Original Article

Comparison of laboratory parameters in mild *vs.* severe cases and died *vs.* survived patients with COVID-19: systematic review and meta-analysis

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Background: This study aimed to summarize the available data on the association between the severity of (COVID-19) and routine blood indicators, inflammatory, biochemical parameters and coagulation parameter.

Methods: A literature search was conducted of PubMed, EMBASE, and Web of Sciences, CNKI, WanFang database providing relevant data. Random-effects meta-analysis was used to pool effect sizes.

Results: In patients with severe symptoms, interleukin-6, [IL-6; standardized mean difference (SMD) =1.15, 95% confidence interval (95% CI): 1.01, 1.29, P<0.001, n=1,121], interleukin-10 (IL-10; SMD =0.92, 95% CI: 0.75, 1.08, P<0.001, n=782), interleukin-4 (IL-4; SMD =0.2, 95% CI: 0.01, 0.39, P=0.04, n=500), procalcitonin (PCT; SMD =1.16, 95% CI: 0.99, 1.33, P<0.001, n=734), C-reactive protein (CRP; SMD =1.42, 95% CI: 1.27, 1.57, P<0.001, n=1,286), serum amyloid A (SAA; SMD =2.82, 95% CI: 2.53, 3.11, P<0.001, n=502) neutrophil count (SMD =0.63, 95% CI: 0.44, 0.82, P<0.001, n=558), alanine aminotransferase (ALT; SMD =2.72, 95% CI: 2.43, 3.02, P<0.001, n=538), aspartate aminotransferase (AST; SMD =2.75, 95% CI: 2.37, 3.12, P<0.001, n=313), lactate dehydrogenase (LDH; SMD =4.01, 95% CI: 3.79, 4.24, P<0.001, n=1,055), creatine kinase (CK; SMD =2.62, 95% CI: 2.2, 3.03, P<0.001, n=230;), CK-MB isoenzyme (CK-MB; SMD =3.07, 95% CI: 2.81, 3.34, P<0.001, n=600, activated partial thromboplastin time (APTT; SMD =0.63, 95% CI: 0.39, 0.87, P<0.001, n=351), and prothrombin time (P-T; SMD =1.83, 95% CI: 1.55, 2.11, P<0.001, n=351) were significantly higher than in patients with mild symptoms. On the contrary, lymphocyte count (SMD =−1.04, 95% CI: −1.21, −0.86, P<0.001, n=805) platelets (SMD =−1.47, 95% CI: −1.7, −1.24, P<0.001, n=653), monocyte count (SMD =−0.56, 95% CI: −0.8, −0.32, P<0.001, n=403), and albumin (SMD =−2.95, 95% CI: −3.21, −2.7, P<0.001, n=637) was significantly lower in patients with severe symptoms than in patients with mild symptoms. IL-6 (SMD =2.62, 95% CI: 2.15, 3.09, P<0.001, n=185), PCT (SMD =0.2, 95% CI: 0.16, 0.23, P<0.001, n=156), creatinine (SMD =2.29, 95% CI: 1.87, 2.7, P<0.001, n=213), and neutrophil counts (SMD =2.77, 95% CI: 2.38, 3.16, P<0.001, n=260) in patients with COVID-19 in the death group were significantly higher than that in patients in the survival group, while the lymphocyte count was significantly lower.

Conclusions: In summary, current evidence show that those laboratory indicators are associated with the severity of COVID-19 and thus could be used as prognostic risk stratification of patients with COVID-19.

Keywords: Coronavirus disease 2019 (COVID-19); laboratory biomarker; prognosis; meta-analysis

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Introduction

Coronavirus disease 2019 (COVID-19) is a self-limiting illness in approximately 80% of patients. However, some patients will develop more severe symptoms, including dyspnea, multifunctional organ failure, and even death (1). With a mortality rate of 1–2%, COVID-19 requires intensive care in 5% of patients (2).

Currently, there is no systemic treatment for COVID-19. Although some drugs, such as hydroxychloroquine, have been included in treatment guidelines or are being developed in interventional studies, treatment of COVID-19 is mainly supportive (3). Aberrant biomarkers help to better understand the biological characteristics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19, and contribute to the development of targeted drugs (4). In the context of out stretched heath care systems and limited resources, risk stratification is important to identify patients who the most need in-hospital and in-depth management. laboratory parameters along with some clinical factors might help to predict disadvantage outcomes among COVID-19 patients. The combination of biomarkers and other clinical parameters could help predict disease progression in COVID-19 patients. These parameters might help in prognostic risk layering of patients with COVID-19. We present the following article in accordance with the MOOSE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-345/rc).

Methods

Inclusion criteria

The inclusion criteria were as follows: (I) The inclusion criteria strictly following PICOS criteria (II) study subjects were patients diagnosed with COVID-19; (III) grouping included a mild symptom group and severe symptom group. The mild group had mild clinical symptoms, accompanied by fever and respiratory symptoms, and pneumonia findings were indicated by imaging examination. The clinical symptoms of patients with severe symptoms were shortness of breath, respiratory rate ≥30 beats/minute, oxygen saturation ≤93% at resting state, and arterial partial pressure of oxygen (PaO_2)/inspired oxygen concentration (FiO_2) ≤300 mmHg. The severity of COVID-19 was defined in accordance with international guidelines for community-acquired pneumonia (5).

Literature search

A total of 152 relevant studies published between April 2020 and October 2021 were identified using the keywords 'COVID-19 Coronary Pneumonia Laboratory Indicators, such as biochemical parameters, coagulation indicators, inflammatory factors' such as IL-6, IL-4, PCT to search PubMed, EMBASE, Web of Science, and CNKI, WanFang database. Finally, 16 articles were included in the study. A flow chart summarizing the inclusion and exclusion of articles is shown in *Figure 1*.

Study selection

Two independent investigators (B Cao and C Wang) assessed the titles and abstracts of the articles obtained from the above databases, and included all literature that met the study criteria. The included data was analyzed using Review Manager 5.3 software for meta-analysis.

Data extraction and statistical analysis

Data from the included articles were extracted in the form of word tables. The extracted contents included the name of the first author of the article, sample size, comorbidities of COVID-19 patients, and standardized mean difference (SMD) values.

The data were saved in Microsoft excel 2007 and then imported into Review Manager 5.3 software to analyze the SMD values of laboratory parameters of patients with mild symptoms and patients with severe symptoms. In cases where studies did not report the SMD of patient biomarkers, the SMD of each mean was calculated using the first quartile (Q1), fourth quartile (Q4), the median, and the number of cases before combining the effect sizes, as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (6). For each study, we calculated their SMD and the corresponding 95% CI, the pooled SMD with 95% CI was summarized to represent the total effect. The presence and amount of heterogeneity were assessed using the χ^2 test and I^2 test, with I^2 of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively (7,8). A two-sided P value of less than 0.05 was considered statistically significant for all analyses. I^2>50%, the heterogeneity is considered high. Considering the age difference, stratified analysis was performed between the mild group patients and the severe group patients with the average age younger than 55 years and elder than 55 years *Table 1*. Publication bias was assessed using funnel plots and

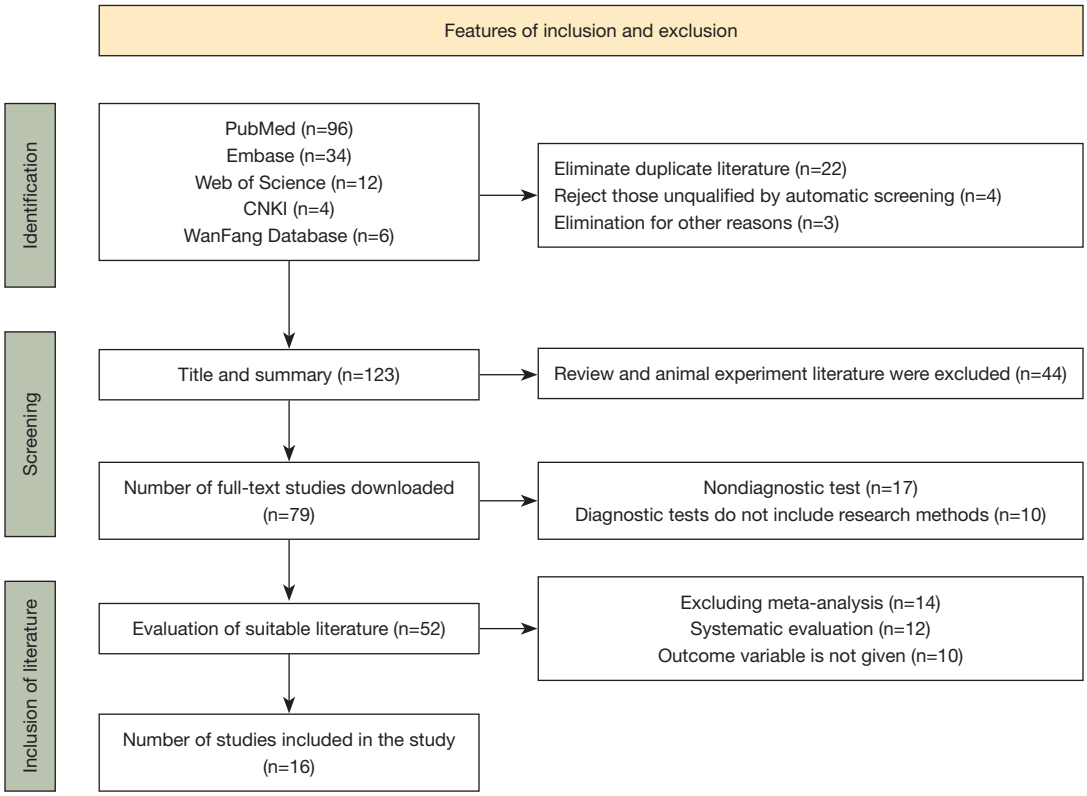

Figure 1 Inclusion and exclusion summary of literature.

Table 1 Stratified analysis of standardized mean difference of biological indicators in meta-analysis for patients with severe and mild disease

Anomaly indicator	Age (years)	SMD (95% CI)	P value	Heterogeneity I^2 (%)	Sample size for mild	Sample size for severe	Included literature
Lymphocyte count	>55	−0.42 (−0.5, −0.34)	<0.001	45	219	171	3
	<55	−0.27 (−0.31, 0.24)	<0.001	48	301	71	3
IL-6	>55	1.54 (1.29, 1.79)	<0.001	72	201	150	4
	<55	3.49 (2.99, 3.98)	<0.001	0	48	160	3
CRP	>55	0.48 (0.08, 0.89)	0.02	38	175	159	3
	<55	3.53 (2.97, 4.08)	<0.001	51	65	325	3
D-D	>55	1.07 (0.79, 1.35)	<0.001	31	71	270	3
	<55	2.7 (2.29, 3.11)	<0.001	37	58	174	3
Neutrophil count	>55	0.44 (0.24, 0.65)	<0.001	80	191	270	4
	<55	1.79 (1.28, 2.3)	<0.001	0	29	68	2

SMD, standardized mean difference; 95% CI, confidence interval; IL-6, interleukin 6; CRP, C-reactive protein; D-D, D-dimer.

Egger's test (P<0.10) (9). The characteristics of the included literature are shown in *Table 2*.

Results

Abnormal routine blood indicators

In patients with severe COVID-19, lymphocyte count [SMD =–1.04, 95% confidence interval (95% CI): –1.21, –0.86, P<0.001, number of patients n=805], monocyte count (SMD =–0.56, 95% CI: –0.8, –0.32, P<0.001, n=403), and platelets (SMD =–1.47, 95% CI: –1.7, –1.24, P<0.001, n=653) were significantly lower compared to patients with mild symptoms. In contrast, the number of neutrophils in patients with severe symptoms (SMD =0.63, 95% CI: 0.44, 0.82, P<0.001, n=558) was higher than that in patients with mild symptoms (*Table 3*). The number of neutrophils in cases of death (SMD =2.77, 95% CI: 2.38, 3.16, P<0.001, n=260) was significantly higher than that in survival cases. However, the number of lymphocytes in the death cases (SMD =–2.1, 95% CI: –2.46, –1.75, P<0.001, n=260) was significantly lower than that in survival cases (*Table 4*).

Lymphocytes in the patients who older than 55 years (SMD =–0.42,95% CI: –0.5, –0.34, P<0.001, n=390) was higher than that in patients who younger than 55years (*Table 1*).

Inflammatory factors

In patients with severe COVID-19, levels of serum interleukin-6 (IL-6; SMD =1.15, 95% CI: 1.01, 1.29, P<0.001, n=1,121), interleukin-4 (IL-4; SMD =0.2, 95% CI: 0.01, 0.39, P=0.04, n=500), interleukin-10 (IL-10; SMD =0.92, 95% CI: 0.75, 1.08, P<0.001, n=782), procalcitonin (PCT; SMD =1.16, 95% CI: 0.99, 1.33, P<0.001, n=734), serum amyloid A (SAA; SMD =2.82, 95% CI: 2.53, 3.11, P<0.001, n=502), and C-reactive protein (CRP; SMD =1.42, 95% CI: 1.27, 1.57, P<0.001, n=1,286) were significantly higher than in the milder COVID-19 patients (*Table 3*). In cases resulting in death, IL-6 (SMD =2.62, 95% CI: 2.15, 3.09, P<0.001, n=185) and PCT (SMD =0.2, 95% CI: 0.16, 0.23, P<0.001, n=156) were significantly higher than that in survival cases (*Table 4*).

Biochemical abnormalities

Aspartate aminotransferase (AST; SMD =2.75, 95% CI: 2.37, 3.12, P<0.001, n=313), alanine aminotransferase (ALT; SMD =2.72, 95% CI: 2.43, 3.02, P<0.001, n=538), and lactate dehydrogenase (LDH; SMD =4.01, 95% CI: 3.79, 4.24, P<0.001, n=1,055) in patients with severe symptoms were significantly higher than in patients with mild symptoms (*Table 3*), while albumin (SMD =–2.95, 95% CI: –3.21, –2.7, P<0.001, n=637) was significantly lower in patients with severe symptoms. The cardiac indexes creatine kinase (CK; SMD =2.62, 95% CI: 2.2, 3.03, P<0.001, n=230) and creatine kinase MB isoenzyme (CK-MB; SMD =3.07, 95% CI: 2.81, 3.34, P<0.001, n=600) in patients with severe symptoms were significantly higher in patients with non-severe symptoms (*Table 3*), while creatinine (SMD =2.29, 95% CI: 1.87, 2.7, P<0.001, n=213) in the survival cases was significantly lower than in patients who had died (*Table 4*).

Coagulation parameters

Patients with severe COVID-19 disease had higher levels of D-dimer (SMD =1.18, 95% CI: 0.96, 1.4, P<0.001, n=573), activated partial thromboplastin time (SMD =0.63, 95% CI: 0.39, 0.87, P<0.001, n=351), and prothrombin time (SMD =1.83, 95% CI: 1.55, 2.11, P<0.001, n=351) compared with patients with mild symptoms (*Table 3*).

Discussion

The results showed that IL-6, IL-4, IL-10, PCT, SAA, CRP, LDH, AST, ALT, D-dimer, P-T, APTT, CK, and neutrophil count of patients with severe COVID-19 were higher than that of patients with mild symptoms. However, the number of lymphocytes, platelets, and monocytes was low in patients with severe symptoms.

Clinical features and inflammatory factors

The most typical clinical features of patients with COVID-19 infection include fever, cough, dyspnea, muscle pain, fatigue, and symptoms of pneumonia (10) and some patients have sputum (11). Studies have shown that older patients and patients with underlying diseases will be more severely ill (12,13). Patients co-infected with COVID-19 and other respiratory pathogens had higher white blood cell count, neutrophil count, D-dimer, CRP, IL-6, and PCT than patients infected with COVID-19 alone (14). Unlike SARS-CoV, the SARS-CoV-2 exhibit a highly contagious even during the asymptomatic period (15). Studies have shown that serum levels of CRP and SAA were higher in patients with severe symptoms than in patients with mild

Table 2 Characteristics of the included literature

Author	Research type	Group	Number of people	Age (years)	Complications
Qian GQ (10)	Multicenter retrospective study	Mild symptom	82	49	Not reported
		Severe symptom	9	66	Not reported
Xie Y (11)	Single retrospective study	Mild symptom	22	58	Not reported
		Severe symptom	7	69	Not reported
Zhu Z (12)	Single retrospective study	Mild symptom	111	49.9±15	High blood pressure 50%, heart disease 12.5%, cancer 6.25%, COPD 12.5%
		Severe symptom	16	57.5±11	Diabetes 9.01%, hypertension 20.72%, heart disease 3.6%, cancer 3.6%, chronic obstructive pulmonary disease 3.6%
Zheng F (13)	Single retrospective study	Mild symptom	131	40	Diabetes 3.8%, hypertension 7.6%, heart disease 1.5%, chronic obstructive pulmonary disease 3.1%, cerebrovascular disease 2.3%, chronic liver disease 3.1%
		Severe symptom	30	57	Diabetes 6.7%, hypertension 40%, heart disease 6.7%, chronic obstructive pulmonary disease 6.7%, cerebrovascular disease 3.3%
Lv Z (14)	Multicenter retrospective study	Mild symptom	115	62	Diabetes 7.83%, hypertension 20%, coronary heart disease 4.35%, chronic obstructive pulmonary disease 1.74%
		Severe symptom	155	61	Diabetes 11.6%, hypertension 21.29%, heart disease 4.52%, chronic obstructive pulmonary disease 1.94%
Zhang G (15)	Single retrospective study	Mild symptom	166	51	Diabetes 9%, hypertension 16.9%, heart disease 5.4%, chronic obstructive pulmonary disease 1.2%, chronic kidney disease 0.6%, cerebrovascular disease 2.4%, chronic liver disease 1.8%, tumor 1.2%,
		Severe symptom	55	62	Diabetes 12.7%, hypertension 47.3%, heart disease 23.6%, chronic obstructive pulmonary disease 7.3%, chronic kidney disease 9.1%, cerebrovascular disease 20%, chronic liver disease 7.3%, tumor 7.8%, immunosuppression 1.8%
Zhang H (16)	Multicenter retrospective study	Mild symptom	9	47±11.7	Not reported
		Severe symptom	4	55.2±6	Not reported
Fu J (17)	Single retrospective study	Mild symptom	22	40.7±9	Hyperlipidemia 4.5%
		Severe symptom	13	60±15.5	Diabetes 23.1%, hypertension 38.5%, chronic obstructive pulmonary disease 7.7%, cerebrovascular
Liu SL (18)	Single retrospective study	Mild symptom	194	43	Not reported
		Severe symptom	31	64	Not reported
Liu Q (19)	Multicenter retrospective study	Mild symptom	59	49	Diabetes 3.4%, chronic kidney disease 4%, cerebrovascular disease 1.7%, chronic obstructive pulmonary disease 3.4%
		Mild symptom	25	52	Diabetes 12%, chronic kidney disease 4%, heart disease 8%, cancer 4%, COPD 12%
Xu B (20)	Single retrospective study	Mild symptom	80	56	Not reported
		Severe symptom	45	60	Not reported
Burgos-Blasco B (21)	Single retrospective study	Mild symptom	35	68.5	Cardiovascular disease 31%, chronic kidney disease 6%, chronic liver disease 6%, tumor 6%
		Severe symptom	27	71	Cardiovascular disease 41%, chronic kidney disease 19%, chronic liver disease 4%, tumor 15%

Table 2 (*continued*)

Table 2 (*continued*)

Author	Research type	Group	Number of people	Age (years)	Complications
Vultaggio A (22)	Single retrospective study	Mild symptom	63	72±13	Cardiovascular disease 41%, chronic kidney disease 19%, chronic liver disease 4%, tumor 15%
		Severe symptom	145	63±15	Diabetes 27%, hypertension 58.7%, chronic lung disease 17.5%, cardiovascular disease 11.1%
Gao Y (23)	Single retrospective study	Mild symptom	28	42.96±14	Diabetes 3.57%, hypertension 25%, heart disease 8%
		Severe symptom	15	45±7.68	Diabetes 40%, hypertension 40%, heart disease 6%
Zeng Z (24)	Single retrospective study	Mild symptom	93	59	Diabetes 18.3%, hypertension 43%, chronic kidney disease 3.2%, tumor 3.2%, chronic respiratory disease 4.3%, heart disease 10.8%
		Severe symptom	167	62	Diabetes 18%, hypertension 36.5%, chronic kidney disease 0.6%, tumor 1.2%, chronic respiratory disease 5.9%, heart disease 10.8%, 8.4%
Liu J (25)	Single retrospective study	Mild symptom	13	59.7±10.1	Diabetes 30.8%, hypertension 38.5%, pituitary adenoma 7.7%
		Severe symptom	27	43.2±12.3	Diabetes 7.4%, hypertension 3.7%, pituitary adenoma 3.7%

COPD, chronic obstructive pulmonary disease.

symptoms, and that SAA better predicts disease severity than CRP (16,17). However, increased SAA levels were not able to indicate the cause or distinguish COVID-19 patients from non-infected patients (18). Therefore, detection of combined laboratory parameters is required to better indicate the development of COVID-19. In addition, these indicators can guide clinicians in assessing and treating patients, as well as assist physicians to better distinguish COVID-19 from other infections (19).

COVID-19 disease can cause multifunctional organ failure in the body accompanied by an increase in systemic blood inflammatory factors (1), with IL-6 one of the key mediators regulating the inflammatory response. Furthermore, SARS-CoV-2 is highly pathogenic, associated with rapid viral replication, and has a tendency to infect the lower respiratory tract, which could cause a severe respiratory distress response caused by IL-6 (20). Effective inhibition of the cytokine storm may contribute to further deterioration of the condition in COVID-9 patients (21). Vultaggio *et al.* reported that in patients with COVID-19 infection, IL-6 can be used as a biomarker for early prediction of disease progression (22). Our results suggested that increased IL-6 levels are important for assessing disease progression. Gao *et al.* reported that a concentration of IL-6 higher than 24.3 pg/mL could indicate the severity of COVID-19 viral pneumonia, with a sensitivity and specificity of 73.3% and 89.3%, respectively (23). The level of various inflammatory factors and liver markers, such as sIL-2R, IL-10, TNF-a, hsCRP, LDH, CK-MB, ALT, were higher in severe patients than in mild patients. (24,25). Infection with COVID-19 is associated with a 'cytokine storm' caused by a systemic immune response *in vivo* (26). After activation by infectious agents such as SARS-CoV-2, macrophages, endothelial cells, and T cells produce IL-6 and activate tissue cells, including endothelial cells and parenchymal cells, to produce inflammatory effector molecules (27). Our study indicated that elevated serum concentrations of IL-6 correlated with disease severity. An increased level of IL-6 is common in patients with respiratory dysfunction (27), which implied that the possible mechanism of cytokine-guided lung injury was caused by COVID-9 viral infection. IL-10, mainly produced by monocytes and T cells, is the most effective cytokine for reducing the inflammatory process and thus limiting tissue damage caused by inflammation (28,29). In this study, the SMD of IL-10 indicated the progression of the disease course from mild disease to severe disease. Huang *et al.* and Zeng *et al.* reported that interleukin-1 receptor antagonist (IL-1RA), interleukin-1 alpha (IL-1a), IL-2, IL-4, IL-6, IL-8, IL-7, IL-10, IL-12, IL-17, interferon gamma-induced protein 10 (IP-10), platelet-derived growth factor (PDGF), tumor necrosis factor α (TNF-a), interferon gamma (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), and hepatocyte growth factor (HGF) were associated with lung injury and disease severity (24,30).

Abnormal myocardial indexes and biochemical indexes

COVID-19 can affect the heart and cause fatal damage

Table 3 Summary results of standardized mean difference of biological indicators in meta-analysis for patients with severe and mild disease

Anomaly indicator	SMD (95% CI)	P value	I^2 (%)	Number of studies	Patients with severe symptoms	Patients with mild symptoms
Inflammatory factors						
IL-6	1.15 (1.01, 1.29)	<0.001	95	10	492	629
IL-4	0.2 (0.01, 0.39)	0.04	0	6	233	267
IL-10	0.92 (0.75, 1.08)	<0.001	98	3	383	399
SAA	2.82 (2.53, 3.11)	<0.001	88	5	101	401
CRP	1.42 (1.27, 1.57)	<0.001	98	11	368	918
Procalcitonin	1.16 (0.99, 1.33)	<0.001	98	5	396	338
Blood coagulation factors						
D-D	1.18 (0.96, 1.4)	<0.001	93	6	129	444
APTT	0.63 (0.39, 0.87)	<0.001	83	4	97	254
P-T	1.83 (1.55, 2.11)	<0.001	89	4	97	254
Routine blood indexes						
Lymphocyte count	−1.04 (−1.21, −0.86)	<0.001	96	7	257	548
Neutrophil count	0.63 (0.44, 0.82)	<0.001	87	6	220	338
Monocyte count	−0.56 (−0.8, −0.32)	<0.001	47	5	96	307
Platelets	−1.47 (−1.7, −1.24)	<0.001	97	6	117	536
Biochemical indicators						
AST	2.75 (2.37, 3.12)	<0.001	91	4	61	252
ALT	2.72 (2.43, 3.02)	<0.001	96	4	92	446
ALB	−2.95 (−3.21, −2.7)	<0.001	93	4	229	408
LDH	4.01 (3.79, 4.24)	<0.001	84	6	351	704
Myocardial indexes						
CK	2.62 (2.2, 3.03)	<0.001	87	4	50	180
CK-MB	3.07 (2.81, 3.34)	<0.001	92	4	138	462

SMD, standardized mean difference; 95% CI, confidence interval; I^2 (%), heterogeneity; IL-6, interleukin 6; IL-4, interleukin 4; IL-10, interleukin 10; SAA, serum amyloid A; CRP, C-reactive protein; D-D, D-dimer; APTT, activated partial thromboplastin time; P-T, prothrombin time; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALB, albumin; LDH, lactate dehydrogenase; CK, creatine kinase; CK-MB, creatine kinase MB isoenzyme.

to other organs. COVID-19 infection causes chronic myocardial damage and severe cardiovascular system damage (31). Han *et al.* reported that high concentrations of biomarkers such as myoglobin, CK isoenzyme, amino-terminal pro-brain natriuretic peptide, and troponin I were associated with disease severity and death (32). Our analysis showed that the serum myocardial injury indexes CK and CK-MB in patients with severe COVID-19 were significantly higher than those in patients with mild COVID-19. Elevated myocardial indexes correlate with the progression of the patient's disease.

In order to better explain the link between COVID-19 and cardiovascular disease, it is necessary to understand the underlying pathological mechanisms of COVID-19 infection, SARS-CoV-2 virus, and cellular transmembrane proteins. Angiotensin-converting enzyme-2 (ACE2), the ACE homologous protein, binds to enter type II alveolar epithelial cells, macrophages, and other types of cells. This process

Table 4 Meta-analysis summary of standardization of laboratory indicators of surviving cases and death cases

Anomaly indicator	SMD (95% CI)	P value	I^2 (%)	Included literature	Death cases	Surviving cases
Inflammatory factors						
IL-6	2.62 (2.15, 3.09)	<0.001	78	2	33	152
PCT	0.2 (0.16, 0.23)	<0.001	39	2	29	127
Routine blood indicators						
neutrophils	2.77 (2.38, 3.16)	<0.001	55	3	54	206
Lymphocyte count	–2.1 (–2.46, –1.75)	<0.001	77	3	54	206
Biochemical indicator						
Creatinine	2.29 (1.87, 2.7)	<0.001	96	2	42	171

SMD, standardized mean difference; 95% CI, 95% confidence interval; I^2 (%), heterogeneity; IL-6, interleukin 6; PCT, procalcitonin.

requires cellular serine protease (TMPRSS2.12) to initiate the priming of the SARS-CoV-2 virus S protein. Therefore, the infection of SARS-CoV-2 requires the co-expression of ACE2 and TMPRSS2 in the same cell type. As a cleavage protein, the viral S protein is a necessary special protein when COVID-19 binds to ACE2 (33). In addition to type II alveolar epithelial cells, ACE2 is highly expressed in pericytes, which may contribute to microvascular dysfunction and explain a greater predisposition to acute coronary syndrome (ACS) (34).

Our results showed that ALT, AST, and LDH were significantly increased in the serum of patients with severe symptoms compared with the mild symptom group. Therefore, in addition to the lungs in patients with severe symptoms, there were other areas of organ dysfunction, including in the liver, kidney, and heart. Significantly lower albumin in patients with severe symptoms suggested that malnutrition is a common feature of COVID-19 patients.

Abnormal routine blood indicators

Alterations in several biological parameters, especially the reduction of lymphocyte counts and neutrophils, are associated with disease progression from severe disease to death (25,35). Moreover, low lymphocyte counts have been reported in other viral respiratory diseases, such as respiratory syncytial virus infection (36). The immune response marked by severe lymphopenia appears to suggest delayed complications following the early massive release of cytokines during SRAS-Cov-2 lung injury (37-39).

Another key finding of this study was thrombocytopenia in severe COVID-19 patients. It was reported that a COVID-19 thrombocytopenia-related mechanism has been proposed. COVID-19 can infect bone marrow cells, thereby reducing platelet production (40). The elevated PCT and neutrophil counts may be associated with disease severity and associated bacterial infection, which may indicate severe progression in patients.

Indicators of abnormal blood coagulation

Disseminated intravascular coagulation (DIC) and pulmonary embolism generally increase D-dimer concentrations and fibrin degradation products in COVID-19, and DIC was observed in 71.4% of patients who died from COVID-19. Currently, massive pulmonary embolism has been reported (41), although the early appearance of DIC features is usually evident. It is notable that the studies from China showed that D-dimer could increase a high degree of prediction of poor COVID-19 outcomes.

The retrospective study reported by Zhou *et al.* indicated that elevated D-dimer levels (>1 g/L) were strongly associated with in-hospital mortality [odds ratio (OR) 18.4, 95% CI: 2.6, 28.6, P=0.003] (42). In addition, it was reported that more discrete changes in D-dimer levels could be observed earlier in rapidly developing disease stages.

There were some limitations in our study. Firstly, due to the limited number of studies, Egger's test and funnel plots were chosen to assess publication bias, rather than forest plots and publication bias was confirmed that (P<0.05). Secondly, although some of the included studies were from outside of China, most were based in China and regional and ethnic differences are not universal.

Conclusions

Some inflammatory factors (IL-6, IL-10, IL-4, SAA, PCT,

and CRP), biochemical indicators (CK-MB, D-dimer, AST, ALT, LDH, and creatinine), and routine blood indicators (lymphocyte count, neutrophil count, and platelets) were significantly associated with the progression of COVID-19 disease. These biomarkers may be useful for predicting the classification of patients at risk for COVID-19 and for further treatment and prognostic assessment.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-345/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-345/coif). The authors have no conflicts of interest to declare.

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