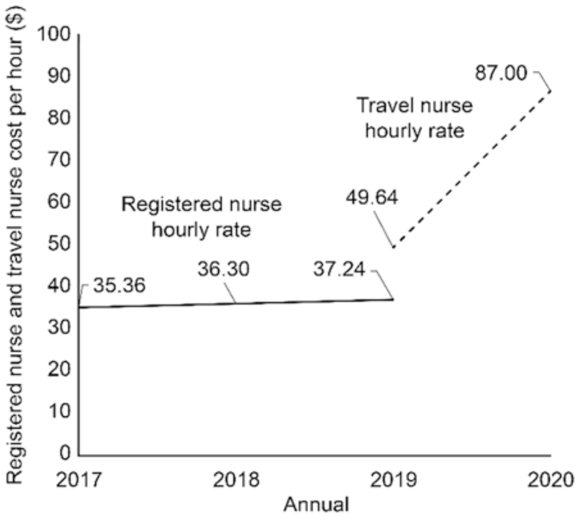

Fig. 3 Real-world COVID-19-induced transaction costs. The registered nurse and travel nurse cost per hour inclusive of transaction costs. (Author's own figure. Data sources for figure https://www.trustedhealth.com/travel-nurse-compensation-report-2019 and https://hitconsultant.net/2020/03/27/coronavirus-outbreak-doubles-travel-nurse-pay-nationwide/#.YD4WIJNKhTb)

Real-World Application of the Simple Model

The real-world data in Fig. 3 suggest that COVID-19 affected health-care assets in a manner that increased the growth of transaction costs. Proprietary data reported by TravelNurseSource.com suggests changes in travel nurse deployment continued through September 2020, with industry data revealing an increase in the demand for ICU nurses that was 59% higher than regular trends. In support of this modeling, TCE regards "changes in price" as incurring a transaction cost linked to adaptation and complexity.

Indicative of this is the case of travel nurse compensation, which displayed a measurable increase in asset value. Higher compensation is associated with higher asset specificity, resulting in higher TCs. There is reason to predict that other specialized labor and assets in the health-care system would, as a result of higher asset value and asset specificity, also have rising transaction costs. The model is constrained by the limited number of data points, yet the trend line of "cost per hour" is indicated by the steepness of the slope.

Simple Model Scale-Up Test

Figure 4 uses real-world data to test the simple model. As Tadelis and Williamson (2010) suggest, the observational evidence produced by a real-world "scaling up" of the simple model can be observed in the simple model if the resulting real-world observed phenomenon is similar to that expected in the simple model.

Tadelis and Williamson proposed real-world "scale-up" testing, as shown in Fig. 4. The simple model can be tested with "respect to scaling up." If the simple

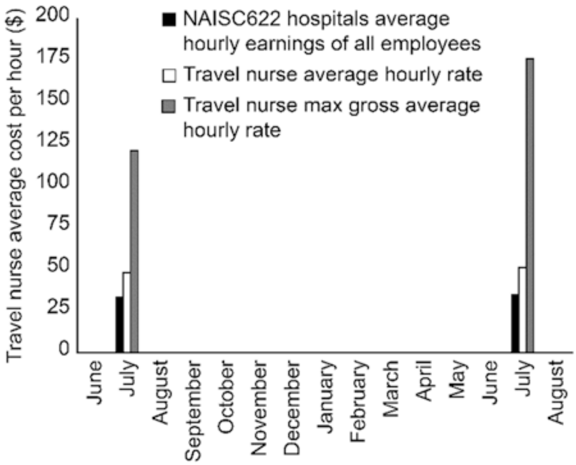

Fig. 4 Testing the simple model—scaling up test. (Author's own figure. https://www.bls.gov/iag/tgs/iag622.htm#earningsguide/how-much-does-a-travel-rn-make/)

model is applicable to a real-world scenario, the outcome of the "repeated application of the basic mechanism" of the simple model will "recognizably describe the phenomena in question."

In our study, the outcome of the simple model is a measure of the TC cost "residual." The cost residual indicates the COVID-19-induced effect on transaction costs and is expressed in the difference in the travel nurse max gross hourly rate between July 2019 and July 2020, as shown in Fig. 4.

Data Findings

Table 1 calculates the residual transaction costs.

"All employees," average hourly earnings of all employees, hospitals, not seasonally adjusted; TN, travel nurse.

- Our study determines the "cost residual" of travel nurse compensation, as indicated in Table 1, as the difference between the 2019 and 2020 residual TC cost, and the result is negative $52 per hour for travel nurses. Expressed as an index, the travel nurse cost residual is −0.58.
- The BLS data regarding the average hourly earnings of all hospital employees in 2019 and 2020 suggest that all employees had similar "cost residual" indices from 2019 to 2020, which were 0.70 and 0.68, respectively. This suggests that COVID-19 did not induce TC changes for all employees in the hospital system.
- The cost residual of all employees for the same period was 0.07/0.68 = 1.03, which reveals a cost residual saving of 0.03.
- These real-world data support the hypothesis that COVID-19 induced a rise in the TCs associated with the private market deployment of travel nurse services between 2019 and 2020. This study suggests that the increase in TCs was great.

Table 1 Residual TC scale-up test

Year	NAISC622 hospitals average HR earnings of "all employees"	"TN HR average"	Residual index "all employees" to "TN HR average"	TN max gross HR average	TN residual TC
2019	$33.38	$48.00	0.70	$121.00	−$73.00
2020	$34.56	$51.00	0.68	$176.00	−$125.00

Author's own work. Data source: https://www.bls.gov/iag/tgs/iag622.htm#earnings and https://blog.nursefly.com/salary-guide/how-much-does-a-travel-rn-make/

Policy Implications of the Result

One might consider that the health-care policy in the United States is created with the notion that ex post actions will be required. That policy "Remediableness" (as defined by Williamson and Tadelis) is implicitly assumed by policy makers. From this notion, it follows that ex post, health-care policy can be regulated in response to market outcomes. The resulting regulations and law and statute interpretations are created to remediate the policy ex post. According to TCE, more complete ex ante contracts can anticipate and limit the need for ex post remediation. This is the value to society of a TC analysis, and it translates into a more efficient provision of health care in response to the public need. Ex post policy remedies are not efficient or economizing according to TCE and our study. Our findings suggest that ex post remedial change to public policy is not economizing due to the high TCs of the assets engaged. The COVID-19-induced economic TC effects on travel nurse compensation reveal the extent to which the private health-care system operates with implicit inefficiency.

Institutional TCE suggests that the most economizing platform of governance when engaging high transaction cost assets is the administratively controlled hierarchy. This study finds that the United States could economize health care if it adopted universal public health care. The pandemic-induced changes to transaction-specific assets suggest that the organizational hierarchy and administrative control of universal health care is an economizing choice. Federal preemption could further facilitate these economizing effects through the promotion of vertical integration, ex ante contract completeness, and organizational collaboration.

Williamson notes that the public policy space often proceeds with the assumption that TCs in governmental operations are zero; this false assumption leads to the reliance on ex post market regulation. This outcome suggests that the "remediableness" of public policy is important to the policy maker; the ability to remediably modify the policy becomes an aspect of its effectiveness. This may be so, although Williamson and Tadelis note that an economic transaction cost analysis might avoid this revision of public policy.

The criticism of the scale-up test conducted in our study as being inductive rather than deductive is reasonable, and we acknowledge the limitations of the inductive method. Our observations indicate the relevance and correlation of the simple model to the real world. The cost "residual" difference can be attributed to COVID-19-induced TCs, similar to the case of Lu and Hsiao (2003), and indicates the effect of the national events considered in the two studies: the introduction of single-payer universal health care in Taiwan and the material effect of COVID-19 on travel nurse TCs.

Post-COVID-19 Consideration of Preemptive and Preventive Actions

Universal health care could be implemented through a governmental action known as federal preemption. The implementation of universal single-payer health care by the issuance of federal preemption might be considered a pandemic preemptive and preventive action. Given the politically partisan nature of the health-care debate in the United States, we believe it is important to consider the implementation of universal health care not only from the perspective of the economizing possibilities of economic TC but also from the perspective of governance. The United States is a federation of states and abides by law established and derived from the Constitution. Given the division of power that exists between the federal and state governments, instigation of universal health care in the United States might require federal preemption to overrule state law.

Sykes and Vanatko (2019) describe the issuance of federal preemption as designed to avert "field preemption" or "conflict preemption." Federal preemption is not an uncommon order of the president of the United States. Constitutionally, a federal preemption is considered the supreme law and supplants individual state laws. As documented online by the US Environmental Protection Agency, former US President Donald Trump has used federal preemptions regarding fuel economy and greenhouse gas emissions standards. This study uses federal preemption as the instigating action that could promote universal health care in the United States.

Preemption instituting universal health care may be required to resolve administrative or policy conflicts of jurisdiction between the federal and state governments. Utilizing the Supremacy Clause of the US Constitution, federal policy makers have the authority to preempt state and local health laws and implement universal health care.

Federal preemption is the a priori assignment of administrative control. Preemption provides conflict avoidance between federal and state law, which can lower the transaction costs associated with incomplete contracts and promote collaboration between organizations. "The most powerful policy rationale for preempting any state law is the potential for conflict between that law and federal law," as quoted from the testimony of McGarity (2009). Lower transaction costs result from the avoidance of conflict between federal and state governments.

The centralized control of government is a divisive issue in America. Hudson and Brown (2020) write in the *National Law Review* (2020) online article (April 24, 2020) the ability of local health-care organizations to meet their needs is noted by Howard Koh, former Assistant Secretary for Health in the US Department of Health and Human Services. Koh suggests that health care is best provided and sustained locally. Koh suggests that government accountability and cooperation between levels of government can be advanced by local control, which fosters innovation and allows diverse communities to best meet their needs because they understand their situation better than a central controller does. Somewhat contrary to Koh's approach, a single-payer model can be adopted to consider the instigation of universal health care; this chapter suggests that the institutional knowledge Koh reveals to be important can be applied and adapted most efficiently from a governance platform of universal health care. Additional benefits of administrative control are in the form of emergency laws and the suspension and assumption by the government of pandemic tort liability. In response to moral hazard and litigation, the federal government instituted tort immunity conditions for pandemic responders.

One is informed by the US Department of Health and Human Services that the federally instituted Public Readiness and Emergency Preparedness Act (codified at 42 USC §247d-6d) and the Coronavirus Aid, Relief, and Economic Security Act (CARES Act) provide immunity from liability for the provision of emergency services during the pandemic. The goal of this law is to allow industries to act with supreme authority without fear of tort. Tort immunity is an emergency response that allows pandemic responders to act with public safety as their highest priority. Krueger and McGuire (2005) suggest tort immunity makes the market a more imperfect vehicle for universal health care, while economizing the cost increases due to collaboration between organizations promoted by homogeneous transaction costs. When local governments face different burdens of transaction costs associated with collaboration, they are less likely to collaborate. It is argued that organizations facing high transaction costs and high competition are unlikely to participate in collaboration and, if they do collaborate, are unlikely to participate at a deep level. Organizational collaboration, which seems beneficial when considering production capabilities, becomes less likely because the differing transaction costs between organizations reduce the economizing effect of organizations working together.

In contrast, "…cooperation in solving common pool resource problems at the local level is significantly enhanced by homogeneous actors…."[10] Organizationally similar transaction costs promote collaboration.

An obstacle to the implementation of single-payer universal health care in the United States is clearly stated by Hsiao (1995): "Unlike in the markets for groceries or clothing, the asymmetry of information between buyers (patients) and sellers (physicians) vastly undermines consumer sovereignty." Hsiao notes the parallel consideration of the need for health care as a phenomenon of choice between buyers

[10] Krueger and McGuire (2005), quoting Keohane and Ostrom (1995).

and sellers that could leave patients (consumers) with few rights and violate their patient sovereignty. Our study notes the adapted role of the make-or-buy choice and the determination that universal health care is a public need and is not efficiently served by the market. However, the complexity of engaging the justice and rights variables within a TC analysis may be considered in future studies.

Conclusion

This study finds that a federal preemption implementing universal health care in the United States would be economizing if the mode of governance chosen is a single-payer system, or a hierarchy. The optimum range of efficient performance and asset specificity exists where there is the greatest opportunity for the government to manage transaction costs ex ante. Our study finds that the transaction costs of adaptation and complexity incurred for travel nurse compensation in the private insurance model during the pandemic are greater than they would be with governance by hierarchy. This study finds that the private health-care model of the United States would economize transaction costs if universal health care were implemented through federal preemption and administrative control. The single-payer universal health-care model would economize transaction costs most significantly through administration, ex ante contract completeness, and vertical integration.

There has been a change in the dialectic. Sweden's former Prime Minister Lofven (2020) is quoted in the Australian newspaper the *Sydney Morning Herald* (2020) as saying that the pandemic is "a reminder that the society affected by the pandemic was not a perfect society; therefore, we will not go back to how everything was before." Such a shift of political and social opinion might support the proposition of a federal preemption instigating universal health care in America. Policy makers could consider four questions when assessing the economizing possibilities of universal health care:

1. Is the event nationally catastrophic?
2. Is the state responsible for the safety of all citizens?
3. Does the state have a fiduciary responsibility to economize?
4. Does the state have economizing choices?

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Assessing the Social Support and Resilience of the Inhabitants of Marginalized Communities amid COVID-19 Pandemic in Iran: A Shiraz Metropolis Case Study

Farzaneh Afifian

Introduction

The new coronavirus, or COVID-19, emerged as an acute respiratory syndrome in Wuhan, China, at the end of 2019 and has now become a pandemic. Our country, Iran, has been officially infected with this virus since *Bahman* 30, 1398 (February 19, 2020) in Qom province. One of the important measures in controlling and inhibiting this disease was social distancing and its implementation in the regions affected by the virus. The rapid spread of this disease worldwide and the increasing number of infected people and the death toll have caused great concern throughout the world, and Iran is no exception to this virus and the damage caused by it. The unknown dimensions of the disease, the uncertainty of the time of the outbreak, the repeatability in the future, and the transformation of human relations and economic activities with the implementation of the social distancing plan affect the whole society. This disease has affected not only the health system but also other areas and has become an economic, political, psychological, cultural, and social issue.

Given the short-term and long-term consequences of this pandemic, it seems necessary to study new pandemic challenges with different approaches in order to provide solutions to manage or reduce their negative consequences. Undoubtedly, the social, psychological, and economic adverse effects of the outbreak of COVID-19 are more present in vulnerable groups, including inhabitants of low-income areas (marginalized communities), child labor centers, centers for correction and

1 This work is adopted from my research project under the contract with *Hajat Mental Health Park Institute*.

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education, nurseries, addiction treatment centers, nursing homes, and so on. Inhabitants of marginalized communities and deprived areas of society are exposed to a lot of damage due to the outbreak of the COVID-19 pandemic in terms of lifestyle and lower social classes. Social support is a necessity in critical situations and acts as a social shock absorber by helping to fulfill the real and emotional needs of individuals. Social support leads to promoting resilience, coping with crises, and increasing social rehabilitation, which is an important factor in reducing anxiety, hope, and generally improving the quality of life. The consequences of the current crisis could be an increase in poverty and inequality and a greater impact on vulnerable groups. A large population in the family dimension, small living space, less attention or inattention to health, financial inability to provide prevention and treatment facilities, type of perspective, and ignorance can double the outbreak of the disease in these areas, and ignoring these areas can affect the whole city. Therefore, appropriate and timely social support measures must be taken in response to this crisis. Accordingly, the evaluation of social support has been conducted and the resilience of the inhabitants of the marginalized areas in the current crisis is found to be very important, and the results of the evaluation can be important in planning, policy-making, and changing methods and procedures to increase resilience and improve the quality of life of the inhabitants in these areas. Assessing the relationship between resilience and social support of marginalized communities amid the COVID-19 pandemic with the variables of age, gender, education, marital status, number of children, employment status, and income and the relationship between social support and its dimensions with the resilience of the inhabitants in these areas are the objectives of this study, based on which the following question is asked:

Is there a relationship between resilience and the social support dimensions of the inhabitants of marginalized communities amid the COVID-19 pandemic and its background variables (age, sex, education, marital status, number of children, employment status, and income)?

Theoretical Framework

Social Support Social support is the love, dignity, comfort, and help that other individuals or groups, including family, friends, colleagues, social organizations, and other groups, grant to the individual. Social support is classified into four categories: emotional, instrumental, informational, and evaluation support (Keivan Ara, 2008). Emotional support with assurance helps people to get rid of negative worries and feelings. Instrumental support helps people to adapt to everyday life and overcome stressful experiences such as physical care and financial aid. Informational support means providing appropriate information in different and stressful situations; evaluation support usually seeks information support, which is the support of individuals when making decisions. In this situation, social support makes it easier for people to decide about their situation (Keivan Ara, 2008).

Resilience The term "resilience" was introduced by the ecological theorist Holling in 1973, who described it as a descriptive and qualitative concept that provides insight into the dynamic properties of a system. Nowadays, resilience is considered a way to strengthen societies by using their capacities (Krrholm et al., 2014). Many theories have been proposed in the field of resilience, including Adger (2000) who considered resilience as the power of groups and societies to adapt to external pressures and the destructions that result from social, political, and other changes. Manyena (2014) stated that resilience is the inherent capacity of the system, community, or society to reduce the risks of accidents and to develop experiences. Davis (2004) described resilience as the ability of societies and endurance against dangers caused by tensions and pressures so that they can quickly step back, accept future threats, and deal with them. In the discussion of resilience, it is also important to pay attention to the social aspects. In Sander's theory of vulnerability reduction (2008) and Norris's theory of social support (2008), social support is considered one of the indicators of resilience. Accordingly, the concept of social resilience has emerged. Adger has defined the term "social resilience" as the ability of groups or communities to cope with external tensions and disorders in the face of social, political, and environmental changes (Adger, 2000). All definitions of social resilience focus on the capacity of individuals, organizations, or societies to tolerate, absorb, and adapt social transformation of any kind (Keck & Sakdapolark, 2013). The existence of social groups with different social and economic conditions and the degree of vulnerability in a community means that the resilience of different groups in society is different to an accident and socially vulnerable groups have less financial and instrumental capacity to deal with disasters.

Marginalized

Marginalized neighborhoods are generally referred to as densely populated neighborhoods, which are formed by a mass of unsanitary and unsuitable houses and do not have sufficient comfort and well-being. People in such neighborhoods live their own ways and usually have false jobs. One of the main characteristics of marginalized communities is uncertain employment status, poor housing status, and poor health, which are more or less common in different parts of the world. Figure 1 provides descriptions of the marginalized areas.

Marginalization in the World

Historically, the first marginalized areas in developed countries, especially in European countries, were called *Jewish ghettos*. After the *Industrial Revolution*, marginalization and slums were increased, following the development of English

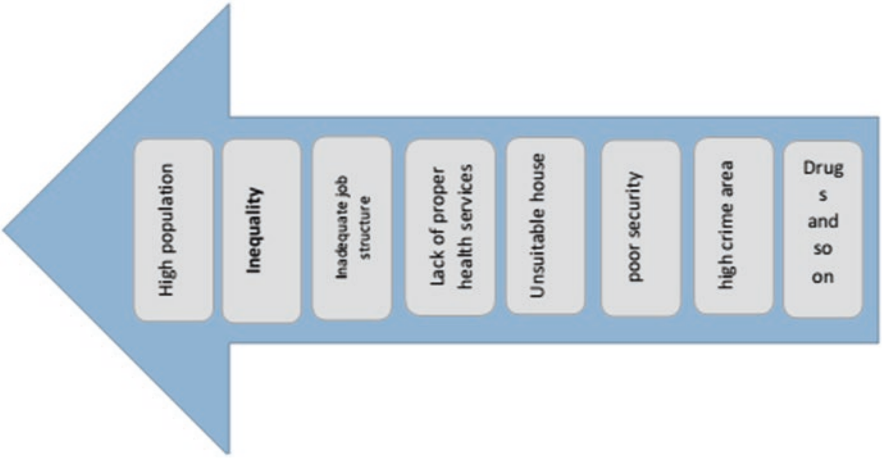

Fig. 1 Different descriptions of marginalized areas (IRIB News Agency, 2018)

cities and then other European cities. This trend in the United States has been accompanied by increasing European immigration from countries such as Britain, Italy, Germany, Hungary, and Ireland to American countries. Marginalization in today's sense, in developing societies, gradually found its existential nature since the beginning of colonialism, and in other words, it can be due to the direct impact of socioeconomic policies and then the urban systems of colonial societies in the occupied countries that with the presence of the Portuguese in the sixteenth century in the ancient continent of Asia, shows its true nature in the face of the cities of today's developing societies. According to the United Nations Center for Human Settlement in 1996, one-fifth of the world's population lacked a home worthy of human life, which included a wide range of homeless people, sleeping streets, and shanty towns (Cale, quoted in Bahmani et al., 2019). After continuing in the next two decades, the rapid growth of urbanization and urbanized tendencies has reached about eight hundred million people to one billion marginalized. The standard of living of the inhabitants of the marginalized areas is lower than the standard line or at least equal to it (Salehi Amiri & Khodaie, 2010). A look at the statistics published in *Habitat* reveals that the five countries of the Central African Republic, Sudan, Chad, Southam, and Guinea-Bissau are ranked first to fifth in the world in terms of marginalized areas. Among the Middle Eastern countries, the presented ranking introduces *Afghanistan* with the highest marginal population equal to 63%. According to the results of 2005 and having 30% marginalization, Iran ranks 70th in the world, 16th in Asia, and 7th in the Middle East (Bahmani et al., 2019).

Marginalization in Iran

In third-world countries, marginalization has emerged with delay usually following the influence of capitalist culture and economics, as well as the implementation of imported reform programs. The phenomenon of marginalization and related problems is a direct result of urban development. In different parts of Iran, the experience of the rapid growth of urbanization and the creation of marginal areas in the last half century has been significant. Accordingly, the urban population of the country increased from 31% in 1957 to 71% in 2012, and subsequently, the rural population of the country decreased from 68% in 1957 to 28% in 2012. This statistic indicates a change in the pattern of traditional living in Iran. Increasing growth, the tendency to live in urban areas in Iran has been recorded while the global urbanization statistics has changed from 34% in the same period (Bahmani et al., 2019). Table 1 shows the latest ranking of Iranian cities in terms of marginal population. According to the statistics and data of 2017, Shiraz, with an area of 240 m^2, had a population of 1869,000 people and the number of its marginalized people is estimated at 374,000 people, that is, 20% of the population.

As can be seen in Table 1, Shiraz is ranked twelfth in terms of the number of marginalized populations, which is estimated at 20% of the population of this marginalized city.

Marginalization and Coronavirus

Marginalization can cause many problems, including economic, social, unemployment, declining incomes, poverty, declining health, and so on. Undoubtedly, the problems of marginalized areas have doubled during the coronavirus outbreak. Following the outbreak of COVID-19, the problems of the inhabitants of these neighborhoods are not limited to the outbreak of coronavirus. The following is a

Table 1 Ranking of cities by marginal population (Udrc.ir, 2019)[a]

The latest ranking of cities in terms of the percentage of marginalized population					
Rank	City	Percent	Rank	City	Percent
1	Karaj	38/5	8	Kerman	28
2	Zahedan	38/5	9	Orumieh	26
3	Kermanshah	33	10	Arak	25
4	Mashhad	30	11	Qom	21
5	Ahwaz	30	12	Tehran-Isfahan-Shiraz	20
6	Hamedan	30	13	Rasht	9
7	Tabriz	28	14		

[a]Urban Regeneration corporation of IRAN

summary of the economic, health, psychological, informative, and sociocultural status of marginalized areas, with an emphasis on the COVID-19 period:

Health status Marginalized areas have dirt alleys, flowing sewage in the yards, as well as small, dense houses built with substandard materials. Houses have neither the characteristics of rural nor urban places, but are an intertwined and heterogeneous complex. The unsanitary condition of sewage in these areas is one of the causes of environmental pollution and disease outbreak. Studies conducted in different countries on marginalization confirm the outbreak of infectious diseases in these areas (Corburn et al., 2020). Improper hygiene of the neighborhood environment, the presence of surface water sludge, and inadequate disposal of municipal sewage through open canals are favorable for the growth of parasitic diseases, and the increase of infectious diseases can be considered a threat to these areas. The outbreak of communicable diseases such as hepatitis, skin diseases, alopecia, and lice are among the characteristics of these areas. In general, reduced health can be considered a consequence of marginalization. Restrictions on hygiene and access to health facilities, which are higher for inhabitants of these areas in normal situations, are exacerbated due to the inability to pay for sanitary items such as soap, masks, gloves, and disinfectants in times of crisis. These areas do not have adequate access to water or do not pay attention to washing their hands or cleaning the environment more due to their inability to pay for water, and in general, the health problems in these areas are much greater during COVID-19. These people have low immunity and are more likely to develop COVID-19 due to poor nutrition and low variation in diet. *They have been affected and intensified by social distancing and the elimination or reduction of nutritional income and food safety*. In poor populations, there are often poorer diets and a higher rate of chronic diseases, for this reason their immunity is lower to other diseases, including COVID-19. A study of marginalized areas in Wuhan, China, found that with rising food prices and declining incomes, poor households reduced their consumption of meat, dairy, vegetables, and fruits to non-core food groups (Riley et al., 2007).

The Economic Status of the Marginalized Areas The attraction of urbanization and urban welfare pulls these people from their hometowns toward industrial hubs and labor markets. Most of them are rural immigrants who go to cities to live better (Zali & Pourfathi, 2013). However, the level of culture, education, and work expertise have affected their job choices, and the lack of adequate jobs and incomes has led to the economic weakness of the inhabitants of these areas. One of the main reasons for people to choose these areas and prefer them to other urban areas is the low value of property, land prices, and housing rents (Veddeld & Siddham, 2020). Therefore, lack of official title deeds and construction permits, inadequacy of infrastructure, inadequate urban services, lack of access to public facilities and services, and unsustainable construction materials are among the physical characteristics of these neighborhoods, which lead to the synergy of their economic problems. Lack of skills and expertise of the workforce in these areas, employment in the informal sectors, low legal age of the labor force, the financial weakness of households, low wages and purchasing power, and high unemployment rates are also among the economic weaknesses of these areas. Most of the people living in these areas do not have job security and some of them are engaged in false, part-time, and seasonal jobs and do not have a fixed income (Vos et al., 2020). Sumner et al. (2020) estimates that COVID-19 could increase poverty in the world due to various factors such as having informal jobs and lack of health insurance, and most of these people are in developing countries, where the most damage due to the COVID-19 outbreak has been observed in terms of income elimination among day laborers (Rozelle et al., 2020). With the onset of the COVID-19 pandemic, some measures such as quarantine in various countries; travel bans; and closing of schools, universities, and shopping malls, had an immediate effect on informal habitats and marginalized areas, and many inhabitants of these areas lost their jobs. Past studies have shown that infectious diseases can affect economic development by creating disease-based poverty, which combines the effects of health on poverty and poverty on health (Bonds et al., 2009).

Psychological status of the marginalized areas: Inadequate living conditions and dilapidated buildings in the marginalized areas are psychologically dangerous for children and also play an important role in juvenile and youth delinquency. Behavioral disorders due to not fulfilling their desires, unfavorable living conditions, and lack of facilities or lack of facilities from childhood have led to psychological problems and provide the ground for delinquency in adolescence and youth. Behavioral disorders are caused by not achieving one's desires and make people aggressive, fierce, and militant (Zali & Pourfathi, 2013). The high population density as well as increasing household size and small living spaces in these areas pose a serious threat to the inhabitants in the face of viral diseases, including COVID-19. Feelings of danger and threat due to a pandemic will undoubtedly double the anxiety and depression of the inhabitants of these areas. The threats posed by COVID-19, on the one hand, and economic and health problems, on the other hand, increase their sense of anger, militancy, and aggression and create great disaster. Changing living conditions in the pandemic created by reducing job opportunities, closing schools, etc., increases violence within families and shakes families. Under normal circumstances, some marginalized people are treated with contempt and are not accepted into communities, which has become more acute in COVID-19 conditions.

Marginalized Information Status Inhabitants of these areas have less access to communication devices due to the weakness of the ICT infrastructure that this challenge highlights even more in times of crisis, such as the COVID-19 outbreak. Lack of awareness and knowledge about prevention and treatment, among other issues, increases the likelihood of infecting them. The digital gap has widened the current crisis for inhabitants of these areas. These people stay away from e-learning if they do not have access to TV and smartphones and worry about paying for electricity. Lack of access to data or lack of reliable data causes these people to be less-attentive or inattentive to the crisis.

Sociocultural Status Population density and housing density in informal habitats create more opportunities for social mixing and the possibility of physical and social distancing is weaker. Observing physical distance is a joke for the inhabitants of these areas (Austrian et al., 2020), because small and dense houses and large family dimensions have caused public areas of these neighborhoods—including grocery stores, bakeries, green spaces and parks, alleys, and passages—to be densely populated, and it is therefore impossible or less possible to maintain a physical distance. It is also difficult or impossible to change traditional relationships between these people and other communication devices. In a study about the flu in Delhi, it was estimated that the epidemic peak was faster and higher due to the exposure rate due to population density in marginalized areas (Chen et al., 2016). Of course, not all marginalized areas are populated, and there are differences between marginalized areas that are more densely populated and marginalized areas that are less densely populated. Among the inhabitants of these areas, there is more traffic in each other's houses in terms of sociocultural structure, and some even share food and sleeping space. Some of them live in the same house with several families and often share a common living space with their grandparents, which increases the risk of transmission.

The majority of the inhabitants of these areas have migrated from the surrounding villages or small towns, who travel between their place of residence and their hometown for work, visiting, etc., and are likely to move COVID-19 to smaller areas. During the *Ebola* pandemic, the disease also spread from these areas to rural areas (Wilkinson, 2020).

The main purpose of this study is to evaluate the social support and resilience of inhabitants of marginalized areas in the face of the COVID-19 outbreak in order to manage social harms (Fig. 2).

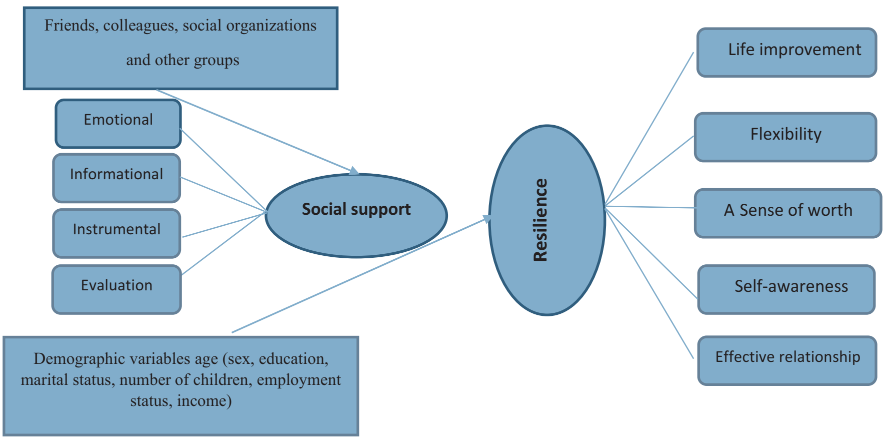

Fig. 2 Theoretical model of research. (Author's own figure)

Literature Review

Considering the importance of the COVID-19 pandemic, there has been a lot of research with different approaches worldwide. Studies on COVID-19 and its impact on the homeless, the elderly, informal settlements, the poor, slum dwellers, etc., show the importance of this issue. Doshmangir et al. (2020) investigated the strategies of East Asian countries in dealing effectively with COVID-19 and assessed the pandemic beyond the health system. Austrian et al. (2020) investigated the knowledge, attitudes, and needs of families in informal settlements in Nairobi, Kenya. The findings highlighted slum dwellers' concerns about virus transmission, job loss and income, and food shortages. Improving communications and information transfer on COVID-19 hazards, recommendations for supporting slum dwellers, ways to increase access to water and sanitation items, and improving waste collection were among their research achievements. Shooshtari (2021) investigated the effect of COVID-19 on marginalized people in metropolitan areas of Iran and the resulting social harms. They analyzed previous research on COVID-19 and marginalization and found that the reasons for the upward trend in the spread of the virus in these areas included inadequate health, and population density, which lead to damage to mental health and widespread poverty. In their work in the United States, Farkas and Romaniuk (2020) also investigated the importance of providing social work services to vulnerable groups during the COVID-19 outbreak. They found that changes have created unexpected challenges, and social workers, along with health-care providers and public and private organizations, are responding to the needs of vulnerable people and must develop emerging programs to mitigate the effects of the crisis. In a study, Neto et al. (2020) stated that the government has abandoned a group of highly vulnerable individuals to combat COVID-19 disease. Ignoring the homeless is not only an inhumane act but also a great danger to public health. These people face sleep deprivation, malnutrition, and severe stress to meet their daily needs and, consequently, have poor immunity. Many homeless people are constantly experiencing psychological pain and distress. For such people, the boundary between health and illness is meeting basic needs, and this is a serious concern exacerbated by the current pandemic.

In their studies on the social distancing plan, Wasdani and Prasad (2020) showed that the implementation of this plan in marginalized areas does not make sense. There is poverty, overcrowding, and dangerous socio-environmental conditions in marginalized areas, and the lack of immunization has led to the transmission of the COVID-19 virus. They offered cash assistance to the vulnerable, information on COVID-19, and the provision of free health kits, and stated that it is necessary to provide economic and social support for low-income people as well as social distancing to prevent a major catastrophe. Auerbach and Thachil (2021) also investigated the impact of COVID-19 on India's slums. Surveys were conducted of slum leaders about their actions in the face of health and livelihood threats. The findings show that pre-pandemic inequalities in infrastructure development make it difficult to maintain social distancing to provide safe services in these areas. Akter et al.

(2021) investigated the resilience of Khulna slums in Bangladesh during the COVID-19 period and found that economic, infrastructural, and health issues related to the pre-pandemic period were compounded by problems such as interruption of municipal services, and unavailable and non-coordinated health services have made slum dwellers more vulnerable. Information sharing and the dissemination of knowledge were among the most common measures, and cash donations from NGOs provided the most material support. But it seems necessary to pay attention to spatial infrastructure in order to deal with the complex problems of slum dwellers for similar events in the future.

There have been many studies on the effect of mediating variables during the outbreak of COVID-19. Alizadehfard and Saffari (2020) investigated the prediction of mental health based on the anxiety and social support caused by the coronavirus. They confirmed the positive and negative psychological and social effects of social distancing and referred to the need for supportive interventions during the COVID-19 pandemic. Kalateh Sadati et al. (2020) stated that one of the most important consequences of the COVID-19 outbreak is social anxiety worldwide and reported that the specific and rapid spread of this disease has caused many social and economic issues to be linked to the outbreak of this disease, turning the pandemic into a socioeconomic issue; therefore, flexibility should be improved at the psychological, social, and individual levels, and vulnerable groups should be supported, including low-income people, the elderly, and the disabled, who suffer from disproportionate damage during epidemics and natural disasters. Eyni et al. (2020) investigated the COVID-19 anxiety model among students based on optimism and resilience and the mediating variable of social support and found that resilience obtained from perceived social support plays an important role in reducing COVID-19-related anxiety in students. Zang et al. (2021) investigated the role of social support and resilience as mediators in interpersonal relationships among Chinese university students and their adaptation during the COVID-19 outbreak. The results showed that interpersonal relationships can directly or indirectly affect student adaptation by increasing social support or resilience in parallel or by increasing resilience through social support.

Many previous studies have investigated the situation of marginalized people during the COVID-19 outbreak and the subsequent damage as well as the effect of social support and resilience on mental health. However, there has been no study on the effect of social support on the resilience of marginalized people. Therefore, the main aim of this study is to address this gap.

Methodology

This research is applied in terms of general methodology and is surveyed in terms of method. The statistical population in this study is the inhabitants of the marginalized areas of Shiraz. The number of marginalized areas of Shiraz is estimated at 374,000 according to the statistics of 1395 (2017). The sample size was 400 people selected from different neighborhoods according to Cochran's formula by proportional cluster sampling method, due to the fact that the marginalized people themselves are different in nature and some live in historical contexts, dilapidated contexts, adjoining villages to the city, and informal habitats. For sampling, the list of marginalized areas of Shiraz in different areas and the population of each neighborhood was extracted based on the 2017 census. Then, the number of samples in each region was determined in relation to the number of marginalized populations in each region, and the number of neighborhoods was selected in proportion to the number of neighborhoods in each region. Finally, the questionnaire was randomly distributed among the individuals. The research measurement tool was a researcher-made questionnaire whose validity was determined using the opinions of a number of experts and specialists in this field. The reliability of the questionnaire was determined using a social-science statistical software and the value of Cronbach's alpha was 0.724. The necessary variables were identified based on the theoretical framework of the research, and a questionnaire with 67 items including contextual variables, information support, emotional support, material-instrumental support, and resilience was designed and finalized based on the tools designed to measure social support and marginalized people's resilience, and prepared and published according to the number of respondents. Then, data were collected from the sample. The collected data were coded and entered into the *Social Science Statistical Software* (SPSS) version 21 and statistical analysis was performed. Descriptive statistics such as frequency and percentage tables and one-sample *t* inferential statistics, one-way analysis of variance, and linear regression were used based on the variables and research questions.

Results

In this section, the frequency distribution of the sample in terms of demographic variables is presented in order to provide an appropriate perspective on the characteristics of the studied subjects. Most of the sample, 67.4%, were male. Also, in terms of age, 149 people (44.6%) in the age group under 30 years had the highest number and people 60 years and older with 12 people (3.6%) had the lowest number. Also, 53% of the general population was single. In terms of education, the number of under diplomas (115) was the highest and the number of PhDs (5 people) was the lowest. The results of the job-based distribution of sample people showed that most of the sample people, that is, 121 people (40%), have free jobs and public sector employees, that is, 21 people (7%), were the least. Also, in terms of the type of ownership, most of the sample people, with 124 people (37.1%), had rent or mortgage ownership. The results of the distribution of sample people based on monthly income showed that most of the sample people, that is, 92 people (27.5%), had less than five hundred thousand Tomans, and also most of the sample people, that is, 115 people (34.4%), had social security insurance.

Table 2 T-sample test results

Paired differences								
				Confidence interval				
Index	Experimental mean	Theoretical mean	Mean difference	Lower bound	Upper bound	*t*	Degrees of freedom	Sig
Social support	3.1981	3	.19808	.1164	.2798	4769	333	.000
Information support	3.4437	3	.44366	.3765	.5109	12,988	333	.000
Emotional support	3.4126	3	.41257	.3122	.5130	8083	333	.000
Material support	3.0094	3	.00937	−.0912	.1099	.183	333	.855

Author's own work

Analysis of Social Support Status and Its Dimensions

In order to examine the social support perceived by the inhabitants of marginalized areas during the crisis of the COVID-19 outbreak, first social support was examined and then the relationship between social support and contextual variables was analyzed (Table 2).

A one-sample *t*-test was used to analyze the status of social support and its dimensions. The results showed that the experimental mean of information support and emotional support was higher than the expected mean (3). The values of *t* for these two dimensions were significant at the level of 0.1 (p-value ≤ 0.01). Therefore, it is concluded that the observed mean is significantly different from the theoretical mean. Because the experimental mean was higher than the theoretical mean, information support and emotional support are higher than the mean. But the material support is lower and moderate.

Analysis of Social Support Status Based on Contextual Variables

Age

A one-way analysis of variance test was used in order to analyze the social support status by age (Table 3). Based on these results, the value of *F* was not significant at the error significance level of less than 5% [p-value ≥05 0.05, $F = 1.835$]. Therefore, it can be said that inhabitants of different ages are not significantly different in terms of social support (Table 4).

Table 3 Results of one-way analysis of variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Social support	Intergroup variance	3138	3	1046	1.835	.141
	Intragroup variance	187,586	329	.570		
	Total variance	190,724	332			

Author's own work

Table 4 The mean scores of the groups

Subset for alpha = 0.05		
Age	*N*	1
60 years and older	12	2794
45–60 years	35	3.0516
Under 30 years	149	3.2325
30–45 years	137	3.2412
Sig.		0.087

Author's own work

Table 5 T-test results for two independent groups

Variable	Gender	Mean	Levine test *F*	Levine test Sig	*t*	Degrees of freedom	The significance level
Social support	Male	3.2226	.000	.991	1.044	327	297
	Female	3.1287					

Author's own work

A comparison of means and their order shows that social support does not increase with age. Another point is that the score for 60 years and above is below average.

Gender (Table 5)

To analyze the status of social support by gender; T-test was used for two independent groups. It was found that the significance level of the Levens test is more than 0.05. Therefore, in interpreting the results, the first-order results are used, which accept the assumption of the equality of variances for the two groups. Since the value of t was not significant at the level of 0.05 [p-value ≤ 0.05, $t = 1.044$], it can be said that there is no significant difference between the social support of male and female inhabitants in the region.

Marital Status

To analyze the status of social support based on marital status, the *t*-test was used between two independent groups, and it was found (Table 6) that the significance level of the Levin test is more than 0.05, so the first-order results that accept the assumption of the equality of variances for the two groups are used in interpreting the results. Considering that the value of *t* was not significant at the level of 0.05 [p-value ≥ 0.05, $t = 1.622$], therefore, it can be said that there is no significant difference between the social support of single and married inhabitants in the region. The comparison of the observed means showed that this value is higher than the average for both groups.

Number of Children

A one-way analysis of variance test was used in order to analyze the status of social support based on the number of children (Table 7). Based on these results, the value of *F* was significant at the level of error significance of less than 5% [p-value ≤ 0.05, $F = 2.716$]. Considering that the value of *F* was significant at the error level, of less than 0.05, it can be said that inhabitants with different numbers of children are significantly different in terms of social support (Table 8).

This table compares pairs of the mean score of social support among inhabitants. According to the results of the significant column, it was found that the mean score of social support among inhabitants with different numbers of children is significantly different, at the error level of less than 0.05 (Table 9).

Comparing the means and their order shows that the social support of the groups, except for those with two children, is higher than the average.

Table 6 T-test results for two independent groups

Variable	Gender	Mean	Levine test		*t*	Degrees of freedom	The significance level
			F	Sig			
Social support	Single	3.2830	.354	.552	1.622	305	.106
	Married	3.1422					

Author's own work

Table 7 Results of one-way analysis of variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Social support	Intergroup variance	11,702	8	1463	2716	.007
	Intragroup variance	155,088	288	.538		
	Total variance	166,790	296			

Author's own work

Table 8 Paired comparisons

					Confidence interval 95%	
Child (*I*)	Child (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Lower bound	Upper bound
0	1	0.12809	0.14258	0.993	−0.3176	0.5737
	2	0.50102	0.16912	0.079	−0.0276	1.0296
	3	−0.34179	0.1446	0.308	−0.7937	0.1102
	4	0.15049	0.21871	0.999	−0.5331	0.8341
	5	−0.21062	0.30448	0.999	−1.1623	0.7411
	6	−0.12224	0.22784	1	−0.8344	0.5899
	7	−0.91896	0.52174	0.708	−2.5497	0.7118
1	8	−0.12729	0.52174	1	−1.758	1.5034
	0	−0.12809	0.14258	0.993	−0.5737	0.3176
	2	0.37293	0.2074	0.683	−0.2753	1.0212
	3	−0.46987	0.18794	0.236	−1.0573	0.1175
	4	0.0224	0.24949	1	−0.7574	0.8022
	5	−0.33871	0.32729	0.982	−1.3617	0.6843
	6	−0.25033	0.25754	0.988	−1.0553	0.5546
	7	−1.04704	0.53537	0.576	−2.7204	0.6263
	8	−0.25538	0.53537	1	−1.9287	1418
2	0	−0.50102	0.16912	0.079	−1.0296	0.0276
	1	−0.37293	0.2074	0.683	−1.0212	0.2753
	3	−0.84280*	0.20879	0.002	−1.4954	−0.1902
	4	−0.35053	0.26555	0.925	−1.1805	0.4795
	5	−0.71164	0.3397	0.479	−1.7734	0.3501
	6	−0.62326	0.27313	0.357	−1.4769	0.2304
	7	−1.41997	0.54304	0.185	−3.1173	0.2773
	8	−0.62831	0.54304	0.965	−2.3256	1069
3	0	0.34179	0.1446	0.308	−0.1102	0.7937
	1	0.46987	0.18794	0.236	−0.1175	1.0573
	2	.84280*	0.20879	0.002	0.1902	1.4954
	4	0.49228	0.25065	0.57	−0.2911	1.2757
	5	0.13116	0.32818	1	−0.8946	1.1569
	6	0.21955	0.25866	0.995	−0.5889	1028
	7	−0.57717	0.53591	0.977	−2.2522	1.0978
	8	0.2145	0.53591	1	−1.4605	1.8895
4	0	−0.15049	0.21871	0.999	−0.8341	0.5331
	1	−0.0224	0.24949	1	−0.8022	0.7574
	2	0.35053	0.26555	0.925	−0.4795	1.1805
	3	−0.49228	0.25065	0.57	−1.2757	0.2911
	5	−0.36111	0.36691	0.987	−1.5079	0.7857
	6	−0.27273	0.30632	0.993	−1.2301	0.6847
	7	−1.06944	0.56047	0.609	−2.8212	0.6823
	8	−0.27778	0.56047	1	−2.0296	1474

(continued)

Table 8 (continued)

Child (*I*)	Child (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
5	1	0.21062	0.30448	0.999	−0.7411	1.1623
	2	0.33871	0.32729	0.982	−0.6843	1.3617
	3	0.71164	0.3397	0.479	−0.3501	1.7734
	4	−0.13116	0.32818	1	−1.1569	0.8946
	5	0.36111	0.36691	0.987	−0.7857	1.5079
	6	0.08838	0.37243	1	−1.0757	1.2524
	7	−0.70833	0.59917	0.96	−2.5811	1.1644
	8	0.08333	0.59917	1	−1.7894	1.9561
6	0	0.12224	0.22784	1	−0.5899	0.8344
	2	0.25033	0.25754	0.988	−0.5546	1.0553
	3	0.62326	0.27313	0.357	−0.2304	1.4769
	4	−0.21955	0.25866	0.995	−1.028	0.5889
	5	0.27273	0.30632	0.993	−0.6847	1.2301
	6	−0.08838	0.37243	1	−1.2524	1.0757
	7	−0.79672	0.5641	0.892	−2.5598	0.9664
	8	−0.00505	0.5641	1	−1.7682	1.7581
7	0	0.91896	0.52174	0.708	−0.7118	2.5497
	1	1.04704	0.53537	0.576	−0.6263	2.7204
	3	1.41997	0.54304	0.185	−0.2773	3.1173
	4	0.57717	0.53591	0.977	−1.0978	2.2522
	5	1.06944	0.56047	0.609	−0.6823	2.8212
	6	0.70833	0.59917	0.96	−1.1644	2.5811
	7	0.79672	0.5641	0.892	−0.9664	2.5598
	8	0.79167	0.73383	0.977	−1.5019	3.0853
8	0	0.12729	0.52174	1	−1.5034	1758
	1	0.25538	0.53537	1	−1.418	1.9287
	2	0.62831	0.54304	0.965	−1.069	2.3256
	3	−0.2145	0.53591	1	−1.8895	1.4605
	4	0.27778	0.56047	1	−1.474	2.0296
	5	−0.08333	0.59917	1	−1.9561	1.7894
	6	0.00505	0.5641	1	−1.7581	1.7682
	7	−0.79167	0.73383	0.977	−3.0853	1.5019

Author's own work

Level of Education

A one-way analysis of variance test was used in order to analyze the status of social support based on the level of education (Table 10). Based on these results, the value of F was not significant at the level of error less than 5% [p-value ≥ 0.05, $F = 1.876$]. Therefore, it can be said that inhabitants with different levels of education are not significantly different in terms of social support (Table 11).

Table 9 Tukey post hoc test results

Subset for alpha = 0.05			
Children	*N*	1	2
2	21	2.7328	
4	12	3.0833	3.0833
1	31	3.1057	3.1057
0	182	3.2338	3.2338
6	11	3.3561	3.3561
8	2	3.3611	3.3611
5	6	3.4444	3.4444
3	30	3.5756	3.5756
7	2		4.1528
Sig.		0.533	0.209

Author's own work

Table 10 Results of the one-way analysis of variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Social support	Intergroup variance	4292	4	1073	1876	.114
	Intragroup variance	180,189	315	.572		
	Total variance	184,482	319			

Author's own work

Table 11 The mean scores of the groups

Subset for alpha = 0.05			
Education	*N*	1	2
PhD	5	2.4667	
High school	115	3.1447	3.1447
Diploma and associate	103	3.1502	3.1502
Master	12		3.2731
Bachelor	85		3309
sig		0.082	0.973

Author's own work

A comparison of means and their order shows that social support does not increase significantly with an increasing level of education. Another point is that the score for all groups is above average.

Job

A one-way analysis of variance was used in order to analyze the status of social support based on the job. These results are shown in Table 12. Based on these results, the value of *F* was significant at the level of error significance of less than

Table 12 Results of the one-way analysis of the variance test

Variable		Total squares	df	Mean squares	F	Sig
Social support	Intergroup variance	28,437	4	7.109	13,516	0.000
	Intragroup variance	155,699	296	.526		
	Total variance	184,136	300			

Author's own work

5% [p-value ≤0.05, $F = 13.516$]. Considering that the value of F was significant at the error level of less than 0.05, it can be said that inhabitants with different jobs are significantly different in terms of social support (Table 13).

This table compares pairs of the mean score of social support among inhabitants. According to the results of the significant column, it was found that the mean score of social support between inhabitants with different jobs is significantly different at the error level of less than 0.05 (Table 14).

Comparing the means and their order shows that the social support of people with jobs and the unemployed is lower than for other people.

Income

A one-way analysis of variance test was used in order to analyze the status of social support based on income. Based on the results (Table 15), the value of F was significant at the level of error significance of less than 5% [p-value ≤0.05, $F = 18.740$]. Therefore, it can be said that inhabitants with different incomes are significantly different in terms of social support (Table 16).

This table compares pairs of the mean score of social support among inhabitants. According to the results of the significant column, it was found that the mean score of social support among inhabitants with different incomes is significantly different at the error level of less than 0.05 (Table 17).

A comparison of means and their order shows that social support is higher than the average for the four groups of income groups.

Resilience Status Analysis

In order to investigate the resilience status of the inhabitants of marginalized areas in the COVID-19 outbreak crisis, first the resilience status of the sample was examined and then the relationship between their resilience and contextual variables was analyzed (Table 18).

One-sample t-test was used to analyze resilience status. The findings showed that the experimental mean of resilience was higher than the expected mean (3) and the value of t was significant at the level of 0.01 (p-value ≤0.01). Therefore, it is

Table 13 Paired comparisons

Job (*I*)	Job (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
Free job	Public sector employee	−.33621*	0.10675	0.015	−0.6292	−0.0432
	Private sector employee	0.00294	0.12119	1	−0.3297	0.3356
	Worker	0.48795	0.19308	0.087	−0.042	1.0179
	Unemployed	.61213*	0.14768	0	0.2068	1.0175
Public sector employee	Free job	.33621*	0.10675	0.015	0.0432	0.6292
	Private sector employee	.33915*	0.11579	0.03	0.0213	0.657
	Worker	.82416*	0.18974	0	0.3034	1.3449
	Unemployed	.94834*	0.14328	0	0.5551	1.3416
Private sector employee	Free job	−0.00294	0.12119	1	−0.3356	0.3297
	Public sector employee	−.33915*	0.11579	0.03	−0.657	−0.0213
	Worker	0.48501	0.19822	0.106	−0.059	1.0291
	Unemployed	.60919*	0.15434	0.001	0.1856	1.0328
Worker	Free job	−0.48795	0.19308	0.087	−1.0179	0.042
	Public sector employee	−.82416*	0.18974	0	−1.3449	−0.3034
	Private sector employee	−0.48501	0.19822	0.106	−1.0291	0.059
	Unemployed	0.12418	0.21544	0.978	−0.4671	0.7155
Unemployed	Free job	−.61213*	0.14768	0	−1.0175	−0.2068
	Public sector employee	−.94834*	0.14328	0	−1.3416	−0.5551
	Private sector employee	−.60919*	0.15434	0.001	−1.0328	−0.1856
	Worker	−0.12418	0.21544	0.978	−0.7155	0.4671

Author's own work

Table 14 Tukey post hoc test results

Subset for alpha = 0.05			
Education	*N*	1	2
Unemployed	31	1	
Worker	65	2.5703	
Private sector employee	63	2.6944	3.1795
Free job	121		3.1824
Public sector employee	21		3.5186
Sig		0.941	0.229

Author's own work

Table 15 Results of the one-way analysis of the variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Social support	Intergroup variance	29.123	3	9708	18,740	.000
	Intragroup variance	149,706	289	.518		
	Total variance	178,830	292			

Author's own work

Table 16 Paired comparisons

Income (*I*)	Income (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
Less than five hundred thousand tomans	Between five hundred thousand tomans to one and a half million tomans	−0.02244	0.11884	0.998	−0.3295	0.2846
	One and a half million to three million tomans	.71753*	0.11325	0	0.4249	1.0102
	Above three million tomans	.47361*	0.1151	0	0.1762	0.771
Between five hundred thousand tomans to one and a half million tomans	Less than five hundred thousand tomans	0.02244	0.11884	0.998	−0.2846	0.3295
	One and a half million to three million tomans	.73996*	0.12525	0	0.4163	1.0636
	Above three million tomans	.49605*	0.12692	0.001	0.1681	0.824
One and a half million to three million tomans	Less than five hundred thousand tomans	−.71753*	0.11325	0	−1.0102	−0.4249
	Between five hundred thousand tomans to one and a half million tomans	−.73996*	0.12525	0	−1.0636	−0.4163
	Above three million tomans	−0.24392	0.12171	0.189	−0.5584	0.0706
Above three million tomans	Less than five hundred thousand tomans	−.47361*	0.1151	0	−0.771	−0.1762
	Between five hundred thousand tomans to one and a half million tomans	−.49605*	0.12692	0.001	−0.824	−0.1681
	One and a half million to three million tomans	0.24392	0.12171	0.189	−0.0706	0.5584

Author's own work

Table 17 Tukey post hoc test results

Subset for alpha = 0.05			
Income	*N*	1	2
One and a half million to three million tomans	72	2.7785	
Above three million tomans	68	3.0225	
Less than five hundred thousand tomans	92		3.4961
Between five hundred thousand tomans to one and a half million tomans	61		3.5185
Sig		0.18	0.998

Author's own work

Table 18 One-sample *t*-test results

Paired differences								
				Confidence interval				
Index	Experimental mean	Theoretical mean	Mean difference	Lower bound	Upper bound	*t*	Degrees of freedom	Sig
Resilience	3. 7320	3	.73204	.6730	.7911	24.391	333	.000

Author's own work

Table 19 Results of the one-way analysis of the variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Resilience	Intergroup variance	2744	3	.915	3.103	.027
	Intragroup variance	96,978	329	.295		
	Total variance	99,722	332			

Author's own work

concluded that the observed mean is significantly different from the theoretical mean. Since the experimental mean was higher than the theoretical mean, it was concluded that the resilience of the inhabitants of the marginal areas is higher than average.

Analysis of Resilience Status Based on Contextual Variables

Age

A one-way analysis of variance test was used in order to analyze the status of resilience by age (Table 19). Based on these results, the value of F was significant at the level of error significance of less than 5% [p-value ≤ 0.05, $F = 3.103$]. Therefore, it can be said that inhabitants of different ages are significantly different in terms of resilience. As can be seen in the table above, the assumption of homogeneity of variances is also observed (p-value ≥ 0.05). Then, the Tukey post hoc test was used to evaluate the differences between the groups (Table 20).

Table 20 Paired comparisons

Age (*I*)	Age (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
Under 30 years	30–45 years	−0.13465	0.06426	0.157	−0.3006	0.0313
	45–60 years	−0.1516	0.10198	0.447	−0.4149	0.1117
	60 years and older	−0.3979	0.16292	0.071	−0.8186	0.0228
30–45 years	Under 30 years	0.13465	0.06426	0.157	−0.0313	0.3006
	45–60 years	−0.01695	0.10283	0.998	−0.2825	0.2486
	60 years and older	−0.26325	0.16345	0.374	−0.6853	0.1588
45–60 years	Under 30 years	0.1516	0.10198	0.447	−0.1117	0.4149
	30–45 years	0.01695	0.10283	0.998	−0.2486	0.2825
	60 years and older	−0.2463	0.18162	0.528	−0.7153	0.2227
60 years and older	Under 30 years	0.3979	0.16292	0.071	−0.0228	0.8186
	30–45 years	0.26325	0.16345	0.374	−0.1588	0.6853

Author's own work

Table 21 Tukey post hoc test results

Subset for alpha = 0.05			
Age	*N*	1	2
Under 30 years	149	3.6484	
30–45 years	137	3783	3783
45–60 years	35	3.8	3.8
60 years and older	12		4.0463
Sig		0.682	0.216

Author's own work

This table compares pairs of the mean resilience score between inhabitants. According to the results of the significant column, it was found that the mean resilience score among inhabitants of different ages is significantly different at the error level of less than 0.05 (Table 21).

A comparison of means and their order shows that resilience increases with age. Another point is that the score is above average for all age groups.

Gender (Table 22)

T-test was used for two independent groups to analyze the status of resilience by gender. Based on the results of the table, it was found that the significance level of the Levin test is more than 0.05, so in interpreting the results, the first-order results

Table 22 T-test results for two independent groups

Variable	Gender	Mean	Levine test		T	Degrees of freedom	The significance level
			F	Sig			
Social support	Male	3.6573	.092	.762	−3.750	327	.000
	Female	3.8980					

Author's own work

Table 23 Test results for two independent groups

Variable	Gender	Mean	Levine test		*t*	Degrees of freedom	The significance level
			F	Sig			
Resilience	Single	3.6780	.008	.928	−1.962	305	.051
	Married	3.8013					

Author's own work

are used, which assumes equality of variances for the two groups. Considering that the value of t was significant at the level of 0.05 [p-value ≤ 0.05, $t = -3.750$], it can be said that there is a significant difference between the resilience of male and female inhabitants in the region. A comparison of the observed means showed that this value is higher for women than men.

Marital Status (Table 23)

T-test was used for two independent groups to analyze the status of resilience based on marriage. Based on the results of the table, it was found that the significance level of the Levin test is more than 0.05, so in interpreting the results, the first-order results are used, which assumes the equality of variances for the two groups. Considering that the value of t was significant at the level of 0.05 [p-value ≤ 0.05, $t = -1.962$], it can be said that there is a significant difference between the resilience of single and married inhabitants in the region. The comparison of the observed mean showed that this value is higher for the married group than for the single group.

Number of Children (Table 24)

The one-way analysis of variance was used in order to analyze the status of resilience based on the number of children. These results are shown in the table. Based on these results, the value of F was significant at the level of error significance of less than 1% [p-value ≤ 0.01, $F = 15.036$]. Therefore, it can be said that inhabitants with different numbers of children are significantly different in terms of resilience (Table 25).

This table compares pairs of the mean resilience score between inhabitants. According to the results of the significant column, it was found that the mean resilience score between inhabitants with a different number of children is significantly different at the error level of less than 0.05 (Table 26).

A comparison of means and their order shows that resilience decreases significantly with the increasing number of children.

Level of Education

A one-way analysis of variance test was used in order to analyze the status of resilience based on education level (Table 27). Based on these results, the value of F was significant at the level of error significance of less than 5% [p-value ≤ 0.05, $F = 22.416$]. Therefore, it can be said that inhabitants with different levels of education are significantly different in terms of resilience (Table 28).

This table compares pairs of the mean resilience score between inhabitants. According to the results of the significant column, it was found that the mean resilience score between inhabitants with different levels of education is significantly different at the error level of less than 0.05 (Table 29).

A comparison of means and their order shows that resilience increases significantly with an increasing level of education.

Job

A one-way analysis of variance test was used in order to analyze the status of resilience by job (Table 30). Based on these results, the value of F was significant at the level of error significance of less than 5% [p-value ≥ 0.05, $F = 2.665$]. Therefore, it can be said that inhabitants with different jobs are significantly different in terms of resilience (Table 31).

This table compares pairs of the mean resilience score between inhabitants. According to the results of the significant column, it was found that the mean

Table 24 The one-way analysis of the variance test results

Variable		Total squares	df	Mean squares	F	Sig
Resilience	Intergroup variance	39,158	8	4.895	15.036	.000
	Intragroup variance	21,486	66	.326		
	Total variance	60,644	74			

Author's own work

Table 25 Paired comparisons

Child (*I*)	Child (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
0	1	.11697	.27586	1000	−1.0089	1.2428
	2	.88215	.25645	.182	−.1645	1.9288
	3	1.22475*	.28957	.035	.0429	2.4066
	4	1.28788*	.24329	.002	.2949	2.2808
	5	1.55114*	.26512	.000	.4691	2.6332
	6	1.64935*	.27586	.000	.5235	2.7752
	7	1.72078*	.27586	.000	.5949	2.8467
	8	2.25253*	.25645	.000	1.2059	3.2992
1	0	−.11697	.27586	1000	−1.2428	1.0089
	2	.76519	.28754	.534	−.4083	1.9387
	3	1.10778	.31743	.166	−.1878	2.4033
	4	1.17091*	.27586	.034	.0450	2.2968
	5	1.43417*	.29529	.007	.2290	2.6393
	6	1.53238*	.30498	.004	.2877	2.7771
	7	1.60381*	.30498	.002	.3591	2.8485
	8	2.13556*	.28754	.000	.9620	3.3091
2	0	−.88215	.25645	.182	−1.9288	.1645
	1	−.76519	.28754	.534	−1.9387	.4083
	3	.34259	.30071	.995	−.8847	1.5699
	4	.40572	.25645	.959	−.6409	1.4524
	5	.66898	.27724	.666	−.4625	1.8005
	6	.76720	.28754	.530	−.4063	1.9407
	7	.83862	.28754	.399	−.3349	2.0121
	8	1.37037*	.26897	.004	.2726	2.4681
3	0	−1.22475*	.28957	.035	−2.4066	−.0429
	1	−1.10778	.31743	.166	−2.4033	.1878
	2	−.34259	.30071	.995	−1.5699	.8847
	4	.06313	.28957	1000	−1.1187	1.2450
	5	.32639	.30814	.997	−.9312	1.5840
	6	.42460	.31743	.985	−.8709	1.7201
	7	.49603	.31743	.961	−.7995	1.7916
	8	1.02778	.30071	.189	−.1995	2.2551
4	0	−1.28788*	.24329	.002	−2.2808	−.2949
	1	−1.17091*	.27586	.034	−2.2968	−.0450
	2	−.40572	.25645	.959	−1.4524	.6409
	3	−.06313	.28957	1000	−1.2450	1.1187
	5	.26326	.26512	.998	−.8188	1.3453
	6	.36147	.27586	.987	−.7644	1.4874
	7	.43290	.27586	.961	−.6930	1.5588
	8	.96465	.25645	.099	−.0820	2.0113

(continued)

Table 25 (continued)

Child (*I*)	Child (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
5	0	−1.55114*	.26512	.000	−2.6332	−.4691
	1	−1.43417*	.29529	.007	−2.6393	−.2290
	2	−.66898	.27724	.666	−1.8005	.4625
	3	−.32639	.30814	.997	−1.5840	.9312
	4	−.26326	.26512	.998	−1.3453	.8188
	6	.09821	.29529	1000	−1.1070	1.3034
	7	.16964	.29529	1000	−1.0355	1.3748
	8	.70139	.27724	.605	−.4301	1.8329
6	0	−1.64935*	.27586	.000	−2.7752	−.5235
	1	−1.53238*	.30498	.004	−2.7771	−.2877
	2	−.76720	.28754	.530	−1.9407	.4063
	3	−.42460	.31743	.985	−1.7201	.8709
	4	−.36147	.27586	.987	−1.4874	.7644
	5	−.09821	.29529	1000	−1.3034	1.1070
	7	.07143	.30498	1000	−1.1733	1.3161
	8	.60317	.28754	.814	−.5703	1.7767
7	0	−1.72078*	.27586	.000	−2.8467	−.5949
	1	−1.60381*	.30498	.002	−2.8485	−.3591
	2	−.83862	.28754	.399	−2.0121	.3349
	3	−.49603	.31743	.961	−1.7916	.7995
	4	−.43290	.27586	.961	−1.5588	.6930
	5	−.16964	.29529	1000	−1.3748	1.0355
	6	−.07143	.30498	1000	−1.3161	1.1733
	8	.53175	.28754	.900	−.6418	1.7053
	0	−2.25253*	.25645	.000	−3.2992	−1.2059
	1	−2.13556*	.28754	.000	−3.3091	−.9620
	2	−1.37037*	.26897	.004	−2.4681	−.2726
	3	−1.02778	.30071	.189	−2.2551	.1995
	4	−.96465	.25645	.099	−2.0113	.0820
	5	−.70139	.27724	.605	−1.8329	.4301
	6	−.60317	.28754	.814	−1.7767	.5703
	7	−.53175	.28754	.900	−1.7053	.6418

Author's own work

resilience score among inhabitants with different jobs is significantly different at the error level of less than 0.05 (Table 32).

Comparing the means and their order shows that the resilience of people with free jobs and workers is lower than other people. Another point is that the score for all groups is above average.

Table 26 Tukey post hoc test results

Subset for alpha = 0.05					
Age	*N*	1	2	3	4
8	2	2.2778			
7	2	2.8095	2.8095		
6	11	2.8810	2.8810		
5	6	2.9792	2.9792		
4	12	3.2424	3.2424		
3	30	3.3056	3.3056	3.3056	
2	21		3.6481	3.6481	3.6481
1	31			4.4133	4.4133
0	182				4.5303

Author's own work

Table 27 One-way analysis of variance test results

Variable		Total squares	df	Mean squares	*F*	Sig
Resilience	Intergroup variance	15,658	4	3.914	22.416	.000
	Intragroup variance	6287	36	.175		
	Total variance	21,944	40			

Author's own work

Income

A one-way analysis of variance was used in order to analyze the status of income-based resilience. These results are shown in Table 33. Based on these results, the value of F was significant at the level of error significance of less than 5% [p-value ≤ 0.05, $F = 6.744$]. Considering that the value of F was significant at the error level of less than 0.05, it can be said that inhabitants with different incomes are significantly different in terms of resilience (Table 34).

This table compares pairs of mean resilience scores between inhabitants. According to the results of the significant column, it was found that the mean resilience score among inhabitants with different incomes is significantly different at the error level of less than 0.05 (Table 35).

A comparison of means and their order shows that people's resilience is lower for low-income groups and increases with income.

The Relationship Between the Dimensions of Social Support and the Resilience of Marginalized Inhabitants in the COVID-19 Crisis

Linear regression test was used to investigate the relationship between the dimensions of social support and resilience using the simultaneous method. The results of this test are as follows:

Table 28 Paired comparisons

Education (*I*)	Education (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
High school	Diploma and associate	−.07143	.21059	.998	−.7549	.6121
	Masters	−.90476*	.23249	.011	−1.6593	−.1502
	Master and above	−.98052*	.20204	.001	−1.6363	−.3248
	PhD	−1.67560*	.21628	.000	−2.3775	−.9736
Diploma and associate	High school	.07143	.21059	.998	−.6121	.7549
	Masters	−.83333*	.22024	.015	−1.5482	−.1185
	Master and above	−.90909*	.18782	.001	−1.5187	−.2995
	PhD	−1.60417*	.20306	.000	−2.2632	−.9451
Bachelor	High school	.90476*	.23249	.011	.1502	1.6593
	Diploma and associate	.83333*	.22024	.015	.1185	1.5482
	Master and above	−.07576	.21208	.998	−.7641	.6126
	PhD	−.77083*	.22568	.035	−1.5033	−.0383
Master and above	High school	.98052*	.20204	.001	.3248	1.6363
	Diploma and associate	.90909*	.18782	.001	.2995	1.5187
	Masters	.07576	.21208	.998	−.6126	.7641
	PhD	−.69508*	.19417	.024	−1.3253	−.0649
PhD	High school	1.67560*	.21628	.000	.9736	2.3775
	Diploma and associate	1.60417*	.20306	.000	.9451	2.2632
	Masters	.77083*	.22568	.035	.0383	1.5033
	Master and above	.69508*	.19417	.024	.0649	1.3253

Author’s own work

Table 29 Tukey post hoc test results

Subset for alpha = 0.05				
Education	*N*	1	2	3
High school	115	2.4286		
Diploma and associate	103	2.5000		
Bachelor	85		3.3333	
Master	12		3.4091	
PhD	5			4.1042

Author’s own work

Table 30 Results of one-way analysis of variance test

Variable		Total squares	df	Mean squares	*F*	Sig
Resilience	Intergroup variance	3257	4	.814	9.594	.000
	Intragroup variance	3310	39	.085		
	Total variance	6568	43			

Author's own work

Table 31 Paired comparisons

Job (*I*)	Job (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95% Lower bound	Upper bound
Unemployed	Worker	−.11905	.14682	.955	−.5937	.3556
	Free job	−.31349	.16209	.454	−.8374	.2105
	Private	−.57359*	.14086	.007	−1.0289	−.1183
	Governmental	−.70996*	.14086	.000	−1.1653	−.2546
Worker	Unemployed	.11905	.14682	.955	−.3556	.5937
	Free job	−.19444	.15355	.807	−.6908	.3019
	Private	−.45455*	.13095	.029	−.8778	−.0313
	Governmental	−.59091*	.13095	.002	−1.0142	−.1676
Free job	Unemployed	.31349	.16209	.454	−.2105	.8374
	Worker	.19444	.15355	.807	−.3019	.6908
	Private	−.26010	.14786	.549	−.7381	.2179
	Governmental	−.39646	.14786	.149	−.8744	.0815
Private	Unemployed	.57359*	.14086	.007	.1183	1.0289
	Worker	.45455*	.13095	.029	.0313	.8778
	Free job	.26010	.14786	.549	−.2179	.7381
	Governmental	−.13636	.12423	.875	−.5379	.2652
Governmental	Unemployed	.70996*	.14086	.000	.2546	1.1653
	Worker	.59091*	.13095	.002	.1676	1.0142
	Free job	.39646	.14786	.149	−.0815	.8744
	Private	.13636	.12423	.875	−.2652	.5379

Author's own work

Table 32 Tukey post hoc test results

Subset for alpha = 0.05				
Job	*N*	1	2	3
Unemployed	31	2.5476		
Worker	65	2.6667	2.6667	
Free	121	2.8611	2.8611	2.8611
Private	63		3.1212	3.1212
Governmental	21			3.2576

Author's own work

Table 33 One-way analysis of variance test results

Variable		Total squares	df	Mean squares	*F*	Sig
Resilience	Intergroup variance	2154	3	.718	6.744	.001
	Intragroup variance	3088	29	.106		
	Total variance	5242	32			

Author's own work

Table 34 Paired comparisons

Income (*I*)	Income (*J*)	Mean difference (*I-J*)	Std. error	Sig.	Confidence interval 95%	
					Lower bound	Upper bound
Less than five hundred thousand tomans	Between five hundred thousand tomans to one and a half million tomans	−.11905	.16445	.913	−.6069	.3688
	One and a half million to three million tomans	−.31349	.18155	.410	−.8521	.2251
	Above three million tomans	−.63420*	.15777	.005	−1.1023	−.1661
Between five hundred thousand tomans to one and a half million tomans	Less than five hundred thousand tomans	.11905	.16445	.913	−.3688	.6069
	One and a half million to three million tomans	−.19444	.17199	.736	−.7047	.3158
	Above three million tomans	−.51515*	.14667	.015	−.9503	−.0800
One and a half million to three million tomans	Less than five hundred thousand tomans	.31349	.18155	.410	−.2251	.8521
	Between five hundred thousand tomans to one and a half million tomans	.19444	.17199	.736	−.3158	.7047
	Above three million tomans	−.32071	.16561	.310	−.8121	.1706
Above three million tomans	Less than five hundred thousand tomans	.63420*	.15777	.005	.1661	1.1023
	Between five hundred thousand tomans to one and a half million tomans	.51515*	.14667	.015	.0800	.9503
	One and a half million to three million tomans	.32071	.16561	.310	−.1706	.8121

Author's own work

Table 35 Tukey post hoc test results

Subset for alpha = 0.05			
Income	*N*	1	2
Less than five hundred thousand tomans	92	2.5476	
Between five hundred thousand tomans to one and a half million tomans	61	2.6667	
One and a half million to three million tomans	72	2.8611	2.8611
Above three million tomans	68		3.1818

Author's own work

Table 36 Summary of regression pattern

Model	*R*	R^2	Adjusted *R*2	Standard error of estimation	Durbin-Watson
Value	.393	.155	.147	.50656	1.544

Author's own work

Table 37 Test of total squares and value of *F* (ANOVA)

Model	Total squares	Degrees of freedom	Mean squares	*F*	Sig
Regression	15,501	3	5.167	20.137	.000
Residual	84,679	330	.257		
Total amount	100,181	333			

Author's own work

In Table 36, which summarizes the statistics related to the model fit, the value of multiple correlation coefficient *R* is equal to 0.393, which indicates the correlation between the dimensions of social support and resilience. *R*2 shows the extent to which variance is explained by the dimensions of social support. One of the problems of *R*2 is that it overestimates the success rate of the model and takes less into account the number of independent variables and sample size, so some researchers prefer to use another index called adjusted *R*2.

In the table above, the adjusted *R*2 value is 0.147, which indicates that the dimensions of social support can explain about 15% of resilience changes. Camera-Watson statistics results confirmed the independence of observations (independence of residual values or errors) from each other. Camera-Watson statistics range from 0 to 4. If there is no consecutive correlation between the residuals, the value of this statistic should be close to 2. If it is close to zero, it indicates a positive correlation, and if it is close to 4, it indicates a negative correlation. In general, if this statistic is between 1.5 and 2.5, there is no need to worry. This statistic in the table is 1.544 (Table 37).

In the table above, a value of *F* was reported at a significant error level of 0.01, which indicates that the dimensions of social support predict changes in resilience and the regression model fits well.

In Table 38, the Beta coefficient for information support was 0.347 and the *t* value for this variable was significant at the error level of 0.01, which means that by increasing a standard deviation in information support, resilience increases by 0.347 standard deviation. The Beta coefficient for emotional support was 0.173 and the *t*

Table 38 Standardized and non-standardized regression coefficients

Variable	Non-standard coefficients		Standard coefficients	t	Sig
	B	Std. error	Beta		
Constant value	2520	.160		15,772	.000
Information support	.305	.060	.347	5119	.000
Emotional support	.102	.044	.173	2342	.020
Material support	−.062	.048	.105	1291	.198

Author's own work

Table 39 Summary of regression pattern

Model	R	R^2	Adjusted $R2$	Standard error of estimation	Camera-Watson
Value	.313	.098	.095	.52178	1.538

Author's own work

Table 40 Test the total squares and the value of F (ANOVA)

Model	Total squares	Degrees of freedom	Mean squares	F	Sig
Regression	9792	1	9792	35.967	.000
Residual	90,389	332	.272		
Total amount	100,181	333			

Author's own work

value for this variable was significant at the error level of 0.05, which means that by increasing a standard deviation in emotional support, resilience increases by 0.173 standard deviation. The Beta coefficient for material support was 0.105 and the t value was not significant for this variable at the error level of 0.05.

The Relationship Between Social Support and Resilience

In Table 39, which summarizes the statistics related to the model fit, the value of the multiple correlation coefficient (R) is equal to 0.313, which indicates the correlation between the dimensions of social support and resilience. In the table above, the adjusted $R2$ value is 0.095, which indicates that social support can explain about 10% of resilience changes. Camera-Watson results confirmed the independence of observations (independence of residual values or errors) from each other. This statistic in the table is 1.538 (Table 40).

In the table above, the value of F was reported at a significant error level of 0.01, which indicates that social support predicts changes in resilience and the regression model fits well (Table 41).

In the table above, the Beta coefficient for social support was 0.313 and the t value for this variable was significant at the error level of 0.01, which means that by

Table 41 Standardized and non-standardized regression coefficients

Variable	Non-standard coefficients		Standard coefficients		
	B	Std. error	Beta	*t*	Sig
Constant value	3010	.124		24,307	.000
Social support	.226	.038	.313	5997	.000

Author's own work

increasing a standard deviation in social support, resilience increases by 0.313 standard deviation.

Recommendations

- Improving the living conditions of the inhabitants of the marginalized areas with cash and non-cash aids so that the maximum number of people will benefit from the relevant organizations, nongovernmental organizations, and charities
- Facilitate access to financial resources of banks (loans) and financial institutions
- Provide conditions for returning to work for those who have lost their jobs in coronavirus conditions or create alternative jobs
- Preparation and distribution of free health kits including masks, disinfectants, and detergents
- Facilitate access to health education and health base for prevention and treatment, access to these specialists can increase their information support and social health
- Preparation of brochures containing useful content, and continuous and constant information using the facilities that everyone has access to, such as mass media, visit these areas, and speaker announcements
- Improvement of the sewage system
- Construction of prefabricated rooms for people with coronavirus for temporary accommodation
- Periodic visits to these areas by the relevant authorities, preparing a report on the current situation and taking action to resolve problems
- Assess the situation of students in these areas, receiving reports from education organizations, schools, and parents on how to transfer curriculum during the corona period and the situation of families in providing the Internet, smartphones, and other necessary facilities
- Assess the situation of students in these areas and examine their problems in receiving virtual education and the support of students who were not supported by their universities during the outbreak of the COVID-19 pandemic
- Case assessment and support for those most affected by the corona period
- Activation of facilitation offices in order to carry out measures outside the assigned tasks due to the COVID-19 pandemic crisis

Finally, it is suggested that research on social support and resilience be conducted in different cities and on the marginalized areas and inhabitants of informal settlements.

Discussion and Conclusion

The COVID-19 pandemic's extent and its high mortality rate have caused different sections of society to behave differently in the face of this crisis, that is, according to the class requirements and socioeconomic status in which they find themselves. One of the important issues about the coronavirus is the different socioeconomic status of citizens in the face of this uninvited and mysterious virus. Therefore, the economic and social support of individuals is very important and effective during both the confrontation and infection of this virus. According to the results of this study, it was found that social support has a direct and forcible effect on the resilience of inhabitants of marginalized areas. In fact, social support in the two dimensions of emotional support and information support has been an effective factor in promoting the ability and tolerance of individuals in the face of a pandemic, but in terms of instrumental support, little effect has been observed on people's resilience. Perhaps the situation during the pandemic effected coronavirus and the material and instrumental aids provided did not have much effect on the endurance of the disappointed and frustrated people.

The findings also showed that among the dimensions of social support, emotional support and information support were above average and material support was average. Thus, it can be assumed that the material support provided was not sufficient to increase individual resilience. Therefore, it is necessary to perform some interventions to improve the situation, in general, the measures that should be taken to increase the level of social support in its various dimensions, which will be kind of strengthening and complementary to each other and will directly or indirectly lead to increasing the resilience of the inhabitants of the marginalized areas. Studies have shown that most people in the sample have free jobs, and no doubt these people have jobs such as agency drivers and vendors, whose income has been affected during the coronavirus and their tables have become emptier. The consequences of the coronavirus have been poverty, hunger, difficult living conditions, and unemployment for these people. The low income of these people, who are mainly under five hundred thousand tomans, and the type of rental ownership of the inhabitants of these areas show the difficult living conditions of these people. Austrian et al. (2020) in their study also mentioned the slum dwellers' concern about losing their jobs and income as one of the most important concerns in the current crisis.

Marginalized inhabitants have faced deprivation, inequality, injustice, and weakness of the urban management system, as well as health and even cultural deficiencies. These people have always been discriminated against by others. The spread of coronavirus and its economic and social consequences have strengthened and intensified this trend. Experiences from past epidemic diseases show that inhabitants of these areas are more vulnerable in critical situations for numerous reasons such as higher population density in poor areas; employment in professions and jobs that create more interaction and contact with the general public, such as peddling and driving and using more public services such as government hospitals, buses, and subways; less attention to the risks of epidemic diseases due to focus on living and vital needs; delay in going to the doctor for treatment due to possible expenses; inability to rest and stay at home due to the type of job and risk of unemployment in case of long absence; lack of access to accurate and reliable information about epidemic diseases due to lack of access to social networks; lack of smartphones or lack of time and skills to surf in these networks; and weaker immune system due to the type of diet and stressful lifestyle (Deghaghele, 2020). Coronavirus also infects the poor and marginalized people more than anyone else.

The psychological problems caused by the current crisis, especially in poor areas, are so high that studies conducted on these people in different countries have also examined psychological issues. In the United States, Farkas and Romaniuk (2020) examined the importance of social workers providing services to vulnerable groups during the COVID-19 pandemic. Neto et al. (2020) stated that a large number of homeless people constantly experience psychological pain and distress, which is exacerbated by this pandemic. Kalateh Sadati et al. (2020) cited social anxiety around the world as one of the most important consequences of the outbreak of coronavirus. Therefore, it is necessary to improve flexibility at the psychological, social, and individual levels, and vulnerable groups should be supported including the low-income people, the elderly, and the disabled, who suffer from disproportionate damage in epidemics and natural disasters. Anxiety due to coronavirus and social distancing affect mental health, and supportive interventions are necessary during coronavirus disease epidemics (Alizadeh Fard & Saffarinia, 2020). Therefore, further evaluation and recognition by relevant organizations are necessary to review and address the situation of residents in these areas. Empathy with these groups leads to improved strength and endurance, improved family relationships, and ultimately improved life.

In addition to emotional support, material and instrumental support should also be on the agenda for these groups. The economic problems of these people have become much greater by imposing periodic restrictions on the peak of illness and the closure or semi-closure of some businesses since the outbreak of the coronavirus, which must be compensated with financial support. Wasdani and Prasad (2020) considered the effects of social distancing on the poorer areas of India to be more of a dream. Because if such a protocol is not accompanied by simultaneous economic support, it is almost impossible for vulnerable communities to distance themselves from society. Most slum dwellers receive a daily wage, which means they do not eat if they do not work. These people are taxi drivers, street vendors, garbage collectors, and domestic workers. Observing social distance for them means starving themselves and their families. Andrade (2020) stated that the economic problems caused by the coronavirus have reached the Brazilian slums before the virus itself. There is poverty, overcrowding, and dangerous socio-environmental conditions in the margins, and the lack of immunization of the margins has become a breeding ground for the transmission of the COVID-19 virus. In order to prevent a catastrophe, the economic and social support of low-income groups is necessary in parallel with social distance, and the poor population, who are more vulnerable in times of crisis, should be given more social support. In *Japan*, the allocation of subsidies to workers and the poor groups and in *Hong Kong*, the distribution of health items to the poor population are examples of social support in these countries in the form of material and instrumental support (Doshmangir et al., 2020).

Steps must be taken to increase people's awareness in the field of information support. A step will be taken to strengthen their sense of worth and the level of emotional support will be raised with the necessary training and raising the level of awareness. In this way, people can strengthen their level of ability to make decisions, solve problems, establish effective relationships, as well as the ability of self-awareness and empathy and cope with emotions and stress, and get through this crisis well. Providing appropriate and timely information is essential. In addition to information on self-care measures for prevention and treatment, appropriate information should be provided about facilities and cash and non-cash aids during COVID-19. Information must be provided via a variety of ways and methods due to the lack of access or poor access of the inhabitants of these areas to the mass media and the relevant channels and groups, and complementary measures should be on the agenda. In summary, strengthening the social support of marginalized inhabitants to increase their resilience seems to be an important strategy in controlling the pandemic and overcoming the crisis.

Research Limitations

In this study, data collection was performed by field method using a questionnaire. In COVID-19 conditions, the collection of questionnaires has been associated with many problems and the collection process has been delayed and closed with the peak of the disease.

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How the Pandemic Crisis May Affect Economic Systems: A Study on the Nexus Between COVID-19 and Entrepreneurial Activities

Shahla Jahangard, Ebrahim Bonyadi, Lida Sarreshtehdari, and Nezameddin Faghih

Abbreviations

ANOVA	Analysis of variance
EB	Established business ownership
GDP	Gross domestic product
GEM	Global Entrepreneurship Monitor
HDI	Human Development Index
IMF	International Monetary Fund
OECD	Organization for Economic Co-operation and Development
TEA	Total early-stage entrepreneurial activities
UNDP	United Nations Development Programme
WEF	World Economic Forum
WEO	World Economic Outlook
WHO	World Health Organization

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Introduction

The world has experienced several crises that have had significant impacts on small and medium-sized enterprises (SMEs), such as the Great Depression of the 1930s, the financial crisis of the early 2000s, and, more recently, the global crisis of COVID-19 (Tsilika et al., 2020). The COVID-19 pandemic experienced worldwide has affected economies and production chains, harming millions of businesses and entrepreneurs. In the face of the global pandemic of COVID-19, entrepreneurs must adapt to new realities. This pandemic is not only a major global health crisis but also affects millions or even billions of people worldwide. This has also caused an unprecedented recession in the world economy.

For example, France has registered the biggest decrease in GDP (around 5.8%). Meanwhile, in the United States, the number of unemployed or underemployed people has now exceeded 40 million. It exposes the fragility of our economies and their foundations. If the world has changed rapidly in a blink of an eye, the different scenarios and realities are not the same depending on where or when you run your business today.

If you are an entrepreneur operating in the United States or Europe, the business environment, facilities, policymakers, public health, and economic responses are very different. If your field of activity is in the online shopping industry, or for example food delivery, or even in video gaming clubs, where business is booming, you will have a completely different image from a business whose activities are mainly in the hotel industry, restaurant, or retail. The entrepreneurs who are running such businesses which are affected by COVID-19 should be prepared to lose 50–80% of their transactions as well as a large part of their market value.

A natural disaster is not a "natural" event. Human and natural systems are affected by natural hazards, such as earthquakes, storms, hurricanes, diseases, floods, and droughts. The most immediate consequences of natural disasters are fatalities and casualties (Hallegatte, 2014). Many human developments have taken place during the last century. An obvious example includes technological innovations in various fields of science, medicine, and industry, and consequently, the high growth of urban society on a global scale. However, despite all these achievements, humans are incapable and weak in the face of many environmental laws like floods, earthquakes, and more unknown diseases.

The widespread and gradual outbreak of the coronavirus (COVID-19) at the beginning of the year 2020 has made us think about future human crises and environmental laws more than ever before.

This deadly virus has spread to many countries of the world in a short period of time (less than a month) and has caused the closure of businesses and unprecedented economic stagnation in many countries worldwide.

Under these circumstances, according to the World Health Organization (WHO), governments and businesses can control this epidemic only by increasing resilience.

According to the World Bank (2013), between 1980 and 2011, disasters have caused 2,275,000 times, almost half of them in low-income countries (vs. 5% in high-income countries). In addition to human losses, natural disasters have economic consequences, which also affect welfare. From an economic point of view, natural disasters can be considered natural events that can disrupt the functioning of the economic system and may also have a significant negative impact on production and employment (Hallegatte, 2012; Subbiah et al., 2008).

Coronavirus, as the most recent disease, has led the world community to stop economic activities at least for a short time. According to the World Economic Forum's (WEF's) Global Risks Report (2020), more than 180 countries and territories have confirmed a case of coronavirus, and the number of cases worldwide has reached more than 870,000. Like a massive roaring wave, the crisis threatens not only to overwhelm health-care systems and economics but also has an effect on different aspects of human life, and it has had a significant impact on the global economy.

Although, it is too early to estimate the economic costs of the COVID-19 crisis with any precision, we can still make some preliminary estimates. In January and February of 2020, China reported a 13.5% drop in value-added (Fig. 1). If we suppose that this negative shock led to a 15% drop in GDP in the first quarter, then after a rapid recovery, the direct shock caused by the coronavirus to the Chinese economy would be a 3.75% drop in GDP at the end of this year (Vox Ukraine Report, 2020).

The spread of COVID-19 around the world has caused many worries, confusion, and challenges. It seems that the depth, breadth, and timing of this crisis are even greater than the economic recessions of 2008 and 1929 (Clingingsmith et al., 2020). According to statistics, this crisis will certainly negatively affect the natural growth of countries. Assuming the pandemic fades in the second half of 2022 and that policy actions taken around the world are effective in preventing widespread firm bankruptcies, extended job losses, and system-wide financial strains, we project global growth at the end of 2022 to rebound to 6.3%. This improvement in 2021 is only marginal as the level of economic activity is projected to be lower than the level the scientists had predicted for 2021 before the virus outbreak. Figure 2 shows that the cumulative loss to global GDP over 2020 and 2021 from the pandemic crisis could be around 9 trillion dollars.

COVID-19 has shown that humans are always facing major unpredictable shocks. According to the World Health Organization, governments and businesses can control such crises only by increasing resilience in economic activities (WEF, 2020). Therefore, governments must think of ways of increasing economic resistance in a country more than ever before.

After the Great Recession post-2008, the concept of resilience was used as a key term to assess global risks. Therefore, in the World Economic Forum's Global Risks Report 2013, resilience was defined as the capacity to "Bounce back faster after stress, tolerate more stress, and be less disturbed by a given amount of stress."

According to Williams and Vorley (2014), resilience is an emerging concept that has been applied to examine economic performance and response to external shocks such as financial crises and recessions. On the other hand, according to Salisu et al. (2020), resilience is often considered the ability of entrepreneurs to adapt to changes in opportunities, new markets, and circumstances. Although several years have

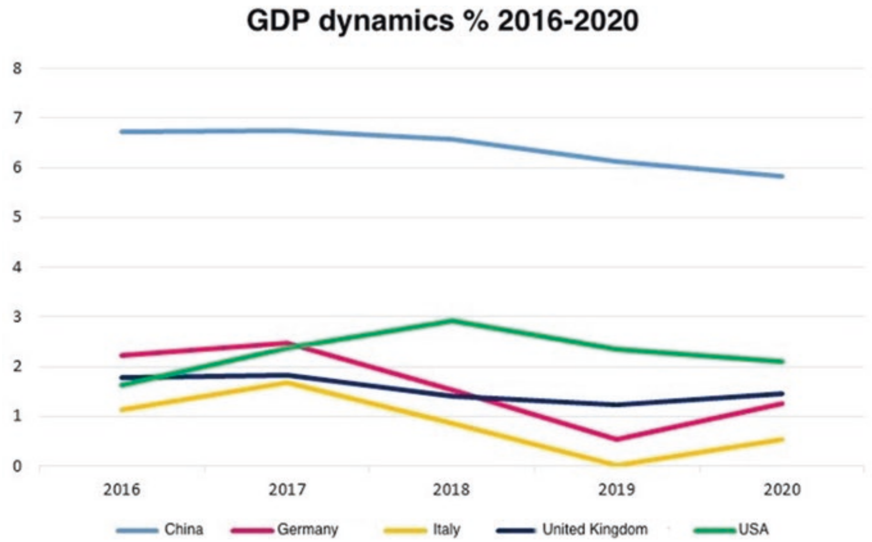

Fig. 1 GDP dynamics in 2016–2019 and growth forecast for early 2020. (Source: Authors' own figure (based on IMF (International Monetary Fund (2019)) and WEO (World Economic Outlook) (2019–2020) reports))

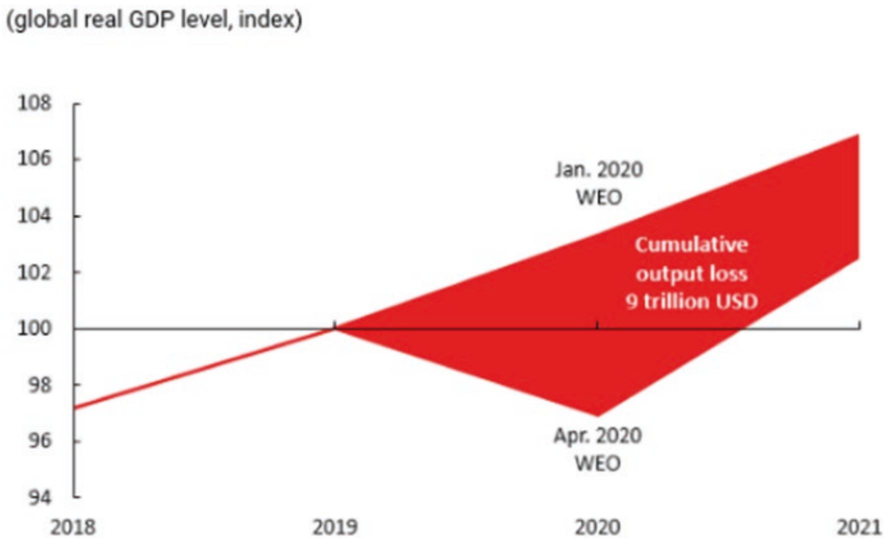

Fig. 2 Estimation of cumulative output loss. (Source: Authors' own figure (based on IMF and WEO staff calculations, 2020))

Table 1 A summary of the economic resilience index and the outbreak of COVID-19

Country	Resilience index		COVID-19 outbreak (May 10, 2020)		
	Rank	Score	Confirmed	Recovered	Death
Norway	1	100	8099	7114	219
Denmark	2	97.2	10,319	8093	526
Switzerland	3	97	30,231	26,400	1532
China	73	46.6	82,901	78,120	4633
Iran	120	18.4	6589	86,064	106 K

Source: Authors' own table (based on FM Global (2019) and WHO (2020) reports)

passed since the outbreak of COVID-19, there is no doubt that it is necessary to deal with crises like this pandemic to prevent the occurrence of global economic recessions (Sawalha, 2020). During the COVID-19 pandemic, the positive and effective resilience property of economic systems can help countries rebound from the toll the virus will take on health care, the economy, education, and employment (World Economic Forum's Global Risks Report).

These days, the world is experiencing special circumstances in the face of the confrontation with COVID-19. Table 1 shows the resilience score and prevalence of coronavirus in several countries.

This table describes and somewhat confirms a relationship between the resilience situation and the global crisis (COVID-19 herein). As is demonstrated, resilience is in a negative relationship with the rate of death which is rooted in COVID-19. For example, Norway which is at the top in terms of resilience index faces with lowest death rate caused by COVID-19 disease.

Hence, discovering factors that positively or even negatively affect the resilience of economies will help societies to focus on increasing the resilience of economies when encountering economic crises. Entrepreneurship, as the driving force of economic growth (Schumpeter, 1965; Faghih et al., 2020a), can be considered the most important factor that may create high economic resilience.

In fact, entrepreneurship is necessary to sustain a dynamic economy. On the other hand, entrepreneurship is considered critical in creating more resilient economies. In point of fact, entrepreneurship is a phenomenon that can promote the diversification and capacity of economic activities leading to more resilient economies.

Objective of This Study

As mentioned, increasing economic resilience will help economies to resist when facing unexpected endogenous and exogenous shocks (Faghih et al., 2021a). Disasters, diseases, wars, etc., might be reasons that lead countries to fail in economic growth. Hence, investigations into factors affecting economic resilience will, in turn, help policymakers and state-run entities to consider the detected factors for increasing economic resilience.

As mentioned in much scholarly research and annual reports, entrepreneurship drives countries toward development. For this reason, to run better strategies in shock times, this study attempts to provide a deep analysis for scrutinizing the relationship between entrepreneurship and economic resilience.

Economic Resilience

At the time of the recent pandemic, COVID-19 has created a wave of positive and negative innovations in the world of entrepreneurship and the business sector. On the other hand, scientific studies, along with the significant risks taken by entrepreneurs, are necessary to end the COVID-19 crisis and provide new techniques to adapt to the post-pandemic world. As COVID has severely affected the quality of life of people, especially the elderly, it has also shocked the global economy incredibly. For example, during the COVID pandemic, the UK employment rate was estimated at 75.5%. This means 1.1% less than before the coronavirus pandemic (December 2019 to February 2020). This may be because many people may not have been actively looking for work due to social distancing.

It should be noted that today, economic vulnerability is one of the most important features that usually results from a set of exogenous shocks that affect a country's economy (Faghih et al., 2020b, 2021b).

In contrast, economic resilience is the economic viability against these external shocks (Korber & McNaughton, 2017). In addition, the amount of an economy's ability to withstand threats and shocks is called economic resilience. Economic resilience is a set of regulations that can act as a supporter and protector of the economic system in times of global crisis. On the other hand, this reflects the fact that the viability of a country's economy depends strongly on its flexibility, which determines how it can withstand internal and external threats and other pressures. The ability to withstand and overcome crises depends on the resilience of economic activities (McKinsey and Company report, 2020; Faghih et al., 2021c) and national resilience (FM Global, 2019).

Every economy has weaknesses when encountering crises. On the other hand, countries' resilience to these crises shows their ability to stand up, compromise, and modernize after the crisis.

The resilience index is a composite index that includes three economic dimensions that after normalization will be between zero and 100.

The closer it is to zero, the lower the resilience and the closer it is to 100, the higher the resilience. According to the 2019 FM Global Report, Norway, Denmark, and Switzerland have the highest resilience scores.

Béné et al. (2012, 2016) propose that resilience emerges as the result of three capacities: absorptive, adaptive, and transformative capacities (Fig. 3).

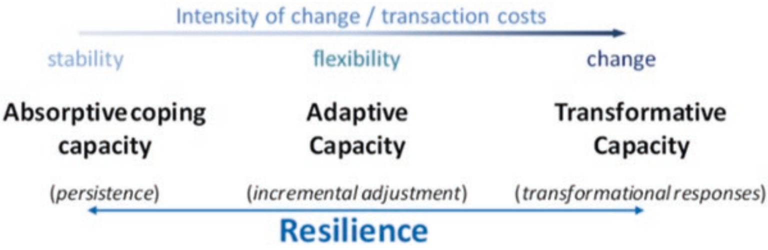

Fig. 3 Subdimensions of resilience. (Source: Authors' own figure)

Economic Resilience and Entrepreneurship

Today, globalization, rapid technological change, deep recessions, and man-made disasters have made it important to do research on regional economic resilience as an important field of recent studies. Due to the existing literature in the field of entrepreneurship, entrepreneurship seems to be effective in all three dimensions of resilience.

The Global Entrepreneurship Monitor (GEM) calculated more than 16 entrepreneurship indicators in every annual survey. These indicators are divided into three layers: activities, perception, and aspiration. Based on the GEM's definition (Table 2) of entrepreneurial activities, entrepreneurs are divided into two main categories: total early-stage activities (TEA) and established business (EB).

In this study, we selected, not so arbitrarily, the rate of the total early-stage activities (TEA) and the establish business (EB) in the entrepreneurial activities layer, the entrepreneurship intention in the perception layer, and innovation in the passion layer to get a reasonable result over the research.

Based on the GEM's definition of entrepreneurial innovation, this indicator is a percentage of those who indicate that their product(s) or service(s) is new to at least some customers and that few/no businesses offer the same product.

On the other hand, the GEM economies in 2017 comprise 67.8% of the world's population and 86.0% of the world's GDP (GEM global report, 2017). The GEM groups the participating economies in two ways: geographic region and economic development level.

First, based on the GEM definition, "start-up activity is measured by the proportion of the adult population (18–64 years of age) in each country that is currently engaged in the process of creating a nascent business. The proportion of adults in each country who are involved in operating a business that is launched less than 42 months measures the presence of the TEA. Second, the rate of the established business is a percentage of the 18 to 64 years-old population who are currently an owner of an established business that has paid salaries, wages, or any other payments to the owners for more than 42 months."

The data used in this study is based on the data collected by the GEM in 2017. The main reason for selecting this old data is because of the big sample size of

Table 2 GEM definitions

Total early-stage entrepreneurial activity	A percentage of the adult population between the ages of 18 and 64 years who are in the process of starting a business (a nascent entrepreneur) or owner-manager of a new business that is less than 42 months old
The established business ownership rate	A percentage of the adult population between the ages of 18 and 64 years who are currently an owner-manager of an established business, i.e., owning and managing a running business that has paid salaries, wages, or any other payments to the owners for more than 42 months
Entrepreneurial intentions rate	A percentage of the 18–64 population (individuals involved in any stage of entrepreneurial activity excluded) who are latent entrepreneurs and who intend to start a business within three years
Entrepreneurship innovation rate	A percentage of those involved in TEA who indicate that their product or service is new to at least some customers *and* that few/no businesses offer the same product

Source: Authors' own table (based on the GEM's official website)

Table 3 Triple classification of economies

	Factor-driven economies	Efficiency-driven economies	Innovation-driven economies
Africa	Madagascar	Egypt, Morocco, South Africa	
Asia and Oceania	*India, Kazakhstan, Vietnam*	China, Indonesia, Lebanon, Malaysia, Saudi Arabia, Thailand	Australia, Israel, the Republic of South Korea, Taiwan, the United Arab Emirates, Japan
Latin America and the Caribbean		Argentina, Brazil, Chile, Colombia, Ecuador, Guatemala, Mexico, Panama, Peru, Uruguay	Puerto Rico
Europe		Bulgaria, Bosnia and Herzegovina, Croatia, Latvia, Poland, Slovakia	Cyprus, Estonia, France, Germany, Greece, Ireland, Italy, Luxembourg, the Netherlands, Slovenia, Spain, Sweden, Switzerland, United Kingdom
North America			Canada, United States

Source: Authors' own table

participant countries during the year. Naturally, the data on economic resilience of the mentioned year has been used to find its relationship with the entrepreneurship factors.

First, it is required to list economies that have participated in the GEM surveys in the year 2017. Table 3 has stratified the GEM member countries based on the triple classification of economies.

According to the classification of the World Economic Forum (WEF), factor-driven economies are less developed. They are heavily dominated by traditional agriculture and non-manufacturing businesses that rely heavily on unskilled labor and natural resources. Efficiency-driven economies have more efficient production processes, which naturally compete with other businesses by increasing the quality of the manufactured product. Among these three groups, innovation-driven economies are the most developed. In these new economies, businesses depend on knowledge and science, and the service sector expands dramatically. The GEM equates economies that are transitioning from factor-driven to efficiency-driven economies, while economies that are transitioning from efficiency-driven to innovation-driven are included in the efficiency-driven category.

Methodology

The COVID-19 crisis stimulated much interest in the impact of previous pandemics on economies. A rapid review of the literature (summarizing the key points) was produced for BEIS (the United Kingdom's Department for Business, Energy, and Industrial Strategy) by Turner and Akinremi (2020). Generally, the findings of this review, for an influenza pandemic's potential impact, suggested a concurrent decline in international trade and global aggregate demand, leading to a further reduction in national income and outputs. Moreover, the potential impact of absenteeism at work, disruption of production processes and business activities, and a shift from business-as-usual to some more costly practices can lead to supply shocks that might affect supply chains nationally and globally. Emergency measures, for example, restrictions and quarantines on trade and travel to mitigate or slow the pandemic, can result in supply chain breakdown and a temporary disruption of logistics and trade services locally and internationally (Bosma & Hart, 2020). The data source of this study is the GEM's annual surveys which are gathered using field methods worldwide.

The purpose of this section is to analyze the relationship between several entrepreneurship indexes and the resilience index. Eleven linear and nonlinear models including Linear, Logarithmic, Inverse, Quadratic, Cubic, S, Exponential, Power, Compound, Growth, and Logistic have been used to detect the best model of the relationship between economic resilience and the considered entrepreneurship indicators. To examine the relationship between the TEA and the economic resilience index, the TEA has been considered as the independent (or effective) variable and the economic resilience index as the dependent variable.

To estimate the best regression model between these two variables, as mentioned, more than 11 regression models (linear and nonlinear models) were fitted and then the best model based on the R-square[1] criterion was selected.

[1] R-square is a statistical tool to determine how much a model is reliable. This parameter is computed for each model separately and its amounts are more than zero and less than one. The lower amount of this parameter shows the weakness of the model and vice versa.

Economic Resilience and TEA

Figure 4 shows the scatter plot of the economic resilience index against the rate of TEA. In the confirmed regression model (a cubic model), which resulted from the data gathered from 52 countries surveyed by the Global Entrepreneurship Monitor in 2017, the R-square is about 47%. This means that the rate of TEA can predict about 47% of the variations of economic resilience across member countries.

This figure also shows as the rate of TEA increases, the rate of economic resilience decreases. This contradiction comes from the quantitative properties of the indicators created by the GEM. Based on the GEM reports, the rate of TEA in factor-driven economies is much more than in innovation-driven economies. Additionally, the rate of exited businesses in factor-driven economies is higher than in innovation-driven economies. In fact, because both the TEA and the rate of exited businesses calculated by the GEM have quantitative properties, naturally, they may lead to contradictory reports.

What seems to be more important in Fig. 4 is the high amount of economic resilience of the economies specified between red vertical lines. In fact, based on the GEM reports and Fig. 4, obviously, the innovation-driven countries that launch innovative entrepreneurial activities will have more resiliency in economic conditions compared to the factor-driven economies.

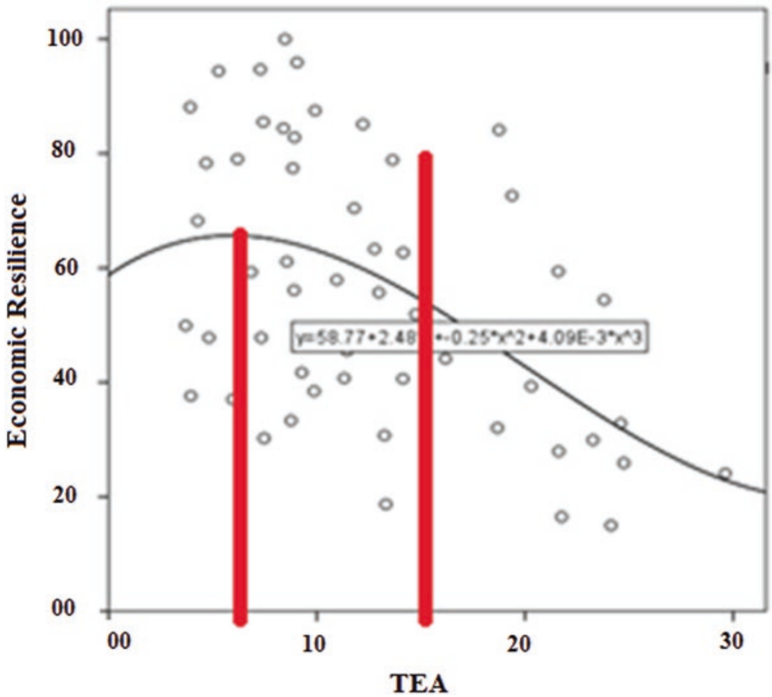

Fig. 4 Scatter plot of the total early-stage activities rate versus the rate of economic resilience. (Source: Authors' own figure)

It can be inferred that in developed countries, it can be expected that with the growth of the TEA rate, the resilience index will also rise. But in underdeveloped countries, this trend is reversed. More precisely, with the growth of entrepreneurship in underdeveloped economies (factor-driven economies), economic resilience is also declining.

As mentioned, according to the GEM's findings, the rate of TEA in underdeveloped countries (factor-driven economies) is higher than in developed countries (innovative-driven economies), so it can be concluded that TEA in underdeveloped countries does not have the necessary quality for improving the level of economic resilience. On the other hand, as Fig. 4 shows, between 7% and 15% of high-quality entrepreneurial activities are required to maximize the level of economic resilience.

Economic Resilience and Established Business

Figure 5 shows the estimated regression model of the relationship between the established businesses rate and the economic resilience index. The analysis of this model is very similar to the previous model. According to the GEM, the rate of EB

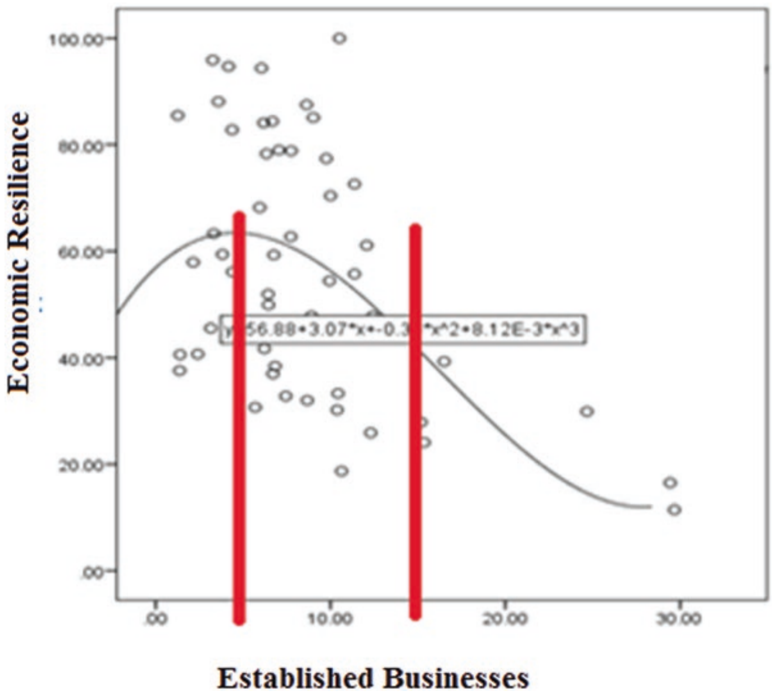

Fig. 5 Scatter plot of the established business rate versus the rate of economic resilience. (Source: Authors' own figure)

in innovation-driven economies is significantly different than the factor-driven economies. As mentioned previously, this factor may make a contradiction.

The fitted model is a cubic model and the coefficient of determination (also called R-square) in this model is 38%.

Interestingly, given the above scatter chart, it can be inferred that most countries with lower EB are more resilient to economic crises. Although, it should be noted that more countries with a high rate of EB are in the factor-driven or efficiency-driven group.

The impact of entrepreneurial activities on economic development mainly reflects the importance of innovation which mainly comes from within individuals and environmental and institutional factors.

In addition to the GEM studies, many scholars like Reynolds et al. (2002), Sternberg (2006), and Faghih et al. (2019) have discussed two varied types of entrepreneurial motivation: necessity entrepreneurship and opportunity entrepreneurship, which have been coined by the GEM (Block and Wagner, 2006).

On the other hand, the GEM's findings prove that the amount of opportunity entrepreneurship rate in the innovation-driven group is significantly more than in the factor-driven group. Besides, a higher level of necessity entrepreneurship has been observed in developing countries (Bosma & Levie, 2010). It seems that the economic resilience index in developed countries is growing due to the high quality of innovation in established businesses. While in underdeveloped countries, due to the lack of an opportunistic approach (despite the high rate of established business), resilience has decreased. As Fig. 5 shows, the range of 5–15% of EB is an almost optimal range for EB activities in innovation-driven economies, and the maximum increase in economic resilience occurs at this level of activities.

Economic Resilience and Entrepreneurship Intention

Entrepreneurship intention, as one of the best predictors of entrepreneurial behavior and activities, has been considered one of the factors confirming the dependency of economic resilience on the business sector (Faghih et al., 2021d). Figure 6 is the nonlinear model showing the relationship between entrepreneurship intention rate and economic resilience.

According to the GEM's findings, the Entrepreneurship Intention Index in factor-driven countries is always higher than in innovation-driven countries.

The scatter plot in Fig. 6, which shows 59% of the detection coefficient in this model (a cubic model), demonstrates that the relationship between these two indicators differs in three categories of economies.

In factor-driven countries as well as innovative-driven countries, with the growth of entrepreneurial intention, the level of economic resilience also increases, while the relationship between these two variables in efficiency-driven countries is quite the opposite.

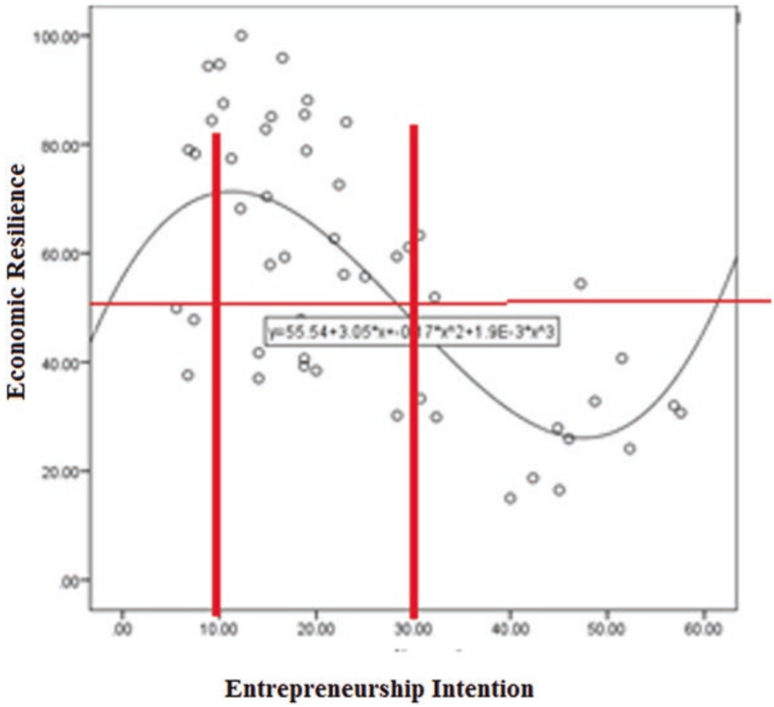

Fig. 6 Scatter plot of the rate of entrepreneurship intention versus the rate of economic resilience. Source: Authors' own figure

In fact, if the entrepreneurship intention rate is between 10% and 30% or more than 60%, the economic resilience of the society will be at an acceptable level of 50%. The highest rate of economic resilience will occur when the entrepreneurship intention is about 10%.

Economic Resilience and Entrepreneurial Innovation

The estimated equation in this regard is a cubic (third-order) formula and its coefficient of detection is more than 33%.

It is worth considering that the rate of economic resilience may increase in each country with effective entrepreneurial activities. This means that with the increase in the number of businesses looking for new products and services in a society, the society always has an adequate capacity for the activities of these types of businesses and welcomes such products and services. These types of businesses affect the economic cycle of society more and prevent the occurrence of economic crises in society to some extent.

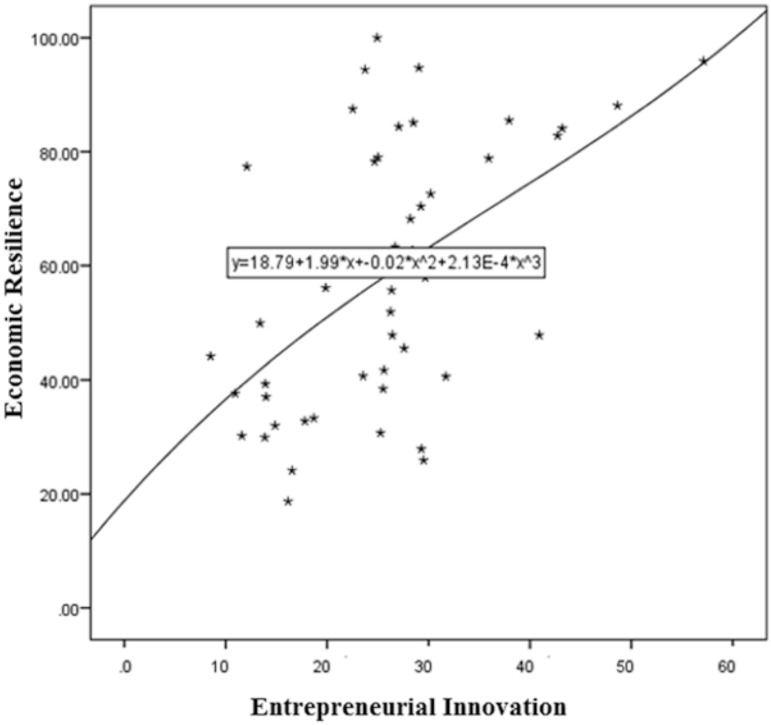

Fig. 7 Scatter plot of the entrepreneurial innovation index versus the rate of economic resilience. (Source: Authors' own figure)

This will increase the sustainability and productivity of the business sector of society. In general, one of the most important factors influencing the country's economic growth and development is innovation, and this will increase economic resilience. To get more understanding of this argument, see Fig. 7.

Results and Discussion

Overview

Can an economic system or business world have positive results during and after COVID? In fact, most of it is happening right before our eyes.

The need for people to remain connected with each other is crucial during a time of crisis. Businesses around the world have come together to serve their community like never before. Despite physical distancing measures, entrepreneurs have discovered solutions to the issues surrounding the pandemic. Business leaders, researchers, and scientists have found a way to foster connectedness even in time of a great disaster.

One of the well-known discoveries of the Global Entrepreneurship Monitor is the relationship between the total early-stage entrepreneurial activity (TEA) and GDP, which is a nonlinear relationship. On the other hand, as mentioned earlier, the relationship between entrepreneurship indicators and the rate of economic resilience is nonlinear. This finding means that the growth of the rates of TEA and EB in the countries does not solely refer to the increase in economic resilience. This may come from the fact that the uncontrolled increase of start-ups and entrepreneurial activities can lead to inefficient allocation of resources which will lead to economic vulnerability.

On the other hand, if opportunistic and innovative entrepreneurship grows, the economic resilience will increase, and also the country will be more resilient when encountering exogenous and endogenous crises. According to Fig. 6, it was shown that if the entrepreneurship intention rate is between 10% and 30% or more than 60%, the economic resilience rate of the country will create a more viable economic system.

What was intended in this study was to outline an indirect link between economic resistance and the natural disasters of countries. COVID-19, which has recently put a lot of pressure on the nations, is a natural crisis that has been linked to economic resistance.

Given the positive and direct relationship between different indicators of entrepreneurship, and also since the planning for the growth and development of entrepreneurship is possible by policymakers, one of the ways to deal with severe damage to the country's economy when encountering natural crises (including coronavirus) is business and entrepreneurship development.

Conclusion

In this study, an indirect relationship between entrepreneurship and global crises (like coronavirus) was estimated and discussed. The positive impact of entrepreneurial activities on economic resilience and, on the other hand, the negative impact of global crises on economic resilience create the idea in the mind of the reader as to how can crises and economic stagnation be avoided during the outbreak of a global crisis.

The estimation of new models of entrepreneurship in the COVID-19 pandemic period, which often occurred due to the issue of distance work, makes us think that high rates of entrepreneurial activities and innovation in businesses are very influential factors that not only save the economic system of a country during global crises but also create new opportunities for entrepreneurs.

Therefore, strengthening the ability to innovate and create new opportunities in the entrepreneurship ecosystem of a country will not only strengthen the poor infrastructure of that country but in difficult days when all countries are involved in financial crises, prosperity and growth will not stop. In the short term, economies have consequently suffered. Research on established businesses and startups in various economies indicates that most entrepreneurs had to require and adopt some measures in dealing with the case of coronavirus disease (Shane et al., 2020). Relief programs, like those reported by the OECD, manifest how significant the initial assistance has been for keeping entrepreneurs in business and for workers to stay in their jobs. Nevertheless, flows of public money face their own boundaries and thus, from the fall of 2020, most economies coped with the newly developed conditions in a different course of action, hoping that the early days of direct relief would also let businesses reconcile, innovate, and adapt, given the newly developed context at hand. Consequently, considering the nature of this crisis, the German and French governments extended the job furlough schemes up to 2022 (Bosma & Hart, 2020). Natural events and incidents, when seriously affecting a giant part of society, undoubtedly cause unpredictable problems. Hence, providing the relevant infrastructure will reduce the destructive damage of those natural crises. The impact of those factors may vary from country to country, but the negative effects of a natural disaster on a country's economy are undeniable. The outbreak of the coronavirus in 2020 was one of those unexpected crises that affected nearly 200 countries around the world. Temporary closure of some factories, companies, business institutions, universities, schools, and even private businesses founded by individuals during the coronavirus outbreak was announced by governments as mandatory (or voluntary). For this reason, the temporary (but severe) economic recession during the fight against this global virus was seen around the world. One of the items that may increase the resilience of countries' economies when facing unexpected and natural disasters is the empowerment and improvement of entrepreneurial and business infrastructure in society. Hence, creating a good entrepreneurial culture in every country won't only result in economic prosperity but will also prevent recessions and economic losses in crisis times.

Methods
This study has used parametric and non-parametric regression models to estimate the nexus between sub-indexes of entrepreneurial activities and economic resilience and finally the effect of these factors on each other in global crises times. Additionally, using the determination coefficient, as a criterion for selecting the best model, the best-fitted models were identified.

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