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Identification of Parameters Representative of Immune Dysfunction in Patients with Severe and Fatal COVID-19 Infection: a Systematic Review and Meta-analysis

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Abstract

Abnormal immunological indicators associated with disease severity and mortality in patients with COVID-19 have been reported in several observational studies. However, there are marked heterogeneities in patient characteristics and research methodologies in these studies. We aimed to provide an updated synthesis of the association between immune-related indicators and COVID-19 prognosis. We conducted an electronic search of PubMed, Scopus, Ovid, Willey, Web of Science, Cochrane library, and CNKI for studies reporting immunological and/or immune-related parameters, including hematological, inflammatory, coagulation, and biochemical variables, tested on hospital admission of COVID-19 patients with different severities and outcomes. A total of 145 studies were included in the current meta-analysis, with 26 immunological, 11 hematological, 5 inflammatory, 4 coagulation, and 10 biochemical variables reported. Of them, levels of cytokines, including IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, IFN-γ, IgA, IgG, and $CD4^+$ T/$CD8^+$ T cell ratio, WBC, neutrophil, platelet, ESR, CRP, ferritin, SAA, D-dimer, FIB, and LDH were significantly increased in severely ill patients or non-survivors. Moreover, non-severely ill patients or survivors presented significantly higher counts of lymphocytes, monocytes, lymphocyte/monocyte ratio, eosinophils, $CD3^+$ T,$CD4^+$T and $CD8^+$T cells, B cells, and NK cells. The currently updated meta-analysis primarily identified a hypercytokinemia profile with the severity and mortality of COVID-19 containing IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, and IFN-γ. Impaired innate and adaptive immune responses, reflected by decreased eosinophils, lymphocytes, monocytes, B cells, NK cells, T cells, and their subtype $CD4^+$ and $CD8^+$ T cells, and augmented inflammation, coagulation dysfunction, and nonpulmonary organ injury, were marked features of patients with poor prognosis. Therefore, parameters of immune response dysfunction combined with inflammatory, coagulated, or nonpulmonary organ injury indicators may be more sensitive to predict severe patients and those non-survivors.

Keywords COVID-19 · Hematological parameters · Immunological indices · Inflammatory responses · Meta-analysis

Abbreviations

ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
Bas	Basophil
COVID-19	Coronavirus disease 2019
CK	Creatine kinase

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cTnI	Cardiac troponin I
CNKI	China National Knowledge Infrastructure
CRP	C-reactive protein
CRN	Creatinine
C3	Complement 3
C4	Complement 4
$CD3^+$ T(ab)	CD3-positive T-lymphocyte absolute count
$CD3^+$ T(%)	CD3-positive T-lymphocyte percentage
CIs	Confidence intervals
ESR	Erythrocyte sedimentation rate
Eos	Eosinophil
FIB	Fibrinogen
ICUs	Intensive-care units
IL-6	Interleukin-6
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IQR	Interquartile range
95%CIs	95% Confidence intervals
LDH	Lactate dehydrogenase
Lym	Lymphocyte
LMR	Lymphocyte/monocyte ratio
Mono	Monocyte
MYO	Myoglobin
MERS-CoV	Middle East respiratory syndrome coronavirus
NLR	Neutrophil/lymphocyte ratio
NOS	Newcastle–Ottawa Scale
NK cells	Natural-killer cells
Neu	Neutrophil
NETs	Neutrophil extracellular traps
PCT	Procalcitonin
PT	Prothrombin time
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAA	Serum amyloid A protein
SMDs	Standardized mean differences
SD	Standard deviation
TBIL	Total bilirubin
TNF-α	Tumor necrosis factor-alpha
WBC	White blood cell

Introduction

As of 27 September 2021, the outbreak of coronavirus disease 2019 (COVID-19) has affected more than 200 countries, with 231,703,120 confirmed cases and 4,746,620 deaths globally [1]. The disease is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which results in a large number of severe/critical ill patients who require rigorous management in intensive-care units (ICUs) [2–4]. Until now, there has been no consensus on an effective method to eradicate SARS-CoV-2. Prompt recognition and supportive care for potentially severe/critical ill patients are the mainstay treatments to save lives.

Our previous study [5] showed that the counts of lymphocytes, T cell subsets, and eosinophils decreased markedly in severely and fatally ill patients. Non-survivors maintained high levels of, or showed an upward trend in, neutrophil (Neu) counts, interleukin-6 (IL-6), procalcitonin (PCT), serum amyloid A protein (SAA), and C-reactive protein (CRP) levels, while levels of these markers held stable or showed a downward trend in survivors. In addition, studies from other research groups have also investigated the correlation between abnormal immune parameters, including white blood cells (WBC), lymphocytes (Lym), and eosinophil (Eos) counts, infection-related variables, serum inflammatory-cytokine levels, and severity or mortality of the disease [5–7]. Indeed, identifying early and sensitive indicators representative of innate and adaptive immune responses to COVID-19 may help predict the disease progression and potential fatal outcomes.

The evidence of immune abnormalities associated with disease severity and mortality in COVID-19 patients has been widely reported in many published observation clinical studies. However, these studies presented a significant heterogeneity in demographic characteristics, genetic features, and therapeutic approaches before hospital admission. Although previous systematic meta-analyses provided evidence of immune signatures in patients with COVID-19 in the early phase of the disease outbreak [8–11], a number of studies have emerged that offer updated data on the immune abnormality associated with poor clinical outcomes [12–16]. Therefore, we aimed to obtain updated, comprehensive evidence of the immune index alongside hematological, biochemical, inflammatory, and coagulation parameters in either a severity or mortality cohort to present the interplay between impaired immune responses and multi-system abnormality contributing to disease progression.

Materials and Methods

Search Strategy and Selection Criteria

This systematic review was conducted according to the Preferred Reporting in Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We previously registered this meta-analysis in PROSPERO, and the study registration number is CRD42020196272. We searched seven databases, PubMed, Scopus, Ovid, Willey, Web of Science, Cochrane Library and the China National Knowledge Infrastructure (CNKI), using the advanced search mode in the field "Title/Abstract," the search terms ["COVID-19"

OR "SARS-COV-2"] AND ["biomarkers" OR "predictors" OR "parameters"] AND ["severity" OR "mortality"], from January 1, 2020 to August 20, 2021, without any language restrictions. After removing duplicates by Endnote, two reviewers independently assessed the title, abstract, and full text of each article to identify eligibility. Any disagreements were solved by a discussion with a third reviewer to reach a consensus. We included observational studies that consisted of two groups: (a) patients with different severities of COVID-19 and/or (b) patients who died from COVID-19 compared to those who survived. Articles with computable data about immune-related variables, including immunological and/or hematological, coagulation, inflammatory, and biochemical variables, were included in the current meta-analysis. The following results were excluded: reviews and meta-analysis, case reports, editorials, preprints, correspondences and letters, data papers, notes, comments, news, short surveys, erratums and retractions, guidelines, and mathematical models. Moreover, we used the Newcastle–Ottawa Scale (NOS) to evaluate the quality of each included publication.

Data Collection

Based on the classifications of the *COVID-19 Diagnosis and Treatment Guideline in China (Interim version 8)* [17], the severity of disease was classified as four types: mild, moderate, severe and critical. As the originally reported clinical groups were highly diverse among the included publications, we attempted to combine them into two groups, severe COVID-19 and non-severe COVID-19, for further meta-analysis. The strategy for this combination was as follows: (1) groups consisting of severe or critical cases, cases treated in ICUs, aggravations, refractory disease, and ARDS cases; and (2) groups consisting of non-severe, mild, moderate, common, ordinary, or general cases, cases not treated in ICUs, no aggravations, and cases without ARDS were placed into the non-severe COVID-19 group. Raw published/publicly available data were extracted, verified in duplication, and combined into a single database. In order to present the detailed characteristics of included studies, we extracted basic information of each study, which included the first author, year of publication, country and region, language, original reported groups, combined groups, average age, gender, and sample size of the "case and control groups." We defined "severe and non-survivors" as "case groups" and "non-severe and survivors" as "control groups." We also described the collected parameters in each study, including immunological and hematological parameters that are closely associated with immune function, and a few indexes reflecting infection, coagulation, and biochemical status. The final item was the quality score of studies, evaluated by the Newcastle–Ottawa Scale, with a higher score meaning higher quality.

Statistical Analysis

All analyses were performed using R software version 3.6.2 (package: meta/metafor; R Project for Statistical Computing, https://www.r-project.org). We divided studies into two separate cohorts for analysis: a severity cohort and a mortality cohort. For the meta-analysis, we transformed the format of laboratory variables presented as "median [interquartile range (IQR)]" into that of "mean [standard deviation (SD)]" [18, 19]. The value of "mean (SD)" of each included variable in the combined groups was calculated with the raw data from the originally reported groups using the formula proposed by Zhang et al. [20]. Standardized mean differences (SMDs) and 95% confidence intervals (95%CIs) were calculated as the primary metrics for each laboratory variable. Laboratory data was pooled whenever two or more publications reported a given variable. We quantified the variations in observed laboratory variables across studies attributable to heterogeneity using the I^2 statistic, a metric ranging from 0% (indicating that all the heterogeneity was spurious) to 100% (indicating that all the heterogeneity was "real" and required further examination or explanation). To probe the sources of heterogeneity, we conducted a meta-regression analysis with three potential factors: the approach of combining disease severity, age, and region. The included variables that presented high heterogeneity ($I^2 > 50\%$) and were reported by an adequate number of studies ($n \geq 10$) were applied to the analysis. In addition, the robustness of the results was applied by performing leave-one-out sensitivity analysis. The funnel plot method was used to test the publication bias.

Results

Figure 1 shows the flow diagram of selecting studies according to the PRISMA guidelines. We identified a total of 8552 records by searching seven databases. After removing duplicates, we screened the title and abstract of 5461 articles and excluded ineligible study designs ($n = 2061$) and unrelated to the topic ($n = 1782$). Then, we assessed 1618 full-text articles and excluded 1473 publications, mainly owing to no targeted groups ($n = 654$) and lacking of available and computable laboratory data ($n = 819$). Ultimately, we included 145 eligible publications in the systematic review and meta-analysis [5, 21–164]. Among the included studies, 91 ones were from China; and 54 studies were from

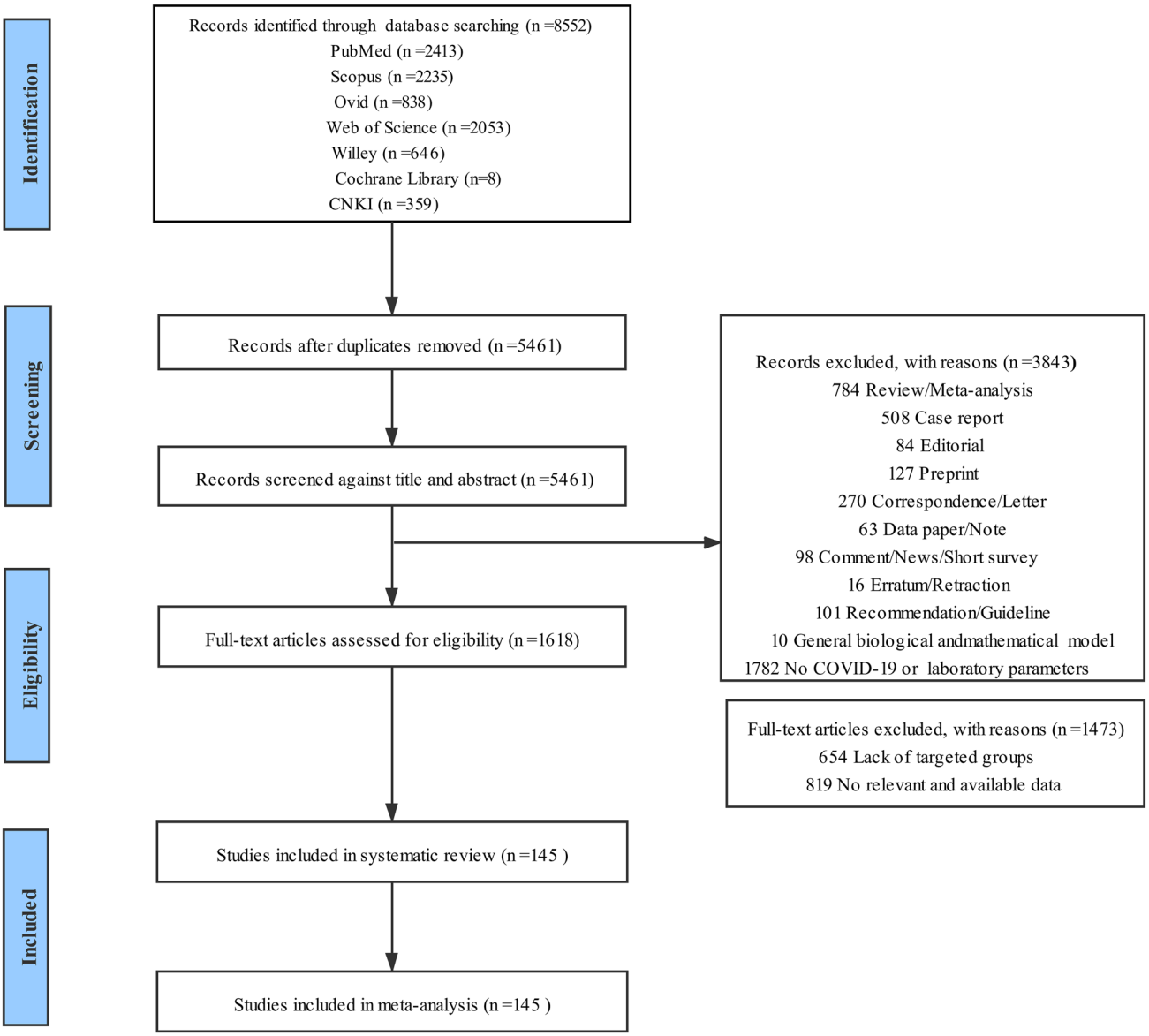

Fig. 1 PRISMA flowchart of the study selection process

America, Pakistan, Japan, Italy, France, Turkey, Korea, UK, Saudi Arabia, Egypt, India, Serbia, Greece, Libya, Spain, Iran, Mexico, Poland, Germany, and the Netherlands. All studies reported that laboratory variables were measured on admission or early during the hospitalization. There were 137 studies published in English and 8 studies published in Chinese. The characteristics of the included studies are presented in Table 1. Detailed results of the quality assessment of the included studies are presented in Fig. E1.

Immunological Results

A total of 26 immunological variables were included for comparisons between patients with severe and those with non-severe COVID-19, including IL-1β, IL-1Ra, IL-2, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, tumor necrosis factor-alpha (TNF-α), interferon-γ (IFN-γ), CD3-positive T-lymphocyte absolute count ($CD3^+$ T[ab]), $CD3^+$ T percentage ($CD3^+$T[%]), $CD4^+$T(ab), $CD4^+$T(%), $CD8^+$T(ab), $CD8^+$T(%), $CD4^+$T(ab)/$CD8^+$T(ab) ratio, B-lymphocyte absolute count (B cell[ab]), Natural-killer cell absolute count (NK[ab]), immunoglobulin A (IgA), IgM, IgG, IgE, C3(Complement 3), and C4. Of these, IL-1β, IL-2, IL-2R, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ, $CD3^+$ T(ab), $CD3^+$ T(%), $CD4^+$ T(ab), $CD4^+$T(%), $CD8^+$ T(ab), $CD8^+$T(%), $CD4^+$T(ab)/$CD8^+$T(ab) ratio, B cell(ab), NK cell(ab), IgA, IgM, IgG, C3, and C4 were available for comparisons between non-survivors and survivors infected with

Table 1 Characteristics of included studies

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Chen 2020	Chongqing, China	Chinese	Critical/Severe/ Moderate	Severe/ Non severe	143 (36/107)	51	20 (55.6)	43	52 (48.6)	IL-6	WBC, Lym, PLT	PCT, CRP	D-dimer	LDH, CK	8
Li 2020	Wuhan, China	Chinese	Critical/Severe/ Moderate	Severe/Non severe	62 (44/18)	55	25 (56.8)	50	7 (38.9)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, B(ab), NK(ab), IgA, IgM, IgE, IgG, C3, C4	WBC, Neu, Lym, PLT	PCT,CRP	APTT, PT	LDH	8
Ling 2020	Shanghai, China	Chinese	Severe/ Non severe	Severe/ Non severe	292 (21/271)	66	19 (90.5)	49	135 (49.8)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab)	WBC, Neu, Lym	ESR,PCT, CRP	D-dimer, FIB	LDH, CK, cTnI, AST, ALT, CRN	9
Lu 2020	Wuhan, China	Chinese	Severe/ Non severe	Severe/Non severe	101 (34/67)	61	17 (50)	41	17 (25.4)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), B(ab), NK(ab), IgA, IgM, IgG, C3, C4	WBC, Neu, Lym, PLT	CRP	NA	LDH, ALT, AST, CRN, BUN	7
Xiang 2020	Jiangxi, China	Chinese	Severe/ Moderate	Severe/Non severe	49(9/40)	53	8 (88.9)	41	25 (62.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), B(ab), NK(ab)	WBC, Neu, Lym, Eos, Mono, PLT, HB	PCT, ESR, CRP, SAA	APTT, PT, D-dimer, FIB	LDH, TBIL, ALB, AST, ALT, CRN, CK	8
Xu 2020	Hefei,China	Chinese	Severe/ Moderate	Severe/ Non severe	155 (30/125)	51	20 (66.7)	40	67 (53.6)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, IL-6	NA	CRP, SAA	APTT	NA	8
Yang 2020	Beijing, China	Chinese	Death/ Survival	Non survivors/ Survivors	94 (13/81)	77	8 (61.5)	66	37 (45.7)	IL-6, IL-8, IL-10, TNF-α	WBC, Neu, Lym	Ferritin	NA	CRN, cTnI	9
Altschul 2020	New York, America	English	Died/ Discharged	Non survivors/ Survivors	2354 (621/ 1733)	73	327 (52.7)	63	771 (44.5)	IL-6	WBC, Lym, PLT	PCT, CRP, Ferritin	D-dimer	AST, ALT, CRN, BUN, cTnI	9
Asghar 2021	Karachi, Pakistan	English	A. ICU/ Ward B. Deceased/ Recovered + Home isolation	A. Severe/ Non severe B. Non survivors/ Survivors	A. 191 (61/130) B. 191 (44/147)	53	NA	NA	NA	NA	LMR, NLR, PLR, HB, PLT	PCT, CRP, Ferritin	NA	LDH	7
Awano 2020	Tokyo, Japan	English	Severe/Non severe	Severe/Non severe	54(21/33)	66	15 (71.4)	41	23 (69.7)	NA	WBC, Lym, Eos	PCT, Ferritin	D-dimer	LDH	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Cai 2020	Shenzhen,China	English	Severe/Non severe	Severe/ Non severe	298 (58/240)	61	39 (67.2)	43	106 (44.2)	IL-6	WBC, Neu, Lym, Eos	PCT, ESR, CRP	D-dimer	AST, ALT, CK, BUN, CRN, LDH, TBIL, MYO	9
Cao 2020	Wuhan, China	English	Critical/Severe/ Moderate	Severe/ Non severe	244 (153/91)	64	89 (58.2)	60	44 (48.4)	$CD4^+$(ab), $CD8^+$(ab)	WBC, Neu, Lym, HB, PLT	PCT, CRP	NA	cTnI, AST, ALT, CRN, CK, LDH, MYO, TBIL	8
Chen 2020	Wuhan, China	English	Severe/ Moderate	Severe/ Non severe	21 (11/10)	61	10 (90.9)	50	7 (70.0)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), B(ab)	WBC, Neu, Lym, HB, PLT	PCT, CRP, Ferritin	APTT, PT, D-dimer	ALT, AST, BUN, CRN, CK, LDH, TBIL	8
Chen 2020	Jiangsu,China	English	Severe or critical/ Mild/ Ordinary	Severe/ Non severe	598 (31/567)	61	302 (53.3)	45	20 (64.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), IL-6	WBC, Neu, Lym, Eos, Mono, PLT, HB	PCT, CRP, ESR	APTT, PT, FIB	AST, ALT, BUN, CRN, LDH, TBIL	8
Chen 2020	Wuhan, China	Chinese	Critical/Severe/ Moderate	Severe/Non severe	29 (14/15)	NA	NA	NA	NA	IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α	Lym	CRP	NA	LDH	7
Chen 2020	Wuhan, China	English	A. Non survivors/ Survivors B. Critical/Severe/ Moderate/Mild	A. Non survivors/ Survivors B. Severe/Non severe	A. 575 (103/445); B. 575 (203/345)	A.67 B.61	A.69 (67.0) B.131 (64.5)	A.54 B.67	A.244 (54.8) B.182 (52.8)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+/CD8^+$, IL-6	WBC, Neu, Lym, Eos, Mono, Bas, NLR, PLR, PLT, HB	PCT, CRP, Ferritin, SAA	APTT, PT, D-dimer	NA	8
Chen 2020	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	55 (19/36)	77	16 (84.2)	72	18 (50.0)	IL-6	WBC, Neu, Lym, PLT	PCT, ESR, CRP	D-dimer	ALT, AST, ALB, CRN, LDH, CK	8
Chen 2020	Wuhan, China	English	Dead/Survive	Non survivors/ Survivors	274(113/161)	69	83 (73.0)	51	171 (62.0)	IL-2R, IL-6, IL-8, IL-10, TNF-α, IgA, IgG, C3, C4	WBC, Neu, Lym, Mono, HB, PLT	PCT, ESR, CRP, Ferritin	APTT, PT, D-dimer	ALT, AST, ALB, BUN, CRN, CK, LDH, cTnI, TBIL	9
Chen 2020	Wuhan, China	English	Critical/Severe/ Moderate	Severe/ Non severe	48 (27/21)	74	24 (88.9)	53	13 (61.9)	IL-6	WBC, Neu, Lym	PCT	NA	CRN, BUN	8
Chi 2020	Nanjing, China	English	Severe/Moderate/ Mild	Severe/ Non severe	66(8/58)	54	5 (63.0)	42	32 (55.2)	IL-1Ra, IL-1β, IL-8, IL-10, IL-18, TNF-α, IFN-r	NA	NA	NA	NA	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Ciceri 2020	Milan, Italy	English	Dead/Discharged	Non survivors/ Survivors	386 (95/291)	75	70 (73.7)	63	207 (71.1)	IL-6	WBC, Neu, Lym, HB, PLT, NLR	PCT,CRP, Ferritin	D-dimer	LDH, CK, cTnI, AST, CRN, TBIL	9
Dong 2020	Wuhan, China	English	Severe/Non severe	Severe/Non severe	147 (53/94)	58	29 (54.7)	43	34 (36.2)	IL-6, IL-10, TNF-α	WBC, Neu, Lym	CRP, ESR,SAA	D-dimer, FIB	ALT, AST, BUN, CRN	8
Du 2020	Wuhan, China	English	Deceased/Survivors	Non survivors/ Survivors	179 (21/158)	70	10 (47.6)	56	87 (55.1)	$CD4^+$(ab), $CD8^+$(ab)	WBC, Neu, Lym	PCT, CRP	APTT, PT, D-dimer	MYO, ALB, TBIL, ALT, AST, CRN, cTnI	8
Feng 2020	Wuhan, China	English	Poor outcome/Good outcome	Non survivors/ Survivors	114 (20/94)	69	13 (65.0)	63	58 (61.7)	$CD4^+$(%), $CD8^+$(%), IL-2, IL-4, IL-6, IL-10, IFN-γ	WBC, Neu, Lym, Mono, HB	CRP,Ferritin	APTT, PT, D-dimer, FIB	ALT, AST, BUN, CRN, CK, LDH, cTnI, TBIL	9
Feng 2020	China	English	Critical/Severe/ Moderate	Severe/Non severe	476(124/352)	59	81 (65.3)	50	190 (54.0)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), TNF-α, IgA, IgM, IgG	WBC, Neu, Lym, HB, PLT	CRP,PCT, ESR	D-dimer, FIB	TBIL, ALB, MYO, CRN, LDH, CK, BUN	8
Guo 2020	Shanghai,China	English	Severe/Non severe	Severe/Non severe	200 (19/181) 348(68/280)	57	46 (67.6)	50	157 (56.1)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+/CD8^+$, IL-6, IgA, IgM, IgG	NA	NA	NA	NA	7
Han 2020	Anhui, China	English	Severe/Mild	Severe/Non severe	154 (32/122)	52	23 (71.8)	40	63 (51.6)	$CD3^+$(ab), CD4 + T(ab), CD8 + T(ab), B(ab), NK(ab), IL-6	WBC, Neu, Lym, PLT, HB	PCT, ESR, CRP, SAA	D-dimer, FIB, PT	ALT, AST, ALB, TBIL, BUN, CRN, CK, LDH	7
He 2020	Wuhan, China	English	Severe/Non severe	Severe/Non severe	204 (69/135)	62	37 (53.6)	42	42 (31.1)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, B(ab), NK(ab), IL-2, IL-4, IL-10, TNF, IFN-γ, IgA, IgM, IgE, IgG, C3, C4	WBC, Neu, Lym, PLT	PCT, CRP	PT, D-dimer	ALT, AST, CRN, LDH, CK, cTnI	7

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Huang 2020	Wuhan, China	English	Dead/Alive	Non survivors/ Survivors	50 (10/40)	38	5 (50.0)	37	18 (45.0)	IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α,	Neu, Lym, Eos, Mono	CRP	APTT, PT, D-dimer, FIB	ALT, AST, cTnI, CK, CRN, BUN	9
Huang 2020	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	151 (15/136)	76	13 (86.7)	59	68 (50.0)	IL-2R, IL-6, IL-8, TNF-α	WBC, Lym	PCT, CRP	NA	AST, ALT, BUN, CRN, MYO	7
Hue 2020	Créteil, France	English	Dead/Alive	Non survivors/ Survivors	38 (13/25)	68	NA	57	NA	IL-6, IL-10	NA	NA	NA	NA	9
Jiang 2020	Wuhan, China	English	Non-survivor/ Survivor	Non survivors/ Survivors	215 (72/143)	70	36 (50.0)	66	69 (48.3)	$CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+$/ $CD8^+$, B(ab), NK(ab)	WBC, Neu, Lym, Mono, HB, PLT	PCT, CRP	APTT, PT, D-dimer, FIB	ALT, AST, ALB, TBIL, LDH, cTnI, CRN, BUN	8
Kazancioglu 2020	Ankara, Turkey	English	Severe/Non severe	Severe/Non severe	120 (35/85)	60	20 (57.1)	44	52 (61.2)	IL-6	WBC, Neu, Lym, Eos, Mono, Bas, HB, PLT	CRP, Ferritin	APTT, PT, D-dimer	ALT, AST, LDH, CK	7
Lei 2020	Guangzhou, China	English	Severe & Critical/ Mild & Moderate	Severe/Non severe	297 (52/245)	60	32 (61.5)	44	111 (45.3)	NA	Lym, Eos	CRP,PCT	NA	TBIL, LDH, ALB	7
Li 2020	Shanghai,China	English	Severe/Non severe	Severe/Non severe	322 (26/296)	68	20 (76.9)	49	147 (49.8)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab)	WBC, Lym, PLT	PCT, CRP	D-dimer	LDH, AST, ALT, TBIL, BUN, CRN, CK	7
Li 2020	Beijing, China	English	Severe/Non severe	Severe/Non severe	69 (26/43)	59	14 (53.8)	40	26 (60.5)	$CD3^+$(ab), $CD4^+$T(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab), IL-1β, IL-6, IL-8, TNF-α	WBC, Neu, Lym, Eos, Mono, Bas	PCT, ESR,CRP, Ferritin	FIB, D-dimer	ALB, AST, ALT, LDH	9
Liao 2020	Wuhan, China	English	Critical/Severe/ Moderate	Severe/Non severe	380(231/149)	67	137 (59.3)	55	69 (46)	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ	WBC, Neu, Lym, Eos, Mono, Bas, HB, PLT	CRP,Ferritin	APTT, PT, D-dimer, FIB	LDH	9
Liu 2020	Wuhan, China	English	Severe/Mild	Severe/Non severe	140 (33/107)	77	25 (75.8)	61	66 (61.7)	IL-6	NA	PCT, CRP	NA	NA	9

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Liu 2020	Wuhan, China	English	Severe/Mild	Severe/Non severe	40 (13/27)	60	7 (53.8)	43	8 (29.6)	IgA, IgM, IgE, IgG, C3, C4	WBC, Neu, Lym, Mono, HB, PLT	CRP,Ferritin, SAA	APTT, PT, D-Dimer, FIB	TBIL, ALT, AST, LDH, CK, BUN, CRN	7
Lu 2020	Shanghai,China	English	Severe and critical/ Mild and moderate	Severe/Non severe	53(9/44)	68	8 (88.9)	53	26 (59.1)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+/CD8^+$, IgA, IgM, IgG, C3, C4	WBC, Neu, Lym, Eos, Mono	CRP,ESR	APTT, PT, D-dimer, FIB	ALB, CRN, TBIL, LDH	8
Luo 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	1018(201/817)	70	133 (66.2)	56	388 (47.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, IL-2R, IL-6, IL-8, IL-10, TNF-α	NA	NA	NA	NA	8
Lv 2020	Wuhan, China	English	Critical/Severe/ Moderate	Severe/Non severe	354(239/115)	60	117 (49.0)	54	58 (50.4)	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, IgA, IgM, IgG, C3, C4	WBC, Neu, Lym	PCT, CRP	D-dimer	BUN, TBIL	8
Mo 2020	Wuhan, China	English	Refractory/General	Severe/Non severe	155(85/70)	61	31 (44.3)	46	55 (64.7)	IL-6	WBC, Neu, Lym, PLT	PCT, ESR, CRP	D-dimer	ALT, AST, ALB, CRN, CK, LDH	9
Park 2020	Daegu, South Korea	English	Fatal cases/Survivor	Non survivors/ Survivors	289 (70/219)	77	42 (60.0)	70	91 (41.6)	NA	WBC, Lym, HB, PLT	CRP,PCT, ESR, Ferritin	PT	CK, AST, ALT, TBIL, BUN, CRN, LDH, ALB	7
Pei 2020	Wuhan, China	English	Critical/Severe/ Moderate	Severe/Non severe	333(189/144)	60	115 (60.8)	51	67 (46.5)	IL-2R, IL-6, IL-10, TNF-α	Neu, Lym, Eos, Mono	ESR, CRP	PT, D-dimer	ALT, AST, cTnI,BUN	9
Qin 2020	Wuhan, China	English	Severe/Moderate	Severe/Non severe	452(286/ 166)	60	155 (54.2)	52	80 (48.2)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+/CD8^+$, B(ab), NK(ab), IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α, IgA, IgM, IgG, C3, C4	WBC, Neu, Lym, Eos, Mono, Bas	PCT, ESR, CRP, Ferritin	NA	NA	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Sinha 2020	Newport and London, UK	English	Non survivors/ Survivors	Non survivors/ Survivors	39 (17/22)	60	14 (82.0)	52	11 (50.0)	IL-6	WBC, Lym, PLT	CRP,PCT, Ferritin	D-Dimer, FIB	ALB, cTnI, LDH, CRN	8
Sun 2020	Jilin, China	English	A. Severe/Non severe B. Died/ Discharged	A. Severe/ Non severe B. Non survivors/ Survivors	A. 57(45/12) B. 36 (11/25)	65	24 (53.3)	58	5 (41.7)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+$/ $CD8^+$, B(ab), NK(ab)	WBC, Neu, Mono, Eos, Bas	NA	NA	NA	8
Sun 2020	Beijing, China	English	Critical/Severe/ Moderate/ Mild	Severe/Non severe	63 (19/44)	59	NA	42	NA	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, NK(ab), IL-6	WBC, Neu, Lym, Eos, Mono, HB, PLT	CRP, ESR, Ferritin	PT, D-dimer, FIB	ALB, TBIL, CRN, ALT, AST, LDH, CK, BUN	8
Urra 2020	Spain	English	ICU/Non ICU	Severe/Non severe	172 (27/145)	66	20 (74.1)	58	84 (57.9)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%)	Neu, Lym, NLR, PLR	CRP,	D-dimer	NA	8
Wan 2020	Chong qing, China	English	Severe/Moderate	Severe/Non severe	123 (21/102)	61	NA	43	NA	$CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab), IL-4, IL-6, IL-10, TNF-α, IFN-γ	WBC, Neu, Lym	NA	NA	NA	8
Wang 2020	Wuhan, China	English	ICU/ Non-ICU	Severe/Non severe	28(14/14)	71	10 (71.4)	66	11 (78.6)	IL-2R, IL-6, IL-8, IL-10, TNF-α	WBC, Neu, Lym, HB, PLT	PCT, ESR, CRP, Ferritin	PT, APTT, D-dimer	CK, LDH, ALT, AST, ALB, TBIL, cTnI, BUN	9
Wang 2020	China	English	Severe/Common	Severe/Non severe	61(24/37)	56	15 (62.5)	51	16 (43.2)	NA	WBC, Neu, Lym, Mono, PLT, LMR, NLR, PLR	PCT,CRP	PT, D-dimer	AST, LDH, ALB, CRN, CK	9
Wang 2020	Wuhan, China	English	Deceased/Alive	Non survivors/ Survivors	119 (16/103)	72	12 (8.2)	59	49 (52.8)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$	WBC, Neu, Lym, Mono, LMR, NLR	PCT,CRP	PT, APTT, D-dimer, FIB	CK, LDH, ALT, AST, CRN, MYO	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Wang 2020	Beijing, China	English	A. Severe/Moderate B. Non survivors/ Survivors	A. Severe/ Non severe B. Non survivors/ Survivors	A. 199(129/70) B. 199(24/175)	A.65 B.72	A.70 (54.3) B.16 (66.7)	A.58 B.62	A.29 (41.4) B.86 (49.1)	IL-1β, IL-2R, IL-8, IL-10, TNF-α	WBC, Neu, Lym, HB, PLT	PCT, CRP, Ferritin	PT, APTT, D-dimer, FIB	AST, ALT, ALB, LDH, TBIL, BUN, CRN	8
Wang 2020	Wuhan, China	English	Death/Survival	Nonsurvivors/ Survivors	339 (65/274)	76	39 (60.0)	69	127 (46.4)	$CD8^+$(ab), IL-6	WBC, Neu, Lym, Mono, HB, PLT	PCT, CRP	PT, APTT, D-dimer	AST, ALT, CRN, CK, cTnI, LDH, BUN	9
Wang 2020	Wuhan, China	English	Severe/Non severe	Severe/Non severe	43(8/35)	6.81	6 (75.0)	6.93	21 (60.0)	$CD3^+$(ab), $CD4^+$(ab), B(ab), NK(ab), IL-2, IL-4, IL-6, IL-10	WBC, Lym	CRP	D-dimer	LDH, CK, ALT, AST, TBIL	8
Wang 2020	Wuhan, China	English	Severe/Mild	Severe/Non severe	69 (14/55)	70	7 (50.0)	40	25 (45.0)	$CD4^+$(%), $CD8^+$(%), IL-2, IL-4, IL-6, IL-10, TNF-α	WBC, Neu, Lym, Mono, Eos, HB, PLT	PCT, ESR, CRP	NA	AST, ALT, LDH, CRN	8
Wang 2020	Wuhan, China	English	Nonsurviving/ Surviving	Non survivors/ Survivors	293(116/ 177)	73	65 (56.0)	50	73 (41.2)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+$/ $CD8^+$, B(ab), NK(ab), NK(%), IgA, IgG, C3, C4	WBC, Neu, Lym	PCT, CRP	PT, APTT, D-dimer	ALT, AST, ALB, CRN, BUN, CK, LDH, MYO, cTnI, TBIL	7
Wu 2020	Wuhan, China	English	A .ARDS/Without ARDS B. Died/ Alive	A. Severe/ Non severe B. Non survivors/ Survivors	A. 201 (84/117) B. 84 (44/40)	A.59 B.68	A.60 (71.4) B.29 (65.9)	A.47 B.49	A.68 (58.1) B.31 (77.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), IL-6	WBC, Neu, Lym, Mono, PLT	ESR, CRP, Ferritin	PT, APTT, D-dimer	TBIL, AST, ALT, ALB, CRN, LDH, BUN	8
Xie 2020	Wuhan,China	English	Severe/Non severe	Severe/Non severe	56 (34/22)	59	6 (27.3)	53	18 (52.9)	$CD3^+$(%), $CD4^+$(%), $CD8^+$(%), $CD4^+$/$CD8^+$	WBC, Neu, Lym, PLT, HB	PCT, CRP	PT, APTT, D-dimer, FIB	ALT, AST, CRN, cTnI, CK, LDH	7
Xiong 2020	Wuhan,China	English	Severe/Non severe	Severe/Non severe	116 (55/61)	64	38 (69.1)	52	42 (68.9)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), IL-6	WBC, Neu, Lym, Mono, HB, PLT	CRP	PT, APTT, D-dimer	CRN, BUN, AST, ALT, TBIL, LDH, cTnI, MYO	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Xu 2020	Wuhan, China	English	A. Died/Discharged B. Critical/Severe/ Mild	A. Non survivors/ Survivors B. Severe/ Nonsevere	A. 145 (28/117) B. 187 (107/80)	A.73 B.64	A.17 (60.7) B.73 (68.2)	A.55 B.56	A.59 (50.4) B.30 (37.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab), IL-1β, IL-6, IL-10, TNF-α	WBC, Neu, Lym, Mono	PCT, CRP, SAA	PT, D-dimer	BUN, CRN, ALT, AST, CK	8
Yan 2020	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	48(39/9)	70	76 (70.4)	49	38 (44.7)	IL-2R, IL-6, IL-8, TNF-α	WBC, Neu, Lym, HB, PLT	PCT, ESR, CRP, Ferritin	PT, APTT, FIB, D-dimer	ALT, AST, ALB, TBIL, CK, LDH, CRN,cTnI, BUN	8
Yang 2020	Wuhan, China	English	Critical/Severe/Mild	Severe/Non severe	52 (19/33)	NA	NA	NA	NA	$CD4^+$(ab), $CD8^+$(ab), IL-6	WBC, Neu, Lym	PCT, CRP	D-dimer	LDH, AST, ALT, CRN, cTnI	8
Yang 2020	Shenzhen, China	English	Critical/Severe/ Moderate	Severe/Non severe	50(36/14)	59	22 (61.1)	50	7 (50.0)	$CD4^+$(ab), $CD8^+$(ab)	WBC, Neu, Lym, PLT	PCT, CRP	NA	AST, ALT, CRN, BUN, CK, LDH, TBIL	8
Yuan 2020	Shenzhen, China	English	Critical/Severe/ Moderate	Severe/Non severe	214 (92/122)	58	59 (64.1)	41	58 (47.5)	$CD4^+$(ab), IL-6	WBC, Neu, PLT	CRP	D-Dimer	ALB	7
Zhang 2020	China	English	Critical/Severe/ Moderate/ Mild	Severe/Non severe	414 (162/251)	44	34 (57.6)	42	11 (37.9)	NA	WBC, Neu, Lym, Mono, LMR, NLR, PLR	NA	NA	NA	7
Jun. Zhang 2020	Wuhan, China	English	Deterioration/ Discharge	Non survivors/ Survivors	111 (18/93)	64	14 (77.8)	38	32 (34.4)	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ	WBC, Neu, Lym, Mono, PLT	CRP	NA	CRN, BUN, ALT, AST	9
Zhang 2020	Wuhan, China	English	Severe/Non severe	Severe/Non severe	74 (27/47)	70	18 (66.7)	61	18 (38.3)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), B(ab), NK(ab), IL-6, IgM, IgE, IgG	WBC, Neu, Lym, Eos, HB, PLT	PCT, ESR, CRP, SAA	D-dimer	CRN, ALB, AST, ALT, CK, LDH, cTnI	7
Zhao 2020	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	539 (125/414)	71	71 (56.8)	52	184 (44.4)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), B(ab), IL-6, IgA, IgG	WBC, Neu, Lym, HB, PLT	PCT, CRP	NA	NA	9
Zhao 2020a	Beijing, China	English	Severe/Mild	Severe/Non severe	71 (18/53)	64	7 (38.9)	45	53 (43.4)	IL-1β, IL-1Ra, IL-2, IL-4, IL-6, IL-10, IL-18, TNF-α	NA	NA	NA	NA	9

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Zheng 2020	Chengdu,China	English	Critical/Moderate	Severe/Non severe	99 (32/67)	64	NA	43	NA	$CD4^+$(ab), $CD8^+$(ab)	WBC, Neu, Lym	CRP	PT, D-dimer	ALT, AST, MYO, cTnI	7
Zhou 2020	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	191 (54/137)	69	38 (70.0)	52	81 (59.0)	IL-6,	WBC, Lym, HB, PLT	PCT, Ferritin	PT, D-dimer	LDH, ALB, ALT, CK, cTnI	8
Zhou 2020	Nanchang, China	English	Aggravation group/ Non aggravation group	Severe/Non severe	17(5/12)	42	0 (0.0)	42	6 (50.0)	$CD4^+$(ab), $CD8^+$(ab)	WBC, Lym	NA	D-dimer	LDH, ALB	8
Zhu 2020	Ningbo, China	English	Severe/Non severe	Severe/Non severe	127 (16/111)	58	9 (56.3)	50	73 (65.8)	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ	WBC, Neu, Lym, NLR, PLR	CRP,ESR	D-dimer, FIB	NA	8
Abers 2020	New York, America	English	Critical/Severe/ Moderate	Severe/Non severe	175 (145/30)	NA	NA	NA	NA	IL-1β, IL-1Ra, IL-2, IL-4, IL-8, IL-18, TNF-α	NA	NA	NA	NA	7
G.Açıksarı 2021	Turkey	English	Non survivors/ Survivors	Non survivors/ Survivors	223 (36/187)	74	15 (12.7)	57	103 (87.3)	NA	WBC, Neu, Lym, Mono, HB, PLT, LMR, NLR, PLR	CRP	NA	NA	8
Alhumaid 2021	Alahsa, Saudi Arabia	English	ICU/Non-ICU	Severe/Non severe	1014(205/809)	53	116 (56.5)	45	466 (57.6)	NA	WBC, Neu, Lym, HB, PLT	CRP,ESR, Ferritin	NA	CK, AST, ALT, LDH, CRN, CK	8
Aly 2021	Egypt	English	Critical/Severe/Non severe	Severe/Non severe	496(311/185)	57	181 (58.2)	38	92 (49.5)	NA	HB, PLT, LMR, NLR, PLR	CRP,Ferritin	D-dimer	NA	8
Bellan 2021	Italy	English	Dead/Discharged	Non survivors/ Survivors	664(211/ 453)	80	144 (68.0)	63	260 (57.0)	NA	WBC, Neu, Lym, Eos, NLR, PLT	NA	NA	NA	7
Bergantini 2021	Italy	English	Severe/Mild to moderate	Severe/Non severe	24(10/14)	65	8 (80.0)	62	11 (78.6)	$CD4^+$(%), $CD8^+$(%), IL-6	WBC, Neu, Lym, Mono, Eos, Bas, PLT	CRP	NA	ALT, AST, LDH	9
Betti 2021	Alessandria, Italy	English	Severec & critical/ Mild & moderate	Severe/Non severe	171 (82/89)	57	54 (65.9)	51	50 (56.2)	NA	WBC, Neu, Lym, Eos, HB, PLT	CRP,Ferritin	APTT, PT, D-dimer, FIB	ALT, AST, LDH, TBIL, CRN, cTnI, BUN	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Bg 2021	Davangere, India	English	Non survivors/ Survivors	Non survivors/ Survivors	100 (25/75)	59	13 (52.0)	43	44 (58.7)	NA	LMR, NLR, PLR	NA	NA	NA	8
Cai 2020	Wuhan, China	English	A. Severe/Non-severe B. Death/ Recovery	A. Severe/ Non-severe B. Non survivors/ Survivors	A. 85(48/37) B. 41(22/19) C. 22(7/15)	A.64 B.67C.70	A.34 (70.8) B.12 (54.5) C.3 (42.9)	A.55 B.50 C.66	A.21 (56.8) B.9 (47.4)C.9 (60.0)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab), IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, IFN-γ	WBC, Neu, Lym, HB, PLT	CRP	APTT, PT, D-dimer	ALB, BUN, CRN, CK, AST, ALT	9
Capdevila-Reniu 2021	Barcelona, Italy	English	Dead/Recovered	Non survivors/ Survivors	159 (53/106)	86	29 (55.0)	83	47 (44.0)	NA	Lym	CRP, Ferritin	D-dimer	LDH	9
Cekerevac 2021	Serbia	English	Severe/Moderate/ Mild	Severe/Non severe	127 (70/57)	61	49 (56.3)	52	38 (66.7)	NA	WBC, Lym, HB, PLT	CRP	FIB	LDH, CK	8
Chen 2020	Taiwan, China	English	Severe/Non severe	Severe/Non severe	55 (24/31)	52.1	NA	NA	NA	IL-1β, IL-1Ra, IL-6, IL-18, TNF-α, IFN-γ	NA	NA	NA	NA	7
Conca 2021	Saudi Arabia	English	Severe/Moderate/ Mild	Severe/Non severe	34 (5/29)	74	5 (100.0)	44	7 (24.1)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab)	WBC	CRP, Ferritin	D-dimer	NA	7
d'Alessandro 2020	Siena, Italy	English	Severe/Non severe	Severe/Non severe	54(14/40)	65	12 (85.7)	65	21 (52.5)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+$/ $CD8^+$, B(ab), NK(ab)	NA	NA	NA	NA	8
Deng 2021	Guangzhou, China	English	Severe & critical/ Mild	Severe/Non severe	166 (17/149)	59	9 (52.9)	48	65 (43.6)	$CD3^+$(%), $CD4^+$(%), $CD8^+$(%), $CD4^+$/$CD8^+$	HB, PLT	NA	PT, APTT, D-dimer, FIB	LDH, CK, CRN	8
Eleni 2021	Greece	English	A. Death/No death B. ICU/No ICU	A. Non survivors/ Survivors B. Severe/ Non severe	A. 5 (9/76) B. 85 (17/68)	A. 71 B. 60	A. 5 (55.6) B. 14 (82.4)	A. 60 B. 60	A. 44 (57.9) B. 35 (51.5)	NA	Lym, PLT	CRP, Ferritin	D-dimer, FIB	ALT, AST, LDH, cTnI	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Elhadi 2021	Libya	English	Non survivors/ Survivors	Non survivors/ Survivors	465(281/184)	69	153 (54.4)	64	87 (47.3)	NA	WBC, Neu, Lym, PLT	CRP,PCT, Ferritin	PT, D-dimer, FIB	cTnI	8
García de Guadiana-Romualdo 2021	Spain	English	A. Non survivors/ Survivors B. Severe/Non-severe	A. Non survivors/ Survivors B. Severe/Non-severe	A. 99 (14/85) B. 99 (25/74)	A. 76 B. 70	A. 10 (71.4) B. 16 (64.0)	A. 64 B. 65	A. 51 (60.0) B. 45 (60.8)	IL-6	WBC, Neu, Lym, NLR, PLT, HB	CRP,PCT, Ferritin	D-dimer	CRN, ALB, ALT, LDH	9
Huang 2021	Wuhan, China	English	Critical/Severe/ Moderate	Severe/ Non severe	218 (102/116)	68	57 (49.1)	56	49 (42)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), B(ab), NK(ab), IL-6	Neu, Lym, Mono, Eos, NLR	NA	NA	NA	8
Karahan 2021	Turkey	English	A. Severe-Critica/ Moderate B. Deceased/ Surviving	A. Severe/ Non severe B. Non survivors/ Survivors	A. 149 (102/47) B. 149 (69/80)	A. 67 B. 68	A. 58 (56.9) B. 41 (59.4)	A. 56 B. 60	A. 23 (48.9) B. 40 (50.0)	NA	WBC, Neu, Lym, HB, PLT	CRP	NA	ALB	8
Karampoor 2021	Iran	English	ICU/Non ICU	Severe/ Non severe	120 (63/57)	61	29 (46.0)	52	35 (61.0)	IL-6, IL-10, IL-18	NA	NA	NA	NA	8
Li 2021	Wuhan, China	English	A. Nonsurvivors/ Survivors B. ICU/ Non ICU	A. Non survivors/ Survivors B. Severe/ Non severe	A. 211 (95/116) B. (211/312)	69	56 (58.9)	56	63 (54.3)	IL-6	WBC, HB	CRP, PCT	NA	BUN, CRN, cTnI, AST, ALT, TBIL, ALB	8
Li 2021	Changchun,China	English	Severe or Critical/ Nonsevere	Severe/Non severe	285 (90/164)	70	57 (63.3)	64	73 (44.5)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab), IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α	WBC, Neu, Lym, Mono, PLT, NLR	CRP,PCT, ESR	APTT, PT, D-dimer, FIB	LDH, cTnI, AST, ALT, TBIL, ALB, CRN	8
Liu 2021	Wuhan, China	English	Severe Common	Severe/Non severe	122 (79/43)	63	46 (58.2)	53	26 (60.5)	IL-6	WBC, Neu, Lym	CRP,PCT, SAA,ESR, Ferritin	APTT, PT, D-dimer, FIB	AST, ALT, CRN, LDH, CK, MYO, cTnI, BUN, TBIL	8
Liu 2020	Nanchang,China	English	Severe/ Mild	Severe/ Non severe	76 (30/46)	NA	NA	NA	NA	$CD4^+$(ab), $CD8^+$(ab), IL-1β, IL-2R, IL-6, IL-8, IL-10	Lym	NA	APTT, PT, D-dimer, FIB	CK, LDH	7

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
López-Escobar 2021	Madrid, Barcelona and Galicia, Spain	English	Non survivors/ Survivors	Non survivors/ Survivors	2088 (321/1767)	82	213(66.4)	66	1032(58.4)	NA	WBC, Neu, Lym, Mono, NLR, PLT	CRP	APTT, PT, D-dimer	AST, ALT, LDH, CRN	7
Lu 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	77 (40/37)	60	29 (73.0)	57	21 (57.0)	NA	WBC, Neu, Lym	CRP,PCT, ESR, Ferritin	APTT, PT, D-dimer	AST, ALT, CRN, LDH, CK, MYO, cTnI, BUN, TBIL	9
Marín-Corral 2021	Spain	English	Critical/Severe/ Moderate	Severe/Non severe	49 (36/13)	51	17 (47.2)	59	7 (53.8)	NA	WBC, Lym	PCT	D-dimer, FIB	LDH	9
Montrucchio 2021	Turin, Northern-Italy	English	Non survivors/ Survivors	Non survivors/ Survivors	57(31/26)	66	28 (90.3)	60	22 (84.6)	NA	WBC, Lym	CRP,PCT	D-dimer	LDH	8
Nakamura 2021	Tokyo, Japan	English	Non survivors/ Survivors	Non survivors/ Survivors	32(11/21)	74	10 (91.0)	67	12 (57.0)	NA	WBC, Neu, Lym, HB, PLT	CRP, Ferritin	D-dimer	CRN, ALB, TBIL, LDH	9
Namendys-Silva 2021	Mexico	English	Dead/ Alive	Non survivors/ Survivors	164 (85/79)	57	59 (69.4)	49	55 (69.6)	NA	WBC, Neu, Lym, PLT	CRP, Ferritin	D-dimer	CRN, TBIL	8
Özdemir 2021	Turkey	English	Deceased/ Surviving	Non survivors/ Survivors	350 (55/295)	73	29 (52.7)	50	165 (55.9)	NA	WBC, Lym, HB	CRP	D-dimer	cTnI, CRN, AST, ALT, ALB	7
Peiro 2021	Spain	English	Non survivors/ Survivors	Non survivors/ Survivors	196 (37/159)	76	23 (62.2)	63	94 (59.1)	NA	WBC, Lym, HB, PLT	CRP	D-dimer	LDH, cTnI	8
Provencio 2021	Spain	English	Died/ Survived	Non survivors/ Survivors	447 (146/301)	68	NA	67	NA	NA	Neu, Lym, Mono, NLR	CRP	D-dimer	LDH, ALB	8
Qin 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	262 (23/239)	69	10 (43.5)	61	113 (47.3)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), C3, C4	WBC, Neu, Lym, Mono	CRP	NA	AST, ALT, CRN, LDH, TBIL	8
Quartuccio 2021	Udine, Italy	English	Patients with P/F < 300/Patients with P/F ≥ 300	Severe/ Non severe	67(22/45)	58	17 (77.3)	59	32 (71.1)	IL-6, IL-18	WBC, Neu, Lym	CRP	D-dimer	LDH, CK	9
Sai 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	47 (15/32)	71	7 (46.7)	70	23 (71.9)	IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α	WBC, Neu, Lym, HB, PLT	CRP,PCT	D-dimer	LDH, AST, CRN, cTnI, TBIL	9
Salto-Alejandre 2021	Seville, Spain	English	Severe/ Moderate/ Mild	Severe/ Non severe	321 (85/236)	74	50 (58.8)	60	119 (50.4)	NA	WBC, Neu, Lym	CRP	D-dimer	CRN, AST, LDH	8

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Scotto 2021	Italy	English	Unfavourable Outcome/ Favourable Outcome	Non survivors/ Survivors	34 (15/19)	NA	NA	NA	NA	IL-6	WBC, Neu, Lym	CRP	D-dimer	NA	7
Song 2021	Hubei, China	English	Critical/Severe/ Mild&moderate	Severe/ Non severe	295 (107/188)	67	67 (62.6)	51	88 (46.8)	IL-6	WBC, Lym, PLT	NA	D-dimer	ALT, AST, BUN, CRN, TBIL	7
Sozio 2021	Italy	English	Death or IOT/Not death and not IOT	Non survivors/ Survivors	111 (28/83)	64	22 (78.6)	62	44 (53.0)	$CD4^+/CD8^+$, IL-1β, IL-6, IL-8, TNF-α	WBC, Neu, Lym	CRP,PCT	D-dimer	LDH, CK, CRN	8
Stachura 2021	Kraków, Poland	English	Severe/ Non severe	Severe/ Non severe	100(47/53)	62.3	30 (63.8)	56.5	33 (62.3)	IL-6	WBC, Neu, Lym	CRP,PCT, Ferritin	APTT, D-dimer	AST, MYO, cTnI, LDH	9
Tang 2021	Wuhan, China	English	Critical/Severe/ Common	Severe/ Non severe	100 (44/56)	49	25 (56.8)	39	31 (55.4)	IL-6	Lym	PCT	NA	NA	8
Tao 2021	Wuhan, China	English	Severe/ Non severe	Severe/ Non severe	222 (20/202)	68	12 (60.0)	54	130 (64.4)	NA	WBC, Neu, Lym, Mono, Eos, Bas, HB, PLT	CRP,PCT, ESR	APTT, PT, D-dimer	MYO, LDH, ALT, AST, TBIL, BUN	8
Tepasse 2021	Germany	English	Critical/Severe/Non severe	Severe/ Non severe	40(31/9)	59	29 (93.5)	55	7 (77.8)	IL-6	WBC	CRP,PCT, Ferritin	D-dimer	CRN, ALT, ALB	8
Viana-Llamas 2021	Spain	English	Deceased /Alive	Non survivors/ Survivors	609 (128/481)	80	85 (66.4)	66	282 (58.6)	NA	WBC, Lym, HB, PLT	CRP, Ferritin	D-dimer, FIB	cTnI, LDH, AST, ALB, CRN	8
Wang 2021	Wuhan, China	English	Critical/Severe/Non severe	Severe/ Non severe	A.211 (100/111) B.112(46/66)	63	63 (68.0)	46	38 (34.2)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD4^+$(%), $CD8^+$(ab), $CD8^+$(%), $CD4^+/CD8^+$, B(ab), NK(ab), IL-2, IL-4, IL-6, IL-10, IFN-γ	WBC, Lym	NA	NA	AST, ALT	8
Wang 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	156 (56/100)	74	32 (57.1)	54	44 (44.0)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$, B(ab), IL-6	WBC, Neu, Lym, HB, PLT	CRP,PCT	D-dimer	CRN, BUN, LDH, AST, ALT, CK, cTnI, TBIL	8
Waris 2021	Pakistan	English	Critical/Severe/ Moderate/Mild	Severe/ Non severe	101 (25/76)	62.1/ 56	17 (68.0)	49.1 /43.24	53 (69.7)	NA	WBC, Lym, HB, PLT, LMR, PLR, NLR	NA	NA	NA	7

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Xiong 2021	China	English	Dead cases/ Recovery cases	Non survivors/ Survivors	190 (85/105)	72	53 (62.4)	59	46 (43.8)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+$/ $CD8^+$, B(ab), NK(ab)	WBC, Neu, Lym, HB, PLT	CRP,PCT	D-dimer	LDH, CRN, CK, AST, ALT, BUN, TBIL	7
Xue 2021	China	English	Severe/ Moderate	Severe/ Non severe	289 (63/226)	62	31 (49.2)	54	99 (43.8)	NA	WBC, Neu, Lym	CRP	NA	NA	8
Yang 2021	Wuhan, China	English	Non survivors/ Survivors	Non survivors/ Survivors	203 (58/145)	67	38 (65.5)	56	77 (53.1)	IL-6	WBC, Neu, Lym	CRP	APTT, PT, D-dimer	CK, MYO, cTnI, LDH, ALT, AST, TBIL, ALB, CRN, BUN	8
Zayat 2021	Heinsberg, German	English	Non survivors/ Survivors	Non survivors/ Survivors	17(8/9)	57	4 (50.0)	57	2 (22.0)	IL-6	WBC, PLT, HB	CRP,PCT	D-dimer, FIB	LDH, CRN, BUN, CK, ALT	9
Zhang 2021	Wuhan, China	English	Died/ Cured	Non survivors/ Survivors	208 (26/182)	69	18 (69.0)	62	111 (61.0)	$CD3^+$(ab), $CD3^+$(%), $CD4^+$(ab), $CD8^+$(ab), B(ab), NK(ab), IL-2R, IL-6, IL-8, IL-10, TNF-α, C3, C4	WBC, Neu, Lym, Mono, Eos, Bas, HB, PLT	CRP,ESR, Ferritin	PT, D-dimer	AST, ALT, LDH, cTnI, BUN, CRN, TBIL	9
Zhao 2021b	Wuhan, China	English	Severe/Mild	Severe/ Non severe	285 (74/211)	67	38 (51.0)	63	96 (45.0)	IL-6	Neu, Lym, Mono, Eos, NLR, PLR, LMR	CRP	PT, D-dimer	ALT, AST, BUN, CRN	8
Ahmad 2021	Northern India	English	Mortality/ Survival	Non survivors/ Survivors	1448(159/1289)	58	128 (12.2)	47	921 (87.8)	NA	HB, WBC, PLT	Ferritin, CRP	D-dimer	ALT, AST, ALB, BUN, CRN, LDH	7
Akdogan 2021	Turkey	English	Severe/Non severe	Severe/Non severe	175(57/118)	52	NA	39	NA	NA	WBC, Lym	CRP	D-dimer	LDH, AST, ALT, BUN	7
Berenguer 2020	Spain	English	Dead/ Alive	Non survivors / Survivors	4037 (1133/ 2904)	79	1119 (68.5)	64	2868 (58.1)	IL-6	HB, WBC, Neu, Lym, NLR, PLT	CRP,PCT, Ferritin	D-dimer	ALT, AST, BUN, CRN, ALB, LDH	7
Albalawi 2021	Saudi Arabia	English	Non-survivors/ Survivors	Non survivors /Survivors	119 (26/93)	61	14 (53.9)	53	66 (71.0)	NA	WBC, Neu, Lym, HB, PLT	CRP	D-dimer, PT, APTT	AST, ALT, BUN, CRN, LDH, ALB	7

Table 1 (continued)

Study	Region	Language	Original reported groups	Combined groups†	Sample size‡	Case groups		Control groups		Collected parameters					Quality score
						Age (y)	Male [n (%)]	Age (y)	Male [n (%)]	Immunological	Hematological	Inflammatory	Coagulation	Biochemical	
Arikan 2021	Turkey	English	Dead/Discharged	Non survivors /Survivor	225/353	71	149 (66.2)	67	203 (57.5)	NA	HB, WBC, Neu, Lym, PLT	Ferritin, PCT	FIB, D-dimer	BUN, CRN, AST, ALT, LDH, ALB	7
Chinnadurai 2020	Bury, UK	English	Deceased/Alive	Non survivors /Survivors	215(86/129)	80	51 (59.3)	68	82 (63.5)	NA	HB, Neu, Lym, NLR, PLT	CRP	D-dimer	ALB, ALT	8
d'Arminio Monforte 2020	Italy	English	Death/ Survival	Non survivors / Survivors	541(174/367)	76	117 (67.2)	61	230 (63.0)	NA	HB, WBC, Lym, PLT	CRP,PCT, Ferritin	D-dimer	LDH, CK, ALT, AST, CRN	8
Gozalbo-Rovira 2020	Spain	English	ICU/pneumology ward	Severe/ Non severe	51 (24/27)	62	18 (75.0)	58	14 (52.0)	IL-6	Lym	CRP, Ferritin	D-dimer	LDH	8
Gupta 2020	India	English	ICU/Non ICU	Severe/ Non severe	200 (32/168)	51	20 (62.4)	38	96 (57.1)	NA	WBC, Lym, HB, PLT	NA	NA	BUN, CRN, AST, ALT	8
Kaal 2021	The Netherlands	English	Severe/Non severe	Severe/ Non severe	142 (41/101)	69	28 (68.3)	58	65 (64.4)	NA	WBC, Lym, PLT	CRP,PCT, Ferritin	NA	CRN, LDH	8
Duan 2020	Chongqing, China	English	Severe/Non severe	Severe/ Non severe	348 (20/328)	58	170 (52.0)	44	14 (70.0)	$CD3^+$(ab), $CD4^+$(ab), $CD8^+$(ab), $CD4^+/CD8^+$	WBC, Lym, NLR, PLT, HB	CRP,PCT	APTT, PT, FIB, D-dimer	ALB, ALT, AST, CRN, BUN, TBIL	8
Li 2020	Wuhan, China	English	Non-survivors/ Survivor	Non survivors/ Survivors	102 (15/87)	68	11 (73.0)	55	48 (55.0)	IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α	WBC, Neu, Lym, HB, PLT	CRP,PCT	D-dimer, PT	cTnI, ALB, LDH, ALT, AST, TBIL, CRN, BUN	8
Li 2021	Jinan, China	English	Non-survivors/ Survivor	Non survivors/ Survivors	99(9/63)	72	6 (66.7)	57	29 (43.9)	IL-6	WBC, Lym, PLT	CRP,PCT	D-dimer	BUN, CRN, CK, LDH	8
Aksel 2021	Turkey	English	Non-survivors/ Survivor	Non survivors/ Survivors	168 (32/136)	70	17 (53.1)	62	73 (53.7)	NA	WBC, Neu, Lym	CRP	NA	NA	8

Data of age are presened as Mean. *NA*: not available. Combined groups†: Case group (Non-survivors/Severe)/Control group (Survivors/Non-severe). Sample size‡: Total sample (Case group sample/Control group sample). Quality score*: The Newcastle–Ottawa Scale was used for assessing the quality score of each article, with more stars meaning a higher score

SARS-CoV-2. The summarized results are presented in Fig. 2. The detailed forest plots are presented in Fig. E2.

1. Severe Versus Non-severe COVID-19

IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, IFN-γ, IgA, and IgG were significantly increased in patients with severe versus those with non-severe COVID-19 (IL-1β = 0.13 [95%CI, 0.03 to 0.24], $P = 0.0121$, $I^2 = 39.1\%$; IL-1Ra = 0.71 [95%CI, 0.45 to 0.98], $P < 0.001$, $I^2 = 28.6\%$; IL-2R = 1.05 [95%CI, 0.65 to 1.44], $P < 0.0001$, $I^2 = 89\%$; IL-4 = 0.53 [95%CI, 0.11 to 0.95], $P = 0.014$, $I^2 = 92.3\%$; IL-6 = 1.07 [95%CI, 0.88 to 1.25], $P < 0.001$, $I^2 = 91.2\%$; IL-8 = 0.69 [95%CI, 0.45 to 0.94], $P < 0.0001$, $I^2 = 69.5\%$; IL-10 = 0.91 [95%CI, 0.61 to 1.20], $P < 0.001$, $I^2 = 92.9\%$; IL-18 = 0.71 [95%CI, 0.37 to 1.05], $P < 0.001$, $I^2 = 63\%$; TNF-α = 0.28 [95%CI, 0.05 to 0.51], $P = 0.0186$, $I^2 = 87.3\%$; IFN-γ = 0.44 [0.07; 0.81], $P = 0.0196$, $I^2 = 89.2\%$; IgA = 0.18 [95%CI, 0.07 to 0.29], $P < 0.001$, $I^2 = 24.2\%$; IgG = 0.11 [95%CI, 0.01 to 0.22], $P = 0.0335$, $I^2 = 46.6\%$); whereas $CD3^+$ T(ab), $CD3^+$ T(%), $CD4^+$ T(ab), $CD4^+$ T(%), $CD8^+$ T(ab), $CD8^+$ T(%), Total B cell(ab), NK cell(ab), and IgM were significantly decreased in patients with severe versus those with non-severe COVID-19 ($CD3^+$ T(ab) = −1.06 [95%CI, −1.24 to −0.89], $P < 0.001$, $I^2 = 77.6\%$; $CD3^+$ T(%) = −0.58[95%CI, −0.87 to −0.29], $P < 0.001$, $I^2 = 78.2\%$; $CD4^+$ T(ab) = −1.09 [95%CI, −1.29 to −0.89], $P < 0.001$, $I^2 = 86.9\%$; $CD4^+$ T(%) = −0.21[95%CI, −0.32 to −0.09], $P < 0.001$, $I^2 = 37.9\%$; $CD8^+$T(ab) = −1.00 [95%CI, −1.20 to −0.80], $P < 0.001$, $I^2 = 86.3\%$; B cell(ab) = −0.70 [95%CI, −1.02 to −0.38], $P < 0.001$, $I^2 = 87.4\%$; NK cell(ab) = −0.56 [95%CI, −0.79 to −0.33], $P < 0.001$, $I^2 = 78.1\%$ and IgM = −0.21 [95%CI, −0.32 to −0.11], $P < 0.001$, $I^2 = 26.1\%$). There were no differences in IL-2, $CD8^+$ T(%), $CD4^+$T/CD8 + T ratio, C3, C4, and IgE between the two groups.

2. Non-survivors Versus Survivors of COVID-19

IL-1β, IL-2R, IL-6, IL-8, IL-10, TNF-α and $CD4^+$T/$CD8^+$T ratio, IgA, and IgG were significantly increased in non-survivors versus survivors of COVID-19 (IL-1β = 0.72 [95%CI, 0.48 to 0.96], $P < 0.001$, $I^2 = 40.6\%$; IL-2R = 1.44 [95%CI, 1.04 to 1.83], $P < 0.001$, $I^2 = 84.3\%$; IL-6 = 1.13 [95%CI, 0.99 to 1.27], $P < 0.001$, $I^2 = 83.6\%$; IL-8 = 1.02 [95%CI, 0.70 to 1.35], $P < 0.001$, $I^2 = 81.6\%$; IL-10 = 1.19 [95%CI, 1.08 to 1.30], $P < 0.001$, $I^2 = 49.1\%$; TNF-α = 0.68 [95%CI, 0.38 to 0.97], $P < 0.001$, $I^2 = 83.8\%$; $CD4^+$T/$CD8^+$T

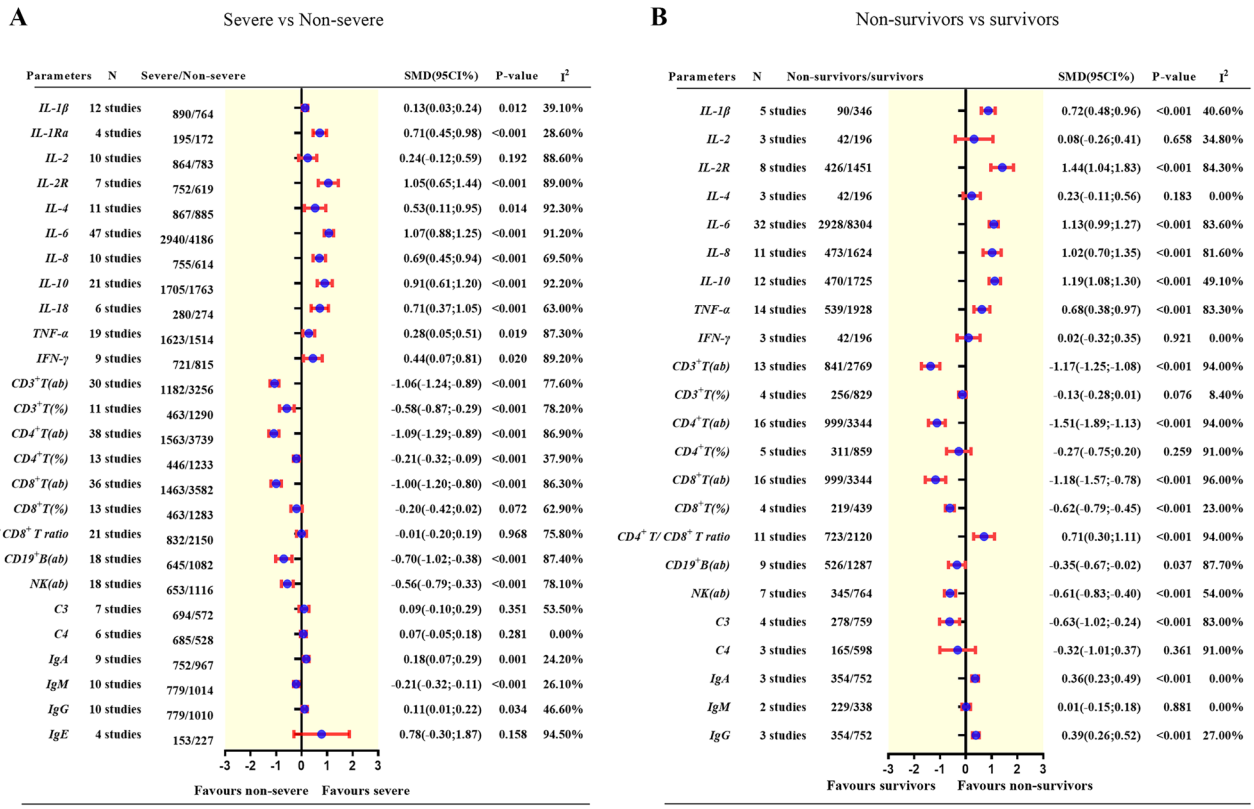

Fig. 2 Summary result of the comparison of immunological parameters between patients with severe COVID-19 and non-severe COVID-19 (**A**), and between non-survivors and survivors with COVID-19 (**B**)

ratio = 0.71[95%CI, 0.30 to 1.11], $P = 0.0007$, $I^2 = 94\%$; IgA = 0.36 [95%CI, 0.23 to 0.49], $P < 0.001$, $I^2 = 0\%$; IgG = 0.39[95%CI, 0.26 to 0.52], $P < 0.001$, $I^2 = 27\%$). $CD3^+$ T(ab), $CD4^+$ T(ab), $CD8^+$ T(ab), $CD8^+$ T(%), B cell(ab), NK cell(ab) and C3 were significantly decreased in non-survivors versus survivors ($CD3^+$ T(ab) = −1.51 [95%CI, −1.89 to −1.13], $P < 0.001$, $I^2 = 94\%$; $CD4^+$ T(ab) = −1.12[95%CI, −1.45 to −0.80], $P < 0.001$, $I^2 = 94\%$; $CD8^+$T(ab) = −1.18[95%CI, −1.57 to −0.78], $P < 0.001$, $I^2 = 96\%$; $CD8^+$ T(%) = −0.62 [95%CI, −0.79 to −0.45], $P < 0.001$, $I^2 = 23\%$; B cell(ab) = −0.35 [95%CI, −0.67 to −0.02], $P = 0.0367$, $I^2 = 87.7\%$; NK cell(ab) = −0.61 [95%CI, −0.83 to −0.40], $P < 0.001$, $I^2 = 54\%$; C3 = −0.63[95%CI, -1.02 to −0.24], $P = 0.0014$, $I^2 = 83\%$). There were no differences in IL-2, IL-4, IFN-γ, $CD3^+$ T(%), $CD4^+$ T(%), C4, and IgM between the two groups.

Hematological Results

Eleven hematological variables, including WBC, neutrophil (Neu), lymphocyte (Lym), eosinophil (Eos), monocyte (Mono), basophil (Bas) absolute counts and platelet (PLT), hemoglobin (HB), neutrophil/lymphocyte ratio(NLR), lymphocyte/monocyte ratio (LMR), and platelet/lymphocyte ratio (PLR), were included in the meta-analysis for comparisons between patients with severe and non-severe COVID-19. All hematological parameters were available for comparisons between non-survivors and survivors of COVID-19. The summarized results are presented in Fig. 3. The detailed forest plots are presented in Fig. E3.

1. Severe Versus Non-severe COVID-19

WBC, Neu, NLR, and PLR counts were significantly increased in patients with severe versus those with non-severe COVID-19 (WBC = 0.48 [95%CI, 0.37 to 0.59], $P < 0.001$, $I^2 = 83.7\%$; Neu = 0.73 [95%CI, 0.63 to 0.84], $P < 0.001$, $I^2 = 80.2\%$; NLR = 0.95 [95%CI, 0.70 to 1.20], $P < 0.001$, $I^2 = 87\%$; PLR = 0.47 [95%CI, 0.27 to 0.68], $P < 0.001$, $I^2 = 77.3\%$), whereas Lym, Mono, LMR, Eos, PLT and HB were significantly decreased in patients with severe versus those with non-severe COVID-19 (Lym = −0.74 [95%CI, −0.87 to −0.61], $P < 0.001$, $I^2 = 89.9\%$; Mono = −0.10 [95%CI, −0.21 to −0.00], $P = 0.0465$, $I^2 = 50.2\%$; Eos = −0.39 [95%CI, −0.55 to −0.22], $P < 0.001$, $I^2 = 79.1\%$; LMR = −0.94 [95%CI, −1.05 to −0.83], $P < 0.001$, $I^2 = 46.8\%$; PLT = −0.27 [95%CI, −0.41 to −0.133], $P < 0.001$, $I^2 = 86.1\%$; HB = −0.21 [95%CI, −0.36 to −0.06], $P = 0.006$, $I^2 = 83.7\%$) There was no difference in the Bas count between the two groups.

2. Non-survivors Versus Survivors of COVID-19

Similarly, WBC, Neu, NLR, and PLR were significantly increased in non-survivors versus survivors of COVID-19 (WBC = 0.74 [95%CI, 0.62 to 0.86], $P < 0.001$, $I^2 = 90.4\%$; Neu = 0.96 [95%CI, 0.82 to 1.10], $P < 0.001$, $I^2 = 89.9\%$; NLR = 0.45 [95%CI, 0.08 to 0.82], $P = 0.0169$, $I^2 = 97.4\%$; PLR = 0.44 [95%CI, 0.02 to 0.86], $P = 0.038$, $I^2 = 84.1\%$), whereas Lym, Eos, LMR, PLT and HB were

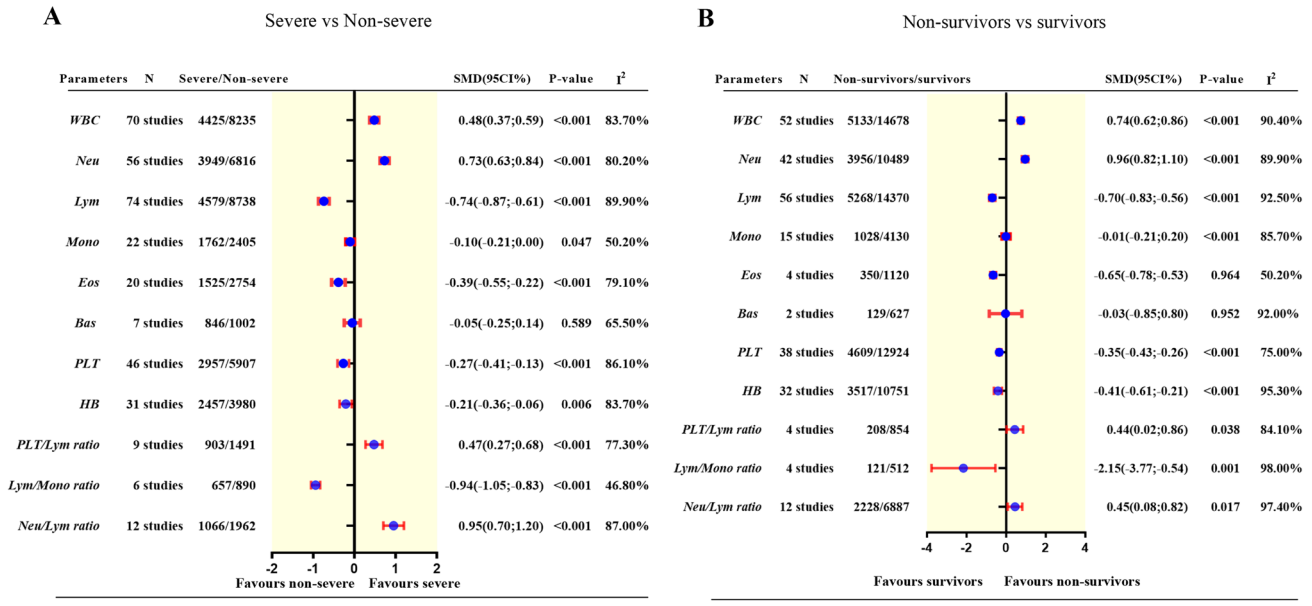

Fig. 3 Summary result of the comparison of hematological parameters between patients with severe COVID-19 and non-severe COVID-19 (**A**), and between non-survivors and survivors with COVID-19 (**B**)

significantly decreased in non-survivors versus survivors (Lym = −0.70 [95%CI, −0.83 to −0.56], $P < 0.001$, $I^2 = 92.5\%$; Eos = −0.65 [95%CI, −0.78 to −0.53], $P < 0.001$, $I^2 = 50.2\%$; LMR = −2.15 [95%CI, −3.77 to −0.54], $P = 0.009$, $I^2 = 98\%$; PLT = −0.35 [95%CI, −0.43 to −0.26], $P < 0.001$, $I^2 = 75\%$; HB = −0.41 [95%CI, −0.61 to −0.21], $P < 0.001$, $I^2 = 95.3\%$). There were no differences in the Mono and Bas count between the two groups.

Other Abnormal Clinical Parameters Deriving from Immune Dysfunction

Beyond immunological and hematological cells, cytokines, antibodies and complements, there are some other laboratory parameters that are related to immune dysfunction and reflect the progression of COVID-19 which have been reported in previous studies [165–168]. In the current study, we simultaneously included coagulation parameters (including prothrombin time(PT), activated partial thromboplastin time(APTT), D-dimer and fibrinogen (FIB)), inflammatory parameters (containing C-reactive protein(CRP), procalcitonin(PCT), erythrocyte sedimentation rate(ESR), serum amyloid A(SAA)) and ferritin, biochemical parameters (including cardiac function related ones such as creatine kinase(CK), cardiac troponin I(cTnI), myoglobin (MYO), lactate dehydrogenase (LDH), liver function related ones such as aspartate aminotransferase(AST), alanine aminotransferase (ALT), total bilirubin(TBIL) and kidney function related ones such as creatinine(CRN), albumin(ALB), blood urea nitrogen(BUN). The summarized results are presented in Fig. 4.

Coagulation Results

Four coagulation variables, namely prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer and fibrinogen (FIB), were included in this study. All coagulation variables were available for comparisons between non-survivors and survivors of COVID-19. The detailed forest plots are presented in Fig. E4.

1. Severe Versus Non-severe COVID-19

The included four coagulation variables were significantly increased in patients with severe versus those with non-severe COVID-19 (PT = 0.60 [95%CI, 0.46 to 0.75], $P < 0.001$, $I^2 = 76.7\%$; APTT = 0.40 [95%CI, 0.13 to 0.67], P = 0.0033, $I^2 = 91.5\%$; D-dimer = 0.79 [95%CI, 0.65 to 0.93], $P < 0.001$, $I^2 = 86.8\%$; FIB = 0.62 [95%CI, 0.43 to 0.81], $P < 0.001$, $I^2 = 79.1\%$).

2. Non-survivors Versus Survivors of COVID-19

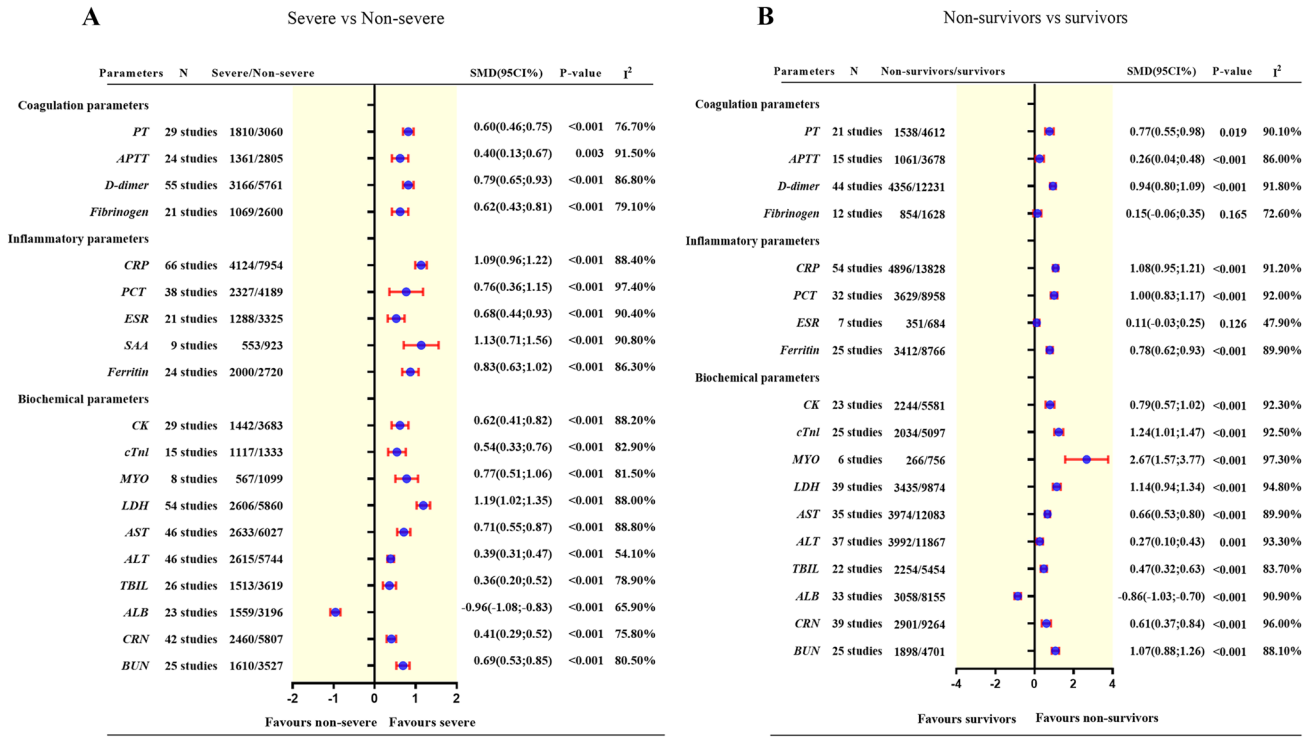

Fig. 4 Summary result of the comparison of coagulation, inflammatory and biochemical parameters between patients with severe COVID-19 and non-severe COVID-19 (**A**), and between non-survivors and survivors with COVID-19 (**B**)

Similarly, all the four coagulation variables were significantly increased in non-survivors versus survivors of COVID-19 (PT = 0.77 [95%CI, 0.55 to 0.98], $P < 0.001$, $I^2 = 90.1\%$; APTT = 0.26 [95%CI, 0.04 to 0.48], $P = 0.0187$, $I^2 = 86\%$; D-dimer = 0.94 [95%CI, 0.80; 1.09], $P < 0.001$, $I^2 = 91.8\%$). However, there was no difference in FIB between the two groups.

Inflammatory Results

Five inflammatory variables, C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), serum amyloid A (SAA) and ferritin, were included for comparisons between patients with severe and those with non-severe COVID-19, Of these, CRP, PCT, ESR and ferritin were available for comparisons between non-survivors and survivors infected with SARS-CoV-2. The detailed forest plots are presented in Fig. E5.

1. Severe Versus Non-severe COVID-19

Levels of all five inflammatory variables were significantly increased in patients with severe versus those with non-severe COVID-19 (CRP = 1.09 [95%CI, 0.96 to 1.22], $P < 0.001$, $I^2 = 88.4\%$; PCT = 0.76 [95%CI, 0.36 to 1.15], $P < 0.001$, $I^2 = 97.4\%$; ESR = 0.68 [95%CI, 0.44 to 0.93], $P < 0.001$, $I^2 = 90.4\%$; ferritin = 0.83 [95%CI, 0.63 to 1.02], $P < 0.001$, $I^2 = 86.3\%$; SAA = 1.13 [95%CI, 0.71 to 1.56], $P < 0.001$, $I^2 = 90.8\%$).

2. Non-survivors Versus Survivors of COVID-19

CRP, PCT, and ferritin were significantly increased in non-survivors versus survivors of COVID-19 (CRP = 1.08 [95%CI, 0.95 to 1.21], $P < 0.001$, $I^2 = 91.2\%$; PCT = 1.00 [95%CI, 0.83 to 1.17], $P < 0.001$, $I^2 = 92\%$; ferritin = 0.78 [95%CI, 0.62 to 0.93], $P < 0.001$, $I^2 = 89.9\%$). There was no difference in ESR between the two groups.

Biochemical Results

Ten biochemical variables, namely creatine kinase (CK), cardiac troponin I (cTnI), myoglobin (MYO), lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL), creatinine (CRN), albumin (ALB), and blood urea nitrogen (BUN), were included in this study. All biochemical variables were available for comparisons between non-survivors and survivors of COVID-19. The detailed forest plots are presented in Fig. E6.

1. Severe Versus Non-severe COVID-19

CK, cTnI, MYO, LDH, AST, ALT, TBIL, CRN, and BUN were significantly increased in patients with severe versus those with non-severe COVID-19 (CK = 0.62 [95%CI, 0.41 to 0.82], $P < 0.001$, $I^2 = 88.2\%$; cTnI = 0.54 [95%CI, 0.33 to 0.76], $P < 0.001$, $I^2 = 82.9\%$; MYO = 0.77 [95%CI, 0.51 to 1.06], $P < 0.001$, $I^2 = 81.5\%$; LDH = 1.19 [95%CI, 1.02 to 1.35], $P < 0.001$, $I^2 = 88\%$; AST = 0.71 [95%CI, 0.55 to 0.87], $P < 0.001$, $I^2 = 88.8\%$; ALT = 0.39 [95%CI, 0.31 to 0.47], $P < 0.001$, $I^2 = 54.1\%$; TBIL = 0.36 [95%CI, 0.20 to 0.52],$P < 0.001$, $I^2 = 78.9\%$; CRN = 0.41 [95%CI, 0.29 to 0.52], $P < 0.001$, $I^2 = 75.8\%$; BUN = 0.69 [95%CI, 0.53 to 0.85], $P < 0.001$, $I^2 = 80.5\%$;), whereas ALB was significantly decreased in patients with severe versus non-severe COVID-19 (ALB = −0.96 [95%CI, −1.08 to −0.83], $P < 0.001$, $I^2 = 65.9\%$).

2. Non-survivors Versus Survivors of COVID-19

Similarly, CK, cTnI, MYO, LDH, AST, ALT, TBIL, CRN, and BUN were significantly increased in non-survivors versus survivors of COVID-19 (CK = 0.79 [95%CI, 0.57 to 1.02], $P < 0.001$, $I^2 = 92.3\%$; cTnI = 1.24 [95%CI, 1.01 to 1.47], $P < 0.001$, $I^2 = 92.5\%$; MYO = 2.67 [95%CI, 1.57 to 3.77], $P < 0.001$, $I^2 = 97.3\%$; LDH = 1.14 [95%CI, 0.94 to 1.34], $P < 0.001$, $I^2 = 94.8\%$; AST = 0.66 [95%CI, 0.53; 0.80], $P < 0.001$, $I^2 = 89.9\%$; ALT = 0.27 [95%CI, 0.10 to 0.43], $P = 0.013$, $I^2 = 93.3\%$; TBIL = 0.47 [95%CI, 0.32 to 0.63], $P < 0.001$, $I^2 = 83.7\%$; CRN = 0.61 [95%CI, 0.37 to 0.84], $P < 0.001$, $I^2 = 96\%$; BUN = 1.07 [95%CI, 0.88 to 1.26], $P < 0.001$, $I^2 = 88.1\%$). In contrast, ALB was significantly decreased in patients with severe versus non-severe COVID-19 (ALB = −0.86 [95%CI, –1.03 to −0.70], $P < 0.001$, $I^2 = 90.9\%$).

Publication Bias

Funnel plots are shown in Figs. E7 and E8. In severe and non-severe patients of COVID-19, the obvious publication bias was presented in B cell (ab), NK cell (ab), IL-1β, IL-4, IL-6, IL-10, TNF-α, NLR, CRP, D-dimer, and cTnI. In contrast, in non-survivors and survivors of COVID-19, obvious publication bias was present in IL-6, IL-8, IL-10, TNF-α, PLT, HB, CRP, Ferritin, ALT, and ALB. Many factors may have led to the publication bias, such as not enough amounts of originally included studies, different characteristics, and the wide ranges of the parameter results.

Sensitivity Analysis

Results of the sensitivity analysis, using the leave-to-out method, showed that most parameters presented good reliability and stability. However, there were also some

parameters showed high sensitivity. Detailed results of each parameter are shown in Figs. E9, E10, E11, E12, and E13.

Investigation of Heterogeneity

A majority of included variables in the current review presented significant heterogeneity ($I^2 > 50\%$). The heterogeneity might have come from various factors, such as demographic and clinical characteristics of included patients, time of the symptom onset and laboratory parameters measured, and treatment intervention before the admission. Therefore, we conducted a meta-regression analysis with three potential factors, including the approach of combining disease severity, age, and region, to identify the sources of heterogeneity. The included variables presenting high heterogeneity ($I^2 > 50\%$) and reported by an adequate number of studies ($n \geq 10$) were applied to the analysis. Regarding the approach of combing disease severity, we identified four subgroups in our severe group according to the originally reported disease severity: severe and critical (severe/critical), severe alone, critical alone, and other. The findings showed that the potential heterogeneity of 16 of 39 variables, including $CD3^+T$(%), B cell(ab), NK(ab), IL-4, IL-6, IL-8, Lym, Eos, HB, NLR, CRP, Ferritin, LDH, ALB, CRN, and BUN, were related to the originally reported disease severity. The detailed results are presented in Table E1. Second, based on the available average age of severely ill patients and non-survivors of COVID-19, we classified the studies into six subgroups (average age ≤ 18 years(y), 30 ~ 49y, 50 ~ 59y, 60 ~ 69y, 70 ~ 79y, and ≥ 80y). In severe patients, the findings showed that the potential heterogeneity of 13 of 38 variables, including $CD3^+T$(%), IL-8, PLT, HB, ESR, Ferritin, APTT, PT, FIB, cTnI, ALB, CRN, and BUN, were related to the different ages of the patients in the included studies. The detailed results are presented in Table E2. Similarly, the potential heterogeneity of 14 of 30 variables in non-survivors, including $CD3^+T$(%), $CD4^+T$(ab), $CD8^+T$(ab), Neu, PLT, CRP, PCT, Ferritin, D-dimer, cTnI, AST, ALT, TBIL, and CRN, were related to the ages of the patients in different included studies. The detailed results are presented in Table E3. Moreover, we divided the four subgroups according to the continents (Asia, Europe, North America and Africa). In severe groups, the findings showed that the potential heterogeneity of 28 of 30 variables, including $CD3^+T$(ab), $CD3^+T$(%), $CD4^+T$(ab), $CD8^+T$(ab), B cell(ab), NK(ab), IL-4, IL-6, IL-8, TNF-α, WBC, Neu, Lym, Eos, HB, NLR, PCT, Ferritin, APTT, PT, FIB, CK, cTnI, LDH, AST, ALT, TBIL, and CRN, were related to the region. The detailed results are presented in Table E4. In non-survivors, the findings showed that the potential heterogeneity of 25 of 27 variables, including $CD4^+T/CD8^+T$ ratio, IL-6, IL-8, TNF-α, WBC, Neu, Lym, PLT, HB, NLR, CRP, PCT, Ferritin, APTT, D-dimer, FIB, CK, cTnI, LDH, AST, ALT, TBIL, ALB, CRN and BUN, were related to the region. The detailed results are presented in Table E5. We considered the major source of heterogeneity as the regional differences among our included studies, while the approach of combining disease severity and the age of patients partially contributed to the marked heterogeneity observed.

Discussion

In the current updated meta-analysis, our synthetic results of 145 included studies identified a hypercytokinemia profile, including IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, and IFN-γ, which was associated with increased severity and mortality in patients with COVID-19 infection. By contrast, patients with non-severe COVID-19 and survivors exhibited functional innate and adaptive immune responses, presenting by higher levels of eosinophils, lymphocytes, monocytes, B cells, NK cells, T cells and its subset $CD4^+$ T, and $CD8^+T$. Furthermore, in line with an elevated concentration of proinflammatory cytokines, augmented information (indicated by increased WBC, Neu, NLR, PLR, PCT, ESR, CRP, ferritin, or SAA), coagulation dysfunction (indicated by abnormal D-dimer, FIB, APTT and PT) as well as myocardial/liver/renal injury (indicated by elevated CK, cTnI, MYO, LDH, ALT, AST, TBIL, ALB, CRN, and BUN) were the main clinical abnormalities of patients with COVID-19 infection in the severe and fatal cohort.

SARS-CoV-2 infection can initiate a potent immune response, which includes innate immune activation and antiviral immune responses [169, 170]. However, the transition between innate and adaptive immune responses is the core of determining the clinical outcomes and prognosis of COVID-19 infection [171]. Early immune responses against COVID-19 primarily play a protective role in viral clearance, whereas exacerbated and dysregulated immune responses, otherwise known as the "cytokine storm," can cause tissue damage contributing to poor disease outcomes [172]. An overreactive immune response releases excess pro-inflammatory cytokines and chemokines of which has been well documented [173]. Of these elevated pro-inflammatory cytokines, IL-6 is the most investigated and is a key driver of cytokine dysregulation, which is responsible for the hyper-inflammation in lungs in patients infected with COVID-19 [174]. A recent meta-analysis showed that the anti-IL-6 agent (Tocilizumab) was associated with a lower relative risk of mortality in patients with COVID-19 infection [175]. Other cytokines, such as IL-8 and IL-10, were also proposed to that play a significant role in the inflammatory cascade [176, 177]. We identified an updated abnormal cytokine profile, including IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, and IFN-γ, relating to

severe COVID-19 infection and fatality. It is well known that cytokine storm and the subsequent inflammation cascade relay on a complex cytokine network. Our synthesis results offer updated evidence on revealing the structure of cytokine networks related to the poor clinical outcomes, which helps clarify the underlying complex inflammatory pathways, so we can target new treatment agents.

Current management of COVID-19 is supportive, and respiratory failure from acute respiratory distress syndrome (ARDS) is the leading cause of mortality [178]. Hyperinflammation is the prominent feature of patients with ARDS and those non-survivors. Our previous longitudinal study of 548 revealed that patients who died from COVID-19 infection commonly showed an upward trend for neutrophils, IL-6, and C-reactive protein [5]. Other inflammatory parameters, including WBC, PCT, ESR, and SAA, were also proposed as the predictors of fatality. Our synthesis agrees with the findings of previous studies [179–183]. All patients with COVID-19, regardless of the severity, should be screened for hyperinflammation as precaution for potential ARDS once increases in these indicators are detected. Identification of the early signs of ARDS is critical for early intervention (such as low tidal volumes and prone ventilation) to improve oxygenation and lung compliance. Currently, the rates of bacterial/fungal co-infection reported in patients with COVID-19 appear to be low. Timothy et al. included nine studies and found that only 8% (62/806) of cases of bacterial/fungal co-infection were reported [184]. Nevertheless, our data observed that an increased infectious parameter profile detected on admission was strongly associated with poor clinical outcomes, which suggested that prompt antibiotic therapy should be considered after a comprehensive infectious assessment. Additionally, a combined assessment of using abnormal inflammatory parameters and increased cytokine levels might better identify the subgroup of patients for whom immunosuppression could improve mortality. Beneficial anti-inflammatory effects should be weighed against the potentially detrimental effects of inhibiting anti-viral immunity, thereby delaying virus clearance and perpetuating illness [185].

In addition, we observed substantial decreases in B cells, NK cells, T cells, and its subsets, including $CD4^+$T cells and $CD8^+$ T cells in patients with severe disease, compared to those with non-severe disease. We also found that decreased $CD3^+$T, $CD4^+$T, $CD8^+$ T cells, and higher ratio of $CD4^+$ to $CD8^+$ T cells were associated with a fatal outcome. Our findings were in line with the results from a recent meta-analysis targeting lymphocytes and their subset counts [186] as well as observations from clinical practice. However, the underlying mechanism of observed lymphopenia in severe or fatal COVID-19 patients remains unclear. Based on the current evidence, it is proposed that lymphopenia be relating to the following causes: (1) suppression by cytokine mediation; (2) T cells infected by the virus; (3) T cell exhaustion (4) T cell expansion interfered with by the virus; and (5) organ inflation. Furthermore, our data supported that eosinopenia was associated with both severe disease and a fatal outcome. Our previous study suggested that dynamic changes in blood eosinophil counts might predict COVID-19 progression and recovery [5]. However, the pathophysiology for eosinopenia in COVID-19 remains unclear but is likely multifactorial [187], involving (1) reduced expression of adhesion/chemokine/cytokine, (2) direct eosinophil apoptosis, (3) blockade of eosinophilopoiesis, and (4) inhibition of eosinophil egress from the bone marrow. The finding that eosinophil levels improved in patients before discharge might serve as an indicator of improving clinical status.

The presence of the hypercoagulable state in patients with COVID-19 was another marked clinical feature of patients with increased mortality and a more severe form of the disease. The underlying pathophysiology mechanism was also associated with impaired immune responses [188]. SARS-CoV-2 infects host endothelial cells through ACE2 (an integral membrane protein) [189]. Patients with COVID-19 tend to exhibit greater numbers of ACE2-positive endothelial cells [190]. Therefore, vascular endothelial injury is commonly presented in patients with COVID-19. Vascular endothelial injury caused by COVID-19 infection would lead to the formation of microvascular microthrombi, which would trigger active tissue factor expression on macrophages and endothelial cells [191] Elevated tissue factor levels alongside local hypoxia from COVID-19 induced ARDS create a positive thromboinflammatory feedback loop, also known as a cytokine storm [191] The strong interaction between coagulation cascade activation and the cytokine storm might be responsible for the increased incidence of thrombotic events and aggressive inflammatory reactions. Based on our meta-analysis, increased APTT, PT, D-dimer, and FIB were identified as the indicators of coagulation dysfunction contributing to the unfavorable clinical outcomes. Simultaneously increased coagulation parameters and immune index might imply the interplay between overreactive immune responses and coagulation dysfunction which might serve as a more sensitive predicted index of a poor prognosis of COVID-19 infection. Additionally, we also identified several abnormal biochemical parameters representative of myocardial, liver, or renal injury in the severe and non-survivors cohort, such as CK, cTnI, MYO, LDH, ALT, AST, TBIL, ALB, CRN, and BUN. Although the pathophysiological mechanisms underlying myocardial/liver/renal injury by COVID-19 are not well-known so far, innate dysfunction and adaptive immune systems driving the cytokine storm seem to play a role in non-pulmonary organ damage [192–196], particularly those with comorbidities of cardiovascular, liver, and renal diseases.

The purpose of this meta-analysis is two-fold. First, to provide robust evidence of identifying a series of abnormal immunological indicators early to distinguish patients with poor clinical outcomes and to offer valuable information for exploring the underlying mechanism of COVID-19 progression. Second, to draw a picture of the interaction between immune abnormality and other body system dysfunction, including coagulation, inflammation, and non-pulmonary function. However, our meta-analysis has limitations. In line with the heterogeneity that characterized these observational studies [197, 198], a majority of included variables presented large I^2 values, indicating significant variations in terms of outcomes observed. Although we attempted to manage this by performing subgroup analysis and meta-regression by disease severity, the age of included patients, and genetic characteristics, the results could not fully explain the source of heterogeneity. We were confined by the methodologies of the studies included, as well as the heterogeneity in characteristics of included patients, such as comorbidities, the therapeutic approach before hospital admission, and the time of symptom onset, which were not provided in the included studies. However, the observed heterogeneity did not impair our main conclusion that severe COVID-19 and mortality were associated with significant abnormalities in the immunological, hematological, coagulation, inflammatory, and biochemical variables. What the heterogeneity suggests is that these abnormalities might show some variation from one country to another, from one city to another, and from one clinical setting to another.

Conclusions

The currently updated meta-analysis primarily identified a hypercytokinemia profile with the severity and mortality of COVID-19, containing IL-1β, IL-1Ra, IL-2R, IL-4, IL-6, IL-8, IL-10, IL-18, TNF-α, and IFN-γ. Impaired innate and adaptive immune responses, reflected by decreased eosinophils, lymphocytes, monocytes, B cells, NK cells, T cells and their subtype $CD4^+$ and $CD8^+$ T cells, and augmented inflammation, coagulation dysfunction, and nonpulmonary organ injury, were marked features of patients with a poor prognosis. Given the strong interplay between immune response dysfunction, aggressive inflammation, coagulation abnormality, and nonpulmonary organ injury, parameters of immune response dysfunction combined with either inflammatory, coagulated, or nonpulmonary organ injury indicators may be more sensitive to predict outcomes in severe patients versus non-survivors.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12016-021-08908-8.

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Author Contribution All the authors conceived and designed the study project. Li He and Rundong Qin performed the literature search and evaluated the study quality. Li He, Rundong Qin, Xinliu Lin, Renbin Huang, Tian Luo, Yukai Liu, Siyang Yao completed the data extraction. Rundong Qin and Li He performed the statistical analysis. This study was drafted by Rundong Qin, Li He, Zhaowei Yang, Nan Jia, Ruchong Chen, Jiaxing Xie, Wanyi Fu, Hao Chen, Jing Li. It was revised following critical review initially by Jing Li, Rundong Qin, Li He and all the co-authors. All the authors gave final approval of the version to be submitted and agreed to be accountable for the whole paper.

Declarations

Ethics Approval As the current study did not involve human subjects, the Ethics Committee at the First Affiliated Hospital of Guangzhou Medical University exempted this study from the need for ethical approval.

Study Registration PROSPERO CRD42020196272.

Competing Interests The authors declare no competing interests.

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