

## REVIEW

# A systematic meta-analysis of immune signatures in patients with COVID-19

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## Summary

Currently severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission has been on the rise worldwide. Predicting outcome in COVID-19 remains challenging, and the search for more robust predictors continues. We made a systematic meta-analysis on the current literature from 1 January 2020 to 15 August 2020 that independently evaluated 32 circulatory immunological signatures that were compared between patients with different disease severity was made. Their roles as predictors of disease severity were determined as well. A total of 149 distinct studies that evaluated ten cytokines, four antibodies, four T cells, B cells, NK cells, neutrophils, monocytes, eosinophils and basophils were included. Compared with the non-severe patients of COVID-19, serum levels of Interleukins (IL)-2, IL-2R, IL-4, IL-6, IL-8, IL-10 and tumor necrosis factor  $\alpha$  were significantly up-regulated in severe patients, with the largest inter-group differences observed for IL-6 and IL-10. In contrast, IL-5, IL-1 $\beta$  and Interferon (IFN)- $\gamma$  did not show significant inter-group difference. Four mediators of T cells count, including CD3<sup>+</sup> T, CD4<sup>+</sup> T, CD8<sup>+</sup> T, CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>-</sup> Treg, together with CD19<sup>+</sup> B cells count and CD16<sup>+</sup>CD56<sup>+</sup> NK cells were all consistently and significantly depressed in severe group than in non-severe group. SARS-CoV-2 specific IgA and IgG antibodies were significantly higher in severe group than in non-severe group, while IgM antibody in the severe patients was slightly lower than those in the non-severe patients, and IgE antibody showed no significant inter-group differences. The combination of cytokines, especially IL-6 and IL-10, and T cell related immune signatures can be used as robust biomarkers to predict disease severity following SARS-CoV-2 infection.

**Abbreviations:** ARDS, acute respiratory distress syndrome; CLIA, chemiluminescence immunoassay; COVID-19, coronavirus disease 2019; CSS, Churg–Strauss syndrome; DCs, dendritic cells; ELISA, enzyme-linked immunosorbent assay; ICU, intensive care unit; IFN, interferon; Ig, immunoglobulin; IL, interleukins; IQR, interquartile range; MERS, Middle East respiratory syndrome; MMFI, multiple microspheres flow immunofluorescence; NK cell, natural killer cell; NOQAS, Newcastle–Ottawa Quality Assessment Scale; PD, programmed cell death protein; PD-L, programmed cell death protein ligand; PRISMA, preferred reporting items for systematic reviews and meta-analyses statement; SARS, severe acute respiratory syndrome; SD, standard deviation; SMD, standardized mean difference; TNF- $\alpha$ , tumour necrosis factor- $\alpha$ .

Kun Liu and Tong Yang contributed equally to this study.

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**KEYWORDS**

antibody, COVID-19, cytokines, disease severity, innate immunity, meta-analysis

## 1 | INTRODUCTION

Currently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission has been on the rise in the worldwide range, with more than 32,000,000 cases and more than 990,000 deaths documented to 28 September 2020. Intensive efforts have been put forward to study the clinical process and outcome of the disease.<sup>1</sup> Predicting outcome in coronavirus disease 19 (COVID-19) remains challenging, and the search for more robust methods continues. A broad range of signs and symptoms have been investigated in COVID-19 to predict the disease outcome, while showing divergent results.<sup>2–6</sup> Inclusion more specific biomarkers is urgently needed to develop a robust algorithm. Previous studies have suggested that lymphocytopenia and inflammatory cytokine storm are typical abnormalities in infections caused by highly pathogenic coronavirus, such as SARS and MERS.<sup>7,8</sup> Similarly, numerous studies on COVID-19 patients have reported a decrease in peripheral blood lymphocyte count and an increase in serum inflammatory cytokines,<sup>9–12</sup> which is suggested that the inflammatory factors may be the main reason for adverse progression and poor treatment response in COVID-19, but mostly proposed from small sample studies.<sup>13</sup> If these biomarkers are validated in a large patient cohort, their incorporation into algorithms might prove sufficiently sensitive and specific to be clinically useful, particularly when they can be related to the disease outcome.

In the current study, we attempted to address these issues by conducting a systematic meta-analysis using the pooled data for the immune indicators that were evaluated at early disease and among patients with various disease severity. The inclusion of various studies allowed more statistical power for a holistic view of SARS-CoV-2-induced immune mediators among patients with different disease severity, and across various geographic locations. This will also help to identify the immune signatures that better distinguish the development of COVID-19 outcome.

## 2 | MATERIALS AND METHODS

### 2.1 | Protocol registration

This systematic review was not registered. The format of the review used the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Table S1), and addressed the

following question: 'Are the immune mediators different in severe and non-severe groups of COVID-19 patients?' according to PICOS (P—Patient, Problem or Population; I—Intervention; C—Comparison, control or comparator; O—Outcome; S—Study design) (Table S2).

### 2.2 | Search strategy and study selection

We performed a comprehensive systematic review and meta-analysis to identify the associations of immune cells, cytokines and the severity of COVID-19. Identification of relevant existing literature was performed by an online search in PubMed, Web of Science and EMBASE, for studies published from 1 January 2020 to 15 August 2020. The MESH headings (keywords) searched were 'nCoV' or 'coronavirus' or 'SARS-CoV-2' or 'COVID' and 'cytokine' or 'immunological' or 'immunity' or 'Cellular immunity' or 'T cell' or 'B cell' or 'NK cell' or 'antibody'. In addition, the same search strategy was applied to the database of bioRxiv and medRxiv for the unpublished studies (Table S3). Two reviewers (TY and XFP) independently screened the list of titles and abstracts, and the full text of chosen manuscripts related the immune mediators. Disagreements on which manuscripts to include during both title and abstract screen, and the subsequent full-text analysis, were discussed until a conclusion was reached with two other reviewers (SML and KL).

### 2.3 | Inclusion and exclusion criteria

All studies evaluating individual measurement of immunological indicators in predicting severe infection (as measured by disease severity criteria, or ICU admission or fatal/survived) were included. All studies of any design, from any time since the outbreak started were eligible. To avoid selection bias, no subjective quality criteria were applied to the studies for inclusion. The immunological signatures that were measured at the acute phase of infection were used, and if there was more than one evaluation for the same patient, only the first test results were used. Only those immune signatures investigated in at least three papers were used in the subsequent analysis. Exclusion criteria included the following: (1) Case reports of individual patients, literature reviews, nonhuman studies, editorials, comments, expert opinions or articles with number of patients  $\leq 10$ ; (2) Studies of exclusively paediatric or pregnant patients, due to the varying presentation of the disease in these groups and (3) Studies

without adequate baseline information, such as age, sex or geographic region.

## 2.4 | Data extraction

All the search results were evaluated according to the PRISMA statement.<sup>14</sup> From each study, various details including the baseline information of study population (age, sex, interval from disease onset to hospitalization, intervals from disease onset to the sample collection, study areas), the number of patients in each study group, the measured immunological indicators and their test methods and the definitions used to measure outcome, were extracted into Microsoft Excel. These details are presented in Table 1. The Newcastle-Ottawa Quality Assessment Scale (NOQAS) was used to assess the quality of the studies included in the meta-analysis and performed by two reviewers (TY and XFP) with a third reviewer (SML) consulted in case of discrepancy.

## 2.5 | Predictors and outcome

The included studies varied in their differentiation of patients' disease status, with classifications of 'mild, moderate, severe and critical', 'ordinary and severe/critical', 'common and severe', 'acute respiratory distress syndrome (ARDS) and non-ARDS' and 'non-severe and severe'. To allow comparability between studies for meta-analysis, these were grouped into a single disease severity, with the outcome measure used was severe (including both severe and critical cases, ICU admission, death, ARDS, etc.) versus non-severe disease (including non-severe, mild disease, ordinary disease, non-ICU admission and non-ARDS, etc.).

## 2.6 | Statistical analysis

Quantitative syntheses and meta-analyses were analysed using the meta package in the R statistical language (Version 3.6.3). First, we collected the mean and standard deviation (SD) from each value of immune mediators in severe and non-severe groups of COVID-19 patients. Where necessary, the mean and SD were converted from the median and interquartile range (IQR) using a previously standard approach.<sup>155</sup> For some articles, data regarding the immunological signature were extracted from the figures by measuring the pixel positions of the electronic figures and then computing the actual values. For box plots, medians and ranges were used to compute means and SDs, and for scatter plots, the individual values were used to compute means and SDs. Second, forest plots were conducted to illustrate the differences in the two groups. For fear of that the recruited studies used different experiment methods, for which means and differences cannot be pooled directly to estimate the effect, we calculated a dimensionless effect measure from each study for the pooling use. The standardized mean

difference (SMD) was computed from means and SDs, and used as the effect size.<sup>156</sup> Finally, we undertook the meta-analyses for each immune mediator. The heterogeneity of the studies was tested by the Cochran Chi-square test and  $I^2$  index, and the pooled SMD were calculated by using the random-effects model. All results were pooled and presented in the forest plots. Leave-one-out sensitivity analysis was applied to detect the robustness of the results. Funnel plot method and Egger's regression were used to test the publication bias. If the funnel plot was asymmetric or  $p < 0.05$ , the trim-and-fill method was adopted to further test publication bias. The statistical testing with  $p < 0.05$  was considered to be significant (two-sided).

## 3 | RESULTS

### 3.1 | Review of the included studies

A detailed flow diagram of study selection and the selected number are shown in Figure 1. Our literature search identified 19,802 records through 15 August 2020. After removing duplicates, the title and abstract of the remaining 19,688 articles were screened, and 16,613 records were excluded. For 3075 potentially relevant studies, full-text was retrieved and evaluated for eligibility, and then 2861 studies were excluded from the meta-analysis: 1305 studies contained data from only case series, 1,312 studies were literature reviews, 52 studies provided no comparison data between disease severity, and 192 studies didn't provide enough data. As five studies were further excluded because the described immune mediators were investigated in <3 studies (Table S4), at last 214 studies were included in the qualitative synthesis. Those remained in the study were collated for the meta-analysis consisted of 149 distinct studies that were performed in China (133), the United States (6), South Korea (2), Singapore (2), the United Kingdom (1), France (1), Germany (1), Italy (1), Spain (1), and both China and USA (1) (Table 1). All the included studies had reported patients with severe patients and non-severe patients. These articles included data from 33,691 patients, 25.96% ( $n = 8746$ ) with severe COVID-19 disease and 74.04% ( $n = 24,945$ ) with non-severe disease. Of these studies, 55 studies had evaluated the data on 10 cytokines, including interleukins 2 (IL-2), IL-2R, IL-4, IL-5, IL-6, IL-8, IL-10, interferon  $\gamma$  (IFN- $\gamma$ ), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and IL-1 $\beta$ ,<sup>1,9,10,15-65,157</sup> 8 studies investigated the antibodies (IgA, IgG, IgM and IgE)<sup>10,16,20,25,66-69</sup> and 40 studies assessed the T cells [CD3<sup>+</sup> T cells count, CD4<sup>+</sup> T cells count, CD8<sup>+</sup> T cells count, CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>-</sup>Treg cells count, CD3<sup>+</sup> T cells ratio, CD4<sup>+</sup> T cells ratio, CD8<sup>+</sup> T cells ratio and CD4<sup>+</sup>/CD8<sup>+</sup> (Th/Ts)],<sup>9-11,15-20,24,27,33,34,41,45,47,48,51-53,56,57,59,61,63,65-67,69-79,157</sup> and 22 studies estimated the B cells and NK cells (CD16<sup>+</sup>CD56<sup>+</sup> NK cells count, CD19<sup>+</sup> B cells count, CD16<sup>+</sup>CD56<sup>+</sup> NK cells ratio and CD19<sup>+</sup> B cells ratio),<sup>10,11,15-20,24,33,34,41,45,47,48,63,67,69,71-73,157</sup> 124 studies on the evaluation of neutrophils, eosinophils and basophils cells (comprised of neutrophils cells counts/cells ratio, monocytes cells counts/cells ratio, eosinophils cells counts and basophils

TABLE 1 Characteristics of the association studies included in the meta-analysis

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
IL-2 (unit: ng/L)									
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	9.48 $\pm$ 4.87	6.7 $\pm$ 4.42
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	2.69 $\pm$ 0.14	2.51 $\pm$ 0.16
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	4.2 (4.0-4.4)	3.8 (3.6-4.3)/3.7 (3.5-4.0)
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	5.12 $\pm$ 1.64	4.47 $\pm$ 0.29
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	1 (0.8-1.9)	1 (0.7-2.0)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.52 (0.33-0.66)	0.36 (0.22-1.23)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-sever	69	135	4.06 (3.28-4.09)	3.55 (3.38-3.65)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	2.8 $\pm$ 0.7	9 $\pm$ 53.4
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	2.9 $\pm$ 0.9	0.93 (0.55-1.73)
IL-2R (unit: ng/L)									
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	902 $\pm$ 51/1185 $\pm$ 80	631 $\pm$ 37
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	1209.33 $\pm$ 421.86	448.97 $\pm$ 186.35
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	1189.0 (901.0-1781.0)	566.5 (448.0-858.3)
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	1166.5 (898.8-1788.5)/1076.5 (671.8-1699.5)	571.5 (353.0-821.8)/454.5 (270.3-563.0)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	757 (528.5-1136.3)	663.5 (473.3-862.8)
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	46	1451 (879-2768)	579 (429-1432)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	5.00 (5.00-25.88)	5.00 (5.00-5.00)
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	766 (595-1050)	546 (455-743)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	1026 (378-1260)	666.77 $\pm$ 334.12
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	2	27	250.23 $\pm$ 750.12	529.00 (385.00-754.50)/2181.75

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	1098 (721-1512)	716 (458-954)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	905.08 $\pm$ 441.45 1077.16 $\pm$ 551.21	787.88 $\pm$ 313.40
IL-4 (unit: ng/L)									
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	3.49 $\pm$ 1.27	2.90 $\pm$ 1.28
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	2.02 $\pm$ 0.10	1.88 $\pm$ 0.24
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	4.5 (4.1-4.8)	4.2 (3.8-4.9)/4.1 (3.8-4.6)
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	1.42 $\pm$ 0.27	1.47 $\pm$ 0.2
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	1.8 (1.4-1.8)	1.8 (1.2-1.8)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MMFI	Severe/no-severe	21	102	1.83 $\pm$ 0.1849	1.69 $\pm$ 0.07049
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.11 (0.00-0.42)	0.24 (0.10-0.48)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	4.30 (4.01-4.60)	3.75 (3.70-3.85)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	2.3 $\pm$ 0.8 8.4 $\pm$ 20	2.6 $\pm$ 1
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	3.25 $\pm$ 0.81	1.49 $\pm$ 0.22
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	1.99 (1.26-2.73)	1.87 (1.43-2.55)
IL-6 (unit: ng/L)									
Cai et al. <sup>36</sup>	2020/4/2	China	Allergy	-	Severe/no-severe	58	240	38.8 (22.7-57.2)	12 (6.4-19.7)
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	52 $\pm$ 11/108 $\pm$ 12	34 $\pm$ 7
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	72.39 $\pm$ 71.64	18.66 $\pm$ 15.80
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	72.0 (35.6-146.8)	13.0 (4.0-26.2)
Gao et al. <sup>37</sup>	2020/4/10	China	J Med Virol	-	Severe/no-severe	15	28	36.1 (23-59.2)	10.6 (5.13-24.18)
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	29.42 $\pm$ 41.34	12.47 $\pm$ 22.05
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	48.4 (12.6-154.1)/65.1 (11.3-154.1)	4.2 (1.9-16.4)/3.3 (1.4-16.7)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	36.52 $\pm$ 5.54	2.61 $\pm$ 0.65
Mo et al. <sup>38</sup>	2020/3/16	China	Clin Infect Dis	-	Severe/no-severe	85	70	64 (31-165)	23 (9-57)
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	9.93 (8.58-11.92)	5.78 (5.10-7.19)/6.03 (5.39-7.93)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	25.2 (9.5-54.5)	13.3 (3.9-41.1)
Ruan et al. <sup>39</sup>	2020/3/3	China	Intensive Care Med	-	Death/no-death	68	82	13.47 $\pm$ 15.89	6.78 $\pm$ 8.78
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	445.83 $\pm$ 204.85	312.61 $\pm$ 24.27
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	24.2 (11.6-47.0)	21.6 (8.7-57.2)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MMFI	Severe/no-severe	18	45	37.77 $\pm$ 7.801	13.41 $\pm$ 1.84
Wu et al. <sup>9</sup>	2020/3/13	China	JAMA Intern Med	-	ARDS/no-ARDS	84	117	7.39 (5.63-10.89)	6.29 (5.36-7.83)
Xiao et al. <sup>40</sup>	2020/2/27	China	Acta Acad Med Mil Tert	-	Severe/no-severe	36	107	15.29 $\pm$ 4.54/28.06 $\pm$ 8.38	6.21 $\pm$ 1.04
Xu et al. <sup>41</sup>	2020/3/8	China	medRxiv	-	Severe/no-severe	25	44	14.8 (7.5-45.3)	5.9 (2.8-10.9)
Zheng et al. <sup>42</sup>	2020/3/17	China	Cellular & Molecular Immunology	-	Severe/no-severe	6	10	28.3 $\pm$ 22.64	50.94 $\pm$ 31.13
Zhou et al. <sup>43</sup>	2020/3/9	China	Lancet	-	Death/no-death	54	137	11 (7.5-14.4)	6.3 (5.0-7.9)
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	46	29.1 (2-89.3)	7.1 (2.79-25.7)
Sun et al. <sup>44</sup>	2020/5/8	China	J Am Geriatr Soc	-	Death/no-death	121	123	75.2 (35.2-162.9)	12.7 (3.3-41.5)
Fan et al. <sup>45</sup>	2020/4/19	China	Metabolism	-	Death/no-death	4	15	195 (127-280)	12 (4-18)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	18.15 (5.91-49.24)	2.21 (0.83-13.22)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	57.33 $\pm$ 111.5/116.47 $\pm$ 141.9	24.69 $\pm$ 39.72
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	154.55 $\pm$ 315.11	9.21 $\pm$ 10.12
Dong et al. <sup>46</sup>	2020/5/29	China	Transbound Emerg Dis	-	Severe/no-severe	53	94	21.85 (11.77-38.68)	8.54 (3.52-17.29)
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	33.22 $\pm$ 31.90/34.09 $\pm$ 26.47	5.26 $\pm$ 1.25/14.17 $\pm$ 11.37
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	22.88 (18.90-27.76)	9.50 (1.79-18.09)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	14.3 (7.8-11.6)	14.0 (7.2-15.3)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	CLIA	Severe/no-severe	26	43	24.6 (17.9-45.0)	8.4 (5.7-15.9)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	150.7 $\pm$ 449.2	64.6 $\pm$ 137.7
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	57.4 $\pm$ 105.6 27.1 (11.8-60.0)	13.2 (3.8-23.1)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	16.9 $\pm$ 25.32 25.35 $\pm$ 33.15	67.71 $\pm$ 56.33
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	44.51 $\pm$ 12.45	7.06 $\pm$ 3.55
Burian et al. <sup>49</sup>	2020/5/18	Germany	J Clin Med	-	ICU/no-ICU	12	25	103.9 $\pm$ 43.6	51.7 $\pm$ 65.6
Gayam et al. <sup>50</sup>	2020/7/16	USA	J Med Virol	-	Death/no-death	132	276	84.5 (53.3-205)	53.1 (23.9-97.4)
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	43.8 (20.1-62.6)	3.9 (2.2-9.6)
Xu et al. <sup>52</sup>	2020/6/13	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	30	125	75.85 $\pm$ 37.64	19.16 $\pm$ 10.53
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	4	27	22.88 (18.90-27.76)	9.50 (1.79-18.09)
Xie et al. <sup>53</sup>	2020/6/13	China	Circ J	-	Severe/no-severe	24	38	14.1 (4.3-26.7)	5.0 (4.3-8.2)
Morrison et al. <sup>54</sup>	2020/7/3	USA	J Autoimmun	-	Death/no-death	16	22	17.5 (8.4-27.9)	6.7 (4.2-9.3)
Wang et al. <sup>55</sup>	2020/3/24	China	Int J Infect Dis	-	Severe/no-severe	25	100	47.5 (15.5-82)	12 (5-32)
Zheng et al. <sup>56</sup>	2020/3/27	China	Int J Infect Dis	-	Severe/no-severe	21	34	39.80 (23.75-60.6)	16.80 (5.55-29.7)
Wang et al. <sup>57</sup>	2020/3/15	China	J Infect	-	Death/no-death	65	274	64.3 (3.8-439)	27.6 (3.6-280)
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	93.8 (35.9-182.3)	10.5 (4.9-18.8)
Chen et al. <sup>58</sup>	2020/4/17	China	Clin Infect Dis	-	Severe/no-severe	27	21	61.1 (29.9-132.2)	10.8 (2.7-37.4)
Liu et al. <sup>59</sup>	2020/7/31	China	Ann Intensive Care	-	Death/no-death	157	1033	5.8 (3.1-16.9)	10.4 (3.8-31.0)
Arunachalam et al. <sup>60</sup>	2020/8/11	China and USA	Science	Flow cytometry	Severe/no-severe	18	4	64.0 (25.6-111.9)	13.2 (7.7-366.2)
Wei et al. <sup>61</sup>	2020/4/16	China	J Infect	-	Severe/no-severe	30	137	31.9 (11.1-1487.0)	9.87 $\pm$ 5.74
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	41.89 $\pm$ 68.33	15.40 (5.05-28.90)
Shi et al. <sup>62</sup>	2020/4/23	China	medRxiv	-	Severe/no-severe	46	88	36.20 (16.25-59.90)	3.82 (2.19-9.87)
								24.11 (1.14-54.37)	5.7 (5.0-9.9)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	11.30 (4.34–28.43)	14.60 (4.21–22.30)
Pereira et al. <sup>64</sup>	2020/4/24	USA	Am J Transplant	-	Severe/no-severe	27	41	17.40 (7.18–50.20)	18 (5–45)
IL-8 (unit: ng/L)									
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	20 $\pm$ 16/30 $\pm$ 16	16 $\pm$ 11
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	61.62 $\pm$ 73.07	24.74 $\pm$ 26.86
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	28.3 (18.7–72.1)	11.4 (7.8–20.2)
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	49.74 $\pm$ 76.59	18.19 $\pm$ 16.24
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	22.0 (14.0–28.4)/27.6 (14.1–64.9)	9.3 (6.4–18.6)/9.4 (5.7–15.9)
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	46	21.5 (5–125.6)	8.66 (5.41–17.5)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	18.4 (11.3–28.4)	13.7 (8.9–21)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	29.05 (14.35–56.75)	9.40 (6.55–15.85)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	CLIA	Severe/no-severe	26	43	13.1 (11.4–15.9)	7.8 (6.4–10.4)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	32.21 $\pm$ 34.88 55.99 $\pm$ 78.34	29.78 $\pm$ 43.11
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	4	27	29.05 (14.35–56.75)	9.40 (6.55–15.85)
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	28.3 (14.7–59.1)	12.5 (6.9–20.8)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	32.58 $\pm$ 23.79 57.23 $\pm$ 61.01	36.55 $\pm$ 54.97
IL-10 (unit: ng/L)									
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	11.0 $\pm$ 9.2/11.4 $\pm$ 2.6	8.0 $\pm$ 3.2
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	10.93 $\pm$ 2.10	6.67 $\pm$ 2.65
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	12.8 (8.8–19.6)	5.0 (5.0–8.4)
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	19.38 $\pm$ 37.95	5.51 $\pm$ 4.31
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	4.9 (4.0–10.0)/8.3 (4.9–17.0)	4.9 (4.0–4.9)/4.9 (4.0–4.9)



TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	5.48 $\pm$ 0.48	3.06 $\pm$ 0.16
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	6.54 (5.96–7.44)	4.93 (4.25–5.55)/4.78 (4.28–5.51)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	6.6 (5.0–11.3)	5 (5.0–7.0)
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	25.43 $\pm$ 12.71	19.21 $\pm$ 1.89
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	6.7 (3.3–8.2)	4.3 (3.0–8.1)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MMFI	Severe/no-severe	21	102	4.59 $\pm$ 0.3777	2.464 $\pm$ 0.08506
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	30.25 (15.57–67.13)	24.79 (16.64–36.92)
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	46	7.32 (<5–11.23)	5 (<5–5.87)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	5.23 (3.31–10.64)	2.34 (1.16–4.41)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	10.16 $\pm$ 4.96	36.55 $\pm$ 54.97
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	23.85 $\pm$ 26.57	4.52 $\pm$ 3.71
Dong et al. <sup>46</sup>	2020/5/29	China	Transbound Emerg Dis	-	Severe/no-severe	53	94	4.50 (3.91–5.45)	4.51 (3.48–6.23)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	22.00 (14.73–60.00)	5.00 (5.00–7.90)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	4.3 $\pm$ 1.7	3.9 $\pm$ 1.8
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	5.6 $\pm$ 3.6	6.37 (5.71–6.67)
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	7.25 (6.20–8.05)	5.0 (5.0–8.1)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	8.0 (5.0–15.1)	13.88 $\pm$ 12.95
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	9.18 $\pm$ 8.52	0.91 $\pm$ 0.7
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	4	27	7.45 $\pm$ 2.64	5.00 (5.00–7.90)
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	22.00 (14.73–60.00)	2.5 (2.5–7.0)
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	10.5 (5.9–18.5)	3.13 (2.15–4.57)

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TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	8.52 (4.90–15.80)	5.00 (4.90–7.16)
TNF- $\alpha$ (unit: ng/L)									
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	10.8 $\pm$ 6.5/10.1 $\pm$ 1.5	8.3 $\pm$ 1.9
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	10.93 $\pm$ 3.30	7.56 $\pm$ 1.85
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	11.8 (8.6–17.6)	7.9 (6.7–9.6)
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	13.0 (8.3–23.3)/21.3 (13.2–28.9)	7.3 (5.6–9.4)/5.7 (3.8–7.9)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	2.26 $\pm$ 0.15	2.11 $\pm$ 0.10
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	2.98 (2.76–3.41)	2.85 (2.51–3.35)/2.89 (2.55–3.28)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	8.7 (7.1–11.6)	8.4 (6.9–10.4)
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	1.23 $\pm$ 0.30	0.93 $\pm$ 0.20
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	12.2 (12.2–54.4)	19.7 (2.5–67.5)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MMFI	Severe/no-severe	21	102	2.948 $\pm$ 0.4432	4.077 $\pm$ 1.588
Zheng et al. <sup>42</sup>	2020/3/17	China	Cellular & Molecular Immunology	-	Severe/no-severe	6	10	97.06 $\pm$ 30.88	202.94 $\pm$ 70.59
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.1 (0.00–0.24)	0.10 (0.10–0.26)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	10.16 $\pm$ 2.94	10.34 $\pm$ 3.12
Dong et al. <sup>46</sup>	2020/5/29	China	Transbound Emerg Dis	-	Severe/no-severe	53	94	13.26 $\pm$ 14.02	2.18 (1.93–2.35)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	23.00 (9.65–44.23)	7.60 (5.65–9.00)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	2.98 (2.63–3.11)	2.50 (2.44–2.73)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	CLIA	Severe/no-severe	26	43	7.4 (6.7–8.7)	5.0 (4.8–6.08)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	5.5 $\pm$ 6.1	5.6 $\pm$ 6.6
								3.2 $\pm$ 2	

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	9.3 (7.6-11.6)	8.1 (6.8-9.8)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	10.41 ± 4.73 4.48 ± 8.13	9.03 ± 4.11
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	1.74 ± 0.4	0.91 ± 0.49
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	4	27	23.00 (9.65-44.23)	7.60 (5.65-9.00)
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	10.7 (7.5-15.9)	8.2 (6.1-10.2)
Arunachalam et al. <sup>60</sup>	2020/8/11	China and USA	Science	Flow cytometry	Severe/no-severe	18	4	7.11 ± 1.65	5.66 ± 2.94
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	1.48 (1.39-1.74)	1.35 (1.12-1.73)
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	94.09 ± 20.40	72.01 ± 20.96
IL-5 (unit: ng/L)									
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	13.61 ± 12.57	12.62 ± 12.75
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	2.22 (2.11-2.33)	2.16 (2.07-2.22)/2.13 (2.05-2.18)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	2.27 (2.12-2.35)	2.39 (2.30-3.05)
IL-1β (unit: ng/L)									
Chen et al. <sup>23</sup>	2020/2/4	China	Chinese Medical Association	ELISA	Severe/no-severe	14	15	5.0 ± 1.1/6.2 ± 2.4	5.5 ± 1.9
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	CLIA	Severe/no-severe	9	7	5.32 ± 0.96	5 ± 0.21
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	1.16 ± 0.54	1.40 ± 1.52
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Death/no-death	26	108	4.5 (4.0-4.9)/4.9 (4.2-4.9)	4.9 (4.0-4.9)/4.9 (4.7-4.9)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	5 (5.0-5.0)	5 (5.0-5.0)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	4.90 (4.90-5.42)/4.90 (4.90-5.61)	4.90 (4.90-5.21)
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	1.65 ± 0.38	0.85 ± 0.14
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	CLIA	Severe/no-severe	26	43	9.9 (6.0-18.3)	7.5 (6.8-8.7)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	7	27	5.00 (5.00-25.88)	5.00 (5.00-5.00)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	46	5.69 (<5-11.6)	5 (<5-10.1)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	CLIA	Severe/no-severe	221	168	6.43 $\pm$ 3.01/10.71 $\pm$ 6.02	5.57 $\pm$ 2.13
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	4	27	5 (5-25.88)	5 (5-5)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	6.48 $\pm$ 3.83/5.32 $\pm$ 0.63	6.11 $\pm$ 2.92
IFN- $\gamma$ (unit: ng/L)									
Huang et al. <sup>1</sup>	2020/1/24	China	Lancet	-	ICU/no-ICU	13	28	16.062 $\pm$ 20.752	0.849 $\pm$ 5.472
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry and ELISA	Severe/no-severe	69	11	2.49 $\pm$ 0.18	1.87 $\pm$ 0.09
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	3.99 (3.61-4.44)	3.76 (3.53-4.19)/3.64 (3.38-4.07)
Shi et al. <sup>17</sup>	2020/3/16	China	medRxiv	-	Severe/no-severe	25	31	5.27 $\pm$ 1.91	4.9 $\pm$ 0.85
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	9 (5.7-24.3)	12.2 (5.8-37.9)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MIFI	Severe/no-severe	21	97	6.904 $\pm$ 1.247	5.132 $\pm$ 0.8413
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	86.37 (47.01-255.91)	80.06 (36.63-129.08)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.58 (0.11-1.69)	0.66 (0.11-1.57)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	3.8 (3.8-3.93)	3.93 (3.51-4.61)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	CLIA	Severe/no-severe	121	131	2.9 $\pm$ 4.5 9.5 $\pm$ 24.7	2.5 $\pm$ 1.1
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	10	30	13.48 $\pm$ 4.84	0.87 $\pm$ 0.72
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	Flow cytometry	Severe/no-severe	16	111	1.93 (1.25-2.29)	1.24 (0.93-1.57)
IgA (unit: g/L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	2.18 (1.84-3.68)	2.38 (1.85-3.04)
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	2.4 (1.6-3.3)	2.1 (1.6-2.8)
Han et al. <sup>67</sup>	2020/3/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	3.08 $\pm$ 1.08	1.01 $\pm$ 0.64
Liu et al. <sup>68</sup>	2020/2/16	China	EBioMedicine	-	Severe/no-severe	13	27	2.4 $\pm$ 0.6	2.2 $\pm$ 0.8
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	1.97 (1.55-2.41)	1.90 (1.41-2.52)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	2.26 (1.57-2.89)	2.14 (1.66-2.71)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	3.30 (1.68-4.50)	2.55 (1.81-3.01)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	2.10 (1.43-2.85)	1.84 (1.45-2.44)
IgG (unit: g/L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	12.4 (10.9-13.8)	11.8 (10.3-13.6)
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	12.3 (10.1-14.5)	11.3 (9.3-13.0)
Han et al. <sup>67</sup>	2020/3/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	12.50 (9.82-15.20)	11.05 (9.34-12.53)
Liu et al. <sup>68</sup>	2020/2/16	China	EBioMedicine	-	Severe/no-severe	13	27	11.5 ± 2	10.8 ± 2
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	12 (10-14)	12 (11-16)/13 (11-15)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	11.7 (9.53-13.8)	11.85 (10.13-13.40)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	12.20 (10.60-14.30)	10.00 (11.70-13.40)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	13.4 (10.5-16.5)	11.6 (9.9-13.8)
IgM (unit: g/L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	0.86 (0.68-0.99)	0.96 (0.69-11.24)
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	1.0 (0.7-1.4)	1.0 (0.7-1.4)
Han et al. <sup>67</sup>	2020/3/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	1.01 ± 0.36	1.01 ± 0.44
Liu et al. <sup>68</sup>	2020/2/16	China	medRxiv	-	Severe/no-severe	13	27	1.1 ± 0.3	1.1 ± 0.5
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	1.05 (0.74-1.52)	1.16 (0.74-1.36)/1.20 (0.96-1.86)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	-	Severe/no-severe	286	166	0.9 (0.69-1.28)	1.02 (0.77-1.37)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	0.93 (0.72-1.16)	0.86 (0.67-1.09)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	0.94 (0.66-1.22)	1.11 (0.86-1.38)
IgE (unit: IU/mL)									
Han et al. <sup>67</sup>	2020/3/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	36.00 (0.00-103.5)	0.00 (0.00-33.98)
Liu et al. <sup>68</sup>	2020/2/16	China	EBioMedicine	-	Severe/no-severe	13	27	43.9 (27-105.5)	26.5 (12.8-76.1)
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	28.0 (17.3-58.0)	17.5 (17.3-98.2)/32.2 (17.3-65.0)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	30.85 (17.3-68.9)	21.9 (17.3-84.3)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
CD3+T cells count (unit: cells/ $\mu$ L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	411.0 (198.0-537.0)	801.0 (561.5-1087.0)
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	294.0 (169.3-415.3)	640.5 (588.3-789.5)
Diao et al. <sup>70</sup>	2020/5/1	China	Front Immunol	-	ICU/no-ICU	43	212	261 (157-457)	652 (351-977)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	378.10 ± 142.33	973.46 ± 298.92
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	461.6 ± 264.7	663.8 ± 291.3
Shi et al. <sup>17</sup>	2020/3/12	China	medRxiv	Flow cytometry	Severe/no-severe	25	19	738 ± 512.15	1073.38 ± 464.14
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	269.0 (158.0-410.0)	504.5 (262.0-918.8)
Wu et al. <sup>9</sup>	2020/3/13	China	JAMA Intern Med	-	ARDS/no-ARDS	84	117	446.50 (231.00-633.75)	633.00 (467.00-846.00)
Xu et al. <sup>41</sup>	2020/3/8	China	medRxiv	Flow cytometry	Severe/no-severe	25	44	306 (185-464)	734 (445-1036)
Zeng et al. <sup>71</sup>	2020/3/8	China	medRxiv	Flow cytometry	ICU/no-ICU	65	113	503 ± 187	1056 ± 191
Zheng et al.(a) <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	530.25 ± 255.417	1245.105 ± 619.531
Zheng et al.(b) <sup>11</sup>	2020/3/19	China	Cell Mol Immunol	-	Severe/no-severe	13	55	583.94 ± 328.97	857.66 ± 737.83
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	427.86 ± 253.74	571.23 ± 270.10
								259.85 ± 155.97	
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	707.55 ± 538.45	1047.17 ± 481.21
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	305 (198-525)	1066 (804-1321)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	378 (258-576)	991 (740-1154)
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	266.5 (173.8-579.8)/ 297.0 (139.0-433.0)	706.0 (491.5-1004.5)/ 657.5 (431.0-1035.3)
Liu et al. <sup>74</sup>	2020/5/13	China	Clin Chim Acta	Flow cytometry	Severe/no-severe	105	49	358.15 (73.71-1019.43)/ 511.78 (120.54-1739.49)	512.03 (118.69-1746.61)
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	522.57 ± 318.73/464.67 ± 339.68	1210.75 ± 408.81/ 808.97 ± 371.22
Liu et al. <sup>59</sup>	2020/7/31	China	Ann Intensive Care	-	Death/no-death	157	1033	367 (267-409)	647 (468-991)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	339.50 (217.50-524.25)	609.00 (410.00-905.00)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	593.00 (412.00-725.00)	894.50 (662.75-1192.00)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
CD4+ T cells count (unit: cells/ $\mu$ L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	198.0 (116.0–340.0)	468.0 (309.5–679.5)
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	177.5 (104.0–249.8)	381.5 (255.0–451.0)
Diao et al. <sup>70</sup>	2020/5/1	China	Front Immunol	-	ICU/no-ICU	43	212	198 (100–279)	342 (192–559)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	230.50 $\pm$ 86.68	610.15 $\pm$ 178.30
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	285.1 $\pm$ 168.0	420.5 $\pm$ 207.8
Shi et al. <sup>17</sup>	2020/3/12	China	medRxiv	Flow cytometry	Severe/no-severe	25	19	384.72 $\pm$ 270.99	616.62 $\pm$ 294.09
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	139.0 (72.0–206.0)	288.5 (142.5–504.0)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	-	Severe/no-severe	21	102	263.2 $\pm$ 28.83	451.3 $\pm$ 23
Wu et al. <sup>9</sup>	2020/3/13	China	JAMA Intern Med	-	ARDS/no-ARDS	84	117	234.00 (136.75–398.00)	371.00 (283.00–572.00)
Xu et al. <sup>41</sup>	2020/3/8	China	medRxiv	Flow cytometry	Severe/no-severe	25	44	201 (127–251)	422 (244–593)
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	329 (200.25–438.5)	559.5 (377–784)
Zeng et al. <sup>71</sup>	2020/3/8	China	medRxiv	Flow cytometry	ICU/no-ICU	65	113	290 $\pm$ 87	599 $\pm$ 163
Zheng et al. <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	140.798 $\pm$ 336.375	416.618 $\pm$ 622.589
Zhou et al. <sup>75</sup>	2020/3/17	China	Ann Palliat Med	-	Aggravation/no-aggravation	5	12	377.2 $\pm$ 229.6	698.2 $\pm$ 267.4
Fan et al. <sup>45</sup>	2020/4/19	China	Metabolism	-	Death/no-death	4	15	168 (108–250)	416 (172–557)
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol	-	Severe/no-severe	30	60	125 (60–107)	462 (239–636)
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	392.27 $\pm$ 267.42	612.83 $\pm$ 296.34
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	257.86 $\pm$ 129.48/270.11 $\pm$ 162.75	689.38 $\pm$ 251.29/436.8 $\pm$ 225.08
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	199 (128–325)	544 (364–667)
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	130.5 (92.0–369.8)/130.0 (103.0–277.0)	396.0 (293.0–599.0)/442.5 (264.5–676.0)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	184 (103–293)	645 (461–794)
Yang et al. <sup>76</sup>	2020/4/29	China	J Allergy Clin Immunol	-	Severe/no-severe	36	14	377 (200.75–492.5)/246 (176–315.5)	561 (367–826)
Liu et al. <sup>74</sup>	2020/5/13	China	Clin Chim Acta	Flow cytometry	Severe/no-severe	105	49	230.24 (40.13–760.24)/315.4 (54.96–1098.12)	311.34 (60.07–1134.24)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Yang et al. <sup>77</sup>	2020/5/15	China	J Med Virol	-	Severe/no-severe	68	65	234.5 (155.5–353.5)	478 (326–571)
Xu et al. <sup>52</sup>	2020/6/13	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	30	125	330.43 $\pm$ 211.00	481.12 $\pm$ 243.60
Zheng et al. <sup>78</sup>	2020/4/6	China	J Clin Virol	-	Severe/no-severe	26	63	273.92 $\pm$ 185.21	553.25 $\pm$ 377.81
Wang et al. <sup>57</sup>	2020/3/15	China	J Infect	-	Death/no-death	65	274	191 (107–282)	349 (217–516)
Liu et al. <sup>59</sup>	2020/7/31	China	Ann Intensive Care	-	Death/no-death	157	1033	211 (275–645)	388 (275–645)
Wei et al. <sup>61</sup>	2020/4/16	China	J Infect	-	Severe/no-severe	30	137	282.00 (183.00–574.75)	490.40 $\pm$ 232.64
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	203.00 (126.50–284.25)	368.00 (246.00–549.00)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	299.00 (249.00–460.00)	573.50 (426.75–771.00)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	168.50 (125.25–255.00)	342.39 $\pm$ 173.91
								244.57 $\pm$ 135.87	146.74 $\pm$ 125
CD8+ T cells count (unit: cells/ $\mu$ L)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	128.0 (65.0–182.0)	217.0 (176.0–415.0)
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	89.0 (61.5–130.3)	254.0 (183.3–312.8)
Diao et al. <sup>70</sup>	2020/5/1	China	Front Immunol	-	ICU/no-ICU	43	212	64.3 (40.7–160)	208 (118–356)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	125.98 $\pm$ 84.71	345.00 $\pm$ 194.10
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	154.7 $\pm$ 116.5	201.9 $\pm$ 107.1
Shi et al. <sup>17</sup>	2020/3/12	China	medRxiv	Flow cytometry	Severe/no-severe	25	19	311.33 $\pm$ 222.67	317.6 $\pm$ 150.67
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	117.0 (59.0–177.0)	234.0 (122.3–367.8)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	-	Severe/no-severe	21	102	179 $\pm$ 23.87	288.6 $\pm$ 14.23
Wu et al. <sup>9</sup>	2020/3/13	China	JAMA Intern Med	-	ARDS/no-ARDS	84	117	157.50 (76.00–289.50)	241.00 (159.0–323.00)
Xu et al. <sup>41</sup>	2020/3/8	China	medRxiv	Flow cytometry	Severe/no-severe	25	44	88 (60–145)	266 (166–401)
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	139 (97–183)	453.5 (232.8–586)
Zeng et al. <sup>71</sup>	2020/3/8	China	medRxiv	Flow cytometry	ICU/no-ICU	65	113	207 $\pm$ 142	455 $\pm$ 127
Zheng et al.(a) <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	109.694 $\pm$ 161.125	312.704 $\pm$ 432.54
Zhou et al. <sup>75</sup>	2020/3/17	China	Ann Palliat Med	-	Aggravation/no-aggravation	5	12	147 (116–446)	364 (111–799)
Zheng et al.(b) <sup>11</sup>	2020/3/19	China	Cell Mol Immunol	-	Severe/no-severe	13	55	206.52 $\pm$ 117.72	336.96 $\pm$ 725.87



TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
Liu et al. <sup>27</sup>	2020/4/10	China	Viral Immunol		Severe/no-severe	30	60	65 (33–112)	267 (210–405)
Fan et al. <sup>45</sup>	2020/4/19	China	Metabolism		Death/no-death	4	15	33 (23–135)	273 (122–377)
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	297.55 ± 223.32	301.03 ± 159.44
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	205.14 ± 153.09/202.22 ± 199.10	462.88 ± 154.43/355.33 ± 166.86
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	121 (54–197)	366 (274–482)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	134 (91–237)	417 (309–539)
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	106.5 (42.0–212.5)/68.0 (52.0–156.0)	268.0 (157.0–396.0)/221.0 (128.3–312.0)
Yang et al. <sup>76</sup>	2020/4/29	China	J Allergy Clin Immunol	-	Severe/no-severe	36	14	146 (97–225.25) 139 (107–171.5)	453.5 (232.8–586)
Liu et al. <sup>74</sup>	2020/5/13	China	Clin Chim Acta	Flow cytometry	Severe/no-severe	105	49	97.34 (21.82–733.95)/220.95 (49.45–833.76)	175.62 (40.73–865.47)
Xu et al. <sup>52</sup>	2020/6/13	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	30	125	233.50 ± 149.63	359.12 ± 191.26
Zheng et al. <sup>78</sup>	2020/4/6	China	J Clin Virol	-	Severe/no-severe	26	63	202.31 ± 144.31	349.13 ± 256.5
Wang et al. <sup>57</sup>	2020/3/15	China	J Infect	-	Death/no-death	65	274	73 (42–160)	204 (97–298)
Liu et al. <sup>59</sup>	2020/7/31	China	Ann Intensive Care	-	Death/no-death	157	1033	129 (87–144)	242 (156–356)
Wei et al. <sup>61</sup>	2020/4/16	China	J Infect	-	Severe/no-severe	30	137	191.00 (135.75–326.50)	316.00 (234.50–452.25)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	145.00 (70.00–213.00)	205.00 (111.00–303.00)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	188.00 (134.00–274.00) L 92.50 (70.75–141.50)	323.50 (232.75–448.75)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight		Severe/no-severe	35	30	156.52 ± 123.91	198.91 ± 120.65

Treg cell count (unit: cells/ $\mu$ L)

Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	4.7 (2.6–5.4)	3.9 (3.6–4.3)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	3.7 ± 1.3	4.5 ± 0.9

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
Shi et al. <sup>17</sup>	2020/3/12	China	Immunology	Flow cytometry	Severe/no-severe	25	19	7.13 ± 2.49	8.54 ± 2.09
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology		Severe/no-severe	25	31	7.15 ± 3.84	8.58 ± 3.19
CD3+ T cells ratio (unit: %)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	55.1 (52.2–60.5)	68.8 (64.7–75.2)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	65.85 ± 2.05	79.27 ± 1.94
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	60 (50–71)	72 (69–77)/73 (69–78)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	60.0 ± 10.8	63.4 ± 8.5
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	29	31	64.75 (52.75–76.36)	66.85 (57.53–75.05)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight		Severe/no-severe	35	30	59.71 ± 15.21	65.58 ± 9.66
								57.77 ± 11.95	
Xie et al. <sup>79</sup>	2020/4/24	China	J Med Virol		Severe/no-severe	34	22	74.68 (70.81–78.92)	77.18 (68.35–82.03)
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	70.2 ± 13.41	70.21 ± 9.88
Zheng et al. <sup>56</sup>	2020/3/27	China	Int J Infect Dis	-	Severe/no-severe	21	34	70.5 (39.5–86.8)	76.8 (62.9–89.6)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	60.49 (45.30–64.45)	69.00 (55.48–74.82)
CD4+ T cells ratio (unit: %)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	36.7 (30.7–37.3)	36.4 (32.0–40.6)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	40.24 ± 1.46	45.61 ± 1.95
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	33 (25–42)	40 (33–43)/40 (37–46)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	37.2 ± 8.4	39.8 ± 7.5
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	38.31 ± 7.31	42.82 ± 7.58
Xie et al. <sup>79</sup>	2020/4/24	China	J Med Virol		Severe/no-severe	34	22	44.92 (40.46–53.49)	46.29 (40.7–52.36)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight		Severe/no-severe	35	30	35.61 ± 8.93	38.47 ± 6.07
								33.06 ± 14.05	
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	20.0 (20.0–30.0)	50.0 (30.0–70.0)
Xie et al. <sup>53</sup>	2020/6/13	China	Circ J	-	Severe/no-severe	24	38	36.7 (30.6–52.6)	41.4 (37.5–50.3)
								42.2 (36.0–50.8)	
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	33.90 (27.09–39.58)	41.46 (32.95–46.58)
CD8+ T cells ratio (unit: %)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	17.4 (14.7–23.4)	25.2 (22.8–34.2)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	23.29 $\pm$ 1.35	32.05 $\pm$ 2.53
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	20 (16-25)	26 (24-30)/26 (23-30)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	19.7 $\pm$ 9.2	19.5 $\pm$ 6.2
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	30.92 $\pm$ 13.32	24.64 $\pm$ 10.68
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	10.0 (10.0-30.0)	30.0 (20.0-40.0)
Xie et al. <sup>53</sup>	2020/6/13	China	Circ J	-	Severe/no-severe	24	38	17.3 (14.1-25.4)/22.8 (17.6-25.4)	27.6 (23.8-31.8)/23.5 (19.2-28.6)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	20.65 (13.36-32.06)	22.20 (16.52-29.90)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	21.76 $\pm$ 8.1	22.85 $\pm$ 9.5
Xie et al. <sup>79</sup>	2020/4/24	China	J Med Virol	-	Severe/no-severe	34	22	23.52 (17.8-30.23)	25.16 (16.15-31.41)
CD4+CD8+ (THTs) ratio (unit: %)									
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	173	1.78 (1.29-2.15)	1.68 (1.23-2.32)
Diao et al. <sup>70</sup>	2020/5/1	China	Front Immunol	-	ICU/no-ICU	43	212	2.43 (1.5-4.25)	1.6 (1.17-2.28)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	2.32 $\pm$ 0.24	1.65 $\pm$ 0.19
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	2.2 $\pm$ 0.6	2.5 $\pm$ 1.5
Shi et al. <sup>17</sup>	2020/3/12	China	medRxiv	Flow cytometry	Severe/no-severe	25	19	1.51 $\pm$ 0.71	2.01 $\pm$ 0.8
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	1.2 (1.1-1.7)	1.2 (0.9-1.6)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	-	Severe/no-severe	21	102	1.509 $\pm$ 0.1701	1.671 $\pm$ 0.05941
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	2.26 (1.35-2.82)	1.71 (1.21-2.17)
Zheng et al.(a) <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	2.277 $\pm$ 3.164	0.965 $\pm$ 1.516
Fan et al. <sup>45</sup>	2020/4/19	China	Metabolism	-	Death/no-death	4	15	5.0 (2.0-6.2)	1.6 (1.3-2.4)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	29	31	1.99 (1.28-3.75)	1.46 (0.78-2.11)
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	1.52 $\pm$ 0.71	2.03 $\pm$ 0.81
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	1.28 $\pm$ 0.76/2.42 $\pm$ 1.56	1.53 $\pm$ 0.41/1.62 $\pm$ 1.86
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	1.57 (1.10-2.36)	1.66 (1.37-2.16)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	1.40 (0.79-2.08)	1.18 (0.96-1.58)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Yang et al. <sup>77</sup>	2020/5/15	China	J Med Virol	-	Severe/no-severe	68	65	1.42 (1-2.02)	1.23 (0-1.68)
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	1.5 (0.9-2.4)	1.6 (1.1-2.4)
Xu et al. <sup>52</sup>	2020/6/13	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	30	125	1.80 $\pm$ 0.92	1.54 $\pm$ 0.67
Wei et al. <sup>61</sup>	2020/4/16	China	J Infect	-	Severe/no-severe	30	137	1.51 $\pm$ 0.71	1.51 (1.11-1.91)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	1.59 (1.13-2.47)	1.93 (1.26-2.68)
Xie et al. <sup>79</sup>	2020/4/24	China	J Med Virol	-	Severe/no-severe	34	22	1.88 (1.39-2.85)	1.99 (1.52-3.19)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	2.17 $\pm$ 1.6 1.66 $\pm$ 1.16	2.14 $\pm$ 1.17
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	1.96 (1.02-2.70)/1.75 (1.06-2.28)	1.68 (0.96-2.18)
CD19 + B cells count (unit: cells/ $\mu$ L)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	184.0 (42.8-273.3)	115.5 (102.8-133.5)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	124.59 $\pm$ 62.64	167.03 $\pm$ 94.32
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	169 $\pm$ 140.9	196.1 $\pm$ 144.9
Shi et al. <sup>17</sup>	2020/3/12	China	medRxiv	Flow cytometry	Severe/no-severe	25	19	131.3 $\pm$ 112.3	187.17 $\pm$ 133.69
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	82 (45.0-149.0)	115.5 (83.0-161.5)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	MMFI	Severe/no-severe	21	102	125.3 $\pm$ 13.49	166 $\pm$ 11.98
Xu et al. <sup>41</sup>	2020/3/8	China	medRxiv	Flow cytometry	Severe/no-severe	25	44	74 (45-196)	124 (72-240)
Zeng et al. <sup>71</sup>	2020/3/8	China	medRxiv	Flow cytometry	ICU/no-ICU	65	113	126 $\pm$ 52	155 $\pm$ 51
Zheng et al. <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	109.5 $\pm$ 57.756	230.21 $\pm$ 217.257
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	Flow cytometry	Death/no-death	14	71	106.00 (55.00-142.75)	128.00 (91.00-187.00)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	91 (54-139)	190 (139-268)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	Flow cytometry	Severe/no-severe	107	80	97.00 (74.00-162.00)/ 73.00 (36.50-101.75)	213.50 (152.25-314.25)
Fan et al. <sup>45</sup>	2020/4/19	China	Metabolism	-	Death/no-death	4	15	84 (34-134)	104 (49-236)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	155.65 $\pm$ 98.21 58.44 $\pm$ 37.21	174.86 $\pm$ 145.77

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	128.83 $\pm$ 42.44/119.38 $\pm$ 59.07	330.71 $\pm$ 177.65/148.92 $\pm$ 89.33
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	92 (56-135)	163 (126-224)
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	88.5 (54.8-175.0)/75.0 (45.0-163.0)	139.0 (91.5-221.5)/ 149.5 (111.3-237.0)
CD16+CD56+ NK cells count (unit: cells/ $\mu$ L)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	60.5 (27.5-109.0)	180.5 (115.0-228.0)
Han et al. <sup>67</sup>	2020/3/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	115.65 $\pm$ 76.06	179.85 $\pm$ 80.27
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	113 $\pm$ 71.8	160.2 $\pm$ 90.8
Shi et al. <sup>17</sup>	2020/3/12	China	Immunology	Flow cytometry	Severe/no-severe	25	19	90.32 $\pm$ 86.02	189.25 $\pm$ 75.27
Song et al. <sup>18</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	42	31	100 (54.0-178.0)	232.5 (100.5-286.3)
Wan et al. <sup>34</sup>	2020/2/10	China	Br J Haematol	Multiple microsphere flow immunofluo rescence	Severe/no-severe	21	102	119.6 $\pm$ 16.5	147 $\pm$ 10.36
Zeng et al. <sup>71</sup>	2020/3/8	China	medRxiv	Flow cytometry	ICU/no-ICU	65	113	239 $\pm$ 133	283 $\pm$ 131
Zheng et al.(a) <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	537.5 $\pm$ 674.557	250.706 $\pm$ 193.328
Zheng et al.(b) <sup>11</sup>	2020/3/19	China	Cell Mol Immunol	-	Severe/no-severe	13	55	105.11 $\pm$ 79.05	188.32 $\pm$ 130
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	Flow cytometry	Severe/no-severe	107	80	93 (60-161)/55.5 (32-91.25)	107.5 (82.75-149.75)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	135	105 (66-168)	144 (93-231)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-sever	35	30	127.42 $\pm$ 107.41	133.92 $\pm$ 101.73
								142.59 $\pm$ 96.63	
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-sever	25	31	89.14 $\pm$ 86.21	192.01 $\pm$ 73.14
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	185.00 $\pm$ 180.11/102.88 $\pm$ 72.28	288 $\pm$ 175.93/203.63 $\pm$ 209.433
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	122 (51-162)	186 (122-302)
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	51.0 (24.3-124.0)/100.0 (40.0-157.0)	132.5 (71.8-196.3)/ 137.5 (81.3-224.8)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	88.00 (39.5-176.25)	119.00 (74.00-171.00) (Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean ± SD or IQR	
						Severe	No-severe	Severe	No-severe
CD19+ B cells ratio (unit: %)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	20.2 (17.6–39.5)	10.8 (10.3–12.4)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	14.63 ± 1.83	14.63 ± 1.46
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	12 (9–22)	12 (10–16)/11 (9–15)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	21.8 ± 12.2	18.5 ± 8.1
Zheng et al. <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	11.448 ± 5.666	12.537 ± 5.571
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	17.30 (10.33–40.30)	15.23 (11.55–21.22)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	29	31	21.59 (12.03–29.31)	14.88 (9.6023.87)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	22.38 ± 12.65/25.62 ± 12	18.49 ± 8.76
CD16+CD56+ NK cells ratio (unit: %)									
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	Flow cytometry	Severe/no-severe	11	10	14.7 (7.5–21.0)	15.1 (11.6–22.8)
Liu et al. <sup>15</sup>	2020/3/1	China	medRxiv	Flow cytometry	Severe/no-severe	69	11	13.87 ± 1.22	3.19 ± 0.82
Nie et al. <sup>16</sup>	2020/3/24	China	medRxiv	-	Severe/no-severe	25	72	18 (12–31)	12 (8–19)/12 (9–19)
Qin et al. <sup>10</sup>	2020/3/12	China	Clin Infect Dis	Flow cytometry	Severe/no-severe	27	17	16.9 ± 10.1	17.2 ± 10.1
Zheng et al. <sup>72</sup>	2020/2/19	China	medRxiv	Flow cytometry	Severe/no-severe	8	95	38.2 ± 18.427	15.128 ± 10.337
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	29	31	7.71 (4.95–16.07)	11.77 (7.53–23.12)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	16.78 ± 10.48	15.03 ± 9.81
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	Flow cytometry	Severe/no-severe	25	31	14.99 ± 6.38	14.22 ± 9.77
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	17.32 (11.59–26.48)	13.24 (8.79–19.03)
Neutrophils count (unit: cells/μL)									
Huang et al. <sup>80</sup>	2020/5/8	China	medRxiv	-	Severe/no-severe	27	321	4.06 (3.26–6.42)	2.85 (2.28–3.79)
Huang et al. <sup>81</sup>	2020/5/8	China	PLoS Negl Trop Dis	-	Severe/no-severe	23	179	4.5 (2.8–5.9)	2.8 (2.1–3.6)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	7.66 (6.16–11.6)	3.65 (2.58–5.80)
Wang et al. <sup>33</sup>	2020/4/23	China	JCI Insight	-	Severe/no-severe	35	30	5.7 ± 3.7	3.8 ± 2.4
								7.7 ± 3.9	
Tan et al. <sup>41</sup>	2020/5/27	China	Immunology	-	Severe/no-severe	25	31	7.21 ± 5.25	4.49 ± 3.64
Xie et al. <sup>79</sup>	2020/4/24	China	J Med Virol	-	Severe/no-severe	34	22	4.31 (2.88–5.47)	2.78 (2.35–3.56)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Dong et al. <sup>46</sup>	2020/5/29	China	Transbound Emerg Dis	-	Severe/no-severe	53	94	3.46 (2.42-5.40)	2.32 (1.75-3.51)
Zhang et al. <sup>82</sup>	2020/5/30	China	Eur Radiol	-	Death/no-death	10	50	8.6 $\pm$ 5.1	5.2 $\pm$ 3.4
Li et al. <sup>83</sup>	2020/5/15	China	Theranostics	-	Death/no-death	25	68	3.8 (2.7-5.2)	2.8 (2.2-3.6)
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	3.76 $\pm$ 1.85/5.54 $\pm$ 3.70	3.25 $\pm$ 0.82/2.70 $\pm$ 1.01
Sun et al. <sup>84</sup>	2020/4/24	China	Clin Chim Acta	-	Severe/no-severe	27	89	6.07 (3.10-7.60)	2.90 (2.15-3.80)
Qi et al. <sup>85</sup>	2020/5/20	China	Gut	-	Death/no-death	5	16	4.01 (1.54-7.45)	2.48 (1.64-4.22)
He et al. <sup>20</sup>	2020/4/14	China	J Clin Virol	-	Severe/no-severe	69	136	3.87 (2.49-6.11)	2.69 (2.03-3.61)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	13	40	5.58 (1.76-5.87)	2.63 (1.98-4.19)
Shang et al. <sup>86</sup>	2020/5/21	China	J Med Virol	-	Severe/no-severe	139	304	4.27 (2.65-6.24)	3.07 (2.35-4.15)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	4.65 (2.11-8.79)	2.83 (1.98-3.51)
Yip et al. <sup>87</sup>	2020/5/18	Singapore	Br J Haematol	-	Severe/no-severe	20	56	4.56 (1.79-14.75)	3.15 (0.98-16.76)
Zhao et al. <sup>88</sup>	2020/5/14	China	EPMA J	-	Death/no-death	29	503	6.3 $\pm$ 3.3	3.8 $\pm$ 2.9
Shi et al. <sup>73</sup>	2020/5/14	China	Diabetes Care	-	Death/no-death	47	259	8.0 (5.1-11.7)/6.6 (4.2-12.4)	3.3 (2.5-4.9)/8.0 (5.1-11.7)
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	4.06 (2.84-5.56)	2.99 (2.14-4.13)
Wang et al. <sup>89</sup>	2020/4/30	China	Crit Care	-	Death/no-death	19	88	5.4 (3.2-8.5)	2.8 (2.0-3.9)
Yang et al. <sup>76</sup>	2020/4/29	China	J Allergy Clin Immunol	-	Severe/no-severe	36	14	2.74 (1.81-3.13)	2.8 (2.17-4.43)
Hou et al. <sup>30</sup>	2020/5/4	China	Clin Exp Immunol	-	Severe/no-severe	221	168	4.71 $\pm$ 2.66	3.43 $\pm$ 2.55
Yu et al. <sup>90</sup>	2020/4/27	China	Clin Ther	-	ARDS/no-ARDS	24	71	3.21 $\pm$ 1.34	3.36 $\pm$ 1.51
Hong et al. <sup>35</sup>	2020/5/7	South Korea	Yonsei Med J	-	ICU/no-ICU	13	85	7.7 $\pm$ 3.3	4.1 $\pm$ 3.2
Wang et al. <sup>91</sup>	2020/2/7	China	JAMA	-	ICU/no-ICU	36	102	4.6 (2.6-7.9)	2.7 (1.9-3.9)
Liu et al. <sup>2</sup>	2020/2/12	China	medRxiv	-	Severe/no-severe	17	44	2.8 (2.3-4.4)	2.4 (1.9-3.4)
Liu et al. <sup>68</sup>	2020/2/12	China	medRxiv	-	Severe/no-severe	13	27	4.7 (3.6-5.8)	2.0 (1.5-2.9)
Huang et al. <sup>92</sup>	2020/5/14	China	J Med Virol	-	Death/no-death	16	283	5.6 $\pm$ 3.4	3.2 $\pm$ 2

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Zheng et al. <sup>(a)</sup> <sup>72</sup>	2020/2/19	China	medRxiv	-	Severe/no-severe	8	95	2.465 $\pm$ 0.91	2.98 $\pm$ 1.26
Fu et al. <sup>93</sup>	2020/5/6	China	Thromb Res	-	Severe/no-severe	16	59	5.63 $\pm$ 3.50	2.92 $\pm$ 1.21
Lu et al. <sup>94</sup>	2020/2/19	China	medRxiv	-	Severe/no-severe	22	243	3.3 (2.7-4.8)	2.8 (2.3-3.8)
Liu et al. <sup>95</sup>	2020/2/23	China	medRxiv	-	Severe/no-severe	7	44	5.2 (3.2-9.9)	3.5 (2.4-5.6)
Feng et al. <sup>3</sup>	2020/2/23	China	medRxiv	-	Progressive/Stable	15	126	3.2 (2.6-5.2)	3.4 (2.2-4.3)
Mao et al. <sup>96</sup>	2020/2/23	China	medRxiv	-	Severe/no-severe	88	126	3.8 (0.0-18.7)	2.6 (0.7-11.8)
Qian et al. <sup>97</sup>	2020/2/25	China	QJM	-	Severe/no-severe	9	82	3.32 (3-5.82)	2.8 (2.18-3.49)
Wang et al. <sup>98</sup>	2020/3/17	China	medRxiv	-	Severe/no-severe	38	72	4.26 (2.84-4.84)	3.38 (2.33-5.24)
Liang et al. <sup>99</sup>	2020/5/12	China	JAMA Intern Med	-	Severe/no-severe	131	1459	6.4 (3.6)	3.9 (1.9)
Rica et al. <sup>100</sup>	2020/6/24	Spain	Microorganisms	-	ICU/no-ICU	21	27	6.76 (3.58)	5.62 (3.12)
Xiong et al. <sup>101</sup>	2020/5/8	China	J Am Soc Nephrol	-	Severe/no-severe	30	101	5.3 (3.4-6.6)	3.7 (2.6-5.6)
Huang et al. <sup>102</sup>	2020/5/5	China	J Med Virol	-	Progressive/stable	45	299	4.7 $\pm$ 3.3	3 $\pm$ 1.7
Giacomelli et al. <sup>103</sup>	2020/5/6	Italy	Pharmacol Res	-	Death/no-death	48	185	5.7 (3.8-8.3)	3.9 (2.8-5.3)
Liu et al. <sup>104</sup>	2020/2/29	China	Chin Med J	-	Progression/ stabilization	11	67	4.69 (2.96-7.06)	2.94 (2.20-4.60)
Li et al. <sup>105</sup>	2020/5/5	China	Invest Radiol	-	Severe/no-severe	25	58	4.36 (2.87-6.48)	3.50 (2.64-4.46)
Ji et al. <sup>106</sup>	2020/5/6	China	Epidemiol Infect	-	Severe/no-severe	69	88	3.3 (2.5-6.1)	3.2 (2.2-4.2)
								8.5 (4.2-10.6)	
Fan et al. <sup>107</sup>	2020/2/29	Singapore	Am J Hematol	-	ICU/no-ICU	9	58	4.40 $\pm$ 4.14	2.8 $\pm$ 1.33
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	2.98 (2.12-3.7)	2.32 (1.75-4.28)
Luo et al. <sup>108</sup>	2020/5/23	China	Clin Infect Dis	-	Death/no-death	84	214	6.92 (4.33-10.79)	3.20 (2.53-4.56)
Buckner et al. <sup>109</sup>	2020/5/22	USA	Clin Infect Dis	-	Severe/no-severe	51	54	5.4 (3.3-8.4)	3.8 (2.8-5.1)
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	24.1 (2.7-5.6)	2.9 (1.9-3.9)
Shi et al. <sup>111</sup>	2020/6/3	China	BMC Med	-	Progressive/Stable	16	69	3.5 $\pm$ 1.5	3.1 $\pm$ 1.6
Gayam et al. <sup>50</sup>	2020/7/16	USA	J Med Virol	-	Death/no-death	132	276	7.2 (4.7-10.35)	5.6 (3.9-8.4)
Lee et al. <sup>112</sup>	2020/7/21	South Korea	Int J Infect Dis	-	Severe/no-severe	137	557	4.57 (3.00)	2.93 (1.36)
Yu et al. <sup>113</sup>	2020/7/17	China	J Infect Public Health	-	Severe/no-severe	864	799	3.9 (2.8-5.7)	3.6 (2.6-4.9)
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	4.7 (3.1-8.7)	3.3 (2.2-4.5)
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	10	40	5.58 (1.76-5.87)	2.63 (1.98-4.19)



TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Chen et al. <sup>114</sup>	2020/5/29	China	medRxiv	-	Severe/no-severe	50	241	3.34 (2.17–4.18)	3.56 (2.55–4.62)/2.80 (2.14–3.56)
Cao et al. <sup>66</sup>	2020/3/4	China	medRxiv	-	ICU/no-ICU	19	174	3.47 (2.97–4.74)	2.81 (2.33–3.81)
Xie et al. <sup>53</sup>	2020/6/13	China	Circ J	-	Severe/no-severe	24	38	3.2 (3.0–3.8)	3.0 (2.1–4.0)
Cao et al. <sup>115</sup>	2020/6/17	China	PLoS One	-	Death/no-death	27	53	3.5 (3.0–4.5)	3.5 (2.5–4.6)
Zhang et al. <sup>116</sup>	2020/3/6	China	J Clin Virol	-	Severe/no-severe	55	166	3.3 (1.9–5.5)	2.2 (1.7–2.8)
Wang et al. <sup>117</sup>	2020/5/19	China	Open Forum Infect Dis	-	Severe/no-severe	45	230	5.4 (2.8–8.4)	2.6 (1.8–4.0)
Liu et al. <sup>118</sup>	2020/5/1	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	42	236	4.4 $\pm$ 3.1	2.8 $\pm$ 1.2
Song et al. <sup>18</sup>	2020/4/9	China	medRxiv	-	Severe/no-severe	42	31	4.9 $\pm$ 2.5	2.9 $\pm$ 1.3
Li et al. <sup>119</sup>	2020/6/1	China	Am J Med Sci	-	Death/no-death	14	60	5.8 (2.8–10.2)	2.8 (1.8–4.1)
Xu et al. <sup>41</sup>	2020/3/5	China	medRxiv	-	Severe/no-severe	25	44	6.3 (2.8–10.0)	5.0 (2.9–7.1)
Zhang et al. <sup>120</sup>	2020/7/8	China	Infect Dis Poverty	-	Severe/no-severe	78	710	2.9 (2.4–4.6)	2.3 (1.8–3.3)
Zheng et al. <sup>78</sup>	2020/4/6	China	J Clin Virol	-	Severe/no-severe	32	67	3.2 (2.6–5.0)	3.6 (2.0–5.0)
Zhang et al. <sup>121</sup>	2020/7/23	China	Int J Lab Hematol	-	Severe/no-severe	162	251	5.8 (2.8–8.0)	2.9 (2.2–3.8)
Qin et al. <sup>10</sup>	2020/3/8	China	Clin Infect Dis	-	Severe/no-severe	286	166	63.81 $\pm$ 16.51	42.51 $\pm$ 15.11
Levy et al. <sup>122</sup>	2020/6/2	USA	medRxiv	-	Severe/no-severe	1185	4048	6.35 $\pm$ 3.96	3.22 $\pm$ 1.67
Myers et al. <sup>123</sup>	2020/4/24	USA	JAMA	-	Death/no-death	113	264	8.39 $\pm$ 3.37	5.02 $\pm$ 3.27
Hadjadj et al. <sup>12</sup>	2020/4/23	France	medRxiv	-	Severe/no-severe	35	15	4.3 (2.9–7.0)	3.2 (2.1–4.4)
Ouyang et al. <sup>124</sup>	2020/4/17	China	Clin Infect Dis	-	Severe/no-severe	6	5	6.36 (4.37–9.13)	5.05 (3.59–7.09)
Gao et al. <sup>37</sup>	2020/4/10	China	J Med Virol	-	Severe/no-severe	15	28	5.6 (3.9–7.4)	4.3 (3.1–5.9)
Gong et al. <sup>125</sup>	2020/4/16	China	Clin Infect Dis	-	Severe/no-severe	28	161	5.37 (3.23–6.38)	3.3 (2.76–4.0)
Lei et al. <sup>126</sup>	2020/4/4	China	EClinicalMedicine	-	ICU/no-ICU	15	19	7.36 (4.54–9.18)	4.1 (3.1–5.8)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Wang et al. <sup>55</sup>	2020/3/24	China	Int J Infect Dis	-	Severe/no-severe	25	100	3.86 $\pm$ 2.18	3.49 $\pm$ 1.62
Wan et al. <sup>127</sup>	2020/3/18	China	J Med Virol	-	Severe/no-severe	40	95	4.1 (3.1-5.7)	3.6 (3.0-3.9)
Feng et al. <sup>128</sup>	2020/4/10	China	Am J Respir Crit Care Med	-	Severe/no-severe	124	352	3.6 (2.59-5.99)	3.39 (2.5-4.64)
Yang et al. <sup>129</sup>	2020/6/26	China	medRxiv	-	Death/no-death	16	53	5.99 (3.47-9.55)	4 (4.00-5.9)
Bai et al. <sup>130</sup>	2020/3/27	China	medRxiv	-	Severe/no-severe	54	79	7.50 (6-8.4)	3.54 $\pm$ 1.9
Yan et al. <sup>131</sup>	2020/3/23	China	medRxiv	-	Severe/no-severe	35	131	4.15 $\pm$ 2.29	2.9 (2.2-3.9)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	4.2 (3.0-7.7)	3.03 $\pm$ 1.53
Wang et al. <sup>132</sup>	2020/3/27	China	medRxiv	-	Death/no-death	15	101	7.34 $\pm$ 4.10	5.2 (2.8-5.7)
Li et al. <sup>26</sup>	2020/3/23	China	medRxiv	-	Severe/no-severe	15	87	8.2 (6.2-10.0)	4.1 (2.8-6.2)
Chen et al. <sup>24</sup>	2020/3/27	China	J Clin Invest	-	Severe/no-severe	11	10	8.0 (3.5-10.6)	2.7 (2.1-3.7)
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	6.9 (4.9-9.1)	3.2 (2.4-4.5)
Huang et al. <sup>133</sup>	2020/3/30	China	BMJ	-	Severe/no-severe	32	93	9.0 (5.4-12.7)	3.26 $\pm$ 1.28
Lo et al. <sup>134</sup>	2020/3/15	China	Int J Biol Sci	-	Severe/no-severe	4	6	3.50 $\pm$ 1.77	2.49 $\pm$ 0.9
Zheng et al. <sup>56</sup>	2020/3/27	China	Int J Infect Dis	-	Severe/no-severe	21	34	3.82 $\pm$ 1.81	2.77 (0.93-5.93)
Wang et al. <sup>57</sup>	2020/3/15	China	J Infect	-	Death/no-death	65	274	3.46 (0.56-9.29)	4.01 (2.63-5.97)
Cai et al. <sup>36</sup>	2020/4/17	China	Allergy	-	Severe/no-severe	58	240	7.65 (4.35-11.74)	6.65 (5.3-8.7)
Xie et al. <sup>135</sup>	2020/4/2	China	Liver Int	-	Severe/no-severe	28	51	7.35 (5.4-9.6)	3.7 (2.7-5.1)
Du et al. <sup>136</sup>	2020/4/7	China	Ann Am Thorac Soc	-	ICU/no-ICU	51	58	3.8 (3.2-5.7)	6.9 $\pm$ 4.1
Wang et al. <sup>32</sup>	2020/6/1	China	Am J Respir Crit Care Med	-	Death/no-death	133	211	8.3 $\pm$ 5.2	3.7 (2.5-5.3)
Feng et al. <sup>137</sup>	2020/4/10	China	medRxiv	-	Severe/no-severe	69	495	8.0 (5.5-12.2)	2.9 (2.2-3.9)
Du et al. <sup>138</sup>	2020/5/7	China	Eur Respir J	-	Death/no-death	21	158	4.4 (2.7-6.8)	3.9 (2.6-6.1)
Zhang et al. <sup>139</sup>	2020/4/11	China	Eur Radiol	-	Severe/no-severe	30	90	7.7 (3.0-11.5)	1.6 $\pm$ 1.1
Jiang et al. <sup>140</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	8	47	3.1 $\pm$ 2.6	3.01 (2.34-3.51)
Wang et al. <sup>141</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	30	131	3.39 (1.82-9.52)	6.69 $\pm$ 3.83
Chen et al. <sup>142</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	8	24	10.51 $\pm$ 5.10	3.3 (2.3-3.8)
Xie et al. <sup>143</sup>	2020/6/20	China	Allergy	-	Severe/no-severe	12	85	3.4 (2.2-4.1)	4.1 (2.8-6.2)
Liu et al. <sup>59</sup>	2020/7/31	China	Ann Intensive Care	-	Death/no-death	157	1033	3.4 (2.2-4.1)	14.7 (9.9-20.3)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Chen et al. <sup>58</sup>	2020/4/17	China	Clin Infect Dis	-	Severe/no-severe	27	21	2.9 (2.0-3.78)/7.1 (5.3-9.2)	3.4 (2.8-4.3)
Yang et al. <sup>144</sup>	2020/4/13	China	Int Immuno pharmacol	-	Severe/no-severe	24	69	7.73 $\pm$ 5.4	4.55 $\pm$ 0.21
Brill et al. <sup>145</sup>	2020/6/25	UK	BMC Med	-	Death/no-death	173	237	6.6 (4.178-9.750)	5.32 (3.48-7.82)
Wei et al. <sup>61</sup>	2020/4/16	China	J Infect	-	Severe/no-severe	30	137	3.93 (2.23)	3.43 (2.39-4.40)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Death/no-death	14	71	10.10 (6.58-13.49)	3.96 (2.85-5.72)
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	-	Severe/no-severe	16	111	3.89 (2.25-6.57)	3.29 (2.54-4.40)
Shi et al. <sup>62</sup>	2020/4/23	China	medRxiv	-	Severe/no-severe	46	88	3.0 (2.3-4.3)	2.9 (2.1-4.0)
Yao et al. <sup>146</sup>	2020/4/24	China	Pol Arch Intern Med	-	Death/no-death	12	96	6.55 (3.39-9.66)	2.53 (1.89-3.78)/3.33 (1.99-5.07)
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	4.87 (3.43-7.64)	3.12 (2.18-4.20)
Pereira et al. <sup>64</sup>	2020/4/24	USA	Am J Transplant	-	Severe/no-severe	27	41	6.14 (3.33-10.15)	4.1 (2.02-5.42)
Neutrophils ratio (unit:%)									
Huang et al. <sup>80</sup>	2020/5/8	China	medRxiv	-	Severe/no-severe	27	321	72.48 $\pm$ 13.70	63.29 $\pm$ 11.44
Zhang et al. <sup>147</sup>	2020/5/9	China	medRxiv	-	ICU/no-ICU	30	105	83.9 (80.7-92.5)	70.0 (59.8-78.9)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	91.1 (82.9-93.8)	77.1 (69.1-82.8)
Li et al. <sup>83</sup>	2020/5/15	China	Theranostics	-	Death/no-death	25	68	74.2 (12.0)	64.7 (11.6)
Yang et al. <sup>76</sup>	2020/4/29	China	J Allergy Clin Immunol	-	Severe/no-severe	36	14	69.3 (57-75.3)/69.3 (66.65-82.1)	58.8 (52.75-71.4)
Sun et al. <sup>148</sup>	2020/5/5	China	J Med Virol	-	Severe/no-severe	15	40	15 $\pm$ 100	29 $\pm$ 72.5
Liu et al. <sup>105</sup>	2020/5/5	China	Invest Radiol	-	Severe/no-severe	5	58	80.08 $\pm$ 9.51	67.84 $\pm$ 10.00
Chen et al. <sup>114</sup>	2020/5/29	China	medRxiv	-	Severe/no-severe	50	241	73.15 (63.45-82.85)	70.30 (59.80-78.40)/62.70 (56.10-70.45)
Shi et al. <sup>149</sup>	2020/5/11	China	Eur Heart J	-	Death/no-death	62	609	91 (86-93)	68 (59-76)
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	76.3 (66.1-84.9)	64.1 (56.6-73.6)
Yang et al. <sup>150</sup>	2020/5/25	China	J Clin Pharm Ther	-	Severe/no-severe	33	103	77.8 (64.1-88.5)	65.9 (57.7-74.6)
Yang et al. <sup>65</sup>	2020/3/2	China	medRxiv	-	Severe/no-severe	34	19	69.95 (61.35-79.93)	60.90 (52.95-69.30)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Yu et al. <sup>113</sup>	2020/7/17	China	J Infect Public Health	-	Severe/no-severe	864	799	70.8 (60.8-79.7)	67.4 (59.0-75.9)
Liu et al. <sup>118</sup>	2020/5/1	China	Zhonghua Wei Zhong Bing Ji Jiu Yi Xue	-	Severe/no-severe	42	236	0.72 $\pm$ 0.13/0.73 $\pm$ 0.14	0.51 $\pm$ 0.12/0.59 $\pm$ 0.11
Li et al. <sup>119</sup>	2020/6/1	China	Am J Med Sci	-	Death/no-death	14	60	0.9 (0.8-0.9)	0.8 (0.7-0.9)
Zhang et al. <sup>121</sup>	2020/7/23	China	Int J Lab Hematol	-	Severe/no-severe	162	251	78.01 $\pm$ 11.31	61.48 $\pm$ 6.65
Qin et al. <sup>10</sup>	2020/3/8	China	Clin Infect Dis	-	Severe/no-severe	286	166	86.79 $\pm$ 6.01	71.02 $\pm$ 12.64
Levy et al. <sup>122</sup>	2020/6/2	USA	medRxiv	-	Death/no-death	1185	4048	77.6 (68.9-86.5)	67.5 (57.8-75.8)
Bai et al. <sup>130</sup>	2020/3/27	China	medRxiv	-	Severe/no-severe	54	79	81.00 (73.47-86.50)	76.25 (68.38-82.30)
Tao et al. <sup>151</sup>	2020/3/23	medRxiv	China	-	Severe/no-severe	22	143	74.60 $\pm$ 13.42	66.94 $\pm$ 12.16
Yan et al. <sup>131</sup>	2020/3/23	China	medRxiv	-	Severe/no-severe	35	132	65.50 $\pm$ 16.15	61.64 $\pm$ 32.24
Xie et al. <sup>143</sup>	2020/6/20	China	Allergy	-	Severe/no-severe	12	85	74.8 (67.6-83.1)	62.1 (55.6-69.2)
Zhu et al. <sup>22</sup>	2020/4/22	China	Int J Infect Dis	-	Severe/no-severe	16	111	71.9 (52.6-77.8)	71.3 (56.2-78.5)
Fu et al. <sup>69</sup>	2020/4/22	China	medRxiv	-	Severe/no-severe	14	71	75.70 (64.53-88.98)	66.50 (59.60-73.90)
Yang et al. <sup>77</sup>	2020/5/15	China	J Med Virol	-	Death/no-death	68	65	89.65 (85.63-92.28)	69.30 (62.10-79.10)
					Severe/no-severe	68	65	76.6 (45.3-97)	58.1 (18-83.2)
Monocytes count (unit: cells/ $\mu$ L)									
Huang et al. <sup>80</sup>	2020/5/8	China	medRxiv	-	Severe/no-severe	27	321	0.50 (0.24-1.07)	0.41 (0.35-0.58)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.33 (0.24-0.56)	0.41 (0.27-0.56)
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	0.33 $\pm$ 0.19/0.37 $\pm$ 0.19	0.46 $\pm$ 0.16/0.55 $\pm$ 0.99
Sun et al. <sup>84</sup>	2020/4/24	China	Clin Chim Acta	-	Severe/no-severe	27	89	0.42 (0.31-0.76)	0.38 (0.29-0.48)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	13	40	0.51 (0.37-0.60)	0.39 (0.31-0.51)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	0.32 (0.14-0.42)	0.39 (0.30-0.50)
Yip et al. <sup>87</sup>	2020/5/18	Singapore	Br J Haematol	-	Severe/no-severe	20	56	0.48 (0.17-1.36)	0.54 (0.19-1.35)
Wei et al. <sup>21</sup>	2020/4/29	China	J Med Virol	-	Severe/no-severe	121	131	0.6 $\pm$ 0.7	0.51 $\pm$ 0.25
					Severe/no-severe	43	102	0.6 $\pm$ 0.3	0.4 (0.3-0.5)
Chen et al. <sup>152</sup>	2020/4/28	China	Infection	-	Severe/no-severe	189	144	0.36 (0.26-0.52)	0.41 (0.30-0.53)
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	16	283	0.38 (0.22-0.49)	0.3 $\pm$ 0.2
Huang et al. <sup>92</sup>	2020/5/14	China	J Med Virol	-	Death/no-death	16	283	0.5 $\pm$ 0.9	0.3 $\pm$ 0.2

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Rica et al. <sup>100</sup>	2020/6/24	Spain	Microorganisms	-	ICU/no-ICU	21	27	0.40 (0.20)	0.58 (0.33)
Huang et al. <sup>102</sup>	2020/5/5	China	J Med Virol	-	Progressive/stable	45	299	0.3 $\pm$ 0.1	0.3 $\pm$ 0.2
Ji et al. <sup>106</sup>	2020/5/6	China	Epidemiol Infect	-	Severe/no-severe	69	88	0.4 (0.2-0.5)	0.5 (0.3-0.6)
								0.3 (0.1-0.6)	
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	0.4 (0.2-0.5)	0.3 (0.2-0.4)
Lee et al. <sup>112</sup>	2020/7/21	South Korea	Int J Infect Dis	-	Severe/no-severe	137	557	0.47 (0.24)	0.45 (0.16)
Yu et al. <sup>113</sup>	2020/7/17	China	J Infect Public Health	-	Severe/no-severe	864	799	0.5 (0.4-0.6)	0.5 (0.4-0.6)
Huang et al. <sup>31</sup>	2020/6/13	China	J Med Virol	-	Death/no-death	10	40	0.51 (0.37-0.60)	0.39 (0.31-0.51)
Wang et al. <sup>117</sup>	2020/5/19	China	Open Forum Infect Dis	-	Severe/no-severe	45	230	0.3 (0.2-0.4)	0.4 (0.3-0.5)
Zhang et al. <sup>121</sup>	2020/7/23	China	Int J Lab Hematol	-	Severe/no-severe	162	251	0.44 $\pm$ 0.23	0.35 $\pm$ 0.1
								0.43 $\pm$ 0.18	0.42 $\pm$ 0.2
Levy et al. <sup>122</sup>	2020/6/2	USA	medRxiv	-	Death/no-death	1185	4048	0.47 (0.30-0.68)	0.46 (0.32-0.65)
Hadjadi et al. <sup>12</sup>	2020/4/23	France	medRxiv	-	Severe/no-severe	35	15	0.35 (0.30-0.43)	0.40 (0.28-0.52)
								0.38 (0.20-0.77)	
Gao et al. <sup>37</sup>	2020/4/10	China	J Med Virol	-	Severe/no-severe	15	28	0.37 $\pm$ 0.16	0.43 $\pm$ 0.19
Lei et al. <sup>126</sup>	2020/4/4	China	EClinicalMedicine	-	ICU/no-ICU	15	19	0.6 (0.3-1.1)	0.5 (0.4-0.70)
Gong et al. <sup>125</sup>	2020/4/16	China	Clin Infect Dis	-	Severe/no-severe	28	161	0.3 (0.3-0.4)	0.4 (0.3-0.5)
Wang et al. <sup>55</sup>	2020/3/24	China	Int J Infect Dis	-	Severe/no-severe	25	100	0.30 (0.235-0.52)	0.36 (0.26-0.51)
Yan et al. <sup>131</sup>	2020/3/23	China	medRxiv	-	Severe/no-severe	35	130	0.4 (0.3-0.6)	0.4 (0.3-0.5)
Han et al. <sup>67</sup>	2020/6/24	China	Aging (Albany NY)	-	Severe/no-severe	24	23	0.39 $\pm$ 0.20	0.61 $\pm$ 0.24
Wang et al. <sup>132</sup>	2020/3/27	China	medRxiv	-	Death/no-death	15	101	0.5 (0.3-0.7)	0.5 (0.4-0.6)
Chen et al. <sup>25</sup>	2020/3/26	China	BMJ	-	Death/no-death	113	161	0.4 (0.2-0.6)	0.4 (0.3-0.5)
Wang et al. <sup>57</sup>	2020/3/15	China	J Infect	-	Death/no-death	65	274	0.32 (0.22-0.49)	0.43 (0.30-0.62)
Jiang et al. <sup>140</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	8	47	0.28 (0.18-0.60)	0.49 (0.40-0.61)
Wang et al. <sup>141</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	30	131	0.43 $\pm$ 0.27	0.50 $\pm$ 0.25
Xie et al. <sup>143</sup>	2020/6/20	China	Allergy	-	Severe/no-severe	12	85	0.6 (0.2-0.7)	0.5 (0.3-0.6)

(Continues)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Yang et al. <sup>144</sup>	2020/4/13	China	Int Immuno pharmacol	-	Severe/no-severe	24	69	0.5 $\pm$ 0.84	0.41 $\pm$ 0.2
Xu et al. <sup>63</sup>	2020/4/18	China	J Infect	-	Severe/no-severe	107	80	0.42 (0.29-0.61) 0.32 (0.18-0.44)	0.39 (0.31-0.52)
Monocytes ratio (unit: %)									
Huang et al. <sup>80</sup>	2020/5/8	China	medRxiv	-	Severe/no-severe	27	321	7.2 (4.0-13.6)	9.5 (7.3-11.3)
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	3.9 (2.6-5.4)	8.8 (5.4-10.0)
Zheng et al.(a) <sup>72</sup>	2020/2/19	China	medRxiv	-	Severe/no-severe	8	95	8.063 $\pm$ 3.478	8.12 $\pm$ 2.92
Liu et al. <sup>105</sup>	2020/5/5	China	Invest Radiol	-	Severe/no-severe	25	58	6.16 $\pm$ 4.00	7.60 $\pm$ 2.23
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	7.0 (4.5-8.8)	7.7 (5.7-9.8)
Yu et al. <sup>113</sup>	2020/7/17	China	J Infect Public Health	-	Severe/no-severe	864	799	8.2 (6.3-10.6)	8.7 (6.9-10.9)
Li et al. <sup>119</sup>	2020/6/1	China	Am J Med Sci	-	Death/no-death	14	60	0.01 (0.04-0.08)	0.01 (0.03-0.06)
Zhang et al. <sup>121</sup>	2020/7/23	China	Int J Lab Hematol	-	Severe/no-severe	162	251	6.1 $\pm$ 2.62/4.7 $\pm$ 1.85	7.54 $\pm$ 2.63/6.94 $\pm$ 2.72
Qin et al. <sup>10</sup>	2020/3/8	China	Clin Infect Dis	-	Severe/no-severe	286	166	6.6 (4.3-8.8)	8.4 (6.5-10.8)
Levy et al. <sup>122</sup>	2020/6/2	USA	medRxiv	-	Death/no-death	1185	4048	12.70 (11.10-14.30)	13.40 (12.20-14.50)
Xie et al. <sup>143</sup>	2020/6/20	China	Allergy	-	Severe/no-severe	12	85	8.3 (5.4-10.1)	7.9 (5.8-9.2)
Eosinophils count (unit: cells/ $\mu$ L)									
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.00 (0.00-0.00)	0.00 (0.00-0.38)
Cheng et al. <sup>153</sup>	2020/4/27	China	medRxiv	-	Severe/no-severe	8	51	0.01 (0.01-0.33)	0.02 0.01-0.026) 0.02 (0.00-0.05)
Sun et al. <sup>47</sup>	2020/4/24	China	J Autoimmun	-	Severe/no-severe	19	44	0.01 $\pm$ 0.00/0.09 $\pm$ 0.14	0.14 $\pm$ 0.06/0.03 $\pm$ 0.04
Sun et al. <sup>84</sup>	2020/4/24	China	Clin Chim Acta	-	Severe/no-severe	27	89	0.01 (0.00-0.02)	0.03 (0.01-0.05)
Zhang et al. <sup>28</sup>	2020/5/21	China	J Med Virol	-	Death/no-death	13	40	0	0.01 (0-0.05)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	0.00 (0.00-0.01)	0.04 (0.01-0.11)
Yip et al. <sup>87</sup>	2020/5/18	Singapore	Br J Haematol	-	Severe/no-severe	20	56	0.01 (0-0.24)	0.05 (0-0.42)
Pei et al. <sup>29</sup>	2020/4/28	China	J Am Soc Nephrol	-	Severe/no-severe	189	144	0.00 (0.00-0.06) 0.00 (0.00-0.01)	0.00 (0.00-0.09)

TABLE 1 (Continued)

Author	Publish date	Country	Journal	Detection method	Patients group	Sample size		Mean $\pm$ SD or IQR	
						Severe	No-severe	Severe	No-severe
Qian et al. <sup>97</sup>	2020/2/25	China	QJM	-	Severe/no-severe	9	82	0.01 (0-0.01)	0.02 (0.01-0.06)
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	0.00 (0.00-0.01)	0.01 (0.00-0.03)
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	0.00 (0.00-0.02)	0.01 (0.00-0.04)
Chen et al. <sup>114</sup>	2020/5/29	China	medRxiv	-	Severe/no-severe	50	241	0.00 (0.00-0.01)	0.02 (0.00-0.06)/0.02 (0.00-0.05)
Wei et al. <sup>154</sup>	2020/7/29	China	BMC Infect Dis	-	Severe/no-severe	14	262	0 (0-0.01)	0.01 (0-0.03)
Levy et al. <sup>122</sup>	2020/6/2	USA	medRxiv	-	Death/no-death	1185	4048	0.00 (0.00-0.01)	0.00 (0.00-0.02)
Yan et al. <sup>131</sup>	2020/3/23	China	medRxiv	-	Severe/no-severe	35	130	0 (0-0.02)	0.04 (0.01-0.1)
Wang et al. <sup>132</sup>	2020/3/27	China	medRxiv	-	Death/no-death	15	101	0.0 (0.0-0.0)	0.1 (0.0-0.1)
Huang et al. <sup>133</sup>	2020/3/30	China	BMJ	-	Severe/no-severe	32	93	0 (0-0)	0.04 (0.1-0.12)
Cai et al. <sup>36</sup>	2020/4/17	China	Allergy	-	Severe/no-severe	58	240	0.01 (0-0.03)	0.02 (0-0.05)
Wang et al. <sup>141</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	30	131	0.00 $\pm$ 0.01	0.04 $\pm$ 0.06
Basophils count (unit: cells/ $\mu$ L)									
Wu et al. <sup>19</sup>	2020/7/15	China	mSphere	-	Severe/no-severe	39	32	0.01 (0.01-0.02)	0.01 (0.00-0.02)
Li et al. <sup>48</sup>	2020/5/19	China	JCI Insight	-	Severe/no-severe	26	43	0.01 (0.01-0.02)	0.01 (0.01-0.03)
Yip et al. <sup>87</sup>	2020/5/18	Singapore	Br J Haematol	-	Severe/no-severe	20	56	0.01 (0-0.10)	0.02 (0-0.09)
Qian et al. <sup>97</sup>	2020/2/25	China	QJM	-	Severe/no-severe	9	82	0 (0-0.01)	0.01 (0.01-0.02)
Wu et al. <sup>110</sup>	2020/5/7	China	Eur Respir J	-	Severe/no-severe	82	217	0.01 (0.01-0.02)	0.01 (0.01-0.01)
Chen et al. <sup>51</sup>	2020/6/4	China	Clin Transl Med	-	Death/no-death	82	578	0.01 (0.01-0.02)	0.01 (0.01-0.02)
Wang et al. <sup>141</sup>	2020/4/14	China	medRxiv	-	Severe/no-severe	30	131	0.02 $\pm$ 0.02	0.02 $\pm$ 0.01

Abbreviations: CLIA, chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; MMFI, multiple microsphere flow immunofluorescence.

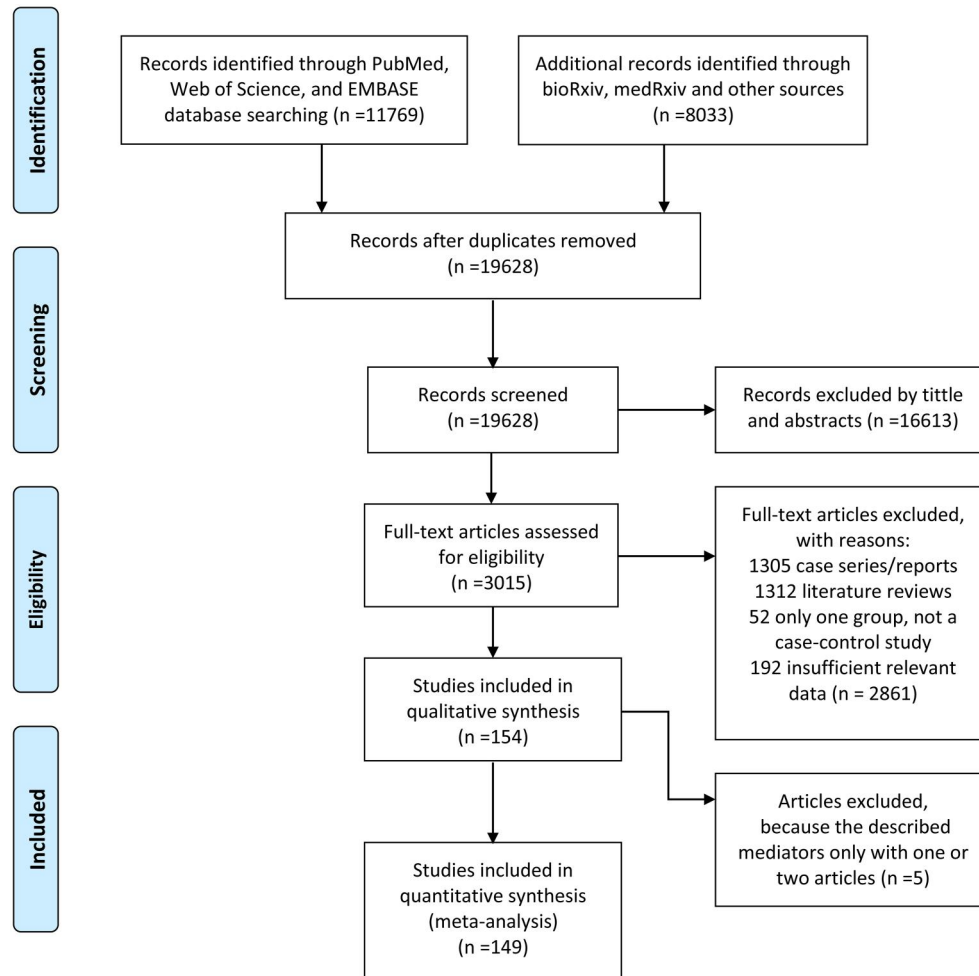


FIGURE 1 A flow diagram of the inclusion criteria for the study selection process

cells counts).<sup>2,3,10,12,18–22,24–26,28–33,35–37,41,46–48,50,51,53,55–59,61–69,72,73,76–79,157,80–154</sup> For each study, various details including the baseline information of study population, study design, the number of patients in each study group, the measured immunological indicators and their test methods, and the definitions used to measure outcome, were extracted into Table S5. For these studies, only the measurements acquired in the acute phase of infection were used for the analysis. Table 1 summarizes the detailed characteristics of the included studies for each immune mediator. The quality scores by NOQAS of the included studies ranged from 5 to 8, and 116 out of 149 was greater than or equal to six stars, indicating good quality (Table S6).

### 3.2 | Cytokines and COVID-19 severity

A total of 55 studies were evaluated 10 mediators of cytokines between the severe ( $n = 3038$ ) and non-severe groups of COVID-19 patients ( $n = 5895$ ), including IL-2, IL-2R, IL-4, IL-5, IL-6, IL-8, IL-10, IFN- $\gamma$ , TNF- $\alpha$  and IL-1 $\beta$  with three or more

studies included (Figure S1).<sup>1,9,10,15–65,157</sup> Compared with the non-severe patients of COVID-19, we found that serum levels of seven cytokines were significantly up-regulated in severe patients, including IL-2 (SMD, 0.40; 95% CI, 0.10–0.71;  $p < 0.01$ ), IL-2R (SMD, 1.12; 95% CI, 0.80–1.44;  $p < 0.01$ ), IL-4 (SMD, 0.71; 95% CI, 0.10–1.33;  $p = 0.02$ ), IL-6 (SMD, 1.16; 95% CI, 0.94–1.38;  $p < 0.01$ ), IL-8 (SMD, 0.75; 95% CI, 0.49–1.00;  $p < 0.01$ ), IL-10 (SMD, 1.26; 95% CI, 0.92–1.59;  $p < 0.01$ ) and TNF- $\alpha$  (SMD, 0.55; 95% CI, 0.32–0.78;  $p < 0.01$ ), respectively (Figure S1a–g). In contrast, serum IL-5, IL-1 $\beta$  and IFN- $\gamma$  did not showed significant inter-group differences with the SMDs of 0 (95% CI, –0.94 to 0.95,  $p = 0.99$ ), 0.33 (95% CI, 0.00–0.67,  $p = 0.05$ ), and 0.46 (95% CI, –0.25 to 1.17,  $p = 0.20$ ), respectively (Figure S1h–j).

### 3.3 | SARS-CoV-2-specific antibodies and COVID-19 severity

Four SARS-CoV-2-specific antibody mediators were included in the meta-analysis between severe and non-severe COVID-19 patients, immunoglobulin A (IgA), IgG, IgM and IgE.<sup>10,16,20,25,66–69</sup> A total of



eight studies evaluated the levels of IgA, IgG and IgM involving 563 severe and 828 non-severe cases, and the levels of IgE involving 131 severe and 257 non-severe cases (Figure S2). Compared with the non-severe patients, the severe patients had significantly higher levels of IgA and IgG with SMDs of 0.39 (95% CI, 0.10–0.68;  $p < 0.01$ ; Figure S2a), and 0.22 (95% CI, 0.01–0.42;  $p = 0.04$ ; Figure S2b), respectively. The level of IgM in the severe patients was slightly lower than those in the non-severe patients of COVID-19 (SMD,  $-0.18$ ; 95% CI,  $-0.32$  to  $-0.03$ ,  $p = 0.02$ ; Figure S2c). No significant differences were noted in the serum levels of IgE between two groups (SMD, 0.16; 95% CI,  $-0.16$  to 0.43,  $p = 0.43$ ; Figure S2d).

### 3.4 | T cells and COVID-19 severity

A total of 40 studies involving 1623 severe cases and 4342 non-severe cases evaluated the T cells count or percent in relation to the COVID-19 disease severity.<sup>9-11,15-20,24,27,33,34,41,45,47,48,51-53,56,57,59,61,63,65-67,69-79,157</sup> Eight measurements of T cells were described in over three studies, including CD3<sup>+</sup> T cells count, CD4<sup>+</sup> T cells count, CD8<sup>+</sup> T cells count, CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>-</sup> Treg cells count, CD3<sup>+</sup> T cells ratio, CD4<sup>+</sup> T cells ratio, CD8<sup>+</sup> T cells ratio and CD4<sup>+</sup>/CD8<sup>+</sup> (Th/Ts) in Figure S3. Compared with the non-severe group, severe group had significantly lower CD3<sup>+</sup> T cells count (SMD,  $-1.14$ ; 95% CI,  $-1.41$  to  $-0.88$ ;  $p < 0.01$ ; Figure S3a) as well as CD4<sup>+</sup> T cells count (SMD,  $-1.16$ ; 95% CI,  $-1.44$  to  $-0.89$ ;  $p < 0.01$ ; Figure S3b), CD8<sup>+</sup> T cells count (SMD,  $-1.03$ ; 95% CI,  $-1.27$  to  $-0.79$ ;  $p < 0.01$ ; Figure S3c), CD4<sup>+</sup>CD25<sup>+</sup>CD127<sup>-</sup> Treg cells count (SMD,  $-0.45$ ; 95% CI,  $-0.76$  to  $-0.13$ ;  $p < 0.01$ ; Figure S3d), CD3<sup>+</sup> T cells ratio (SMD,  $-1.10$ ; 95% CI,  $-1.77$  to  $-0.42$ ;  $p < 0.01$ ; Figure S3e), and CD4<sup>+</sup> T cells ratio (SMD,  $-0.61$ ; 95% CI,  $-1.02$  to  $-0.19$ ;  $p < 0.01$ ; Figure S3f). In contrast, no significant difference was attained for CD8<sup>+</sup> T cells ratio (SMD,  $-0.61$ ; 95% CI,  $-1.35$  to 0.12;  $p = 0.10$ ; Figure S3g), or CD4<sup>+</sup>/CD8<sup>+</sup> (Th/Ts) (SMD, 0.16; 95% CI,  $-0.10$  to 0.42;  $p = 0.23$ ; Figure S3h).

### 3.5 | The B cells, NK cells and COVID-19 severity

A total of 22 studies on the evaluation of B cells and NK cells between severe and non-severe COVID-19 patients were included.<sup>10,11,15-20,24,33,34,41,45,47,48,63,67,69,71-73,157</sup> As shown in Figure S4, the CD19<sup>+</sup> B cells count and CD16<sup>+</sup>CD56<sup>+</sup> NK cells count in the severe group were significantly lower than those in the non-severe group with SMDs of  $-0.74$  (95% CI,  $-1.05$  to  $-0.42$ ;  $p < 0.01$ ; Figure S4a), and  $-0.61$  (95% CI,  $-0.84$  to  $-0.38$ ;  $p < 0.01$ ; Figure S4b), respectively. In contrast, the CD19<sup>+</sup> B cells ratio and CD16<sup>+</sup>CD56<sup>+</sup> NK cells ratio were significantly higher in the severe patients than in the non-severe patients with SMDs of 0.35 (95% CI, 0.15–0.55;  $p < 0.01$ ; Figure S4c), and 1.19 (95% CI, 0.30–2.07;  $p < 0.01$ ; Figure S4d), respectively.

### 3.6 | The neutrophils, monocytes, eosinophils, basophils and COVID-19 severity

About 124 studies on the evaluation of neutrophils, monocytes, eosinophils and basophils cells between severe and non-severe COVID-19 patients were included.<sup>2,3,10,12,18-22,24-26,28-33,35-37,41,46-48,50,51,53,55-59,61-69,72,73,76-79,157,80-154</sup> As shown in Figure S5, the neutrophils cells count and neutrophils cells ratio in the severe group were significantly higher than those in the non-severe group with SMDs of 0.72 (95% CI, 0.61–0.82;  $p < 0.01$ ; Figure S5a), and 0.62 (95% CI, 0.35–0.88;  $p < 0.01$ ; Figure S5b), respectively. The monocytes cells ratio and eosinophils cells count were significantly lower in the severe patients than in the non-severe patients of COVID-19 with SMDs of  $-0.36$  (95% CI,  $-0.51$  to  $-0.21$ ;  $p < 0.01$ ; Figure S5c), and  $-0.45$  (95% CI,  $-0.59$  to  $-0.31$ ;  $p < 0.01$ ; Figure S5d), while the monocytes cells count and basophils cells count were comparable between the two groups with SMDs of  $-0.06$  (95% CI,  $-0.15$  to 0.04;  $p = 0.24$ ; Figure S5e), and  $-0.14$  (95% CI,  $-0.43$  to 0.15;  $p = 0.34$ ; Figure S5f), respectively.

### 3.7 | Sub-analysis of only peer reviewed studies

The sub-analysis considering only peer-reviewed studies for each immune mediator was performed, and the results were presented in Table 2, but without obvious difference with those of all the included literatures analysed.

### 3.8 | Sensitivity analysis

The results showed that none of the exclusions altered the results of the previous analysis for cytokines (except for IL-4 and IL-10), four specific antibodies, T cells, B cells, NK cells (except for CD16<sup>+</sup>CD56<sup>+</sup> NK cells ratio), neutrophils, monocytes, eosinophils and basophils, indicating the good reliability and stability of the results of this meta-analysis (Figure S6). For IL-4, one study by Hong et al.<sup>35</sup> had a strong influence on the result of the meta-analysis. For IL-10, Wan et al.<sup>37</sup> study had a strong influence on the result of the meta-analysis. For CD16<sup>+</sup>CD56<sup>+</sup> NK cells ratio, one study by Liu et al.<sup>15</sup> had a strong influence on the result of the meta-analysis. However, the results of meta-analysis were not badly altered to be the opposite.

### 3.9 | Publication bias

The  $p$  value from Egger's regression and funnel plots suggested that the publication bias presented in seven mediators including IL-2R, IL-6, IL-10, CD4<sup>+</sup> T cells count, CD3<sup>+</sup> T cells ratio, CD8<sup>+</sup> T cells ratio and CD16<sup>+</sup>CD56<sup>+</sup> NK cells ratio (Table S5 and Figure S7). Therefore, we adopted the trim-and-fill method to further test publication bias. As shown in Table S6, the results showed that there was

TABLE 2 The results of meta-analyses for each immune indicator in the study

Variables	Number of studies included	Heterogeneity $I^2$	SMD (95% CI)	$p^*$	Publication bias	
					T	$p^\#$
Cytokines						
IL-2	9	77%	0.40 (0.10, 0.71)	<0.01	0.721	0.495
IL-2R	12	89%	1.12 (0.80, 1.44)	<0.01	3.146	0.011
IL-4	11	95%	0.71 (0.10, 1.33)	0.02	1.406	0.193
IL-6	54	94%	1.16 (0.94, 1.38)	<0.01	2.435	0.018
IL-8	13	80%	0.75 (0.49, 1.00)	<0.01	1.301	0.220
IL-10	27	95%	1.26 (0.92, 1.59)	<0.01	3.236	0.003
TNF- $\alpha$	26	88%	0.55 (0.32, 0.78)	<0.01	0.856	0.400
IL-5	3	92%	0.00 (-0.94, 0.95)	0.99	1.052	0.484
IL-1 $\beta$	13	79%	0.33 (0.00, 0.67)	0.05	0.841	0.425
IFN- $\gamma$	12	96%	0.46 (-0.25, 1.17)	0.20	1.724	0.116
Specific antibodies						
IgA	8	79%	0.39 (0.10, 0.68)	<0.01	1.902	0.106
IgG	8	59%	0.22 (0.01, 0.42)	0.04	0.626	0.555
IgM	8	22%	-0.18 (-0.32, -0.03)	0.02	0.376	0.719
IgE	4	26%	0.16 (-0.11, 0.43)	0.24	3.307	0.081
T cells						
CD3+ T cells count	22	88%	-1.14 (-1.41, -0.88)	<0.01	-0.712	0.485
CD4+ T cells count	32	92%	-1.16 (-1.44, -0.89)	<0.01	-2.857	0.008
CD8+ T cells count	32	89%	-1.03 (-1.27, -0.79)	<0.01	-0.938	0.356
CD4+CD25+CD127- Treg cells count	4	0%	-0.45 (-0.76, -0.13)	<0.01	1.317	0.319
CD3+ T cells ratio	10	92%	-1.10 (-1.77, -0.42)	<0.01	-3.268	0.012
CD4+ T cells ratio	10	85%	-0.61 (-1.02, -0.19)	<0.01	-1.125	0.293
CD8+ T cells ratio	10	95%	-0.61 (-1.35, 0.12)	0.10	-3.784	0.005
CD4+/CD8+ (Th/Ts)	23	87%	0.16 (-0.10, 0.42)	0.23	0.575	0.571
B cells, NK cells						
CD19 <sup>+</sup> B cells count	17	86%	-0.74 (-1.05, -0.42)	<0.01	0.798	0.437
CD16 <sup>+</sup> CD56 <sup>+</sup> NK cells count	17	74%	-0.61 (-0.84, -0.38)	<0.01	0.664	0.517
CD19 <sup>+</sup> B cells ratio	8	0%	0.35 (0.15, 0.55)	<0.01	0.113	0.913
CD16 <sup>+</sup> CD56 <sup>+</sup> NK cells ratio	9	95%	0.19 (0.30, 2.07)	<0.01	5.821	0.001
Neutrophils, monocytes, eosinophils and basophils						
Neutrophils cells count	114	91%	0.72 (0.61, 0.82)	<0.01	1.590	0.115
Neutrophils cells ratio	25	96%	0.62 (0.35, 0.88)	<0.01	0.793	0.436
Monocytes cells count	36	70%	-0.06 (-0.15, 0.04)	0.24	-1.148	0.259
Monocytes cells ratio	11	79%	-0.36 (-0.51, -0.21)	<0.01	-0.418	0.686
Eosinophils cells count	19	62%	-0.45 (-0.59, -0.31)	<0.01	0.079	0.937
Basophils cells count	7	62%	-0.14 (-0.43, 0.15)	0.34	-1.332	0.254

Note:  $p^*$ ,  $p$  value for the variable in the forest plot analysis;  $p^\#$ :  $p$  value for the variable in the publication bias analysis.

Abbreviations: IFN- $\gamma$ , interferon  $\gamma$ ; IL, interleukin; SMD, standardized mean difference; TNF- $\alpha$ , tumour necrosis factor  $\alpha$ .

no significant change in the pooled value change before ( $p < 0.05$ ) and after ( $p < 0.05$ ) trim-and-fill, indicating that the original pooled SMD was relatively robust.

## 4 | DISCUSSION

Inflammation is the body's first coordinated line of defense against tissue damage caused by either injury or infection, involving both the innate and adaptive immune responses.<sup>57</sup> However, exuberant immune responses following infection have been frequently associated with excessive levels of pro-inflammatory cytokines and widespread tissue damage including ARDS.<sup>158-160</sup>

In most previous studies, patients with SARS-CoV-2 infection are associated with a cytokine storm, which is characterized by increased production of IL-2, IL-7 and IL-10, granulocyte-colony stimulating factor, interferon- $\alpha$ -inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1 alpha and TNF- $\alpha$ .<sup>16,18,157</sup> However, there had been conflicting opinion as to whether the cytokine storm was responsible for the severe outcome. One argument was that the pathological process of severe COVID-19 disease was mainly due to the direct lung injury that induced the subsequent ARDS, and respiratory depression. In addition to the virus-induced direct lung injury, it is also considered that COVID-19 invasion triggers the immune responses that lead to the activation of immune cells to release many pro- and anti-inflammatory cytokines including TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and so on. Overwhelming secretion of cytokines causes severe lung damage, which manifest as extensive damage of pulmonary vascular endothelial and alveolar epithelial cells as well as increased pulmonary vascular permeability, leading to the pulmonary oedema and hyaline membrane formation.<sup>15,25,36,66</sup>

Multiple studies have been conducted to characterize the profiles of immune mediator during different phases of the COVID-19 disease in different geographic locations.<sup>43,161-163</sup> However, results varied, which might be due to the difference in clinical sample preparations, assay platforms and recursion criteria of the patients among studies. Here by performing meta-analysis on studies that explored the association between cytokine storm and disease severity, we have determined that several cytokines, including IL-2, IL-2R, IL-4, IL-6, IL-8, IL-10 and IFN- $\gamma$ , were induced to significantly higher levels in severe cases than in non-severe cases, but not for IL-1 $\beta$  or TNF- $\alpha$ .

It is notable that IL-6 and IL-10 were two of the cytokines that were most consistently enhanced in severe patients, and with large intergroup differences. The direction of association remained consistent in 20 of the 22 studies for IL-6, and in all 13 studies for IL-10. Extensive studies have been conducted to characterize the profile of IL-6 in patients with SARS-CoV-2 infection, as well as for their relation with the clinical outcome.<sup>9,10,15,23-25,36-39,66</sup> For example, IL-6 was reported to be elevated during the acute phase of SARS-CoV-2 infection,<sup>9,25,26</sup> and also associated with high viremia in COVID-19 patients. The plasma IL-6 level was increased dramatically

in SARS-CoV-2-infected patients with cardiac injury, which was associated with fatal outcome induced by fulminant myocarditis.<sup>164</sup> Significantly elevated systemic level of IL-6 have been reported in several COVID-19 patient cohorts and shown to correlate with disease severity.<sup>165</sup> IL-6 level diverges profoundly between non-survivors and survivors in the third week after symptom onset and is a predictor of COVID-19 severity and in-hospital mortality,<sup>15,58</sup> which suggest that IL-6 production might play a more important role than viral burden in the pathogenesis COVID-19, since high viral loads were observed at the early clinical process.<sup>65,166-168</sup> In a consistent manner, a study performed on medical staff with COVID-19 disease in Wuhan disclosed normal IL-6 levels on admission were favourable for discharge after infection.<sup>169</sup> Until now, there had been only two studies that showed a reversed direction for the IL-6-severe disease association according to our meta-analysis.<sup>18,42</sup> All these evidences had supported a critical role of IL-6 in determining the outcome. Transcriptional profiling found that SARS-CoV-2 infection in addition to activating type-I interferon and IL-6-dependent inflammatory responses, also results in robust engagement of the complement and coagulation pathway activation.<sup>170</sup> As a simple, fast and readily available screen, we propose it reasonable to take an immediate evaluation of IL-6 and IL-10 levels upon hospital admission of COVID-19 patients, due to its potential benefits to assess worsening clinical features and disease progression in COVID-19. For example, a notably elevated IL-6 value over a certain level by using a predetermined detection kit and following a standard protocol should alert clinicians to adopt aggressive therapeutic approaches without delay.

Accompanying the inflammatory process is the lymphopenia depressed CD4<sup>+</sup>, CD8<sup>+</sup> T cells, NK and B cells in COVID-19 patients. Studies found that acute SARS-CoV-2 infection resulted in broad immune cell reduction including T, NK, monocyte, and dendritic cells (DCs).<sup>171</sup> In the meta-analysed studies, lymphopenia was ubiquitous in severe COVID-19 infection and was associated with adverse outcome. CD3<sup>+</sup>, CD4<sup>+</sup> and CD8<sup>+</sup> T cells counts were always below normal range, and CD19<sup>+</sup> B cells and CD16<sup>+</sup>56<sup>+</sup> NK cells counts were consistently depressed in the severe versus non-severe cases. Recently studies have shown that the extent of lymphopenia seemingly correlates with COVID-19-associated disease severity and mortality.<sup>2,4,24,68,70,71,172-175</sup> Patients with mild symptoms, however, typically present with normal or slightly higher T cell counts.<sup>176,177</sup> The presence of lymphopenia and depressed T cell counts seems to correlate with serum IL-6, IL-10 and TNF- $\alpha$ , which might also act as a signature of severe COVID-19.<sup>34,70</sup> SARS-CoV-2-specific antibodies production in COVID-19 patients suggested the mounting of humoral responses, especially with a higher level of IgA antibody in the severe patients. However, insignificant difference of IgG, IgM or IgE antibody between severe and non-severe patients was observed. The role of adaptive immunity in COVID-19 patients cannot be deciphered according to the current analysis.

These findings have potential application in the effective therapy choice. Until recently, anti-viral drugs with proven safety profiles are lacking, thus targeting the hyper-inflammation might be promising

and critical for reducing mortality. For example, Tocilizumab, a monoclonal antibody targeting the IL-6 receptor, is currently being investigated for the treatment of patients with COVID-19-CSS.<sup>159</sup> The approved randomized controlled trial that evaluates the efficacy and safety of tocilizumab in the treatment of COVID-19 might bring about potential benefit soon. The lymphopenia plays an important role in the pathogenesis of the disease, thus the drugs targeting lymphocyte proliferation or apoptosis (IL-7 and PD1/PD-L1 inhibitors) could help to restore lymphocyte counts in severe patients suffering COVID-19.

The recruited studies evaluated by NOQAS in the meta-analysis revealed good quality, which provided the strong evidence for the association between immune signatures and SARS-CoV-2 infection. However, our study was subject to limitations that were inherent to meta-analysis. All types of severe diseases, such as ARDS development, ICU entrance, the critical ill patients, were pooled into one for comparison. This broad range of severe disease, although been defined according to standard criteria, might cause bias away from the actual estimation of the association. However, with all association with these complications undoubtedly toward the same direction, we would consider these results adaptable for the disease severity prediction. Age and comorbidities are important risk determinants of severity and mortality of COVID-19 patients, which effects however was not measured, as there were only few literatures presenting the subgrouping data on the immune signatures and disease severity, based on age or comorbidities. We also failed to consider the effect of therapy on the disease outcome, because most of the therapy information was missing from the included studies, for which further investigation are warranted.

## 5 | CONCLUSION

Our systematic review and meta-analysis are the first to reveal that multiple immune mediators were significantly associated with clinical outcome in COVID-19 patients in a comprehensive way. A dysregulated immunological response with hypercytokinemia and lymphopenia assembled among severe COVID-19 disease was disclosed. The screening for the currently significant biomarkers, especially cytokine of IL-6, IL-10 and the T cells counts, have important implication in assisting prompt recognition of severe patients and guiding early treatment.

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## CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## AUTHOR CONTRIBUTIONS

Wei Liu, Jing-Yun Li and Qing-Bin Lu conceived the idea. Tong Yang and Xue-Fang Peng searched the studies. Kun Liu, Tong Yang, Xue-Fang Peng, Shou-Ming Lv, Tian-Shuo Zhao, Xiao-Lei Ye, Jia-Chen Li and Zhong-Jun Shao collected and analysed the data. Wei Liu and Kun Liu wrote the manuscript. All authors read and approved the final manuscript.

## DATA AVAILABILITY STATEMENT

All data used for analysis are available upon a proper request from the corresponding author Wei Liu at [lwbime@163.com](mailto:lwbime@163.com).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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