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Clinical and Laboratory Predictors of Severity, Criticality, and Mortality in COVID-19: A Multisystem Disease

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Abstract

Coronavirus disease 2019 (COVID-19) pandemic continues devastating effects on healthcare systems. Such a crisis calls for an urgent need to develop a risk stratification tool. The present chapter aimed to identify laboratory and clinical correlates of adverse outcomes in patients with COVID-19. To this end, we conducted a systematic evaluation of studies that investigated laboratory abnormalities in patients with COVID-19 and compared i. patients with a severe form of disease and patients with a non-severe form of the disease, ii. patients who were in critical condition and patients who were not in critical condition, and iii. patients who survived and patients who died. We included 54 studies in the data synthesis. Compared to patients with a non-severe form of COVID-19, patients

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who had a severe form of disease revealed higher values for white blood cells (WBC), polymorphonuclear leukocytes (PMN), total bilirubin, alanine aminotransferase (ALT), creatinine, troponin, procalcitonin, lactate dehydrogenase (LDH), and D-dimer. By contrast, platelet count, lymphocyte count, and albumin levels were decreased in patients with a severe form of COVID-19. Also, patients with a severe phenotype of disease were more likely to have diabetes, chronic heart disease, chronic obstructive pulmonary disease (COPD), cerebrovascular disease, hypertension, chronic kidney disease (CKD), and malignancy. Compared to patients who survived, patients who died had higher WBC, PMN, total bilirubin, ALT, procalcitonin, IL-6, creatinine, PT, lymphocyte count, platelet count, and albumin. Also, non-survivors revealed a higher prevalence of diabetes, chronic heart disease, COPD, cerebrovascular disease, and CKD. Meta-analyses identified several laboratory parameters that might help the prediction of severe, critical, and lethal phenotypes of COVID-19. These parameters correlate with the immune system function, inflammation, coagulation, and liver and kidney function.

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Keywords

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22.1 Introduction

In December 2019, pneumonia cases with unknown etiology emerged in Wuhan, China (Lu et al.). Lower respiratory tract sampling and sequencing process could reveal a novel coronavirus from the family of betacoronavirus, which was subsequently named 2019 novel coronavirus (2019-nCoV) (Zhu et al. 2020). This family also included severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), which have caused outbreaks over the last two decades (Ksiazek et al. 2003; de Wit et al. 2016; Jabbari et al. 2020). Coronavirus disease 2019 (COVID-19) has rapidly spread throughout the world, posing a global emergency (Hanaei and Rezaei 2020; Rezaei 2020a).

The Chinese Centers for Disease Control and Prevention (CDC) has suggested classifying COVID-19 patients according to their clinical state into three categories. Mild disease manifestations include no pneumonia or mild pneumonia and occur in 81% of cases. Severe disease characterized by dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio < 300, and/or lung infiltrates >50% within 24–48 h is present in 14% of cases. Critical conditions accompanied by respiratory failure, septic shock, and/or multiple organ dysfunction or failure occur in 5% of cases (The Novel Coronavirus Pneumonia Emergency Response Epidemiology 2020). While most patients experience mild respiratory illness, some cases, especially the old population and patients with comorbid conditions, develop a severe form of disease requiring intensive management (Guan et al. 2020b; Lotfi and Rezaei 2020). Chinese CDC has reported an overall case fatality rate of

2.3%, with the majority of deceased patients being 60 years old and above and having preexisting comorbid conditions such as hypertension, cardiovascular disease, and diabetes (The Novel Coronavirus Pneumonia Emergency Response Epidemiology 2020; Shamshirian and Rezaei 2020). Accordingly, the resistance and susceptibility to disease are governed by genetic factors and nongenetic factors such as biological age, pregnancy, and chronic conditions, which affect the expression of the receptors which mediate virus entry, i.e., angiotensin-converting enzyme 2 (ACE2), and the function of the immune system (Yousefzadegan and Rezaei 2020; Ahmadi et al. 2020; Ahanchian et al. 2020; Darbeheshti and Rezaei 2020; Babaha and Rezaei 2020; Mirbeyk and Rezaei 2020).

With the increasing number of people infected with the virus, the burden of COVID-19 on healthcare systems has been overwhelming. Thus, early and efficient detection of high-risk patients is a priority for maximizing the utilization of limited resources, while current diagnostics are not as rapid and as reliable as the current pandemic condition needs (Basiri et al. 2020a). Furthermore, no clinically proven specific antiviral agent has been confirmed for COVID-19. However, approaches targeting the immune system and virus entry, computational methods of drug discovery, regenerative medicine, medical biotechnology, and picotechnology offer hope for the future amid the pandemic (Mohamed et al. 2020b; Rezaei 2020b; Rabiee et al. 2020; Basiri et al. 2020b; Sharifkashani et al. 2020; Lotfi et al. 2020; Mansourabadi et al. 2020; Pashaei and Rezaei 2020; Fathi and Rezaei 2020; Jahanshahlu and Rezaei 2020b). Thus supportive management, including oxygen therapy and conservative fluid management, along with anti-inflammatory and antiviral agents, remains to be the most important management strategy (Cascella et al. 2020; Saghazadeh and Rezaei 2020b). Dynamic changes of laboratory parameters, as well as clinical and imaging findings of patients infected with COVID-19, have been depicted in the literature (Zhou et al. 2020a; Liu et al. 2020a). Results are, however, not consistent. The present chapter aims to identify laboratory and clinical correlates of adverse outcomes in patients with COVID-19. For this purpose, a systematic evaluation of literature was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

22.2 Methods

22.2.1 Search Strategy

The published literature was searched from December 2019 to April 20, 2020. Databases including EMBASE, MEDLINE via PubMed, and Scopus were searched for observational studies of COVID-19. The keywords for search strategy included "Wuhan seafood market pneumonia virus," "COVID19," "2019-nCoV," "novel coronavirus," "coronavirus disease-19," "severe acute respiratory syndrome coronavirus 2," "SARS-CoV-2," "characteristic," "finding," "lab," "imaging," "comorbidit*," "sever*," "critical," "hospital*," "ICU," "non-ICU," "death," "mortality," and "surviv*." Detailed search strategies are presented in Table 22.1.

22.2.2 Study Selection

The studies identified were imported into an EndNote library. After duplicate removal, the two groups (three reviewers in each group) performed the screening titles and abstracts for inclusion and then reviewing the full text of potentially relevant articles. Any questions or conflicts were resolved through discussion with the members of the other group. Concerning studies with overlapping samples, the study that had the largest sample size was included in the final analysis. Studies that i. included subjects with confirmed COVID-19 based on laboratory testing; ii. evaluated individual laboratory characteristics, symptoms, and comorbidities in predicting severe COVID-19 infection or mortality caused by COVID-19 infection; and iii. were written in English were eligible to be included in the systematic review. If the criteria for disease severity were not determined, then the study was excluded

Table 22.1 Search strategy

Database	Search date	Search strategy	Number of search results
Embase	March 20, 2020	(characterist* OR finding$ OR feature$ OR lab OR labrat* OR imaging? OR radiolog* OR "ct scan" OR "computed tomograph*" OR clinical OR comorbidit* OR symptom* OR discript*) AND (sars2 OR "covid-19" OR "2019-ncov" OR "coronavirus disease 2019" OR "novel coronavirus" OR "coronavirus disease-19" OR "severe acute respiratory syndrome coronavirus 2" OR "sars-cov-2" OR "Wuhan coronavirus" OR "ncov-2019" OR "Wuhan seafood market pneumonia virus" OR "covid19 virus") AND ((sever* OR critical OR hospital* OR icu OR intensive) AND care OR death OR mortality OR surviv* OR fatal* OR "disease progression" OR "invasive management" OR outcome OR predic* OR prognos* OR "risk factor" OR (risk NEAR/2 factor NEAR/2 (mortality OR sever*)) OR correlat* OR (risk NEAR/2 death) OR "non-icu" OR "mechanical ventilation" OR "respiratory failure") AND [english]/lim AND [2019–2020]/py	162
Scopus	March 20, 2020	(characterist* OR finding OR feature OR lab OR labrat* OR imaging OR radiolog* OR ct_scan OR computed_ tomograph* OR clinical OR comorbidit* OR symptom* OR discript*) AND (sars2 OR covid_19 OR 2019_ncov OR coronavirus_disease_2019 OR novel_coronavirus OR coronavirus_disease-19' OR severe_acute_respiratory_syndrome_ coronavirus_2 OR sars_cov_2 OR wuhan_coronavirus OR ncov_2019 OR wuhan_seafood_market_pneumonia_virus OR covid19_virus) AND ((sever* OR critical OR hospital* OR icu OR intensive) AND care OR death OR mortality OR surviv* OR fatal* OR 'disease AND progression' OR invasive_management OR outcome OR predic* OR prognos* OR risk_factor OR (risk W/2 factor W/2 (mortality OR sever*)) OR correlat* OR (risk W/2 death) OR non_icu OR mechanical_ventilation OR respiratory_failure) AND (LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019)) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SUBJAREA, "MEDI"))	195
PubMed	March 20, 2020	((((characteristic) OR (finding) OR (feature) OR (lab) OR (laboratory) OR (imaging) OR (radiolog*) OR (CT scan) OR (computed tomography) OR (clinical) OR (comorbidit*) OR (symptom))) AND ((SARS2) OR (Wuhan seafood market pneumonia virus) OR (COVID19 virus) OR(COVID-19) OR (2019-nCoV) OR (coronavirus disease 2019) OR (novel coronavirus) OR (coronavirus disease-19) OR (severe acute respiratory syndrome coronavirus 2) OR (SARS-CoV-2) OR (Wuhan coronavirus) OR (nCoV-2019))) AND ((sever*) OR (critical) OR (hospital*) OR (ICU) OR (non-ICU) OR (intensive care) OR (death) OR (mortality) OR (surviv*) OR (fatal*) OR (disease progression) OR (invasive management) (predic*) OR (prognosis)OR (risk factor)OR (risk factor n2 mortality) OR (risk factor n2 sever*) OR (correlat*) OR (influencing factors) OR (risk n2 death) OR (outcome) OR (PaO2/FiO) OR (mechanical ventilation) OR (respiratory failure))	104

Table 22.2 The definition of outcome and population

	Definition
Laboratory-confirmed case	The laboratory-confirmed case was defined as the presence of SARS-CoV-2 in respiratory specimens (including nasal and pharyngeal swabs) detected by the reverse-transcriptase polymerase chain reaction (RT-PCR), according to the protocol established by the World Health Organization
Severe disease	The following criteria defined severe disease: 1) respiratory distress (respiratory rate ≥ 30 breaths/minute); 2) an oxygen saturation (SpO2) ≤ 93% in the resting state; 3) hypoxemia defined as an arterial partial pressure of oxygen divided by the fraction of inspired oxygen (PaO2/FiO2 ratio) ≤ 300 mmHg; 4) the presence of radiographic progression, defined as ≥50% increase of target lesion within 24–48 hours. The criterion was based on the Chinese COVID-19 prevention and control program (seventh edition, http://en.nhc.gov.cn/2020-03/29/c_78469.htm) and American Thoracic Society guideline (Mandell et al. 2007) and World Health Organization interim guidance

(Table 22.2). Also, types of articles other than original observational studies, e.g., opinion, editorial, case report, book chapter, review, and meta-analysis, studies confined to the pediatric population or pregnant women, and studies rated as low-quality evidence were not included.

22.2.3 Data Extraction and Quality Assessment

We used the Newcastle-Ottawa scale (NOS) and its modified version for the assessment of the quality of retrospective cohort studies and cross-sectional studies. This scale gives the maximum score of 9 points for the least risk of bias in four domains: the selection of study groups (4 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points). Age and sex were defined as the most relevant covariate for comparability. For the cross-sectional studies, we used the modified NOS, which gives a maximum of 10 scores for the least risk of bias in three domains: the selection of study groups (5 points), comparability of groups (2 points), and ascertainment of exposure and outcomes (3 points).

Three authors independently extracted the data by a predesigned spreadsheet in Excel, including the author's name, publication year, setting (country/hospital name), study design, sample size, clinical and laboratory and comorbidities, and severity criteria.

22.2.4 Data Synthesis

All between-group meta-analyses were performed using Comprehensive Meta-Analysis. For the continuous type of outcome, we entered the number of participants in two groups and the mean and standard deviation (SD) of laboratory data. We used methods described in Luo et al. (2018) and Wan et al. (2014) to estimate mean and SD based on median (IQR). A meta-analysis was conducted for data on laboratory and clinical characteristics, comorbidities, and vital status when there were at least three between-group comparisons for each variable. Because studies used different measurement scales, we employed the standardized mean difference (SMD) as effect size (ES) measure. For categorical data, we used the dichotomous method to calculate the odds ratio (OR) with its 95% confidence interval as ES measure. As explained by Higgins and Green et al., the ES of 0.2, 0.5, and 0.8 represent small, moderate, and large effect estimates, respectively (Higgins and Wells 2011).

We investigated heterogeneity across studies by Cochran's Q test, which is calculated by the weighted sum of squared differences between individual study ES estimates. A P-value of 0.10 or less indicates the presence of heterogeneity. The I2 index was used to get a more precise estimate of heterogeneity. If the I2 is less than 40%, the heterogeneity is considered to be not significant. The fixed-effects model is the preferred method of meta-analysis. However, if I2 estimates exceeded 40%, the random-effects approach was applied as the meta-analysis model. We based our analysis on the different outcome stratification including critical/ICU vs noncriti-

cal/non-ICU, severe/critical vs non-severe, and survivors vs non-survivors. Subgroup analysis was performed to explore the potential sources for heterogeneity. We also applied univariate meta-regression analyses to investigate the effect of potential moderators, e.g., sample size, the difference in the mean age of two groups (years), and percentage of female patients on the effect size and heterogeneity. Finally, to identify studies exerting excessive influence on the results or causing high heterogeneity among studies, we conducted a sensitivity analysis by systematically excluding each study at a time and then rerunning the analysis to assess the change in ES.

We assessed publication bias visually by the degree of funnel plot asymmetry and used Begg-Mazumdar Kendall's tau (Begg and Mazumdar 1994) and Egger bias test to quantify it (Duval and Tweedie 2000). A P-value of 0.10 or less suggests the presence of publication bias across studies. The trim and fill method was used to adjust effect sizes in cases that there was evidence of publication bias (Duval and Tweedie 2000).

22.3 Results

22.3.1 Characteristics of Selected Studies

The database search resulted in 461 records. After the removal of duplicates (n = 60) and retrieval of additional 14 studies through hand search of additional references, the title/abstract of 415 search results was screened for potential eligibility. Three hundred forty papers were excluded through screening. Seventy-five full-text articles were reviewed in detail, and 32 met the inclusion criteria. Moreover, an updated search was conducted and resulted in the inclusion of 22 studies. In total, 54 studies were included in the meta-analysis. Figure 22.1 provides an overview of study selection for systematic review and meta-analysis according to PRISMA guidelines.

22.3.2 Study and Patient Characteristics

As summarized in Table 22.3, all included studies were from China, except two studies, which were from Singapore (Young et al. 2020; Fan et al. 2020). All studies were designed as retrospective cohort studies except two with a prospective cohort design (Liu et al. 2020b; Momtazmanesh et al. 2020) and one which was a cross-sectional study (Zhang et al. 2020b). Tables 22.4 and 22.5 show the results of the quality assessment for studies included in the data synthesis.

There were 16 studies that compared critical or severe vs non-severe patients (Zhao et al. 2020; Zhang et al. 2020a; Guan et al. 2020b; Li et al. 2020a; Zhou et al. 2020b; Cai et al.; Tian et al. 2020; Liu et al. 2020b, d; Wu et al. 2020; Feng et al. 2020c; Wan et al. , 2020; Xu et al. 2020; ; Han et al. 2020b; Wang et al. 2020d); 3 studies compared 3 groups of patients, namely, critical, severe, and non-severe (Feng et al. 2020b; Liu et al. 2020c; Han et al. 2020a); 20 studies compared severe vs non-severe patients (Qu et al. 2020; Zhang et al. 2020b, c; Wang et al. 2020e; Cao 2020; Gao et al. 2020; Chen et al. 2020a, e; Liu et al. 2020a; lei and Jian-ya 2020; Lu et al. 2020; Chu et al. 2020; Ji et al. 2020; Xie et al. 2020; Zheng et al. 2020a; c; Li et al. 2020c; Gong et al. 2020; Young et al. 2020; Qin et al. 2020; Nie et al. 2020); 6 studies compared critical/ICU vs noncritical/non-ICU patients (Wang et al. 2020a; Fan et al. 2020; Du et al. 2020; Yan et al. 2020; Huang et al. 2020; Chen et al. 2020b); and 9 studies compared survivor vs non-survivor patients (Tang et al. 2020; Yang et al. 2020; Zhou et al. 2020a; Wu et al. 2020; Momtazmanesh et al. 2020; Chen et al. 2020c, d; Li et al. 2020c; Wang et al. 2020c; Cao et al. 2020). Two studies were not entered into analysis because of the shared samples (Chen et al. 2020c; Huang et al. 2020). A total of 8603 patients were included in the meta-analysis. Tables 22.6, 22.7, 22.8, 22.9, 22.10, 22.11, and 22.12 provide a summary of the

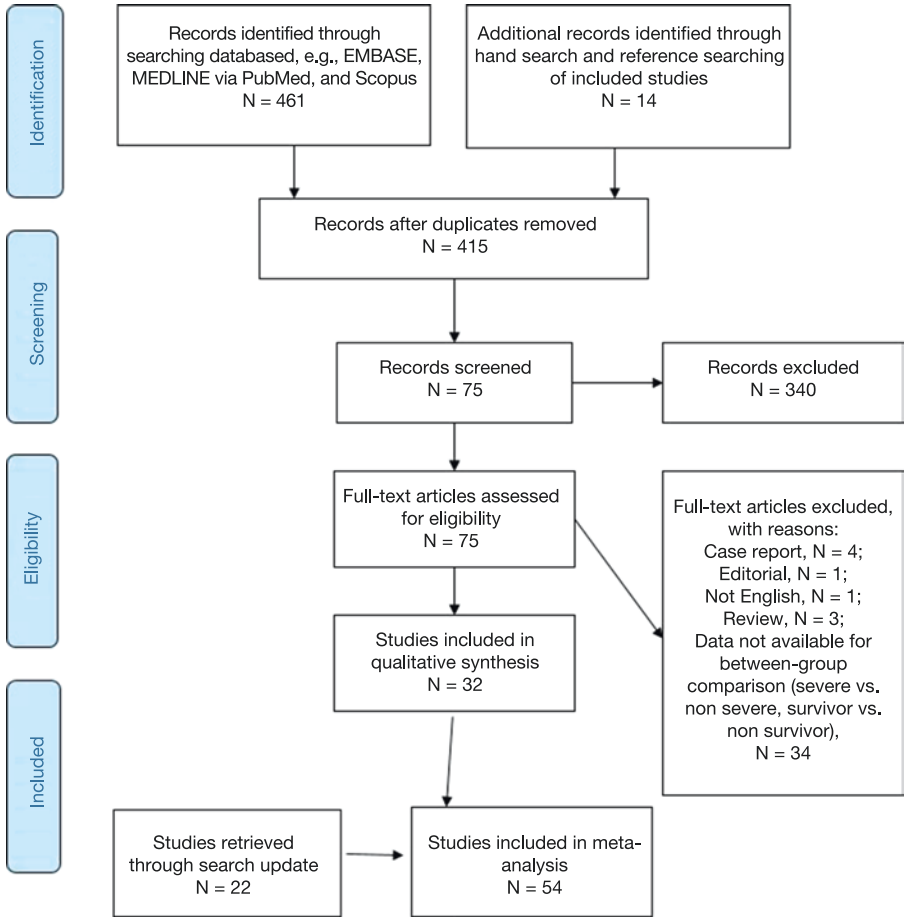

Fig. 22.1 PRISMA flow diagram of study selection

results of meta-analyses, subgroup analyses, and meta-regressions.

22.3.3 Laboratory Findings

22.3.3.1 Severity Analysis

Twenty-seven studies provided data on white blood cell (WBC) values for patients with severe (n = 1131) and non-severe (n = 3293) COVID-19. Meta-analysis showed that patients with non-severe outcome had lower WBC compared to patients with severe COVID-19 (SMD −0.40; 95% CI, −0.58, −0.21; P < 0.0001). There was no evidence of publication bias (Begg's P = 0.77; Egger's P = 0.10). Significant heterogeneity existed across studies (I2 = 84%), and therefore, the random-effects model was applied. Meta-regression analyses demonstrated no significant effect of percentages of female patients, the difference in the mean age, and sample size on the heterogeneity. Neither subgroup meta-analyses nor sensitivity analysis showed a significant effect of specific outcome or study on the effect size and related heterogeneity. Meta-analysis of data on four studies showed that critical COVID-19 patients (n = 131) had higher WBC than noncritical COVID-19 patients (n = 348) (SMD −0.58; 95% CI, −0.79, −0.37; P < 0.0001). There was no significant heterogeneity and evidence of publication bias as well.

Pooled data from 22 studies, including 2215 non-severe and 1109 severe COVID-19 patients, demonstrated that polymorphonuclear (PMN)

Table 22.3 Characteristics of studies included in the systematic review

Study	Setting			Sample size	Outcomes	Adverse outcome			Non-adverse outcome		
	Country	City	Hospital			Patients (%)	Age	Female %	Patients (%)	Age	Female %
Zhao et al.	China	Four institutions in Hunan province		101	Non-severe vs severe	14 (13.86%)	53.71 (12.6)	44.83%	87 (86.14%)	42.94 (11.7)	42.86%
Zhang et al.	China	Wuhan	Zhongnan Hospital of Wuhan University	221	Non-severe vs severe	55 (24.89%)	62.0 (52.0–74.0)	36.36%	166 (75.11%)	51 (36.0–64.3)	56.02%
Guan et al.	China	552 hospitals in 30 provinces		1099	Non-severe vs severe	173 (15.74%)	52.0 (40.0–65.0)	42.20%	926 (84.26%)	45.0 (34.0–57.0)	41.82%
Li et al.	China	Multicenter		83	Non-severe vs severe	25 (30.12%)	53.7 (12.3)	40.00%	58 (69.88%)	41.9 (10.6)	50.00%
Zhou et al.	China	Wuhan	CentralHospital of Wuhan	377	Non-severe vs severe	117 (31.03%)	65.63 (14.03)	41.88%	260 (68.97%)	48.35 (16.17)	60.77%
Cai et al.	China	Shenzhen	Third People's Hospital of Shenzhen	298	Non-severe vs severe	58 (19.46%)	62.5 (56–66)	43.10%	240 (80.54%)	41 (31–56)	53.75%
Tian et al.	China	57 hospitals across Beijing		262	Non-severe vs severe	46 (17.56%)	61.4 (1–94)	43.48%	216 (82.44%)	44.5 (1–93)	53.24%
Liu et al.	China	Wuhan	Central Hospital of Wuhan	109	Non-severe vs severe	53 (48.62%)	61 (52–70)	47.17%	56 (51.38%)	49 (37–59)	44.64%
Liu et al.	China	Beijing	Beijing Ditan Hospital	61	Non-severe vs severe	17 (27.87%)	56 (34–73)	41.18%	44 (72.13%)	41 (1–76)	52.27%
Wu et al.	China	Wuhan	Jinyintan Hospital	201	Non-severe vs severe	84 (41.79%)	58.5 (50.0–69.0)	28.57%	117 (58.21%)	48.0 (40.0–54.0)	41.88%
				84	Survivor vs non-survivor	44 (52.38%)	68.5 (59.3–75.0)	34.09%	40 (47.62%)	50.0 (40.3–56.8)	22.50%
Feng et al.	China	Changsha	Third Xiangya Hospital, Changsha Public Health Treatment Center, Second People's Hospital of Hunan	141	Non-severe vs severe	15 (10.64%)	58 (44–66)	53.33%	126 (89.36%)	41 (33–52)	48.41%

Wan et al.	China	Chongqing	Three Gorges Central Hospital	123	Non-severe vs severe	21 (15.22%)	61.29 ± 15.55	47.62%	102 (73.91%)	43.05 ± 13.12	46.08%
Xu et al.	China	Single center		50	Non-severe vs severe	13 (26%)	60.2 (34–85 range)	46.15%	37 (74%)	36.75 (3–62 range)	40.54%
Wan et al.	China	Chongqing	Three Gorges Central Hospital	135	Non-severe vs severe	40 (29.63%)	56 (52–73)	47.50%	95 (70.37%)	44 (33–49)	45.26%
Han et al.	China	Wuhan	Renmin Hospital of Wuhan University	47	Non-severe vs severe	24 (51.06%)	65.08 (31–87)	29.17%	23 (48.94%)	64.74 (41–81)	60.87%
Qu et al.	China	Huizhou	Huizhou Municipal Central Hospital	30	Non-severe vs severe	3 (10%)	60 ± 5.29	NA	27 (9%)	49.44 ± 14.86	NA
Zhang et al.	China	Wuhan	No. 7 Hospital of Wuhan	140	Non-severe vs severe	58 (41.43%)	64 (25–87)	43.10%	82 (58.57%)	51.5 (26–78)	53.66%
Wang et al.	China	Wuhan	Union Hospital	69	Non-severe vs severe	14 (20.29%)	70.5 (62.0–77.0)	50.00%	55 (79.71%)	37.0 (32.0–51.0)	54.55%
Cao et al.	China	Xiangyang	Xiangyang No 1 Hospital	128	Non-severe vs severe	21 (16.41%)	NA	42.86%	107 (83.59%)	NA	55.14%
Gao et al.	China	Fuyang	Fuyang Second People's Hospital	43	Non-severe vs severe	15 (34.88%)	45.20 ± 7.68	40.00%	28 (65.12%)	42.96 ± 14.00	39.29%
Chen et al.	China	Wuhan	Tongji Hospital	21	Non-severe vs severe	11 (52.38%)	61.0 (56.5–66.0)	9.09%	10 (47.62%)	52.0 (42.8–56.0)	30.00%
Liu et al.	China	Wuhan	Union Hospital	40	Non-severe vs severe	13 (32.5%)	59.7 ± 10.1	46.15%	27 (67.5%)	43.2 ± 12.3	70.37%
Liu et al.	China	Chongqing	Three Gorges Hospital	51	Non-severe vs severe	7 (13.73%)	52 (44–60)	42.86%	44 (86.27%)	44 (33–49)	36.36%
Zhang et al.	China	Chongqing	Chongqing Public Health Medical Center	43	Non-severe vs severe	14 (32.56%)	61.7 ± 9.22	64.29%	29 (67.44%)	44.34 ± 15.84	41.38%
Lu et al.	China	Wuhan	Wuhan Hankou Hospital	577	Non-severe vs severe	100 (17.33%)	61 (49–71)	50.00%	338 (58.58%)	57 (43–65)	54.44%
Chu et al.	China	Wuhan	Tongji Hospital	54	Non-severe vs severe	43 (79.63%)	38 (26–66)	30.23%	11 (20.37%)	47 (36–73)	45.45%

(continued)

Table 22.3 (continued)

Study	Setting			Sample size	Outcomes	Adverse outcome			Non-adverse outcome		
	Country	City	Hospital			Patients (%)	Age	Female %	Patients (%)	Age	Female %
Ji et al.	China	Fuyang and Beijing	Fuyang Second People's Hospital, Fifth Medical Center of Chinese PLA General Hospital	208	Non-severe vs severe	40 (19.23%)	57.7 ± 15.9	30.00%	168 (80.77%)	40.7 ± 14.7	47.02%
Xie et al.	China	Wuhan	Jinyintan Hospital	79	Non-severe vs severe	28 (35.44%)	62.5 (50.5–67.8)	NA	51 (64.56%)	59.0 (46.0–66.0)	NA
Zheng et al.	China	Changsha	North Hospital of Changsha First Hospital (Changsha Public Health Treatment Center)	161	Non-severe vs severe	30 (18.63%)	57 (46.5–66)	50.00%	131 (81.37%)	40 (31–51)	41.22%
Zheng et al.	China	Chengdu	Chengdu Public Health Clinical Medical Center	99	Non-severe vs severe	32 (32.32%)	63.81 ± 16.51	40.63%	67 (67.68%)	42.51 ± 15.11	52.24%
Li et al.	China	Wuhan	Department of Thoracic Surgery of Tongji Hospital	25	Non-severe vs severe	9 (36%)	NA	33.33%	16 (64%)	NA	62.5%
				25	Survivor vs non-survivor	5 (20%)	NA	20%	20 (80%)	NA	60%
Gong et al.	China	Guangzhou and Wuhan	Guangzhou Eighth People's Hospital, Zhongnan Hospital of Wuhan University, and the Third Affiliated Hospital of Sun Yat-sen University, China	372	Non-severe vs severe	28 (7.53%)	63.5 (54.5–72.0)	42.86%	161 (43.28%)	45.0 (33.0–62.0)	55.28%

Young et al.	Singapore	4 hospitals in Singapore		18	Non-severe vs severe	6 (33.33%)	56 (47–73)	66.67%	12 (66.67%)	37 (31–56)	41.67%
Feng et al.	China	Wuhan, Shanghai and Anhui Province	Jinyintan Hospital, Shanghai Public Health Clinical Center and Tongling People's Hospital	476	Non-severe vs severe	124 (26.05%)	58.54 ± 14.38	34.68%	352 (73.94%)	50.29 ± 19.35	46.02%
Liu et al.	China	6 hospitals in Anhui province		67	Non-severe vs severe	24 (32.81%)	46.55 ± 14.30	58.33%	43 (67.19%)	33.4 ± 12.2	34.88%
Han et al.	China	Wuhan	Renmin Hospital of Wuhan University	273	Non-severe vs severe	75 (27.47%)	58.68 ± 14.80	65.33%	198 (72.52%)	58.95 ± 10.8	64.14%
Nie et al.	China	Wuhan	Renmin Hospital	67	Non-severe vs severe	25 (25.77%)	58 (47–67)	48.00%	72 (74.23%)	37 (29–55)	70.83%
Qin et al.	China	Wuhan	Tongji Hospital	452	Non-severe vs severe	286 (63.27%)	61 (51–69)	45.80%	166 (36.73%)	53 (41.25–62)	51.81%
Wang et al.	China	Suzhou	Suzhou Fifth People's Hospital	69	Non-severe vs severe	18 (26.09%)	46.0 (37.3–60.3)	27.78%	51 (73.91%)	41.0 (35.0–57.0)	43.14%
Wang et al.	China	Wuhan	Zhongnan Hospital	138	ICU vs non-ICU	36 (26.09%)	66 (57–78)	38.89%	102 (73.91)	51 (37–62)	48.04%
Fan et al.	Singapore	NA	National Centre for Infectious Diseases (NCID)	67	ICU vs non-ICU	9 (13.43%)	54 (47–62)	33.33%	58 (86.57%)	41 (32–53)	46.55%
Du et al.	China	Wuhan	Wuhan Pulmonary Hospital, Tianyou Hospital, Central Hospital of Wuhan	109	ICU vs non-ICU	51 (46.79%)	68.4 ± 9.7	29.41%	58 (53.21%)	72.7 ± 11.6	34.48%
Yan et al.	China	Hainan province	Hospital of Hainan Medical University	168	Critical vs noncritical	36 (21.43%)	61 (50.3–68)	41.67%	132 (78.57%)	49 (34–60)	54.55%

(continued)

Table 22.3 (continued)

Study	Setting			Sample size	Outcomes	Adverse outcome			Non-adverse outcome		
	Country	City	Hospital			Patients (%)	Age	Female %	Patients (%)	Age	Female %
Tang et al.	China	Wuhan	Tongji Hospital	183	Survivor vs non-survivor	21 (11.48%)	64.0 ± 20.7	23.81%	162 (88.52%)	52.4 ± 15.6	50.62%
Yang et al.	China	Wuhan	Jinyintan Hospital	52	Survivor vs non-survivor	32 (61.54%)	64·6 ± 11·2	34.38%	20 (38.46%)	51·9 ± 12·9	30.00%
Zhou et al.	China	Wuhan	Jinyintan Hospital and Wuhan Pulmonary Hospital	191	Survivor vs non-survivor	54 (28.27%)	69.0 (63.0–76.0)	29.63%	137 (71.23%)	52.0 (45.0–58.0)	40.88%
Du et al.	China	Wuhan	Wuhan Pulmonary Hospital	179	Survivor vs non-survivor	21 (11.73%)	70.2 ± 7.7	52.38%	158 (88.27%)	56.0 ± 13.5	44.94%
Chen et al.	China	Wuhan	Tongji Hospital	274	Survivor vs non-survivor	113 (41.24%)	68.0 (62.0–77.0)	26.55%	161 (58.76%)	51.0 (37.0–66.0)	45.34%
Wang et al.	China	Wuhan	Tongji Hospital	344	Survivor vs non-survivor	133 (38.66%)	70 (62–77)	44.36%	211 (61.34%)	57 (47–69)	50.24%
Cao et al.	China	Wuhan	Wuhan University Zhongnan Hospital	102	Survivor vs non-survivor	17 (16.67%)	72 (63–81)	23.53%	85 (83.33%)	53 (47–66)	52.94%
Huang et al.	China	Wuhan	Jinyintan Hospital	41	ICU vs non-ICU	13 (31.71%)	49·0 (41·0–61·0)	15.38%	28 (68.29%)	49·0 (41·0–57·5)	32.14%
Chen et al.	China	Shanghai	Shanghai Public Health Clinical Center (SPHCC)	249	ICU vs non-ICU	22 (8.84%)	NA	NA	227 (91.16%)	NA	NA
Chen et al.	China	Wuhan	Zhongnan Hospital of Wuhan University	55	Survivor vs non-survivor	19 (34.55%)	77 (median)	15.79%	36 (65.45%)	72 (median)	50.00%
Chen et al.	China	Guangzhou	Guangzhou Eighth People's Hospital	57	Mild vs severe	18 (31.58%)	NA	NA	39 (68.42%)	NA	NA

Table 22.4 The results of quality assessment for cohort studies included in the systematic review

Study	Selection	Comparability	Outcome
Wang et al. (2020a)	***	*	**
Wang et al. (2020d)	***	*	**
Cao (2020)	***	*	*
Huang et al. (2020)	***	**	***
Chen et al. (2020b)	***	**	***
Gao et al. (2020)	****	**	*
Guan et al. (2020a, b)	***	--	**
Yang et al. (2020)	***	--	***
Li et al. (2020a)	***	*	**
Xu et al. (2020)	***	*	---
Fan et al. (2020)	***	*	**
Zhou et al. (2020a, b)	****	**	***
Cai et al.	***	**	**
Liu et al. (2020d)	***	*	***
Tian et al. (2020)	***	*	**
Liu et al. (2020b)	***	**	***
Wu et al. (2020)	***	**	***
Liu et al. (2020a)	***	*	**
Zhang et al. (2020a)	***	--	**
Zhang et al. (2020c)	***	--	**
Qu et al. (2020)	***	*	**
Tang et al. (2020)	****	--	**
Zhao et al. (2020)	***	--	**
Feng et al. (2020b)	****	*	***
Zhang et al. 2020b)	***	**	**
lei and Jian-ya (2020)	***	*	***
Wan et al. (2020)	***	--	**
Momtazmanesh et al. (2020)	****	**	***
Chen et al. (2020e)	***	--	**
Lu et al. (2020)	***	**	***
Chu et al. (2020)	**	*	**
Ji et al. (2020)	****	**	***
Li et al. (2020b)	***	*	**
Liu et al. (2020c)	***	--	**
Wang et al. (2020b)	****	*	***
Xie et al. (2020)	***	**	**
Zheng et al. (2020a)	***	*	**
Chen et al. (2020c)	***	*	**
Chen et al. (2020d)	****	--	*
Han et al. (2020b)	***	*	***
Feng et al. (2020a)	***	**	***
Wan et al.	***	*	**
Du et al. (2020)	***	*	**
Han et al. (2020a)	***	--	**
Zheng et al. (2020b)	***	--	**
Yan et al. (2020)	***	*	**
Cao et al. (2020)	****	*	***
Young et al. (2020)	***	--	***
Gong et al. (2020)	***	*	***

(continued)

Table 22.4 (continued)

Study	Selection	Comparability	Outcome
Nie et al. (2020)	***	*	***
Qin et al. (2020)	***	*	**
Wang et al. (2020c)	***	**	**
Chen et al. (2020a)	***	*	**

Table 22.5 The results of quality assessment for a cross-sectional study included in the systematic review

Author	Selection	Comparability	Outcome
Zhou et al. (2020a, b)	***	*	**

cell counts were increased in severe compared to non-severe patients (SMD −0.72; 95% CI, −0.88, −0.57; P < 0.0001). There was significant heterogeneity among studies (I2 = 64%). No evidence of publication bias was observed (Begg's P = 0.498; Egger's P = 0.496). Meta-analysis for data derived from four studies comparing critical and noncritical COVID-19 patients showed a similar result with the SMD of −0.74 (95% CI, −1.10 to −0.39; P < 0.0001). Critical patients had higher PMN compared to the noncritical group.

Patients with severe outcomes (n = 1890) had lower lymphocyte count compared to non-severe patients (n = 4035) (SMD 0.68; 95% CI, 0.53, 0.84; P < 0.0001). Heterogeneity was high (I2 = 80%). Also, critical patients had lower lymphocyte counts than noncritical patients.

Patients with severe disease (n = 2288) had significantly lower platelets than non-severe cases (n = 627) with an SMD of 0.21 (95% CI, 0.06, 0.35; P = 0.004). Moderate heterogeneity was present (I2 = 50.5%). No evidence of publication bias was observed (Begg's P = 0.707; Egger's P = 0.241).

Eight studies documented CD4 counts for 506 non-severe and 587 severe patients. Because of evidence of publication bias (Begg's P = 0.009), the ES was adjusted using trim and fill method, resulting in an ES of 0.80 (95% CI, −0.06, 1.62), which showed no significant difference between severe and non-severe patients in regard to CD4 counts. Heterogeneity was high (I2 = 96%).

Total bilirubin (TB) was investigated in 15 studies, with a total of 1528 non-severe and 650 severe individuals. Severe patients had higher TB compared to the non-severe group (SMD −0.33; 95% CI, −0.46, −0.21, P < 0.0001), and no substantial heterogeneity was seen (I2 = 31%).

Alanine transaminase (ALT) was documented in 23 studies accounting for a total of 1875 non-severe and 775 severe patients. ALT levels were higher in severe patients than non-severe patients (SMD −0.52; 95% CI, −0.77, −0.27; P < 0.0001). There was evidence of publication bias (Begg's P = 0.009). The ES was adjusted using the trim and fill method and estimated to be about −0.56 with 95% CI, −0.79, −0.32. There was high heterogeneity across studies (I2 = 85.5%). A sensitivity analysis showed that I2 dropped to 49% with the associated ES of −0.36 (95% CI, −0.50, −0.22) when the study (Zheng et al. 2020a) was excluded. Similarly, AST levels were higher in severe patients compared to non-severe patients (SMD −0.79; 95% CI, −1.00, −0.58; P < 0.0001). Heterogeneity was high (I2 = 74.5%). Critical patients had higher AST and ALT levels compared to noncritical patients (SMD −0.78; 95% CI, −1.27, −0.29; and SMD −0.45; 95% CI, −0.68, −0.22), respectively.

Creatinine was increased in severe patients (n = 751) compared to non-severe patients (n = 2320) (SMD −0.21; 95% CI, −0.34, −0.08; P = 0.001). No evidence of publication bias was found (Begg's P = 0.785; Egger's P = 0.282). Moderate heterogeneity was seen (I2 = 52%). Furthermore, BUN was higher in severe patients than non-severe patients (SMD −0.55; 95% CI, −0.93, −0.17; P < 0.0001).

Severe patients showed no difference in potassium levels compared with non-severe patients (SMD = 0.18, p = 0.269). However, the exclusion of a study (Feng et al. 2020b) could resolve heterogeneity (I2 = 0.0), and the ES became significant (SMD 0.25; 95% CI, 0.12, 0.39; P < 0.0001). Sodium levels were not different between severe and non-severe patients, and sensitivity analysis

Table 22.6 Summary of the results of meta-analyses of clinical and laboratory characteristics of patients with COVID-19: patients who survived versus patients who died

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Survived	Died	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger's test
WBC	5	707	365	−1.01	−1.33	−0.696	<0.0001	78.57	18.67	0.001	0.327	0.356
PMN	4	570	311	−1.05	−1.53	−0.584	<0.0001	87.76	24.52	<0.0001	0.734	0.191
Lymphocyte	6	727	397	0.97	0.52	1.43	<0.0001	89.79	48.97	<0.0001	0.024	0.0437
Platelet	5	569	376	0.45	0.19	0.70	0.001	67.56	12.33	0.015	0.0864	0.0717
Hb	3	318	199	0.08	0.10	1.26	0.383	0.00	0.59	<0.0001	1	0.713
Ferritin	3	259	223	−1.03	−1.23	−0.83	<0.0001	0.00	22.64	<0.0001	0.296	0.422
TnI	3	415	277	−3.08	−1.041	−0.722	<0.0001	0.00	1.038	<0.0001	0.296	0.149
CRP	4	554	296	−4.09	−1.49	−0.4	0.001	90.47	31.49	<0.0001	0.734	0.171
PCT	4	622	301	−1.05	−1.27	−0.83	<0.0001	48.37	5.81	0.121	0.734	0.320
CK	3	504	298	−0.78	−0.93	−0.63	<0.0001	0.00	1.74	0.418	1.00	0.636
AST	4	570	311	−0.52	−1.066	0.027	0.062	91.46	35.14	<0.0001	0.734	0.115
ALT	5	705	365	−0.36	−0.54	−0.17	<0.0001	44.65	7.22	0.124	0.462	0.236
TB	5	590	343	−0.79	−1.01	−0.56	<0.0001	49.29	7.88	0.096	0.308	0.097
Alb	5	496	232	0.88	0.46	1.30	<0.0001	87.95	33.21	<0.0001	0.086	0.091
PT	7	880	418	−0.78	−1.89	−0.37	<0.0001	88.54	52.36	<0.0001	1.00	0.345
PTT	4	521	199	0.26	−0.62	0.41	0.695	86.19	21.72	<0.0001	0.308	0.903
Cr	5	590	343	−0.34	−0.77	0.09	0.123	87.55	32.13	<0.0001	1.00	0.898
IL-6	4	498	284	−1.22	−1.38	−1.07	<0.0001	0.00	2.80	0.422	0.734	0.541
D-dimer	5	677	349	−0.66	−1.10	−0.22	0.003	89.02	36.44	<0.0001	0.22	0.32
Fever[a]	7	601	551	1.077	0.70	1.65	0.735	0.00	2.71	0.844	0.763	0.437
Cough	7	489	414	0.82	0.26	2.56	0.739	92.58	80.92	<0.0001	1.00	0.464
Fatigue	5	752	338	0.75	0.57	0.90	0.042	17.64	4.85	0.302	0.806	0.549
Dyspnea	5	590	343	0.34	0.25	0.46	<0.0001	33.68	6.03	0.197	1.00	0.732
Diarrhea	4	503	236	1.33	0.85	2.09	0.206	0.00	2.21	<0.0001	0.734	0.369
Nausea/vomiting	4	318	199	1.14	0.54	2.39	0.71	0.00	1.39	<0.0001	1.00	0.79
Myalgia/arthralgia	5	561	237	0.95	0.63	1.42	0.811	32.99	5.97	0.201	0.806	0.552
Headache	3	339	166	0.66	0.20	2.17	0.500	60.59	5.07	0.079	1.00	0.720
Sputum production	4	610	311	0.84	0.50	1.43	0.535	61.83	7.86	0.049	0.730	0.630
DM	7	812	414	0.49	0.36	0.67	<0.0001	14.60	7.02	0.318	0.071	0.098

(continued)

Table 22.6 (continued)

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Survived	Died	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger's test
CHD	6	654	393	0.31	0.13	0.72	0.006	61.11	12.85	0.025	1.00	0.651
COPD	3	368	192	0.13	0.052	0.34	<0.0001	0.00	0.38	0.824	1.00	0.669
Cerebrovascular disease	3	266	162	0.125	0.034	0.465	0.002	0.002	0.32	0.852	0.29	0.047
CKD	3	383	184	0.095	0.023	0.391	0.001	0.00	0.49	0.782	1.00	0.747
HTN	6	792	382	0.48	0.22	1.03	0.061	85.87	35.38	<0.0001	0.45	0.63
Malignancy	4	561	237	0.44	0.15	1.3	0.149	0.00	1.34	<0.0001	0.089	0.061
Gender (female)	8	974	435	1.45	0.97	2.16	0.066	51.46	14.42	0.044	0.901	0.825
Age	8	974	435	−1.07	−1.35	−0.78	<0.0001	77.49	31.04	<0.0001	0.710	0.648
PR	4	550	299	−0.037	−0.822	0.066	0.095	86.03	21.48	<0.0001	1.00	0.820

WBC white blood cells, *PMN* polymorphonuclear leukocytes, *Hb* hemoglobin, *TnI* troponin I, *CRP* C-reactive protein, *PCT* procalcitonin, *CK* creatine kinase, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *TB* total bilirubin, *Alb* albumin, *PT* prothrombin time, *PTT* partial thromboplastin time, *Cr* creatinine, *IL-6* interleukin 6, *DM* diabetes mellitus, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *HTN* hypertension, *PR* pulse rate, *No*. number, *SMD* standardized mean difference, *OR* odds ratio, *CI* confidence interval

[a]Reported as a categorical variable

Table 22.7 Summary of the results of meta-analyses of laboratory measures in patients with COVID-19: patients with a severe form of COVID-19 versus patients with a non-severe form of COVID-19

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Non-severe	Severe	SMD /OR	95%CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger's test
WBC	27	3293	1131	−0.40	−0.58	−0.21	<0.0001	83.86	161.12	<0.0001	0.77	0.010
PMN	22	2215	1109	−0.72	−0.88	−0.57	<0.0001	63.72	67.07	<0.0001	0.498	0.496
Lymphocyte	31	4035	1890	0.68	0.53	0.84	<0.0001	79.92	149.93	<0.0001	0.586	0.298
Monocytes	11	872	575	0.17	0.57	0.428	0.003	30.70	14.43	0.154	0.640	0.073
Eosinophil	3	164	86	0.23	−0.03	0.50	0.086	33.50	3.00	0.2222	0.296	0.064
CD4 cells	8	506	587	1.80	1.17	2.57	<0.0001	96.17	181.82	<0.0001	0.009	0.062
CD8 cells	8	862	593	1.46	0.81	2.10	<0.0001	95.86	168.91	<0.0001	0.035	0.084
CD3 cells	4	521	176	1.18	0.67	1.69	<0.0001	84.77	19.70	<0.0001	0.308	0.250
Platelet	18	2288	627	0.21	0.06	0.35	0.004	50.47	34.32	0.008	0.707	0.241
Hb	12	1827	472	0.24	0.14	0.34	<0.0001	33.61	16.57	0.121	0.731	0.677
Ferritin	4	470	489	−0.88	−1.26	−0.51	<0.0001	69.82	9.94	0.019	1.00	0.226
D-dimer	17	1954	727	−0.93	−1.12	−0.74	<0.0001	72.77	58.77	<0.0001	0.901	0.619
TnI	3	585	199	−0.98	−1.18	−0.77	<0.0001	0.00	1.31	0.519	1.00	0.370
CRP	23	1677	906	−1.23	−1.48	−0.98	<0.0001	87.20	172.00	<0.0001	0.072	0.004
ESR	7	357	252	−0.71	−1.13	−0.29	0.001	91.74	72.85	<0.0001	0.071	0.054
PCT	13	1170	707	−0.81	−1.07	−0.55	<0.0001	81.08	63.43	<0.0001	0.200	0.202
CK	13	1222	448	−0.50	−0.75	−0.26	<0.0001	74.94	47.88	<0.0001	1.00	0.782
AST	20	1569	630	−0.79	−1.00	−0.58	<0.0001	74.49	74.48	<0.0001	0.922	0.640
ALT	23	1875	775	−0.52	−0.77	−0.27	<0.0001	85.45	151.28	<0.0001	0.009	0.206
TB	15	1528	650	−0.33	−0.46	−0.21	<0.0001	31.00	20.29	0.121	0.766	0.972
Alb	13	1719	868	1.02	0.81	1.23	<0.0001	76.46	50.97	<0.0001	0.760	0.954
Pt	11	796	415	−0.30	−0.64	0.03	0.074	84.18	63.22	<0.0001	0.755	0.689
PTT	9	644	273	0.05	−0.29	0.39	0.772	79.03	38.15	<0.0001	0.251	0.330
LDH	17	1590	587	−1.33	−1.54	−1.17	<0.0001	68.41	50.65	<0.0001	0.433	0.086
Fibrinogen	5	533	193	−0.95	−1.59	−0.31	0.003	87.01	30.79	<0.0001	0.220	0.160
Cr	21	2320	751	−0.21	−0.34	−0.08	0.001	52.31	41.93	0.003	0.785	0.282
BUN	9	821	294	−0.55	−0.93	−0.17	<0.0001	84.97	53.23	<0.0001	0.251	0.143
Sodium	6	1470	381	0.33	−0.05	0.72	0.096	87.33	39.48	<0.0001	1.000	0.413

(continued)

Table 22.7 (continued)

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Non-severe	Severe	SMD /OR	95%CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger's test
Potassium	6	1473	375	0.18	−0.13	0.49	0.269	79.74	24.68	<0.0001	1.00	0.516
Glucose	5	451	322	−1.02	−1.30	−0.74	<0.0001	44.07	7.15	0.128	0.462	0.608
CK-MB	9	1156	487	−0.44	−0.71	−0.18	0.001	80.40	40.83	<0.0001	0.602	0.590
C3	4	288	384	−0.17	−0.49	0.14	0.291	53.17	6.4	0.093	1.00	0.515
C4	4	288	384	−0.20	−0.79	0.37	0.484	85.58	20.81	<0.0001	0.734	0.709
IgM	5	502	374	0.18	0.02	0.33	0.020	0.00	0.85	0.932	0.220	0.085
IgG	5	502	374	−0.001	−0.15	0.15	0.994	6.66	4.28	0.369	0.462	0.318
IgA	5	502	374	−0.47	−1.04	0.08	0.094	88.30	34.19	<0.0001	0.027	0.282
TNFα	3	310	201	−0.47	−1.00	0.05	0.077	59.53	4.94	0.084	0.296	0.185
IL-6	10	863	532	−1.67	−2.39	−0.95	<0.0001	96.15	234.19	<0.0001	0.371	0.051
IL-10	5	376	355	−3.49	−5.46	−1.47	<0.0001	98.22	224.95	<0.0001	0.220	0.105
IL-4	3	203	60	−0.28	−0.55	0.007	0.056	0.00	0.27	0.871	1.000	0.860

WBC white blood cells, *PMN* polymorphonuclear leukocytes, *Hb* hemoglobin, *TnI* troponin I, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *PCT* procalcitonin, *CK* creatine kinase, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *TB* total bilirubin, *Alb* albumin, *PT* prothrombin time, *PTT* partial thromboplastin time, *Cr* creatinine, *LDH* lactate dehydrogenase, *BUN* blood urea nitrogen, *CK-MB* creatine kinase-MB, *C3* complement component C3, *C4* complement component C4, *IgM* immunoglobulin M, *IgG* immunoglobulin G, *IgA* immunoglobulin A, *TNFα* tumor necrosis factor-alpha, *IL-6* interleukin 6, *IL-6* interleukin 10, *IL-6* interleukin 4, *No.* number, *SMD* standardized mean difference, *OR* odds ratio, *CI* confidence interval

Table 22.8 Summary of the results of meta-analyses of clinical characteristics and comorbidities in patients with COVID-19: patients with a severe form of COVID-19 versus patients with a non-severe form of COVID-19

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Non-severe	Severe	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P value of Begg's test	P-value of Egger'stest
Age	28	4006	1493	−0.89	−1.05	−0.72	<0.0001	76.61	115.43	<0.0001	0.797	0.051
Gender (female)	35	4635	1707	1.32	1.17	1.49	<0.0001	18.19	41.56	0.175	0.690	0.799
History of smoking	9	1800	428	0.53	0.38	0.73	<0.0001	0.00	7.045	0.532	0.602	0.795
HTN	25	1787	1322	0.40	0.30	0.52	<0.0001	45.33	43.90	0.008	1.000	0.964
DM	25	3197	1322	0.36	0.26	0.52	<0.0001	47.44	45.66	0.005	0.005	0.038
CHD	20	3036	1259	0.34	0.25	0.45	<0.0001	1.35	19.26	0.440	0.381	0.611
CKD	8	1871	792	0.35	0.18	0.68	0.002	14.09	8.14	0.320	0.901	0.383
Cerebrovascular disease	10	2298	886	0.30	0.18	0.50	<0.0001	0.00	7.41	0.594	0.474	0.892
COPD	15	2607	742	0.20	0.12	0.33	<0.0001	0.00	8.00	0.889	0.022	0.087
Chronic liver disease	12	2126	788	0.71	0.37	1.36	0.309	18.67	13.52	0.260	0.631	0.762
Malignancy	9	1910	748	0.42	0.24	0.72	0.002	0.00	5.58	0.693	0.117	0.480
Immunodeficiency	3	1444	282	0.76	0.15	3.80	0.740	0.00	0.03	0.984	1.000	0.323
Fever[a]	27	3484	1339	0.70	0.41	1.18	0.185	80.74	135.02	<0.0001	0.559	0.097
Fever[b]	8	1579	441	−0.38	−0.67	−0.09	0.010	81.12	37.08	<0.0001	0.386	0.690
RR	6	632	181	−0.78	−1.26	−0.30	0.001	83.29	29.92	<0.0001	1.000	0.825
PR	4	256	107	−0.33	−0.56	−0.09	0.007	0.00	2.26	0.519	0.089	0.025
Chill	5	1037	260	0.62	0.42	0.93	0.023	0.00	2.65	0.616	1.000	0.617
Cough	28	3367	1327	0.78	0.60	1.01	0.064	53.45	58.01	<0.0001	0.441	0.019
Sputum production	18	2247	947	0.66	0.55	0.79	<0.0001	34.46	25.94	0.076	0.939	0.313
Chest pain	10	625	302	0.58	0.28	1.20	0.146	39.37	14.84	0.095	1.000	0.935
Myalgia/arthralgia	15	2248	864	0.79	0.62	1.009	0.060	35.53	21.71	0.085	0.766	0.693
Nausea/vomiting	12	1885	765	0.75	0.51	1.10	0.151	39.55	18.19	0.077	0.837	0.966
Diarrhea	22	2630	1029	0.90	0.57	1.40	0.644	55.48	47.17	0.001	0.283	0.491
Sore throat	16	2422	930	1.01	0.76	1.35	0.903	0.00	11.39	0.724	0.162	0.229
Dyspnea	25	3016	1334	0.22	0.14	0.33	<0.0001	73.50	90.56	<0.0001	0.075	0.083
Headache	17	2500	871	0.83	0.64	1.08	0.178	0.00	11.02	0.808	0.174	0.168
Hemoptysis	4	1519	602	0.25	0.11	0.55	0.001	0.00	0.52	0.914	0.308	0.169
Fatigue	20	2519	981	0.71	0.52	0.97	0.032	54.64	41.89	0.002	0.581	0.273

(continued)

Table 22.8 (continued)

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Non-severe	Severe	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P value of Begg's test	P-value of Egger'stest
Abdominal pain	6	538	460	0.49	0.24	0.98	0.045	0.00	4.44	0.488	0.259	0.101

DM diabetes mellitus, *CHD* coronary heart disease, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *HTN* hypertension, *RR* respiratory rate, *PR* pulse rate, *No.* number, *SMD* standardized mean difference, *OR* odds ratio, *CI* confidence interval

[a]Reported as a categorical variable

[b]Reported as a continuous variable

Table 22.9 Summary of the results of meta-analyses of clinical and laboratory characteristics of patients with COVID-19: patients who either were in critical condition or required ICU admission versus patients who neither were in critical condition nor required ICU admission

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Noncritical	Critical	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger'stest
WBC	4	348	131	−0.58	−0.79	−0.37	<0.0001	15.29	3.54	0.315	1.00	0.806
PMN	4	347	131	−0.74	−1.10	−0.39	<0.0001	60.88	7.66	0.053	1.00	0.854
Lymphocyte	4	346	131	0.53	0.09	0.98	0.018	75.56	12.27	0.006	0.308	0.382
Monocyte	3	346	131	0.16	−0.37	0.69	0.556	74.68	7.9	0.019	0.296	0.160
Platelet	4	350	131	0.15	−0.15	0.46	0.946	50.68	6.08	0.108	0.734	0.555
D-dimer	3	191	102	−0.74	−1.14	−0.34	<0.0001	57.15	4.66	0.097	1.00	0.85
LDH	3	260	76	−1.64	−2.38	−0.89	<0.0001	80.52	10.27	0.006	0.296	0.330
AST	3	235	116	−0.78	−1.27	−0.29	0.002	76.70	8.58	0.014	1.000	0.567
ALT	3	241	118	−0.45	−0.68	−0.22	<0.0001	0.00	0.99	0.608	1.000	0.838
PTT	3	229	114	0.11	−0.12	0.34	0.347	10.73	2.24	0.326	1.000	0.794
PT	3	229	113	−0.27	−0.50	−0.46	0.019	0.00	1.17	0.556	1.000	0.928
Cr	3	248	117	−0.03	−0.75	0.68	0.926	89.91	19.82	<0.0001	1.000	0.879
BUN	3	253	116	−0.42	−1.28	0.42	0.325	92.64	27.19	<0.0001	1.000	0.539
Age	3	292	123	−0.17	−0.85	−0.50	0.614	91.90	24.69	<0.0001	1.000	0.784
Gender (female)	3	292	123	1.46	0.93	2.29	0.094	0.00	0.25	0.879	0.296	0.046
RR	3	292	123	−0.45	−0.99	0.08	0.100	83.58	12.18	0.002	1.000	0.359
PR	3	292	123	−0.55	−0.97	−0.12	0.012	73.51	7.55	0.023	1.000	0.399
Fever[a]	3	292	123	0.41	0.19	0.86	0.019	0.00	0.46	0.793	1.000	0.817
Cough	3	292	123	0.94	0.60	1.48	0.818	0.00	0.25	0.878	1.000	0.534
Fatigue	3	292	123	0.80	0.29	2.21	0.676	78.04	9.11	0.011	1.000	0.600
Dyspnea	3	292	123	0.22	0.06	0.71	0.012	73.46	7.53	0.023	1.000	0.693
Diarrhea	3	292	123	0.59	0.32	1.08	0.088	0.00	0.74	0.700	1.000	0.332
Myalgia/arthralgia	3	292	123	0.81	0.45	1.43	0.475	0.00	1.93	0.380	1.000	0.834
Headache	3	292	123	0.61	0.28	1.32	0.21	0.00	0.51	0.775	1.000	0.208
Sputum production	3	292	123	1.19	0.74	1.91	0.454	0.00	0.15	0.924	1.000	0.341
DM	3	292	123	0.31	0.12	0.82	0.018	59.21	4.90	0.086	0.296	0.005
Chronic liver disease	3	292	123	1.10	0.14	8.34	0.921	49.44	3.95	0.138	0.296	0.012
CKD	3	292	123	0.70	0.06	8.26	0.77	68.62	6.37	0.041	1.000	0.676

(continued)

Table 22.9 (continued)

Factor	No. of pairwise	No. of subjects		Meta-analysis				Heterogeneity			Publication bias	
		Noncritical	Critical	SMD /OR	95% CI		P-value	I2%	Chi2	P-value	P-value of Begg's test	P-value of Egger'stest
HTN	3	292	123	0.398	0.12	1.30	0.128	83.73	12.29	0.002	1.000	0.525
Malignancy	3	292	123	1.02	0.38	2.72	0.961	23.69	2.62	0.270	1.000	0.728

WBC white blood cells, *PMN* polymorphonuclear leukocytes, *LDH* lactate dehydrogenase, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *PT* prothrombin time, *PTT* partial thromboplastin time, *Cr* creatinine, *BUN* blood urea nitrogen, *DM* diabetes mellitus, *CKD* Chronic kidney disease, *HTN* hypertension, *RR* respiratory rate, *PR* pulse rate, *No.* number, *SMD* standardized mean difference, *OR* odds ratio, *CI* confidence interval

[a]Reported as a categorical variable

Table 22.10 Summary of the results of meta-analyses of subgroups of patients with a severe and non-severe form of COVID-19

Factor	Between-group comparison	No. of pairwise	Meta-analysis				Heterogeneity		
			SMD /OR	95% CI		P-value	I2%	Chi2	P-value
WBC	A[a]	12	−0.39	−0.67	−0.12	0.004	88.29	93/98	<0.0001
	B[b]	15	−0.40	−0.66	−0.14	0.001	78.88	66.29	<0.0001
PMN	A	10	−0.74	−0.89	−0.59	<0.0001	45.35	16.17	0.063
	B	12	−0.73	−1.01	−0.45	<0.0001	75.93	45.70	<0.0001
Lymphocyte	A	14	0.81	0.60	1.03	<0.0001	85.09	87.22	<0.0001
	B	17	0.55	0.32	0.79	<0.0001	72.64	58.48	<0.0001
CD4 cells	A	4	2.89	1.35	4.43	<0.0001	98.29	176.20	<0.0001
	B	4	0.79	061	0.96	<0.0001	0.00	2.73	0.434
CD8 cells	A	4	2.24	0.86	3.62	0.001	98.07	155.52	<0.0001
	B	4	0.60	0.31	0.89	<0.0001	35.40	4.64	0.200
Platelet	A	6	0.29	0.04	0.55	<0.0001	72.07	17.90	0.003
	B	12	0.12	−0.002	0.26	0.054	0.00	8.18	0.697
Hb	A	3	0.31	0.17	0.45	<0.0001	0.00	1.13	0.566
	B	8	0.22	0.04	0.41	0.016	36.89	11.09	0.135
CRP	A	7	−1.20	−1.49	−0.91	<0.0001	72.32	21.67	0.001
	B	16	−1.26	−1.61	−0.91	<0.0001	89.02	136.62	<0.0001
PCT	A	4	−1.27	−1.63	−0.62	<0.0001	86.83	22.78	<0.0001
	B	9	−0.61	−0.88	−0.34	<0.0001	61.69	21.04	0.007
Ferritin	B	3	−0.90	−1.49	−0.31	0.003	65.83	5.85	0.054
	A	5	−0.43	−0.75	−0.16	0.008	77.29	17.61	0.001
CK	B	8	−0.56	−0.96	−0.16	0.006	75.37	28.43	<0.0001
	A	7	−0.89	−1.13	−0.66	<0.0001	65.06	17.17	0.009
AST	B	13	−0.70	−1.04	−0.36	<0.0001	78.07	54.72	<0.0001
	A	8	−0.35	−0.61	−0.10	<0.0001	73.13	26.05	<0.0001
ALT	B	15	−0.62	−1.02	−0.22	0.002	88.32	119.86	<0.0001
TB	A	5	−0.36	−0.52	−0.21	<0.0001	0.00	1.29	0.863
	B	8	−0.25	−0.50	−0.01	0.035	48.91	13.07	0.057
Alb	A	6	0.92	0.67	1.17	<0.0001	70.38	16.88	0.005
	B	7	1.14	0.78	1.49	<0.0001	79.04	28.62	<0.0001
PT	A	5	−0.65	−0.91	−0.38	<0.0001	53.90	8.67	0.070
	B	6	−0.001	−0.445	0.442	0.95	76.17	20.98	0.001
PTT	A	4	−0.30	−0.71	0.11	0.151	80.60	15.46	0.001
	B	5	0.45	−0.10	1.02	0.114	75.01	16.01	0.003
LDH	A	7	−1.23	−1.57	−0.90	<0.0001	82.13	33.58	<0.0001
	B	10	−1.41	−1.59	−1.22	<0.0001	20.92	11.38	0.250
Cr	A	9	−0.31	−0.48	−0.22	<0.0001	66.85	24.13	0.002
	B	12	−0.09	−0.23	0.03	0.139	0.00	10.25	0.50
BUN	A	3	−1.04	−1.21	−0.87	<0.0001	0.00	0.50	0.778
	B	6	−0.25	−0.71	0.20	0.270	73.67	18.99	0.002
D-dimer	A	8	−1.05	−1.29	−0.81	<0.0001	75.82	28.95	<0.0001
	B	9	−0.79	−1.10	−0.49	<0.0001	67.66	24.73	0.002
Sodium	A	4	0.46	−0.01	0.95	0.058	91.99	37.48	<0.0001
Potassium	A	4	0.06	−0.28	0.41	0.731	84.66	19.56	<0.0001

(continued)

Table 22.10 (continued)

Factor	Between-group comparison	No. of pairwise	Meta-analysis				Heterogeneity		
			SMD /OR	95% CI		P-value	I2%	Chi2	P-value
IL-6	A	3	−3.07	−5.20	0.94	0.005	98.77	162.79	<0.0001
	B	7	−1.11	−1.69	−0.54	<0.0001	86.82	45.54	<0.0001
CK-MB	A	6	−0.58	−0.84	−0.32	<0.0001	75.94	20.78	0.001
	B	3	−0.11	−0.78	0.59	0.746	82.49	11.42	0.003

WBC white blood cells, *PMN* polymorphonuclear leukocytes, *Hb* hemoglobin, *CRP* C-reactive protein, *PCT* procalcitonin, *CK* creatine kinase, *AST* aspartate aminotransferase, *ALT* alanine transaminase, *TB* total bilirubin, *Alb* albumin, *PT* prothrombin time, *PTT* partial thromboplastin time, *LDH* lactate dehydrogenase, *Cr* creatinine, *BUN* blood urea nitrogen, *IL-6* interleukin 6, *CK-MB* creatine kinase-MB, *SMD* standardized mean difference, *OR* odds ratio, *CI* confidence interval

[a]Stduies comparing patients with a severe form of disease or patients who were in a critical condition and patients with a non-severe form of disease or patients who were not in a critical condition

[b]Stduies comparing patients with a severe form of disease and patients with a non-severe form of the disease

Table 22.11 Adjusted ES using trim and fill methods

Factor	Comparison group	ES	95% CI
Lymphocyte	Survived vs died	1.20	1.06 to 1.34
Alb	Survived vs died	1.23	0.79 to 1.69
Cerebrovascular disease	Survived vs died	0.17	0.05 to 0.51
Malignancy	Survived vs died	0.30	0.11 to 0.78
Monocytes	Severe vs non-severe	0.08	−0.020 to 0.185
Eosinophil	Severe vs non-severe	0.05	−0.170 to 0.285
CD4 cells	Severe vs non-severe	0.80	−0.006 to 1.62
CD8 cells	Severe vs non-severe	0.59	−0.15 to 1.33
CRP	Severe vs non-severe	−0.64	−1.02 to -0.25
ESR	Severe vs non-severe	−0.71	−1.13 to −0.29
ALT	Severe vs non-severe	−0.56	−0.79 to −0.32
LDH	Severe vs non-severe	−1.39	−1.62 to −1.16
IgM	Severe vs non-severe	0.20	0.06 to 0.34
IgA	Severe vs non-severe	−0.47	−1.03 to 0.08
IL-6	Severe vs non-severe	−0.53	−1.29 to 0.22
COPD	Severe vs non-severe	0.42	0.27 to 0.64
Fever	Severe vs non-severe	1.36	0.83 to 2.23
Dyspnea	Severe vs non-severe	0.31	0.20 to 0.49
Cough	Severe vs non-severe	1.10	0.84 to 1.43
PR	Severe vs non-severe	−0.39	−0.61 to −0.16
Age	Severe vs non-severe	−0.59	−0.76 to −0.41
Chronic liver disease	Critical vs no-critical	0.25	0.03 to 2.10
DM	Survived vs died	0.59	0.45 to 0.79
	Critical vs noncritical	0.69	0.24 to 2.01
	Severe vs non-severe	0.48	0.32 to 0.71

Alb albumin, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *ALT* alanine transaminase, *LDH* lactate dehydrogenase, *IgM* immunoglobulin M, *IgA* immunoglobulin A, *IL-6* interleukin 6, *COPD* chronic obstructive pulmonary disease, *PR* pulse rate, *DM* diabetes mellitus, *ES* effect size, *CI* confidence interval

Table 22.12 Summary of the results of meta-regressions

Variable	Moderator	No of pairwise	Meta-regression						The proportion of total between-studyvariance explained
			Coefficient	SE	95% CI		z	P-value	R2 analog
WBC	Sample size	20	0.0006	0.0004	−0.0001	0.0014	1.6	0.1085	0.27
	Age difference	18	0.018	0.0236	−0.0284	0.0643	0.76	0.4467	0
	Gender	20	0.0219	0.0142	−0.0059	0.0497	1.54	0.1226	0
D-dimer	Sample size	12	0.0005	0.0007	−0.0008	0.0018	0.79	0.4324	0
	Age difference	12	−0.0234	0.0179	−0.0585	0.0117	−1.31	0.1908	0.46
	Gender	12	−0.0097	0.0116	−0.0323	0.013	−0.83	0.4039	0.15

No, number, *SE* standard error, *CI* confidence interval

showed no significant effect of any individual study.

Troponin I (TnI) was higher in severe patients (n = 199) than non-severe patients (n = 585) (SMD −0.98; 95% CI, −1.18, −0.77). Thirteen studies reported data on albumin levels, including 868 severe patients and 1719 non-severe patients. Severe patients had lower albumin levels (SMD 1.02; 95% CI, 0.81, 1.23; P < 0.0001). Also, severe (n = 1170) patients had higher procalcitonin levels compared to non-severe patients (n = 707) (SMD −0.81; 95% CI, −1.07, −0.55; P < 0.0001).

A meta-analysis of 11 studies providing data on prothrombin time (PT) showed that patients with severe disease were not different from non-severe patients (SMD −0.30; 95% CI, −0.64, 0.03; P = 0.074). Also, PTT showed no significant difference between the two groups (SMD = 0.05; 95% CI, −0.29 to 0.39; P = 0.772). Critical patients had higher PT compared to non-critical patients (SMD −0.27; 95% CI, −0.50, −0.46, P = 0.019), though PTT was not different between two critical and noncritical groups (SMD 0.11; 95% CI, −0.12, 0.34; P = 0.347).

Seventeen studies reported data on LDH levels, and the meta-analysis revealed that severe patients had higher LDH levels than non-severe patients (SMD −1.33; 95% CI, −1.54, −1.17; P < 0.0001). There was moderate heterogeneity (I2 = 68.41). Also, severe patients had significantly higher D-dimer levels compared to non-severe patients (SMD −0.93; 95% CI, −1.12, −0.74; P < 0.0001). Heterogeneity among studies was relatively high (I2 = 72.77%), but meta-regression analysis could not find any significant potential moderators.

22.3.3.2 Survival Analysis

A total of five studies reported the white blood cell count concerning survival outcomes. Non-survivor patients (n = 707) had significantly higher WBC than survivors (n = 365) with an ES of −1.01 (95% CI, −1.33, −0.69). No evidence of publication bias was observed (Begg's P = 0.327; Egger's P = 0.356). Heterogeneity was high (I2 = 79%). Sensitivity analysis was performed, leaving out a study that only included patients with ARDS (acute respiratory syndrome) (Wu et al. 2020), and as a result, heterogeneity was abolished, and ES became −1.18 (95% CI, −1.33, −1.03).

Analysis of four studies with a total number of 570 survivors and 311 non-survivors revealed significantly higher PMN counts in non-survivor patients compared to survivors (SMD −1.05; 95% CI, −1.53, −0.58; P < 0.0001). Heterogeneity was high (I2 = 87.76%). When removing the abovementioned study (Wu et al. 2020), heterogeneity dropped to 55%, and the ES remained significant −1.32 (SMD −1.32; 95% CI, −1.59, −1.06).

Patients who survived (n = 727) had significantly higher lymphocyte than non-survivors (n = 397) (SMD 0.97; 95% CI, 0.52, 1.42). Significant publication bias was observed (Begg's P = 0.024 Egger's P = 0.043). The trim and fill method was used to adjust the ES (SMD 1.20; 95% CI, 1.06, 1.34). No individual study showed a significant influence on the ES.

Compared to non-survivors (n = 376), survivors had significantly higher platelet counts (SMD 0.45; 95% CI, 0.19, 0.70; P = 0.001). Heterogeneity was relatively high (I2 = 67.56%). When the study (Yang et al. 2020) was removed, there was no heterogeneity across studies further (I2 = 0%), while the pooled effect remained significant.

Non-survivor patients showed higher ALT (SMD −0.36, P < 0.0001) and total bilirubin (SMD = −0.79, p < 0.0001) than survivors. Albumin levels were measured in five studies. Survivor patients showed higher albumin levels compared to non-survivors (SMD = 0.88, p < 0.0001). However, heterogeneity was high (I2 = 87.95). Sensitivity analysis showed a robust ES. Additionally, with the exclusion of two studies (Wu et al. 2020; Momtazmanesh et al. 2020), I2 reduced to 58.41% (Wu et al. 2020; Momtazmanesh et al. 2020).

IL-6 (SMD −1.22; P < 0.0001) and procalcitonin (SMD −1.05; P < 0.0001) levels were significantly higher in non-survivors than survivors. For both analyses, there was no evidence of publication bias and significant heterogeneity.

A meta-analysis of data from five studies showed no difference between non-survivors (n = 343) and survivors (n = 590) regarding creatinine levels (SMD −0.34; 95% CI, −0.77, 0.09; P = 0.123). However, there was high heterogeneity (I2 = 87.55). Sensitivity analysis excluding two studies reduced heterogeneity to I2 = 0%, though the ES remained not significant (SMD 0.016; 95% CI, −0.18, 0.21; P = 0.876).

PT was significantly higher in non-survivors than survivors (SMD −0.78; 95% CI, −1.89, −0.37; P < 0.0001). However, there was no difference regarding PTT between survivors and non-survivors (SMD 0.26; 95% CI, −0.62, 0.41; P = 0.695).

22.3.4 Symptoms and Vital Status

22.3.4.1 Severity Analysis

Compared to severe patients, non-severe patients were less likely to have chills (OR 0.62; 95% CI, 0.42, 0.93), sputum production (OR 0.66; 95% CI, 0.54 to 0.79), dyspnea (OR 0.22; 95% CI, 0.14, 0.33), hemoptysis (OR 0.25; 95% CI, 0.11, 0.55), fatigue (OR 0.71; 95% CI, 0.52, 0.97), and abdominal pain (OR 0.49; 95% CI, 0.24, 0.98). Patients with severe outcomes had significantly higher fever than non-severe patients (SMD −0.38; 95% CI, −0.67, −0.09; P = 0.01).

22.3.4.2 Survival Analysis

The only symptoms that showed a difference between survivors and non-survivors were dyspnea and fatigue, which were less likely to occur in survivors (OR 0.34; 95% CI 0.25, 0.46; and OR 0.75; 95% CI 0.57, 0.90).

22.3.5 Comorbidities and Demographic Characteristics

22.3.5.1 Severity Analysis

Severe patients (n = 4006) were significantly older than non-severe patients (n = 1493) (SMD −0.59; 95% CI, −0.76, −0.41). A meta-analysis of data derived from nine studies showed that non-severe patients were less likely to be smokers than severe patients (OR 0.53; 95% CI, 0.38, 0.73). Male patients had a higher risk of developing the severe disease compared to females (OR 1.32; 95% CI, 1.17, 1.49). Non-severe patients were less likely to have diabetes (OR 0.36; 95% CI, 0.26 to 0.52), chronic heart disease (OR 0.34; 95% CI, 0.25, 0.45), COPD (OR 0.20; 95% CI, 0.12, 0.33), cerebrovascular disease (OR 0.30; 95% CI, 0.18, 0.50), hypertension (OR 0.40; 95% CI, 0.30, 0.52), CKD (OR 0.35; 95% CI, 0.18, 0.68), and malignancy (OR 0.42; 95% CI, 0.24, 0.72) than severe patients. For all analyses, there was low to moderate heterogeneity, with I2 ranging from 0 to 47%.

22.3.5.2 Survival Analysis

A meta-analysis of data from eight studies demonstrated that non-survivors (n = 435) were older than survivors (n = 974) with the SMD of −1.07 (95% CI, −1.35, −0.78; P < 0.0001). Male patients were not different from females concerning survival (p = 0.066; I2 = 51.46).

Patients who survived were less likely to have diabetes (OR 0.49, 0.36 to 0.67), chronic heart disease (OR 0.31; 95% CI, 0.13–0.72), COPD (OR 0.13; 95% CI, 0.052–0.34), cerebrovascular disease (OR 0.125; 95% CI, 0.034–0.46), and CKD (OR 0.095; 95% CI, 0.023–0.39). For all analyses, there was low to moderate heterogeneity, with I2 ranging from 0 to 61%.

22.4 Discussion

Hundreds of thousands of deaths due to COVID-19 during only a few months have placed a heavy burden on the shoulder of each medical researcher by explicitly proving that our knowledge, at the present condition of the pandemic, can seldom offer a useful product to humanity unless all data are collected from other disciplines and then it would be entirely fair to arrive at conclusions from the accumulation of this data (Momtazmanesh et al. 2020; Mohamed et al. 2020a; Rzymski et al. 2020; Moradian et al. 2020; Kafieh et al. 2020). For example, medical doctors initially described COVID-19 as a disease of the respiratory system. It did not take long when a wave of studies reporting anosmia in patients with COVID-19 emerged, putting forward the neurotropism of COVID-19 (Yazdanpanah et al. 2020b; Jahanshahlu and Rezaei 2020a; Saleki et al. 2020). The next wave was actually of two sources of studies in parallel. One was studies that reported stroke events in young patients with COVID-19, and the other was studies that provided evidence of a high incidence of thromboembolic events in patients with COVID-19. Therefore, the second wave strongly confirmed that the involvement of the central nervous system might be why patients with COVID-19 die from acute respiratory failure in a few days as well as suggested coagulopathies as another significant contributor to death from COVID-19. In the meantime, many disciplinary perspectives on the immunology of COVID-19 come into the competition, and the perspective which is already dominant deals inflammatory cells and molecules widely distributed throughout the critical organs to mediate COVID-19 pathogenesis (Pourahmad et al. 2020; Bahrami et al. 2020; Yazdanpanah et al. 2020a; Mansourabadi et al. 2020; Saghazadeh and Rezaei 2020a; Pashaei and Rezaei 2020; Nasab et al. 2020; Saghazadeh and Rezaei 2020b; Rokni et al. 2020). As a result, taking a look at the current evidence links us to a variety of biomarkers and clinical features that might predict the prognosis of COVID-19. The present chapter aimed to offer the most reliable predictors, and for this, we performed a systematic synthesis of the data.

We have stratified patients according to their diverse outcomes: survivor vs non-survivor, critical vs noncritical, and severe vs non-severe. The analysis by severity outcome demonstrated that higher levels of WBC with PMN dominancy might be related to disease severity and subsequent mortality. In the analysis of the WBC in severe patients, a relatively high amount of heterogeneity was observed. Meta-regression of the sample size could only explain 28% of that heterogeneity, and the two other moderators, including the difference in age between two groups and percentages of female patients, could not explain heterogeneity significantly.

We could not find a significant difference regarding CD4+ and CD8+ cell counts between severe and non-severe patients. However, previous investigations have shown that the depletion of T cells occurs during the COVID-19 course (Diao et al. 2020; Fathi and Rezaei 2020). The study (Zheng et al. 2020b) has shown extensive lymphocyte subset reduction in the blood of patients infected with COVID-19 compared to patients with other types of pneumonia. CD45+ lymphocytes, CD3+ lymphocytes, CD4+ T cells, CD8+ T cells, and CD19+ B cells were significantly lower in patients with COVID-19 than those in non-COVID-19-infected pneumonia patients with the same radiological stage.

In line with previous studies, thrombocytopenia was found to be associated with the severity, mortality, and critical outcomes of COVID-19

(Lippi et al. 2020). However, the most remarkable effect size was observed for comparison between survivors and non-survivor patients, which showed moderate ES. Previous literature recognized thrombocytopenia as an indicator that occurs in critically ill patients and is associated with mortality (Williamson et al. 2013). Therefore, COVID-19 can be more challenging in patients whom themselves suffer from immune thrombocytopenia (Sahu et al. 2020).

Acute-phase reactants, including ESR, CRP, ferritin, and procalcitonin, were significantly increased in patients with severe disease compared to patients with the non-severe disease and in patients who died compared to patients who survived. In contrast, negative phase reactants such as albumin, on the other hand, were decreased in patients with severe disease and in patients who died.

Liver enzymes were increased in severe, critical, and deceased patients compared with their counterparts without adverse outcomes. Given the relatively low prevalence of chronic liver disease before infection with COVID-19, studies suggest that increased liver enzymes, as seen in severe patients, might result from a dysregulated immune response against the virus rather than underlying liver comorbidity (Mantovani et al. 2020). Studies postulating the same hypothesis emphasize an inflammatory storm having played a role in immune dysregulation. Other studies believe that respiratory distress syndrome-induced hypoxia and subsequent hepatic ischemia and hypoxia-reperfusion dysfunction might contribute to liver dysfunction in COVID-19 (Feng et al. 2020a).

Our findings pointed to a higher level of TnI in both severe patients and non-survivors. A cohort of 416 hospitalized patients with COVID-19 established that 19.7% of these patients had a cardiac injury and showed an independent correlation between cardiac injury and a higher risk of mortality in patients with COVID-19 (Shi et al. 2020). Several mechanisms could be responsible for cardiac injury, including increased myocardial demand relative to the blood supply and hypoxia, systemic inflammation derived from cytokines, and direct cardiac damage due to COVID-19 (Guo et al. 2020).

On the other hand, there was not a significant difference regarding creatinine neither between severe and non-severe patients nor between survivors and non-survivors. BUN, on the other hand, was significantly increased in severe patients compared to the non-severe group. The authors in Wang et al. (2020b) evaluated the kidney function of patients with COVID-19 over 4 weeks and found that patients with COVID-19 experienced no acute renal injury and only showed a mildly elevated BUN and creatinine. However, there is controversy around acute kidney injury in severe patients.

Electrolytes, including sodium and potassium, showed no significant difference between severe and non-severe patients. However, there was high heterogeneity in studies reporting potassium, and during sensitivity analysis, a significant ES was observed indicating hypokalemia in severe cases. Studies report hypokalemia to be present in a majority of critically ill patients. It can be attributed to increased urine potassium excretion due to the renin-angiotensin system (RAS) disturbances and enhanced delivery of sodium and water to distal tubules (Li et al. 2020b).

Also, PT and PTT in severe patients were not significantly different from non-severe patients. However, PT was higher in critical patients and non-survivors compared to noncritical and survivors, respectively. It might be due to the measurement time of coagulation parameters, which mostly was at the time of admission, while it would undergo significant change over the disease course. D-dimer, on the other hand, was significantly increased in patients with poor outcome.

Patients with poor outcomes, e.g., severe disease and mortality, were more likely to have COPD, CHD, DM, HTN, CKD, cerebrovascular disease, and underlying malignancy compared to their counterparts. A nationwide analysis of 1590 patients in China reported that after adjusting for age and smoking status, COPD, diabetes, hypertension, and malignancy predicted increased admission to ICU, need for invasive ventilation, and death rate (Guan et al. 2020a).

Finally, patients with dyspnea at baseline were about four times more likely to progress to severe or critical condition. Also, hemoptysis increased the likelihood of developing a severe disease by about four times.

22.5 Conclusion

The current pandemic of COVID-19 has affected the healthcare system profoundly (Moazzami et al. 2020), and this effect can take a long time to compensate for it, and as the risk of reinfection is possible (Jabbari and Rezaei 2020), we must work at practice management. Early and efficient detection of high-risk patients is a priority for maximizing the utilization of limited resources. The present chapter aimed to offer the most reliable predictors, and for this, we performed a systematic synthesis of the data. Meta-analyses identified several laboratory parameters (WBC, PMN, IL-6, total bilirubin, ALT, creatinine, troponin, procalcitonin, LDH, and D-dimer), comorbidities (diabetes, chronic heart disease, COPD, cerebrovascular disease, hypertension, CKD, and malignancy), and symptoms (dyspnea and hemoptysis) that might help the prediction of severe, critical, and lethal phenotypes of COVID-19. These parameters correlate with the immune system function, inflammation, coagulation, and liver and kidney function, supporting the view that COVID-19 is a multisystem disorder.

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