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REVIEW ARTICLE

Experimental Technologies in the Diagnosis and Treatment of COVID-19 in Patients with Comorbidities

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Abstract

The COVID-19 pandemic has impacted the whole world and raised concerns about its effects on different human organ systems. Early detection of COVID-19 may significantly increase the rate of survival; thus, it is critical that the disease is detected early. Emerging technologies have been used to prevent, diagnose, and manage COVID-19 among the populace in the USA and globally. Numerous studies have revealed the growing implementation of novel engineered systems during the intervention at various points of the disease's pathogenesis, especially as it relates to comorbidities and complications related to cardiovascular and respiratory organ systems. In this review, we provide a succinct, but extensive, review of the pathogenesis of COVID-19, particularly as it relates to angiotensin-converting enzyme 2 (ACE2) as a viral entry point. This is followed by a comprehensive analysis of cardiovascular and respiratory comorbidities of COVID-19 and novel technologies that are used to diagnose and manage hospitalized patients. Continuous cardiorespiratory monitoring systems, novel machine learning algorithms for rapidly triaging patients, various imaging modalities, wearable immunosensors, hotspot tracking systems, and other emerging technologies are reviewed. COVID-19 effects on the immune system, associated inflammatory biomarkers, and innovative therapies are also assessed. Finally, with emphasis on the impact of wearable and non-wearable systems, this review highlights future technologies that could help diagnose, monitor, and mitigate disease progression. Technologies that account for an individual's health conditions, comorbidities, and even socioeconomic factors can drastically reduce the high mortality seen among many COVID-19 patients, primarily via disease prevention, early detection, and pertinent management.

Keywords Cardiovascular · Pulmonary · Immune system · Wearables · Non-wearables · Innovation

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1 Introduction

COVID-19 has over 125 million confirmed infections worldwide, with over 2.75 million deaths, as of March 26, 2021 [1]. The rapidly progressive disease is caused by the strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is likely to originate from the populous Huanan Seafood Wholesale Market in Wuhan, Hubei Province of China [2–4]. However, COVID-19 is not the first coronavirus strain to emerge quickly and severely. The first coronavirus outbreak, named severe acute respiratory syndrome coronavirus (SARS-CoV), occurred in the Guangdong Province of China during 2002–2003 [3, 5]. Ten years later, a second novel strain, Middle East respiratory syndrome coronavirus (MERS-CoV) first emerged on the Arabian Peninsula [6]. This strain has periodically resurfaced, causing outbreaks across several nations in the Middle East and Europe [6]. Initially, COVID-19 was deemed primarily to be a respiratory disease. However, it can affect various organ systems; the severity of the disease strongly depends on the patient's preexisting health conditions and comorbidities. The exact transmissibility of SARS-CoV-2 is not known. However, early estimates of the first reproduction number (R0) vary between 2 and 3 [2]. Person-to-person transmission can occur via respiratory droplets or close contact with infected persons, and with approximately 50% of patients being asymptomatic, the virus can readily spread unknowingly [7]. Additionally, coronaviruses can undergo rapid mutation and recombination [3].

Several research groups have investigated mechanisms by which SARS-CoV-2 may enter the human host around the globe [8, 9]. These reports indicated that as a first step, the viral surface spike glycoprotein (S protein) attaches to the ACE2, which is highly expressed on pneumocytes (type 2) in the lung, particularly in smokers [8, 9]. The second step is highly subjected to the host cell proteases, especially the type 2 transmembrane serine protease (TMPRSS2). Studies showed that besides SARS-CoV-2, other coronaviruses and influenza viruses rely on host TMPRSS2 activity during virus entry, including SARS-CoV and influenza H1N (1918 and 2009 influenza pandemics) [10–12]. Multiple scRNA-seq datasets revealed a high expression of human's ACE2 and TMPRSS2 in the nasal goblet and ciliated cells [13]. These work findings may explain why among symptomatic and asymptomatic patients, nasal swabs have yielded higher viral loads than throat swabs [14]. Moreover, this discovery suggested that nasal epithelium may function as a potential primary infection place and a possible source of virions for dissemination among humans [14]. The ACE2 and TMPRSS2 co-expression in other tissues could suggest existing alternative transmission routes already observed clinically (e.g., fecal–oral or nasolacrimal duct transmission) [9, 15]. Recent studies provided new insight into and attempted to explain the high transmissibility of SARS-CoV-2 [14, 16]. Based on the results, SARS-CoV-2 presented more efficient replication in pulmonary cells than SARS-CoV, which can be associated with differences in the amino acid composition of the S protein (70% amino acid identity) [14, 16]. Another study showed a 10- to 20-fold higher binding affinity between SARS-CoV-2 spike protein and human ACE2 compared

to SARS-CoV [17]. The high receptor-binding ability of SARS-CoV-2 to pulmonary cells may lead to more efficient virus transmission in the general population.

ACE2 is a membrane-bound, counter-regulatory enzyme to ACE, which breaks down angiotensin 2 to angiotensin 1–7, with high levels of ACE2 expressed in the gastrointestinal system, heart, and kidneys [18]. Unlike ACE, ACE2 does not respond directly to ACE inhibitors or angiotensin receptor blockers (ARBs) which usually block the ACE activity or its receptor and are commonly used to treat hypertension. Once the viruses use ACE2 to enter the cell; the ACE2 enzyme is functionally deactivated, which thereby increases circulating levels of angiotensin 2 [19]. Various theories surround the ultimate contribution of ACE2 upregulation seen in patients on antihypertensives to the pathogenesis of SARS-CoV-2. Recent studies made arguments for the possible protective role of ACE2-increasing drugs against COVID-19 [20–23]. Patients on ACE inhibitors have excess free angiotensin 2 that in the setting of viral particles occupying the ACE2 receptor are now enabled to bind the angiotensin 2 receptor type 1 (AT1R) in the lungs, causing increased pulmonary vascular permeability, further mediating the pathology seen in SARS-CoV-2. Figure 1 shows the flowchart of pathogenesis and possible points of interventions. These mechanisms, as well as the contribution of varying ACE2 polymorphisms, are areas currently under investigation [24].

The symptoms and epidemiological factors of COVID-19 can pave the way for the development of novel systems, especially for those with underlying comorbidities, which can better predict, diagnose, and treat the disease. For example, wearable technologies present as an emerging solution to battle COVID-19. As of April 2020, there are approximately 356.8 million users worldwide of wearable technology and 39.1 million users within the USA alone (https://www.statista.com). Many sensors and subsystems (e.g., pulse oximeters, optical heart rate sensors, and 1-lead electrocardiogram) that were previously limited to clinical settings are integrated into such wearable technologies like smartwatches, smart rings, fitness trackers, and cardiorespiratory monitoring patches. In this review article, we (i) summarize the current understanding of SARS-CoV-2 pathogenesis, highlighting the essential comorbidities and organ systems involved; (ii) present examples of developing research to detect early stages of disease based on pulmonary, cardiovascular, and immunologic factors using wearable and non-wearable technology; and (iii) outline the next steps for future diagnosis and disease monitoring that could potentially mitigate disease spread, secondary complications, and mortality.

1.1 Literature Search Strategy

References for this narrative review were established with four search engines (PubMed, Scopus, Web of Science, and medRxiv) with listed keywords: COVID-19 pandemic, COVID-19 epidemiology, emerging technologies, wearables, nonwearable, artificial intelligence, machine learning, 3D printing. The literature covered the period from January 2020 to March 2021. This review includes articles published only in English.

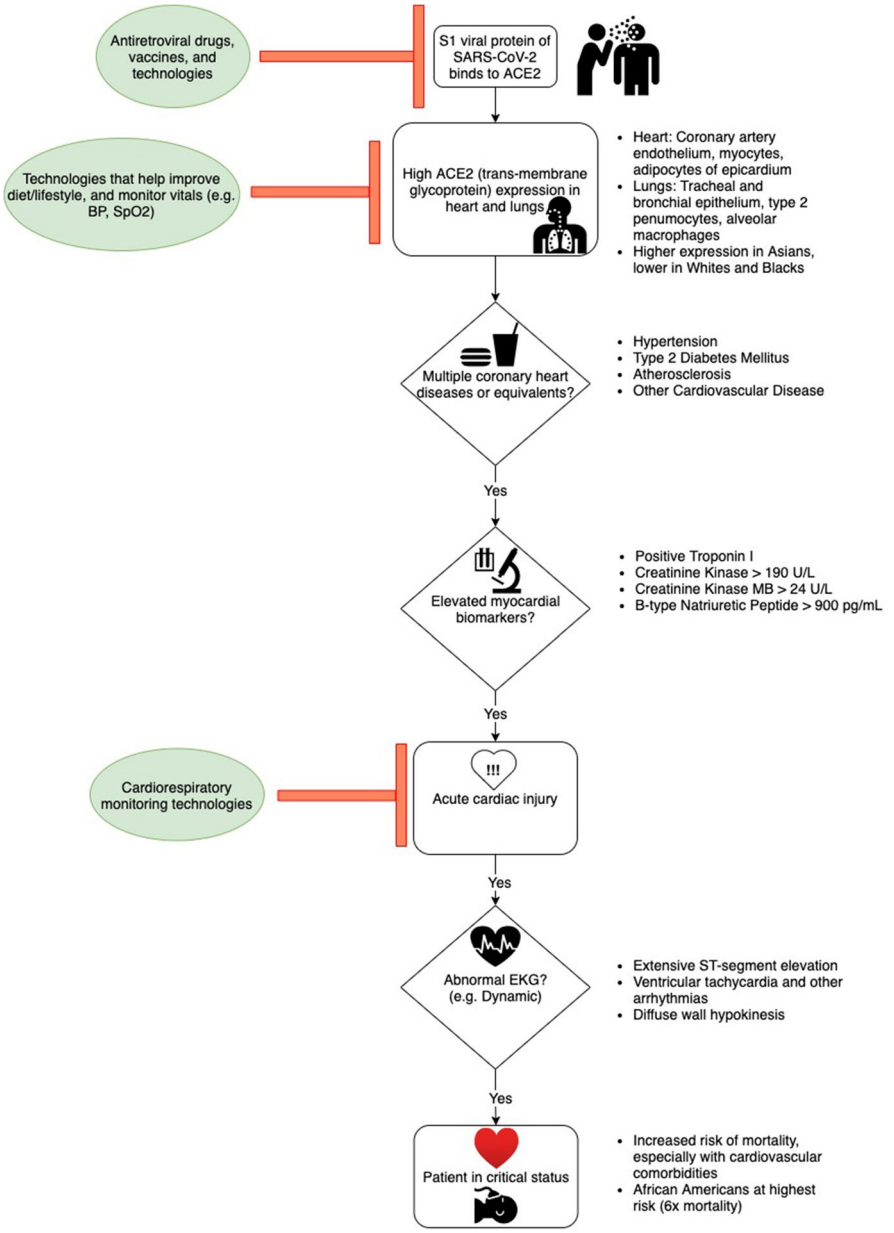

Fig. 1 Proposed flowchart of ACE2, acute cardiovascular disease progression, and potential interventional stages

Methodology: A total of ~ 500 papers were pre-identified in the initial search, a total of 6 people screened ~ 250 papers and they worked in teams of 2; they divided the papers by topics of interest, e.g., cardiovascular, respiratory, and immune

system. Fleiss' Kappa was used to measure the agreement between the two raters (0 indicates no agreement and 1 indicates perfect inter-rater agreement); a Kappa of > 0.61 was used (good agreement) as a decision factor to include a paper. A total of 120 papers were included in the final version of this literature review.

2 COVID-19 and the Cardiovascular System

Cardiovascular disease is emerging as a comorbidity in SARS-CoV-2, and it was previously associated with SARS-CoV and Middle East respiratory syndrome (MERS) pathogenesis. When considering the one study that aimed to identify early disease features for better triage of COVID-19-positive patients, it showed that hypertension (56.6%,) was the most common feature among the 5700 patients admitted to the hospital, followed by obesity (41.7%) and diabetes (33.8%) [25]. However, this study showed the high prevalence of hypertensive patients to be on angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), which was associated with higher mortality. The mortality rate among the hypertensive patients was 26.7% for patients not taking an ACEi or ARBs, 32.7% for patients taking an ACEi, and 30.6% for patients taking an ARB [25]. One review study that investigated the effect of preexisting hypertension on mortality showed a range of hazard ratios ranging from 1.7 to 3.05 [26], indicating a possible increase in mortality rate among hypertensive patients. However, these studies did not adjust for potential confounders [27].

Richardson et al. reported presenting symptoms at triage included fever (30.7%) respiratory rate above 24 breaths/min (17.3%), tachycardia (43.1%), and for some, elevated troponin levels (22.6%) indicating underlying myocardial injury [25]. In a study of COVID-19 hospitalized patients, 15% progressed to having fatal pneumonia, while 6% were in intensive care, especially those older than 60 with hypertension, diabetes mellitus, cardiovascular disease, and other underlying comorbidities [2]. The data pointed out the potential of poorer outcomes of patients with preexisting hypertension, especially in hypertensive elderly patients who will have the compounded risk of cardiovascular disease and age [2, 4]. The mortality in patients with cardiovascular diseases (CVD) and normal troponin T test (TnT) versus patients with CVD and elevated TnT showed to be 13.3% and 69.4%, respectively [28]. The prevalence of the underlying cardiovascular disease in individuals with SARS-CoV, MERS, and SARS-CoV-2 is 10%, 30%, and up to 40% in hospitalized COVID-19 patients [3].

Inflammatory burden is linked to SARS-CoV-2, potentially leading to myocarditis, arrhythmias, and especially in patients with underlying cardiovascular disease, destabilization of coronary plaques, and aggravated hypoxia [28]. The SARS-CoV-2 myocardial injury mechanism is still under investigation, although early reports pointed to the possibility of both direct myocardial damage mediated by ACE2, as well as injury secondary to inflammatory processes including cytokine storm and secondary hemophagocytic lymphohistiocytosis [28, 29]. The cytokine storm could be mediated by an abnormal response from type 1 and type 2 helper T cells [30],

and the mechanisms of cardiac injury and inflammatory response could be potentially correlated.

Zhou et al. [31] showed that the human cardiac troponin I (hc-TnI) level was not only lower in COVID-19 survivors following symptom onset, but it remained stable throughout treatment while COVID-19 non-survivors showed marked upward trends of up to 290.6 pg/mL by day 22 from the onset of illness. Moreover, the troponin rise observed with an increase in inflammatory plasma markers, including D-dimer, ferritin, IL-6, and lactate dehydrogenase [31]. This may indicate that systemic inflammatory changes contribute to disease more so than the myocardial injury alone [29]. However, as evidenced by cases of myocarditis or stress cardiomyopathy due to COVID-19 without coinciding inflammatory signs, a second postulate is that the virus damages the heart via direct injury without much contribution from systemic inflammation [29, 32].

While the overwhelming majority of patients presented with fever, malaise, dry cough, and dyspnea, there have been reports of individuals presenting with predominantly cardiac symptoms, suggesting a different illness pattern [29]. These patients may present with chest pain and ST-segment elevation in the absence of coronary obstruction. Microvascular inflammation and subsequent dysfunction, contributing to myocardial infarction with non-obstructive coronary arteries (MINOCA), could be a result of pericyte infection with the virus [33]. Similarly, some COVID-19 patients, including those previously healthy without the preexisting cardiac disease, have developed fulminant myocarditis via direct viral insult to the heart [29]. A subset of patients in China presented with palpitations and chest pain rather than the common fever and cough [34]. There are also instances of patients presenting with chest pain and cough in the setting of heart failure, cardiogenic shock or in the background of heart transplantation with the concomitant abnormal electrocardiogram (ECG) and echo findings in addition to the hallmark COVID-19 lung opacities [35].

According to Shi et al., patients with cardiac injury showed higher median leukocyte counts, CRP, procalcitonin, CK-MB, myohemoglobin, and hs-TNI [36]. In this study, 28% of patients with a cardiac injury received an ECG at the time of their cardiac biomarker elevations; 14 patients had abnormal results, including ischemia, T-wave depression and inversion, and ST-segment elevation and Q waves. In this same study of 416 patients, only 14 (3.4%) presented with chest pain. The mortality rate was found to be higher among patients with cardiac injury (51.2%), and it increased in association with elevated hs-TNI [36]. He et al. investigated the ECG manifestations in COVID-19 patients and found varying degrees of heart block (e.g., Mobitz type I, right bundle branch block) [37]. The extensive ST-segment elevations seen in inferior leads and leads V1-V4 of the ECG indicated more than just one coronary artery, suggesting a more diffuse myocardial injury like acute myocarditis [37]. Furthermore, several hospitalized COVID-19 patients experienced arrhythmias that changed from one type to another (i.e., dynamic), which resulted in a poorer prognosis [37]. Patients with cardiac injury possessed higher white cell count but a lower number of lymphocytes. A study of 41 admitted individuals with COVID-19 revealed ARDS (29%), viremia (15%), and acute cardiac injury (12%) to be among the most common complications [3]. Wang et al. found that among the 26.1% of transfers to the ICU for complications, 44% were due to arrhythmias [38].

Disseminated intravascular coagulation (DIC) and pulmonary embolism have gained clinical prevalence with DIC observed in 71.4% of survivors [33, 39]. The rise of a potential new Kawasaki-like disease in children related to COVID-19 has additional cardiovascular implications. A group in Italy documented ten cases of this child-afflicting vasculitis during their pandemic's peak, reflecting a monthly incidence 30-fold higher than the previous 5 years [40, 41]. Among those ten children, five presented with fewer classic Kawasaki findings. Additionally, the study showed a high proportion of shock and more than the usual requirement of high-dose corticosteroids to treat the illness, which usually subsides with intravenous immunoglobulin [40, 41].

Historical data showed that more patients die of cardiovascular-related complications than of pneumonia-influenza causes in most influenza epidemics [42]. Inflammatory infiltrates on autopsy were associated with regions of cardiomyocyte necrosis; however, thus far, the presence of SARS-CoV-2 within myocardial tissue is yet to be investigated [43].

2.1 Early Detection Technologies

Reliable continuous cardiorespiratory monitoring systems represent a promising frontier in addressing cardiopulmonary demise, especially now considering the rapid deterioration of COVID-19 patients. Several wearable devices have emerged in efforts to downsize the gold standard ECG for non-invasive assessment of CVD, and to digitize cardiac pathology detection, thus replacing the human-factor-dependent stethoscope with PCG (phonocardiogram) and similar technologies. Many sensors for measuring respiratory function involve obtrusive devices such as face masks or nasal cannula pressure monitors. A novel approach engineered by Klum et al. combines single-lead ECG, PCG, and impedance pneumography into a 55-mm wearable device, termed the "multimodal patch stethoscope" [44]. The impedance pneumograph measures the respiratory volume and rate via a relationship between respiratory depth and thoracic impedance change. This technology could be an alternative approach for early diagnosis of COVID-19.

Shahshahani et al. utilized a single sensor for cardiac and respiratory monitoring via a different modality—ultrasounds by way of a PZT-4 piezo transducer [45]. The monitoring of cardiac changes is not limited to ECG or ultrasound, seismocardiography (SCG) also provides increased sensitivity for detecting anatomic and physiologic coronary artery disease. The technique records chest wall vibrations in response to blood flow through vessels as it corresponds to each heartbeat. The SCG has re-emerged for study with recent advances in signal processing to increase clinical utility [46]. The wearable by Inan et al. employs SCG in combination with graph mining techniques to analyze cardiac response in the setting of exercise to detect heart failure [47].

Strategies that interrogate cardiovascular disease from the standpoint of hypertension include the first wrist-worn blood pressure monitor released in 2019 by Omron Corporation (https://omronhealthcare.com/), cleared by the Food and Drug Administration (FDA) and last year put into clinical trials [48]. The

company additionally has blood pressure and ECG combination devices in their product development pipeline. Wearables such as these, similar to the familiar Holter monitor, could provide meaningful long-term data for measuring hypertensive changes. Currently valued at $500, one must consider the ease with which many of those suffering from hypertension will be able to ascertain such products.

Point-of-care diagnostics is another area of great potential for combating disease in multiple realms, including cardiovascular disease. Cardiac troponin remains the biomarker of choice for detecting myocardial injury. Highly sensitive tests were first introduced in Europe in 2010 and are now becoming available in the USA, providing higher precision and lower limits of detection [49]. The hope is to someday detect myocardial injury with the same ease as diabetics measure blood glucose. The Abbott iSTAT® (https://www.pointofcare.abbott/), for instance, has been tested among groups including emergency medical services (EMS) teams within the last 2 years for validity and usability, with generally promising results [50, 51].

Public health departments of countries around the world are attempting various methods to control COVID-19 infectivity among the populace via digital surveillance through smartphone software [52]. There are two approaches to digital smartphone surveillance: a centralized approach where location history and personal information may be obtained, sometimes without the user's consent, and a decentralized approach where users are informed of proximity (not exact location) to infected individuals and consent needs to be obtained in order to share personal information with the government [52]. East Asian (e.g., China, Taiwan, South Korea) and some European countries (e.g., Italy, France, UK) favor the former centralized approach for COVID-19 digital tracing, whereas Austria, Germany, and Switzerland favor the decentralized, more private approach. Within the USA, both Apple and Google have collaborated to provide a decentralized approach within their iOS and Android software ecosystems, respectively, but the federal government does not favor a nationwide policy yet [52]. Digital tracing is not meant to replace traditional infection prevention measures such as physical distancing, wearing masks in public, regular testing, and isolation/quarantine, but rather to complement such practices [52]. Besides digital surveillance, various other applications exist to educate users and health professionals regarding preventive and behavioral measures, and methods of self-isolation [53]. In one study of 52 smartphone apps in Brazil, 76.9% were for Apple iOS, 15.4% for Google Android, and 7.7% were available for both platforms [53]. This was observed to be an effective means of educating the public about COVID-19, especially since up to 90.4% of Brazilian households relied on smartphones as their primary means of accessing the Internet [53]. Prolonged isolation can negatively impact mental health, especially among the geriatric population (> 65 years), who are also the most susceptible to COVID-19. To mitigate mental illnesses, mobile technologies can help older adults stay connected to family/friends (e.g., FaceTime, Skype) and obtain meal delivery services. With the expansion of Medicare reimbursement policies to include telehealth by the Centers for Medicare & Medicaid Services, older adults can now continue to remotely receive medical care for chronic conditions [54].

3 COVID-19 Effects on the Pulmonary System

Clinical features related to patients with COVID-19 differ among individuals, but the majority present a mild form of respiratory illness with no or flu-like symptoms (e.g., dry cough, fever, and fatigue). Other symptoms may include sore throat, headache, joint pain, anosmia, nausea, and diarrhea [14, 15, 55, 56].

People suffering from chronic obstructive pulmonary disease (COPD) have a high risk of morbidity and mortality due to pneumonia [57]. Regarding COVID-19, COPD patients showed an elevation in the ACE2 levels [58, 59]. Based on results presented in the meta-analysis, COPD is associated with an over five-fold increased risk of severe COVID-19 infection [60]. This study showed that patients suffering from COPD should follow more restrictive actions for minimizing potential exposure to SARS-CoV-2. Other studies indicate that smoking is associated with increased risks of severe COVID-19 infection [61, 62]. Data shows that smoking individuals have a 1.4 times higher risk of severe COVID-19 symptoms, and 2.4 times more often require mechanical ventilation or die than non-smokers [63].

Guidelines for SARS-CoV-2 testing are modifying as the disease spreads in the general population. Currently, the Centers for Disease Control and Prevention (CDC) recommends a reverse transcriptase-polymerase chain reaction (RT-PCR) technique to detect COVID-19 cases [64]. According to CDC guidelines, specimens for testing are collected from an upper respiratory swab—nasopharyngeal (N.P.) sample. While RT-PCR testing is considered the gold standard due to its high specificity, it is a very time-consuming and complicated manual process.

3.1 Imaging Technologies

Radiography examination has been recently proposed as an alternative screening method for COVID-19 [65, 66]. Early reports demonstrated that patients infected with COVID-19 present characteristic visual abnormalities in chest radiography images that are typical visual indicators of those infected with COVID-19 [67, 68]. To facilitate this process, a group of researchers introduced an open-source deep convolutional neural network invented for the identification of COVID-19 (COVID-Net) cases based on chest X-ray (CXR) image analysis. COVID-Net development may improve the diagnostic and treatment of COVID-19 and lead to deep learning solutions for detecting COVID-19 cases from CXR images [69].

Pneumonia appears to be a more severe form of the disease, leading in severe cases to respiratory failure, acute respiratory distress syndrome (ARDS), and multiorgan failure, and is associated with high mortality in patients infected with SARS-CoV-2 [14, 63, 70, 71]. True definitive clinical assessment of ARDS depends on histopathological techniques to determine lung tissue destruction. Once the diagnosis is made, therapy is monitored with a sequential physical exam and current imaging modalities plus pulmonary function tests (PFTs). To continuously sample lung tissue to track repair or destruction over time would be invasive and unfeasible. Bronchiolar lavage as well, though less invasive, does not always yield useful

results or precisely differentiate between pathological cell profiles. Promising new technology such as intravital probe-based confocal-laser endomicroscopy (pCLE) could provide high-resolution images to enable multiplex screening of proteases and microbes, simultaneously allowing for longitudinal lung monitoring [72]. Commercial catheters ranging from 300 microns to 1.5 mm containing a bundle of up to 30,000 optical fiber microprobes have been used in the endobronchial approach. Such modalities are ushering-in the promise of alveolaroscopy and optical biopsy, highly sought-after modalities that allow for precision in the care of lung injured patients [72].

Lung ultrasound, specifically ultrasound lung comets (ULCs), is also emerging as a potential technique in ARDS-evaluation. ULCs evaluate the measurement of extravascular water in the lung, which suggests alveolar wall thickening, a prominent feature in the pathogenesis of ARDS [73–75]. While chest radiography may fail to capture ARDS, lung ultrasound tends to miss the detection of pathology at the distant pleura [70]. The use of ultrasound is promising for this purpose, although more data is needed, especially on patients who are not critically ill. While authors suggested that ultrasound should be used complementarily, not in place of chest radiographs, ultrasound possesses significant value for its unique features, ease of use, the omission of radiation, and economic cost [70, 71, 73]. Benefits of these imaging modalities include portability, fast acquisition, innocuity and especially in the case of pCLE, high spatial resolution and penetrance [72].

Nuclear magnetic resonance (NMR) metabolomics addresses the problem above regarding a lack of precision in assessing microbial burden on bronchiolar lavage [76, 77]. This imaging modality presents another novel approach to delineating prognosis in ARDS, a real clinical challenge with current methods (e.g., bronchiolar lavage, traditional imaging, biopsy). Viswan et al. demonstrated the ability of NMR metabolomics to discriminate between patients with mild, moderate, and severe ARDS using a biomarker model [78]. Though the Berlin criteria currently defines ARDS based on just the patient's oxygen levels, future technologies using imaging or biomarkers could be more informative methods to rapidly assess pulmonary function.

4 COVID-19 and the Immune System

While COVID-19 manifests by harming several organ systems, unfolding data suggest that aberrant immune function plays a critical role in the progression of this disease [79, 80]. The current theory is that a locally triggered immune response involving macrophages and monocytes leads to the cell-mediated response by lymphocytes. In severe cases, a dysregulated response can then lead to systemic pathology. The local response is pro-inflammatory, involving many players such as IL-6, IFN-γ, MCP1, and IP-10 [79]. Besides, lung deterioration with ground-glass opacities is becoming known as a hallmark [81]. The reasoning behind this may be the pulmonary recruitment of immune cells from the blood and lymphocytic infiltrate into the respiratory system [79]. Furthermore, patients with cardiac injury possessed higher white cell count, but a lower number of lymphocytes [36]. Lymphopenia is

mostly associated with worse outcomes for COVID-19 patients [31, 82]. Patients with higher levels of troponin and acute phase reactants had concomitantly higher amounts of leukocytes but lower levels of lymphocytes in several studies [3, 34, 36].

Presepsin (PSP) is a regulatory factor that modulates immune responses by interaction with T and B lymphocytes. A study involving 69 SARS-CoV-2 patients showed that higher values of PCP were associated with longer ICU stays [83]. PSP has particular value as a prognostic biomarker because of its physiologic pattern of response to pathogens. The host–pathogen interaction results in a dose–response that occurs initially at pathogen recognition and remains elevated for several days based on disease severity [83]. Biomarkers such as PSP that show potential for risk stratification are an ideal basis for technologies that seek to harness immunologic tracking for disease prognosis.

While many individuals can recover via neutralizing antibodies with minimal inflammation and damage, current data estimates severe disease in approximately 14% of those infected [84]. The ensuing respiratory distress is likely the result of excessive leukocyte and T cell infiltration, systemic cytokine storm, pulmonary edema and pneumonia, and widespread inflammation and multiorgan damage [79]. A reduction in ACE2 post-infection may contribute to renin-angiotensin system dysfunction, inducing blood pressure, fluid and electrolyte imbalances that further enhance inflammation, and vascular permeability in the respiratory system [79].

Cytokine storm, in particular, mediates lung inflammation and is thus a potential target for emerging immune-sensing technology and immune-targeted systemic therapy [79], and it is implicated in both infectious and non-infectious diseases. The concept of cytokine storm, involving graft-versus-host disease, was developed during the H5N1 avian influenza outbreak of 1993 [85]. Since then, it has been implicated in infectious disease research from Epstein-Barr virus–associated hemophagocytic lymphohistiocytosis to severe acute respiratory syndrome coronavirus in SARS-CoV and now SARS-CoV-2. In severe respiratory infections, the inflammatory markers seen in the peripheral blood more likely represent an even more pervasive immunopathology occurring deep within the respiratory tissues [85]. The process's importance in the context of COVID-19 is highlighted by the FDA's recent approval of a blood purification system [86]. This system combines Terumo BCT's Spectra Optia Apheresis System and specific filters from Marker Therapeutics AG to detoxify COVID-19 patients' blood from the proteins released in a cytokine storm. Groups such as Wear Optimo (https://www.wearoptimo.com/) proposed a micro wearable sensor to monitor IL-6 in the skin interstitium, which could be useful as a sharp peak as this cytokine typically signals an emerging cytokine storm [25]. This marker is low in those with mild symptoms and could provide a basis for the prediction of severe respiratory failure. Additionally, a group at MIT is working on a solution specifically to combat cytokine storm from within the body via injectable water-soluble proteins that mimic the structure of cytokine receptors [87]. Although not explicitly engineered for COVID-19, such solutions could be valuable as the inflammatory component in the disease process of SARS-CoV-2 grows in its importance.

5 Future Methods of COVID-19 Diagnosis and Prevention

Novel approaches to inpatient diagnostics have great potential for addressing the need for more continuous monitoring of heart and lung health at a cellular level while under stress, as in the case of severely ill COVID-19 patients who experience a rapid decline. Onboard health data can be aggregated (i.e., crowdsourcing), compared anonymously in real-time with other users' data, and analyzed using various machine learning algorithms (e.g., predictive analytics) embedded into the device's microprocessor [37].

Presently, detecting new positive COVID-19 cases require RT-PCR, which is labor-intensive and is burdened with the risk of false-negative error. Antibody-based tests have also been introduced on the market, but they heavily suffer from a lack of sensitivity and specificity. For this reason, it is imperative to create new diagnostic techniques allowing for both more accurate and much faster recognition with COVID-19 patients. To overcome those challenges, utilizing artificial intelligence–driven (AI) strategy for developing new diagnosis and treatment approaches has enticed note since the incipience of the COVID-19 pandemic. The outbreak has forged new demands where AI can significantly support physicians regarding diagnosis and treatment and assist the already experiencing difficulty in healthcare facilities.

Artificial intelligence algorithms, using data from all users, can analyze such parameters to help indicate whether the user is "sick" or "not sick," and guide the user on next steps (e.g., go to the emergency department or quarantine at home) [88]. One review study critically assessed 31 prediction models used for diagnosis and prognosis of COVID-19 [89]. Of the 10 prognostic models, the most frequently reported predictors of severe prognosis in COVID-19 patients included demographics (age, sex), specific computerized tomography (C.T.) scan-derived features, and the serum C-reactive protein, lactate dehydrogenase, and lymphocyte count. Other technologies that can be used to diagnose and treat possible COVID-19 include the ability to measure ACE2 plasma activity [90, 91] or ACE2 in the mucosa of the oral cavity as predictors of entry of the virus into the cell to cause the final infection [92].

Machine learning, a subset of AI, has been utilized to develop a more precise diagnosis approach for COVID-19 patients. The algorithm uses 151 peer-reviewed studies and focuses on patient symptoms and laboratory test results. The paper reveals a link between male sex and high levels of neutrophils and lymphocytes in blood serum. As claimed by the authors, patients with COVID-19 can be gathered into subgroups according to the immune cells' number in serum and symptoms and gender. Researchers used the XGBoost algorithm, which characterizes with high sensitivity and specificity (92.5% and 97.9%, respectively) [93].

In other studies, the COVID-19 has been diagnosed using a machine learning strategy and laboratory blood tests [94, 95]. Brinati et al. utilized a machine learning approach and hematological information acquired from routine blood sample tests to identify COVID-19 patients [96]. Researchers have proven that the method provides good precision.

In another study, researchers from Brazil applied a multipurpose machine learning strategy to predict the possibility of occurrence of the critical condition in patients with confirmed SARS-COV2 infection [97]. Scientists used routine, clinical, laboratory, and demographic information to learn five algorithms (extreme gradient boosting, extreme gradient boosting, artificial neural networks, random forests, catboost, and extra trees). Lymphocyte/C-reactive protein and C-reactive protein/Braden Scale ratio were the most significant for algorithms [97].

Due to the sudden emergence of COVID-19, the first stage of addressing the pandemic involves prevention of even contracting the virus in the first place. In hospital and clinic scenarios, case isolation is performed, identifying close contacts, environmental disinfection, and prompt usage of personal protective equipment (PPE) like face masks and shields [4]. Outside the hospital, the recommendation is to wear face masks, cover coughs/sneezes, apply min. 60% alcohol-based hand sanitizer, maintain an appropriate distance from others, and avoid touching the eyes, nose, and mouth with unwashed hands [4]. However, the authors do not mention whether wearable (e.g., smartphone-based) or non-wearable technology (e.g., 3D printing) could be used to ensure that people maintain social distancing and improve treatment and diagnosis.

5.1 Wearable Technologies

Carefully and precisely tracking emerging hotspots is a critical task for maximizing the efficient use of social distancing and healthcare resources. One approach currently being investigated for tracking the spread of COVID-19 and the emergence of hotspots is through a network of smart thermometers in collaboration with commercial vendors like Kinsa [98]. Kinsa already has 1,000,000 + consumer thermometers in use that report recorded temperatures and geolocation to its cloud service, and anomalies in this data can be used to more closely monitor emerging hotspots. At least one research group is using smartphone-recorded audio of coughs to detect COVID-19 and, in a non-peer-reviewed preprint, is reporting that they can obtain up to 81% specificity while maintaining > 99% sensitivity (or can obtain up to 89% sensitivity while maintaining > 99% specificity) for detecting COVID-19 on their dataset of COVID-19, pertussis, bronchitis, and healthy coughs [99]. However, generalizability in a prospective clinical trial still needs to be demonstrated [99]. In theory, this technology need not be restricted to use only in a medical center and could be a way for individuals to self-test in isolation. Another wearable technology is the Oura Ring (Oura; https://ouraring.com/), which tracks respiratory rate, body temperature, and heart rate to better detect early signs of COVID-19 infection, deployed in collaboration with University of California, San Francisco.

5.2 Innovative Non-wearable Technologies

Three-dimensional (3D) printing is a novel and innovative technology uniquely well-positioned to support challenges arising during the COVID-19 pandemic. 3D printing can be used to produce a tailored seal in N95 respirators masks. The mask

seal could be customized based on anthropometric data improving its comfort and fit. In a study using personalized mask seal prototypes, subjects showed improved contact pressure compared with commercially available respirator masks [100]. Currently, the FDA, National Institute of Health (NIH) 3D Print Exchange, and the United States Veterans' Association are making efforts to develop a 3D printed N95 mask prototype. It is worth noting that many researchers propose and test numerous face mask designs with variable degrees of success (Copper3D, https://copper3d.com/; Gladius Friends, http://gladius.si/; Lowell Makes, https://lowellmakes.com). It is important to remember that currently, only prototypes of N95 masks developed on 3D printing platforms are available, and local essential testing procedures assessing the quality of personal protective equipment (PPE) may have been modified from previously established N95 testing. Further modifications on PPE include protective surgical face shields securing the user's eyes and mouth. Shields are made of transparent, lightweight biomaterials that provide high optical clarity and can easily be printed using 3D technology [101]. A research group at MIT and Harvard (http://news.mit.edu/) are currently developing a mask that has embedded sensors which exhibit a fluorescent signal when a person with COVID-19 coughs, sneezes, or even breathes, in an effort to notify surrounding individuals. The group is in early stages of modifying the sensor so it can detect presence of SARS-CoV-2 genome when the user wears the mask and exhales, as a form of rapid detection.

After hospitalization, current diagnostic methods focus on determining the likelihood of a hospitalized patient progressing to ARDS, which is a significant fatal risk factor [88]. Regional shortages of crucial equipment for non-invasive ventilation have been recently observed due to the COVID-19. 3D printing technology can be successfully used to produce single-use ventilator valve sets using available biomaterials. Venturi valves [102], a crucial component of such equipment delivering oxygen at fixed concentrations for patients with ARDS, became difficult to reproduce or substitute during the observed increased demand. This extraordinary situation has successfully developed methods for producing these valves by the engineers at an Italian 3D printing startup [103]. However, manufacturing automated ventilators using 3D printing technology is still a challenge for engineers across the globe. Illinois Rapid-Vent (https://rapidvent.grainger.illinois.edu/) has designed a prototype of the open-source automated ventilator with flow-driven, pressure-controlled respiratory support systems featuring necessary valves and flexible membranes. While 3D-printed ventilators are still a work in progress, the alternative solution currently being applied is the production of 3D-printed ventilator splitters which allows a single ventilator to support multiple patients [104].

To confirm the diagnosis in a patient with suspected infection, RT-PCR helps to detect the nucleic acids of SARS-CoV-2 in the sputum, throat swabs, and lower respiratory tract samples [4]. 3D printing technology can also be implemented to improve the diagnostic process. COVID-19 testing capacity could be potentially increased by supporting manufacturing specimen collection kits with 3D-printed test swabs and it can be made from a flexible biomaterial with the micro-fine customized tip using design software.

It is expected that robust technologies constructed of cost-effective and readily available materials would lead to a more democratized medicine, especially

considering patients of varying socioeconomic backgrounds. However, at least within the USA, there is increasing disparity in healthcare access and resources between the wealthy and poor, despite progressive improvements in innovative technologies. Within the USA, individuals with the lowest incomes and education have consistently showed to be the least healthy among the populace, especially among both non-Hispanic Whites and Blacks [105]. It is commonplace that those of higher socioeconomic status tend to be early adopters and benefiters from the technologies above, as several studies have shown [106–108]. Importantly, this is not necessarily due to a difference in access but in societal structure and economics that put the disadvantaged often as an after-thought for stakeholders, assuming that benefits of emerging technology will trickle down equally [109].

5.3 Social Epidemiology and COVID-19 Complications

Understanding the social epidemiology of COVID-19 can help guide technology development by tailoring to highly susceptible populations, especially for those with increased comorbidities. A lack of data on population-based rates [11, 13] and systematic testing in the USA has led to an inability to draw exact conclusions from the available COVID-19-positive estimates [49]. Individuals of all ages succumbed to severe illness; those 65 and older [110] or with underlying comorbidities were affected the most according to international data [31]. China, Italy, and the USA reported higher death numbers of males [25]. The median age of infected patients in one study was 59 years [4]. As data emerges, several states show that black and Hispanic individuals make up a disproportionately high number of cases and deaths [111, 112]. The data from New York shows death rates among Blacks (265.0 deaths per 100,000 population as of May 13, 2020) and Hispanic/Latino persons (259.2) were substantially higher than that of Whites (130.3) or Asians (121.8) [113]. Reports within the USA indicate that African Americans are both three times more likely to get infected and six times more likely to die from COVID-19 when compared to American Caucasians [114]. For instance, in severely affected areas like Chicago, Louisiana, and Michigan, Blacks make up between 14 to 35% of the population but can account for up to 70% of deaths due to COVID-19 [114]. When considering the root causes of increased risk in these vulnerable populations, several factors have historically contributed to poorer health outcomes. Higher prevalence of associated comorbidities like hypertension, diabetes, body mass index (BMI > 30), and other cardiovascular diseases contribute to this disproportionate impact on Black and Hispanic Americans [3]. Additionally, Black populations are more prone to living in denser metropolitan areas plagued with "food deserts." Lack of proper nutrition and reduced access to healthcare are two factors known to result in increased comorbidities and mortality for Black Americans [114]. Often, Blacks do not occupy jobs that offer "privileges" such as teleworking or social isolation, but rather work in service sector jobs that rarely have the opportunity to maintain social distancing [114]. With the unfortunate combination of increased comorbidities plus adverse social determinants of health, Blacks are disproportionately facing the brunt of COVID-19 infections and mortality within the USA [114]. Taking all

this into account, any novel technical solution used for early detection and triage of COVID-19 cases should ideally be affordable, accessible, and applicable to susceptible populations [114].

Though a small percentage of the overall cases, COVID-19 can affect children. Of the 1.2 million cases within the pediatric population (age 0 to 17) by the end of 2020, children under four accounted for 7.4% of cases [115]. By March 2021, the number of pediatric cases rose to nearly 3.34 million across 49 states [116]. Similar to adult populations, ethnic minorities like Hispanics and Blacks were disproportionately affected, accounting for up to 41.3% of total pediatric cases [115]. In one study of 7480 children, boys and girls were affected almost equally, and presented primarily with fever, chills, and cough, with about 2% of children admitted to pediatric intensive care units [117]. Overall, COVID-19 appears to be milder in children than adults, likely due to less number of comorbidities at such young ages. In another study of 145 children, patients younger than 5 were observed to have equivalent or increased SARS-CoV-2 nucleic acid in their upper respiratory tract compared with adults or older children [118] However, early school closures within the USA likely thwarted an even higher surge in household cases due to school-age children spreading the virus to household members [115]. Multisystem inflammatory syndrome in children (MIS-C) is a rare condition associated with COVID-19 infection where various internal organs (e.g., heart, lungs, kidneys) incur inflammation, and children may exhibit fever, gastrointestinal upset, and lethargy [119]. In one study of 1116 children, MIS-C cases were more likely between 6 to 12 years of age, and of non-Hispanic Black ethnicity, with over 56% of patients having some form of cardiorespiratory involvement [120].

6 Conclusion

Wearable technology can be extremely helpful in disease prevention by tracking the infection chain, identifying infected patients, and maintaining social distancing (e.g., smartwatches, smart rings, smart thermometers, GPS-enabled fitness trackers). Some cellphone manufacturers have recently implemented contact tracing software within their operating systems, though this may also prompt future research studies into user privacy of technologies in disasters such as pandemics. Other non-wearable technologies could be crucial for drastically reducing the mortality observed among COVID-19 patients with cardiovascular and pulmonary comorbidities, (e.g., AI predictive algorithms, convolutional neural network, 3D printing). Emerging technologies can augment traditional prophylaxis such as social distancing, washing hands, refraining from touching one's face, and wearing face masks in public.

This is the first review study to outline and review preventative, diagnostic, and management technologies used against COVID-19, especially for patients with cardiovascular and pulmonary comorbidities. A flowchart of ACE2, cardiovascular disease progression, and appropriate stages of technological intervention are proposed. Novel cardiorespiratory systems, immunosensors, connected biomedical devices, and other innovations are discussed as points of intervention. This review emphasizes the need to develop future technologies that address patients from different

socioeconomic backgrounds, since there is an apparent disparity of mortality among different segments of the population. This is especially true since those with adverse social determinants of health are significantly more likely to be infected and die from COVID-19, as highlighted above. Therefore, innovative firms, researchers, and clinicians need to collaborate and develop novel cost-effective, attainable, and rapidly deployable solutions that mitigate the deadly consequences of COVID-19 and account for the socioeconomic disparities among affected populations.

Availability of Data and Material Not applicable.

Code Availability Not applicable.

Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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