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Research Article

Associations between Serum Interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) and Disease Severity of COVID-19: A Systematic Review and Meta-Analysis

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Background. To investigate the association between interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) and the disease severity of coronavirus disease 2019 (COVID-19). *Materials and Methods*. We systematically searched records investigating the role of interleukins (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) in COVID-19 patients in Web of Science, Pubmed, and Embase through December 2020. Data were extracted and pooled, and the weighted mean difference (WMD) and its 95% confidence interval (CI) were calculated. The funnel plot and the nonparametric trim and fill method were used to visualize and adjust the publication bias. *Results*. In total, 61 studies enrolled 14,136 subjects (14,041 patients and 95 healthy subjects) were enrolled in this meta-analysis. Our results showed that serum IL-2, IL-4, IL-6, and IL-10 levels were elevated in COVID-19 patients compared to healthy controls, and IL-6, IL-8, and IL-10 levels were increased in severe COVID-19 cases compared to nonsevere patients. Additionally, the levels of IL-1β, IL-6, and IL-8 were elevated in nonsurvivor patients compared to survivors. For patients in the intensive care unit (ICU), IL-6 and IL-8 levels were increased than that in non-ICU patients. *Conclusions*. Elevated levels of IL-6, IL-8, and IL-10 were associated with the disease severity of COVID-19, and elevated levels of IL-1β, IL-6, and IL-8 were related to the prognosis of COVID-19 patients, which could be used to evaluate COVID-19 patients' disease severity and prognosis.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) occurred and spread rapidly in Wuhan, China, in 2019, which has received wide attention [1]. As the spread of SARS-CoV-2, the confirmed coronavirus disease 2019 (COVID-19) cases increased dramatically, leading to a public health emergency [2–5]. Fever, dry cough, and muscle aches were common symptoms of COVID-19 cases, and the manifestations varied greatly in critically ill COVID-19 patients [6, 7]. With the development of the detection method, the COVID-19 cases could be confirmed timely to achieve early diagnosis and treatment [8]. Although therapeutic strategies for COVID-19 have advanced greatly, including antiviral drugs, vaccines, and immunomodulatory agents [9], older COVID-19 patients tend to develop severe disease status [10]. Hence, more effective treatment approaches for COVID-19 were warranted.

Immune responses were demonstrated to be involved in the initiation and development of COVID-19, and cytokine storm may cause a poor prognosis in COVID-19 patients [11–13]. Mehta et al. proposed that cytokine storm syndrome may be associated with the disease severity of COVID-19 patients, and immunosuppression could be a therapy option for COVID-19 patients [11]. Increasing evidence demonstrated that interleukins (ILs) played an important role in the progression of COVID-19. Compared to mild COVID-19 cases, serum interleukins levels increased greatly in severe and critical patients [13–17]. Additionally, the cytokine profiles were different between survivors and nonsurvivors of COVID-19 patients [18]. IL-6 level was reported to be associated with patients' clinical manifestations, including

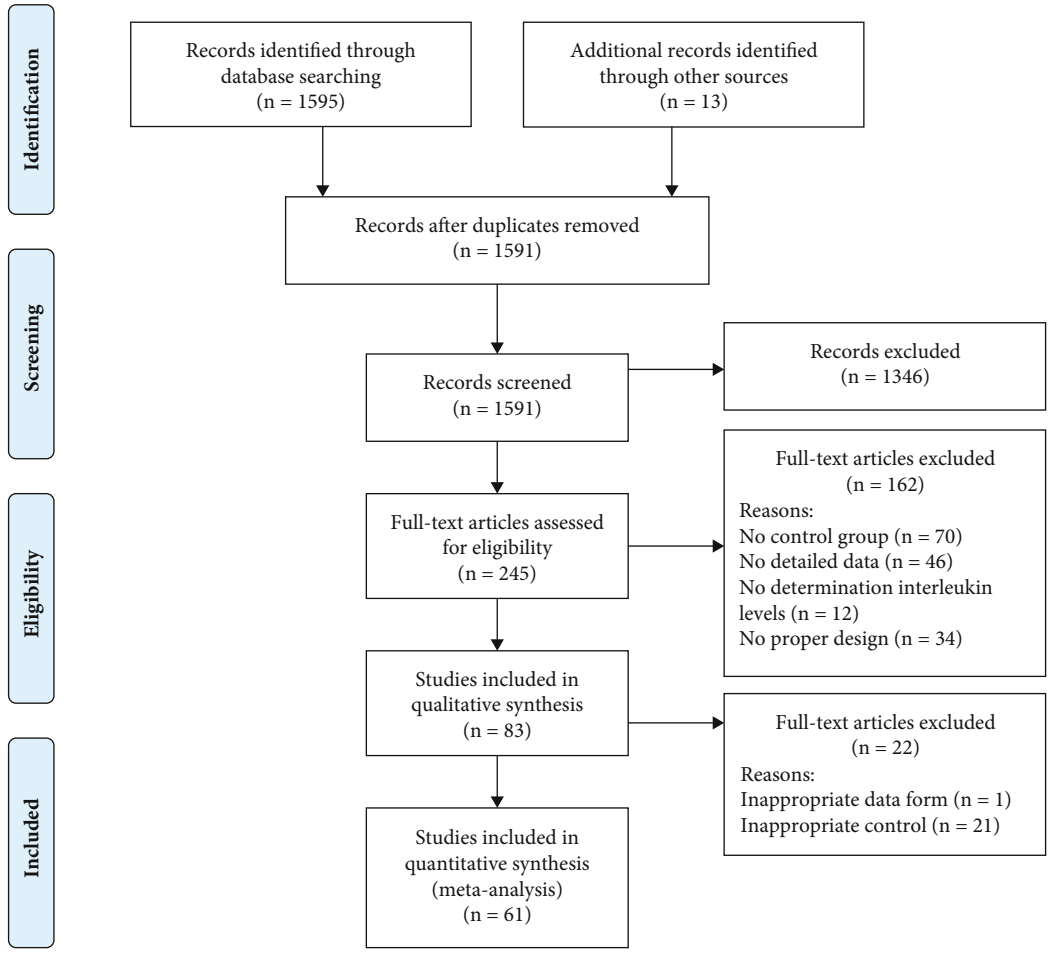


Figure 1: The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

body temperature and blood oxygen saturation, and COVID-19 patients with higher IL-6 levels had a poorer prognosis [19]. Therapeutic agents targeting IL-6 have been applied to clinical practice, which improved the outcomes of severe and critical COVID-19 patients [20, 21]. Thus, immunomodulatory agents targeting immune mediators provided novel clues for the treatment of COVID-19.

In this meta-analysis, we comprehensively analyzed the levels of serum interleukins in COVID-19 patients according to disease severity. Our results showed that elevated levels of IL-6, IL-8, and IL-10 were associated with the disease severity of COVID-19, and elevated levels of IL-1β, IL-6, and IL-8 were associated with the prognosis of COVID-19 cases, and more studies were needed to elucidate the roles of interleukins in the progression and prognosis of COVID-19 to improve the outcomes of patients.

2. Materials and Methods

2.1. Search Study. All procedures in this study were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. Records in Web of Science, Pubmed, and Embase were searched up to December 15, 2020. We used the following search strategy: ("novel coronavirus" OR "SARS-CoV-2" OR "2019-nCoV" OR "COVID-19" OR "coronavirus disease 2019") AND ("IL-1" OR "interleukin-1" OR "IL-2" OR "interleukin-2" OR "IL-4" OR "interleukin-4" OR "IL-6" OR "interleukin-6" OR "IL-8" OR "interleukin-8" OR "IL-10" OR "interleukin-10").

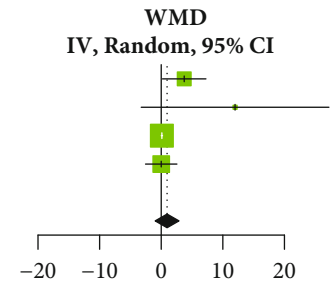
Two investigators (Y.M.C.) and (M.R.B.) researched all relevant articles, and articles that fulfilled the inclusion criteria were included. Any disagreement would be discussed until an agreement was reached. The disease severity of COVID-19 was already defined in the included studies based on clinical criteria, which was according to the Novel Coronavirus Pneumonia Diagnosis and Treatment Plan, the Novel Coronavirus Pneumonia Diagnosis and Treatment Guidance, and World Health Organization (WHO) guidance [23–26], and COVID-19 patients with acute respiratory distress syndrome (ARDS) was defined as severe disease.

2.2. Study Selection and Data Extraction. The inclusion and exclusion criteria were used to identify relevant articles. Case reports, commentaries, meta-analyses, letters, reviews, animal trials, and editorials were excluded. The inclusion criteria were listed below: (i) patients with COVID-19 were confirmed by laboratory test; (ii) subgroup analysis was conducted according to disease severity; (iii) serum interleukin levels (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) were detected,

Severe versus non-severe patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Li SH 2020	11.40	9.1111	26	7.67	1.4074	43	19.0%	3.73 [0.21, 7.26]
Zhao Y 2020	35.25	31.2889	18	23.27	17.8815	53	1.6%	11.99 [−3.25, 27.22]
Xu B 2020	5.11	0.4800	107	5.00	0.2296	80	52.1%	0.11 [0.00, 0.21]
Li XL 2020	3.77	8.3704	56	3.77	8.3704	159	27.3%	0.00 [−2.55, 2.55]
Total (95% CI)			**207**			**335**	**100.0%**	**0.95 [−0.98, 2.88]**

Heterogeneity: Tau² = 1.86; Chi² = 6.40, df = 3 (P = 0.09); I² = 53%
Test for overall effect: Z = 0.97 (P = 0.33)

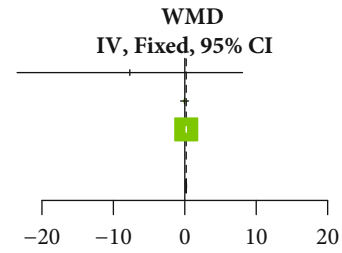


(a) Severe versus nonsevere patients

Non-survivor versus survivor patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Ke CJ 2020	2.89	6.9000	46	10.59	97.1600	148	0.0%	−7.70 [−23.48, 8.08]
Mandel M 2020	0.64	0.7700	12	0.67	1.3800	59	0.6%	−0.03 [−0.59, 0.53]
Mikami T 2020	0.73	0.5926	806	0.53	0.3704	2014	99.4%	0.20 [0.16, 0.24]
Total (95% CI)			**864**			**2221**	**100.0%**	**0.20 [0.15, 0.24]**

Heterogeneity: Tau² = 0; Chi² = 1.61, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 8.87 (P < 0.01)



(b) Nonsurvivor versus survivor patients

Figure 2: IL-1β levels in COVID-19 patients. A significant difference in IL-1β levels between severe and nonsevere COVID-19 patients was not found ($P = 0.33$) (a), while IL-1β levels were increased in (b) nonsurvivor patients compared to survivors.

which were expressed as median (q1-q3) or mean ± standard deviation (SD). The exclusion criteria were as follows: (i) patients were not diagnosed as COVID-19 cases or pediatric and pregnant COVID-19 cases; (ii) subgroup analysis was not conducted according to patient disease severity; (iii) data were not expressed as median (q1-q3) or mean ± SD, or data could not be transformed into mean ± SD; (iv) relevant serum interleukin (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) levels were not detected; and (v) repetitive publication. Two reviewers (Y.M.C) and (M.R.B) extracted the data from the selected studies, and the following items were extracted: first author, publication, country, number of subjects, median age, time of blood sampling, mean, SD, median, or interquartile of interleukins levels. The Newcastle-Ottawa Scale (NOS) tool was used to evaluate the quality of the included studies [27].

2.3. Statistical Analysis. All procedures were conducted in the R software. For data presented as median (q1-q3), the formulas mean = (q1 + m + q3)/3 and SD = (q3 − q1)/1.35 were used to transform the data into mean ± SD [28]. The weighted mean difference (WMD) and corresponding 95% confidence interval (CI) were calculated to compare the difference in serum interleukin levels between the two groups. The heterogeneity was assessed by I^2, and a fixed-effects model was applied when $I^2 < 50\%$; otherwise, a random-effects model was adopted. The funnel plot and nonparametric trim and fill method were used to visualize and adjust the publication bias [29]. $P < 0.05$ (two sides) was recognized as significant difference.

3. Results

3.1. Basic Information of Included Studies. Initially, 1591 articles were searched. After reviewing the titles and abstracts, 245 records were included, and 1346 records were excluded. Finally, after reviewing the full length, 61 studies including 14,136 subjects (14,041 patients and 95 healthy individuals), were integrated into our meta-analysis. [18, 30–89]. The PRISMA chart and checklist showed the whole process of our meta-analysis (Figure 1 and Supplemental Table 1). Data in the 61 studies were presented in Supplemental Tables 2–7, and the NOS scores of the included 61 studies were shown in Supplemental Table 8.

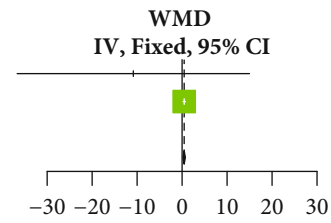
3.2. Alterations of IL-1β, IL-2, and IL-4 in COVID-19 Patients. To comprehensively elucidate the relationship between serum interleukins and disease severity of COVID-19 cases, we compared serum interleukin levels in COVID-19 patients with different disease severities. Our results showed that serum IL-1β levels were not elevated in severe COVID-19 patients compared to nonsevere patients ($P = 0.33$) (Figure 2(a)), while levels of IL-1β were elevated in nonsurvivor COVID-19 patients compared to survivors (WMD = 0.20, 95% CI: 0.15-0.24, and $P < 0.01$) (Figure 2(b)).

For IL-2 in COVID-19 patients, increased serum IL-2 levels were observed in nonsevere and severe patients than that in healthy controls (WMD = 0.46, 95% CI: 0.20-0.73, and $P < 0.01$; WMD = 0.70, 95% CI: 0.50-0.89, and $P < 0.01$) (Figures 3(a) and 3(b)), while no significant difference in IL-2 levels between severe and nonsevere patients ($P = 0.54$) (Figure 3(c)).

Non-severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Zhao Y 2020	39.88	19.2074	53	50.72	54.7778	18	0.0%	−10.85 [−36.68, 14.98]
Han H 2020	3.38	0.6741	42	2.91	0.5704	45	100.0%	0.46 [0.20, 0.73]
Total (95% CI)			**95**			**63**	**100.0%**	**0.46 [0.20, 0.73]**

Heterogeneity: Tau² = 0; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 3.44 (P < 0.01)

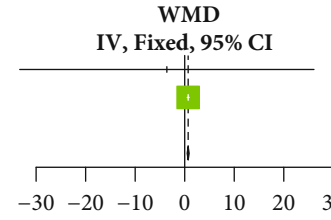


(a) Nonsevere patients versus healthy controls

Severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Zhao Y 2020	47.12	33.6593	18	50.72	54.7778	18	0.0%	−3.60 [−33.3, 26.10]
Han H 2020	3.61	0.4000	60	2.91	0.5704	45	100.0%	0.70 [0.5, 0.89]
Total (95% CI)			**78**			**63**	**100.0%**	**0.70 [0.5, 0.89]**

Heterogeneity: Tau² = 0; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 7.00 (P < 0.01)

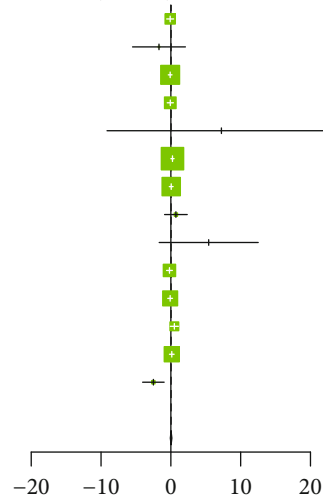


(b) Severe patients versus healthy controls

Severe versus non-severe patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Yuan XH 2020	3.37	1.2148	54	3.46	1.4074	53	4.9%	−0.10 [−0.60, 0.40]
Lv ZH 2020	4.00	2.4300	239	5.70	20.6500	115	0.1%	−1.70 [−5.49, 2.09]
Wu YJ 2020	0.50	0.2444	39	0.60	0.7481	32	16.7%	−0.10 [−0.37, 0.17]
Zhu Z 2002	0.99	0.8370	16	1.07	0.8741	111	6.3%	−0.08 [−0.52, 0.36]
Zhao Y 2020	47.12	33.6593	18	39.88	19.2074	53	0.0%	7.24 [−9.14, 23.63]
Han H 2020	3.61	0.4000	60	3.38	0.6741	42	23.5%	0.23 [0.01, 0.46]
Yi P 2020	1.24	0.6370	49	1.19	0.7778	51	15.7%	0.05 [−0.23, 0.33]
Dayarathna S 2020	1.74	2.1704	8	1.01	1.2000	15	0.5%	0.72 [−0.90, 2.35]
Dayarathna S 2020	6.42	10.2000	8	1.00	1.1630	15	0.0%	5.42 [−1.67, 12.51]
Zhang BC 2020	3.27	0.2963	16	3.47	0.8148	17	7.1%	−0.20 [−0.61, 0.21]
Zhang BC 2020	3.27	0.2963	5	3.37	0.5926	27	10.4%	−0.10 [−0.44, 0.24]
Zhang BC 2020	3.87	0.7407	34	3.37	0.9630	13	3.6%	0.50 [−0.08, 1.08]
Zhang BC 2020	3.87	0.1481	12	3.73	0.8148	24	10.7%	0.13 [−0.20, 0.47]
Jin XH 2020	1.44	1.8370	40	3.95	7.4889	105	0.5%	−2.50 [−4.04, −0.96]
Total (95% CI)			**598**			**673**	**100.0%**	**0.03 [−0.08, 0.15]**

Heterogeneity: Tau² = 0.04; Chi² = 23.92, df = 13 (P = 0.03); I² = 46%
Test for overall effect: Z = 0.62 (P = 0.54)



(c) Severe versus nonsevere patients

Figure 3: IL-2 levels in COVID-19 patients. The levels of IL-2 were increased in (a) nonsevere and (b) severe COVID-19 patients compared to healthy subjects, while no significant difference in IL-2 levels between (c) severe and nonsevere COVID-19 patients.

Serum IL-4 levels were elevated in nonsevere COVID-19 patients compared to healthy individuals (WMD = 0.43, 95% CI: 0.20-0.65, and $P < 0.01$) (Figure 4(a)), while no significant difference in IL-4 levels was observed between healthy controls and severe patients, as well as between severe and nonsevere COVID-19 patients ($P > 0.05$) (Figures 4(b) and 4(c)).

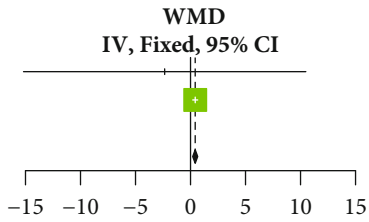
3.3. Alterations of IL-6, IL-8, and IL-10 in COVID-19 Patients. Our results indicated that serum IL-6 levels were not elevated in nonsevere COVID-19 cases compared to healthy controls ($P = 0.13$) (Figure 5(a)), while IL-6 levels were elevated in severe patients compared to healthy controls (WMD = 25.05, 95% CI: 6.92-43.17, and $P < 0.01$) (Figure 5(b)). We also found that the levels of IL-6 were elevated in intensive care unit (ICU), severe, and nonsurvivor patients than that in non-ICU, nonsevere, and survivor patients (WMD = 73.02, 95% CI: 27.16-118.88, and $P < 0.01$; WMD = 19.43, 95% CI: 16.55-22.30, and $P < 0.01$; WMD = 31.06, 95% CI: 25.18-36.93, and $P < 0.01$) (Figures 5(c) and 6(a) and 6(b)).

The serum IL-8 levels were elevated in ICU, severe, and nonsurvivor COVID-19 patients compared to non-ICU, nonsevere, and survivor patients (WMD = 42.55, 95% CI:

Non-severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Zhao Y 2020	32.51	22.7100	53	34.86	24.4200	18	0.0%	−2.35 [−15.18, 10.48]
Han H 2020	3.36	0.4519	42	2.94	0.6222	45	100.0%	0.43 [0.20, 0.65]
Total (95% CI)			**95**			**63**	**100.0%**	**0.43 [0.20, 0.65]**

Heterogeneity: Tau² = 0; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 3.67 (P < 0.01)

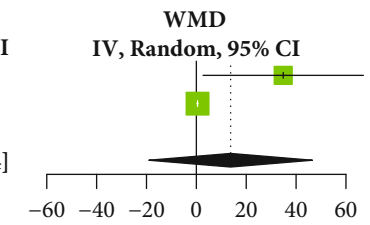


(a) Nonsevere patients versus healthy controls

Severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Zhao Y 2020	69.70	65.1600	18	34.86	24.4200	18	38.6%	34.84 [2.69, 66.99]
Han H 2020	3.41	0.6600	60	2.94	0.6222	45	61.4%	0.47 [0.23, 0.72]
Total (95% CI)			**78**			**63**	**100.0%**	**13.74 [−19.05, 46.54]**

Heterogeneity: Tau² = 456.02; Chi² = 4.39, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.82 (P = 0.41)

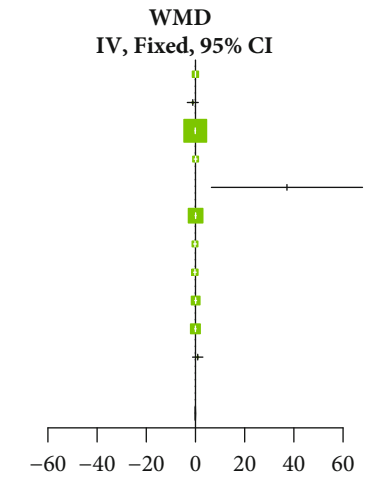


(b) Severe patients versus healthy controls

Severe versus non-severe patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Yuan XH 2020	2.91	1.3926	54	2.94	1.3111	53	3.6%	−0.03 [−0.54, 0.49]
Lv ZH 2020	3.51	1.7600	239	4.61	12.1100	115	0.2%	−1.10 [−3.32, 1.12]
Wu YJ 2020	0.18	0.3111	39	0.27	0.2815	32	49.7%	−0.10 [−0.23, 0.04]
Zhu Z 2002	1.99	1.0889	16	1.95	0.8296	111	3.1%	0.04 [−0.51, 0.60]
Zhao Y 2020	69.70	65.1600	18	32.51	22.7100	53	0.0%	37.19 [6.47, 67.91]
Han H 2020	3.41	0.6600	60	3.36	0.4519	42	20.3%	0.05 [−0.17, 0.26]
Zhang BC 2020	3.27	0.5185	16	3.47	1.0370	17	3.1%	−0.20 [−0.75, 0.35]
Zhang BC 2020	3.27	0.4444	5	3.50	0.8889	27	3.6%	−0.23 [−0.75, 0.28]
Zhang BC 2020	3.20	0.5185	34	3.13	0.5926	13	7.1%	0.07 [−0.30, 0.43]
Zhang BC 2020	3.63	0.2222	12	3.67	0.7407	24	9.1%	−0.03 [−0.36, 0.29]
Jin XH 2020	3.41	6.1926	40	2.50	4.3407	105	0.2%	0.91 [−1.18, 3.00]
Total (95% CI)			**533**			**592**	**100.0%**	**−0.05 [−0.15, 0.05]**

Heterogeneity: Tau² = 0; Chi² = 9.81, df = 10 (P = 0.46); I² = 0%
Test for overall effect: Z = −1.02 (P = 0.31)



(c) Severe versus nonsevere patients

Figure 4: IL-4 levels in COVID-19 patients. IL-4 levels were elevated in (a) nonsevere COVID-19 patients compared to healthy subjects, while no significant difference in IL-4 levels between (b) severe patients and healthy controls, as well as between (c) severe and nonsevere COVID-19 patients.

8.09-77.01, and $P = 0.02$; WMD = 11.72, 95% CI: 6.41-17.02, and $P < 0.01$; WMD = 23.61, 95% CI: 15.61-31.60, and $P < 0.01$) (Figures 7(a)–7(c)).

For IL-10, we found that serum IL-10 levels were increased in nonsevere and severe cases with COVID-19 compared to healthy subjects (WMD = 1.08, 95% CI: 0.60-1.56, and $P < 0.01$; WMD = 2.27, 95% CI: 1.26-3.29, and $P < 0.01$) (Figures 8(a) and 8(b)). However, IL-10 levels were not elevated between ICU and non-ICU patients, as well as between nonsurvivor and survivor patients ($P > 0.05$) (Figures 8(c) and 8(e)). Additionally, the serum IL-10 levels were higher in severe patients compared to nonsevere patients (WMD = 2.29, 95% CI: 1.16-3.41, and $P < 0.01$) (Figure 8(d)).

3.4. Publication Bias. In our meta-analysis, the potential publication bias was assessed and adjusted by funnel plot and the nonparametric trim and fill method, and Supplemental Figure 1 showed the publication bias for our meta-analysis, which was adjusted by the nonparametric trim and fill method.

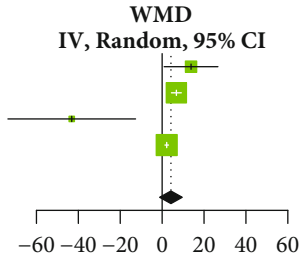
4. Discussion

In this meta-analysis, we analyzed serum levels of IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10 in COVID-19 patients with different disease severities. Our main findings were as follows: (i) levels of IL-2, IL-4, IL-6, and IL-10 were elevated in COVID-19 patients compared to healthy subjects; (ii) levels

Non-severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Kerget B 2020	39.40	30.7000	53	25.60	22.4000	20	12.6%	13.80 [0.97, 26.63]
Liu Q 2020	11.45	8.3333	59	4.65	2.9259	30	40.7%	6.80 [4.43, 9.17]
Zhao Y 2020	29.42	15.2296	53	72.57	65.3556	18	2.9%	−43.15 [−73.62, −12.68]
Han H 2020	6.91	2.5259	42	4.73	1.3630	45	43.8%	2.18 [1.32, 3.04]
Total (95% CI)			**207**			**113**	**100.0%**	**4.20 [−1.18, 9.59]**

Heterogeneity: $Tau^2 = 17.04$; $Chi^2 = 24.42$, df = 3 ($P < 0.01$); $I^2 = 88\%$
Test for overall effect: Z = 1.53 (P = 0.13)

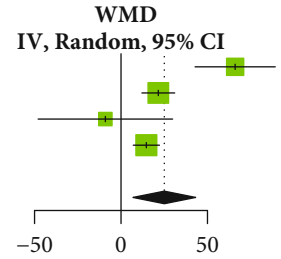


(a) Nonsevere patients versus healthy controls

Severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Kerget B 2020	91.60	63.4000	35	25.60	22.4000	20	22.1%	66.00 [42.81, 89.19]
Liu Q 2020	26.22	24.0296	25	4.65	2.9259	30	31.7%	21.57 [12.09, 31.04]
Zhao Y 2020	63.52	53.0370	18	72.57	65.3556	18	13.4%	−9.05 [−47.93, 29.84]
Han H 2020	19.37	29.8200	60	4.73	1.3630	45	32.8%	14.64 [7.08, 22.20]
Total (95% CI)			**138**			**113**	**100.0%**	**25.05 [6.92, 43.17]**

Heterogeneity: $Tau^2 = 246.18$; $Chi^2 = 19.29$, df = 3 ($P < 0.01$); $I^2 = 84\%$
Test for overall effect: Z = 2.71 ($P < 0.01$)

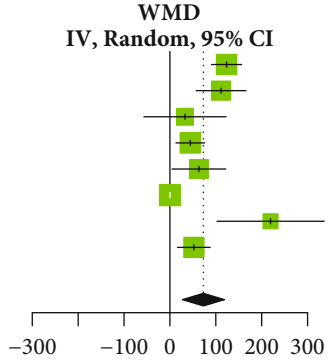


(b) Severe patients versus healthy controls

ICU versus non-ICU patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
McElvaney OJ 2020	169.40	70.7000	20	45.90	24.8000	20	14.2%	123.50 [90.66, 156.34]
Wang F 2020	129.83	99.8519	14	18.40	27.7037	14	12.6%	111.43 [57.15, 165.71]
Liu SP 2020	137.77	275.5556	41	104.97	224.5926	214	9.7%	32.80 [−56.75, 122.35]
Carlino MV 2020	58.51	48.6300	10	14.03	19.2100	18	14.3%	44.48 [13.06, 75.90]
Effenberger M 2020	93.93	113.7778	15	30.73	46.6667	81	12.3%	63.20 [4.73, 121.67]
Maeda T 2020	0.16	0.1793	57	0.04	0.0387	167	15.3%	0.12 [0.07, 0.17]
Guirao JJ 2020	248.36	168.5200	8	29.02	8.9700	42	7.7%	219.34 [102.53, 336.15]
Burian E 2020	103.90	43.6000	12	51.70	65.6000	25	14.0%	52.20 [16.57, 87.83]
Total (95% CI)			**177**			**581**	**100.0%**	**73.02 [27.16, 118.88]**

Heterogeneity: $Tau^2 = 3576.61$; $Chi^2 = 104.77$, df = 7 ($P < 0.01$); $I^2 = 93\%$
Test for overall effect: Z = 3.12 ($P < 0.01$)



(c) ICU versus non-ICU patients

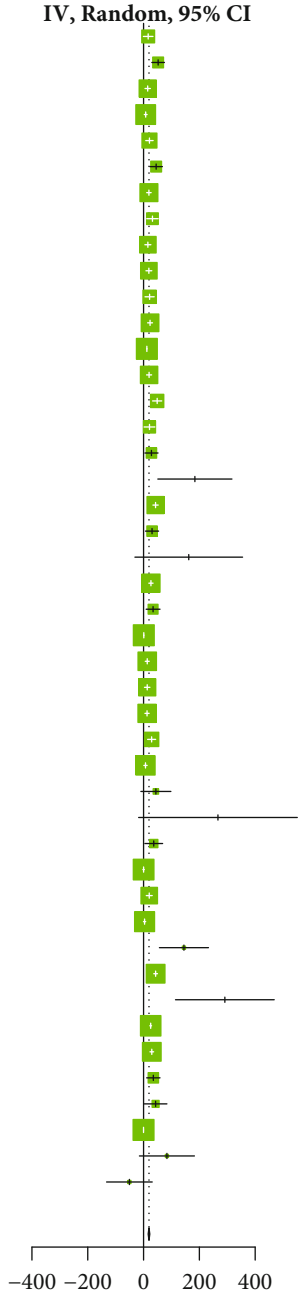
Figure 5: IL-6 levels in COVID-19 patients and healthy controls. No significant difference in serum IL-6 levels between (a) nonsevere COVID-19 patients and healthy controls, while IL-6 levels were elevated in (b) severe patients compared to healthy subjects, and levels of IL-6 were increased in (c) ICU patients compared to non-ICU patients.

Severe versus non-severe patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Xu X 2020	19.62	56.1900	41	3.05	3.1556	47	1.7%	16.57 [−0.65, 33.80]
Kerget B 2020	91.60	63.4000	35	39.40	30.7000	53	1.2%	52.20 [29.63, 74.77]
Liu Q 2020	26.22	24.0296	25	11.45	8.3333	59	3.0%	14.77 [5.11, 24.43]
Yuan XH 2020	17.67	16.5852	54	10.06	9.2741	53	4.0%	7.61 [2.53, 12.69]
Sun Y 2020	33.63	28.6400	19	12.55	10.8400	44	2.3%	21.08 [7.81, 34.35]
Zhang QH 2020	51.80	58.9481	27	6.69	7.6593	47	1.2%	45.11 [22.76, 67.45]
Li SH 2020	29.17	20.0741	26	10.00	7.5556	43	3.3%	19.17 [11.13, 27.21]
Lv ZH 2020	49.32	152.1900	239	17.44	38.2900	115	1.4%	31.88 [11.36, 52.40]
Liu FF 2020	27.20	25.7100	23	11.76	8.7200	42	2.8%	15.44 [4.61, 26.27]
Wu YJ 2020	24.43	32.0963	39	5.42	9.1778	32	2.8%	19.01 [8.45, 29.58]
Yang F 2020	33.43	36.0000	19	11.83	9.5556	33	1.8%	21.60 [5.09, 38.11]
Zou L 2020	34.17	30.9704	52	10.89	10.6963	69	3.2%	23.27 [14.49, 32.06]
Li T 2020	18.70	4.5000	105	6.90	3.8000	207	4.5%	11.80 [10.80, 12.80]
Shi PY 2020	26.63	31.4815	46	6.87	3.6296	88	3.1%	19.77 [10.64, 28.90]
Wang WL 2020	51.62	59.2889	50	2.85	2.0593	73	1.8%	48.77 [32.33, 65.21]
Zhu Z 2002	26.54	39.4296	16	5.29	5.6889	111	1.5%	21.25 [1.90, 40.60]
Liu Y 2020	40.13	64.6667	30	11.86	16.9704	46	1.1%	28.27 [4.62, 51.92]
Jurado A 2020	241.16	597.9200	78	57.27	35.6900	176	0.0%	183.89 [51.09, 316.69]
Liu QQ 2020	50.85	69.8000	217	7.87	9.3333	91	3.0%	42.98 [33.50, 52.47]
Chen XH 2020	45.48	58.1500	27	15.07	20.1481	21	1.1%	30.41 [6.85, 53.98]
Kwon JS 2020	174.03	278.2222	8	12.10	16.8500	23	0.0%	161.93 [−30.98, 354.85]
Zeng ZL 2020	39.91	53.6800	224	13.47	14.5926	93	3.4%	26.44 [18.81, 34.07]
Zhao Y 2020	63.52	53.0370	18	29.42	15.2296	53	1.0%	34.10 [9.26, 58.95]
Chen RC 2020	8.48	3.8000	203	7.62	3.0741	345	4.5%	0.86 [0.24, 1.47]
Li XJ 2020	22.53	26.7407	67	9.33	13.4074	67	3.5%	13.20 [6.04, 20.36]
Huang HH 2020	25.70	21.4815	21	12.60	11.5556	43	3.0%	13.10 [3.28, 22.92]
Han H 2020	19.37	29.8200	60	6.91	2.5259	42	3.4%	12.46 [4.87, 20.04]
Yi P 2020	45.38	48.5259	49	16.47	17.8074	51	2.1%	28.91 [14.47, 43.35]
Xu B 2020	20.62	27.2500	107	13.70	13.4000	80	3.8%	6.92 [0.98, 12.86]
Dayarathna S 2020	48.04	77.4519	8	3.92	5.9852	15	0.3%	44.12 [−9.63, 97.88]
Dayarathna S 2020	267.64	410.1407	8	1.05	0.7111	15	0.0%	266.58 [−17.62, 550.79]
Zhang BC 2020	44.07	64.7407	16	7.57	5.9259	17	0.7%	36.50 [4.65, 68.35]
Zhang BC 2020	6.37	2.6667	5	6.20	2.6667	27	4.4%	0.17 [−2.38, 2.71]
Zhang BC 2020	31.47	26.9630	34	11.13	10.5185	13	2.8%	20.33 [9.62, 31.05]
Zhang BC 2020	10.40	6.7407	12	6.77	3.5556	24	4.1%	3.63 [−0.44, 7.70]
Dreher M 2020	168.00	215.5556	24	23.33	44.4444	26	0.1%	144.67 [56.75, 232.58]
Li CZ 2020	48.07	50.1481	219	4.83	6.2222	770	3.6%	43.23 [36.58, 49.89]
Guirao JJ 2020	320.45	220.9600	6	29.16	15.2800	44	0.0%	291.29 [114.43, 468.15]
Wan SX 2020	28.24	7.1400	21	2.66	0.0879	102	4.3%	25.58 [22.52, 28.63]
Tang YT 2020	33.34	26.2400	60	3.83	0.7400	60	3.6%	29.51 [22.87, 36.15]
Sun H 2020	45.66	72.3500	40	10.63	22.6300	28	1.1%	35.03 [11.09, 58.97]
Chen G 2020	60.17	66.2222	11	17.00	17.2593	10	0.5%	43.17 [2.60, 83.74]
Chen JX 2020	0.07	0.0889	5	0.16	0.7800	113	4.5%	−0.09 [−0.25, 0.07]
Li XL 2020	167.10	360.7407	56	83.39	181.4815	159	0.1%	83.71 [−14.90, 182.31]
Jin XH 2020	89.49	184.4741	40	140.24	306.0889	105	0.1%	−50.75 [−132.58, 31.08]
Total (95% CI)			**2490**			**3775**	**100.0%**	**19.43 [16.55, 22.30]**

Heterogeneity: $Tau^2 = 47.64$; $Chi^2 = 1488.39$, df = 44 ($P < 0.01$); $I^2 = 97\%$

Test for overall effect: $Z = 13.23$ ($P < 0.01$)



(a) Severe versus nonsevere patients

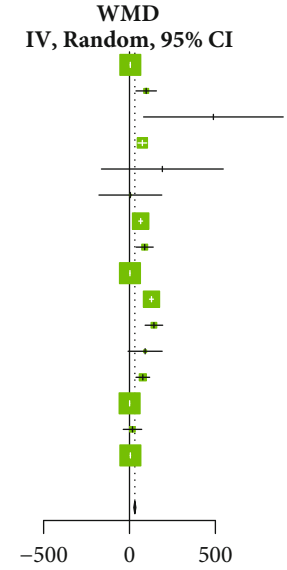
Figure 6: Continued.

Non-survivor versus survivor patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
Fan H 2020	9.73	4.5185	47	5.07	1.7037	26	17.0%	4.67 [3.22, 6.11]
Ke CJ 2020	130.85	201.6600	46	33.72	75.2400	148	0.9%	97.13 [37.61, 156.65]
Mandel M 2020	605.69	710.9900	12	117.24	229.4800	59	0.0%	488.45 [81.94, 894.96]
Chen H 2020	80.47	100.8148	60	5.57	7.1111	795	4.0%	74.90 [49.39, 100.41]
Quartuccio L 2020	276.00	441.4815	6	84.73	66.1481	18	0.0%	191.27 [−163.30, 545.84]
Gadotti AC 2020	877.67	324.4444	18	872.67	329.6296	38	0.1%	5.00 [−177.89, 187.89]
Luo M 2020	72.81	82.3852	201	7.84	10.0222	817	10.4%	64.97 [53.56, 76.38]
Laguna−Goya R 2020	110.33	151.8519	36	22.00	28.8889	465	1.3%	88.33 [38.66, 138.01]
Chen RC 2020	10.16	4.2148	103	7.53	3.1111	445	17.1%	2.63 [1.77, 3.49]
Mikami T 2020	178.43	166.4444	806	50.50	43.7778	2014	10.2%	127.93 [116.28, 139.58]
Guirao JJ 2020	166.46	97.3600	14	24.31	9.9000	36	1.2%	142.15 [91.05, 193.25]
Trecarichi EM 2020	125.00	189.0000	14	34.00	22.0000	34	0.3%	91.00 [−8.28, 190.28]
Tu WJ 2020	110.27	99.1111	25	32.70	53.7037	149	1.9%	77.57 [37.77, 117.36]
Hue S 2020	5.50	0.7000	13	4.90	1.0000	25	17.1%	0.60 [0.05, 1.15]
Guo HQ 2020	73.56	164.5300	46	56.17	67.7800	28	1.1%	17.39 [−36.38, 71.16]
Zhang L 2020	10.03	5.3000	101	5.04	1.6074	33	17.1%	4.99 [3.82, 6.16]
Total (95% CI)			**1548**			**5130**	**100.0%**	**31.06 [25.18, 36.93]**

Heterogeneity: $Tau^2 = 52.30$; $Chi^2 = 735.75$, df = 15 ($P < 0.01$); $I^2 = 98\%$

Test for overall effect: $Z = 10.36$ ($P < 0.01$)



(b) Nonsurvivor versus survivor patients

Figure 6: IL-6 levels in COVID-19 patients. The serum levels of IL-6 were increased in (a) severe and (b) nonsurvivor patients compared to nonsevere and survivor patients.

of IL-6, IL-8, and IL-10 were elevated in severe COVID-19 cases compared to nonsevere patients, while no significant difference in IL-1β, IL-2, and IL-4 levels between severe and nonsevere patients; (iii) elevated levels of IL-1β, IL-6, and IL-8 were found in nonsurvivor COVID-19 patients compared to survivor ones; (iv) levels of IL-6 and IL-8 were elevated in ICU patients compared to non-ICU patients. Taken together, levels of IL-6, IL-8, and IL-10 were associated with the disease severity of COVID-19, and levels of IL-1β, IL-6, and IL-8 were correlated with the prognosis of COVID-19 patients, which may be used to predict the disease severity of COVID-19.

Since the outbreak of COVID-19, an increasing number of COVID-19 cases were confirmed. The cytokine storm occurred in COVID-19, and interleukins and IFN-γ were involved in the process of hyperinflammation [90]. Immune mediators including interleukins were demonstrated to play an important role in the development of COVID-19 [17, 91]. Tocilizumab, a kind of antibody that targeted the IL-6 signaling pathway, was demonstrated to be effective in treating severe COVID-19 patients, and biomarkers including C-reactive protein, procalcitonin, D-dimer, and lymphocyte levels were decreased after receiving tocilizumab administration [20, 92]. Hence, deepening the understanding of interleukins in the development of COVID-19 may contribute to its diagnosis and treatment.

In this study, we systematically analyzed the serum levels of IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10 in COVID-19 patients with different disease severities, as well as in healthy controls. Our results indicated that serum levels of IL-2, IL-4, IL-6, and IL-10 were increased in COVID-19 patients compared to healthy subjects. Additionally, we compared the levels of interleukins in severe and nonsevere COVID-19 patients, and the results indicated that the levels of IL-6, IL-8, and IL-10 were elevated in severe COVID-19 patients compared to nonsevere patients, while no significant difference in IL-1β, IL-2, and IL-4 levels between severe and nonsevere COVID-19 patients, implying that IL-6, IL-8, and IL-10 might be related to the disease severity of COVID-19. Then, we analyzed IL-1β, IL-6, IL-8, and IL-10 levels in nonsurvivor and survivor COVID-19 patients, and our results suggested that the levels of IL-1β, IL-6, and IL-8 levels were elevated in nonsurvivor patients compared to survivor patients, which indicated that IL-1β, IL-6, and IL-8 might be related to COVID-19 patients' prognosis. Compared to non-ICU patients, IL-6 and IL-8 levels were increased in ICU patients, which further demonstrated the important role of IL-6 and IL-8 in the pathogenesis of SARS-CoV-2 [93]. Taken together, these results showed that IL-6 and IL-8 were associated with the disease severity of COVID-19 patients, which may be used to predict patients' prognoses.

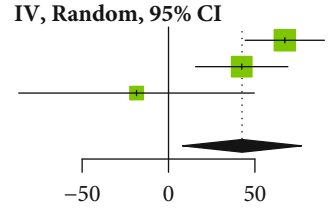
In conclusion, we found that serum levels of IL-6, IL-8, and IL-10 were associated with the disease severity of COVID-19 patients, and serum levels of IL-1β, IL-6, and IL-8 were associated with the prognosis of COVID-19 patients. Herein, more studies were needed to explore the immunological alterations underlying COVID-19 to improve its diagnosis and treatment.

The advantage of the meta-analysis was that more studies and more COVID-19 cases were included in our study, and we compared the levels of interleukins between COVID-19 cases and healthy subjects. Additionally, the COVID-19 patients included in our meta-analysis were from many countries, which makes the results to be more applicable worldwide. The limitation lies in that we used a random-effects model when great heterogeneity exists between

ICU versus non-ICU patients

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	WMD IV, Random, 95% CI
McElvaney OJ 2020	115.50	46.4000	20	48.20	24.0000	20	42.8%	67.30 [44.41, 90.19]
Wang F 2020	55.57	49.7778	14	13.20	11.1111	14	40.0%	42.37 [15.65, 69.08]
Liu SP 2020	99.33	194.8148	41	117.87	246.6667	214	17.2%	−18.53 [−86.71, 49.64]
Total (95% CI)			**75**			**248**	**100.0%**	**42.55 [8.09, 77.01]**

Heterogeneity: Tau² = 586.27; Chi² = 6.33, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 2.42 (P = 0.02)

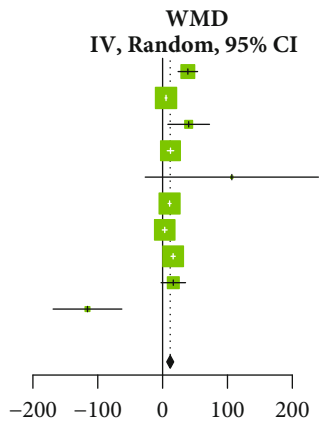


(a) ICU versus non-ICU patients

Severe versus non-severe patients

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	WMD IV, Random, 95% CI
Xu X 2020	46.45	155.0000	411	7.57	4.1481	47	7.4%	38.88 [23.85, 53.92]
Li SH 2020	13.47	3.3333	26	8.20	2.9630	43	17.7%	5.27 [3.71, 6.82]
Liu Y 2020	50.70	89.3333	30	10.52	8.9556	46	2.4%	40.18 [8.11, 72.25]
Liu QQ 2020	29.63	28.5300	217	17.50	16.0741	91	15.4%	12.13 [7.10, 17.16]
Kwon JS 2020	125.73	192.6667	8	19.01	5.8400	23	0.2%	106.72 [−26.81, 240.25]
Zeng ZL 2020	20.41	17.5000	224	9.67	0.8889	93	17.3%	10.74 [8.44, 13.04]
Li XJ 2020	17.10	9.0370	67	13.83	12.8889	67	16.4%	3.27 [−0.50, 7.04]
Li CZ 2020	26.23	24.0000	210	10.00	6.3704	754	16.8%	16.23 [12.96, 19.51]
Chen G 2020	33.83	23.1111	11	17.33	20.8889	10	5.5%	16.50 [−2.32, 35.32]
Li XL 2020	33.03	62.1481	56	148.89	324.4444	159	0.9%	−115.85 [−168.85, −62.86]
Total (95% CI)			**1260**			**1333**	**100.0%**	**11.72 [6.41, 17.02]**

Heterogeneity: Tau² = 40.90; Chi² = 94.04, df = 9 (P < 0.01); I² = 90%
Test for overall effect: Z = 4.33 (P < 0.01)

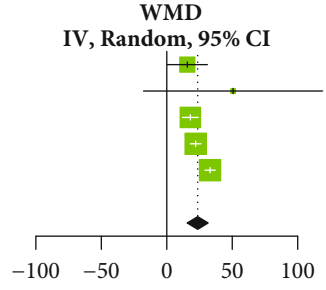


(b) Severe versus nonsevere patients

Non-survivor versus survivor patients

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	WMD IV, Random, 95% CI
Ke CJ 2020	44.11	44.6200	46	28.47	51.8300	148	14.5%	15.64 [0.28, 31.00]
Mandel M 2020	102.24	117.9000	12	51.62	59.2700	59	1.3%	50.62 [−17.78, 119.02]
Chen H 2020	29.50	23.7037	60	11.50	8.2222	795	26.5%	18.00 [11.98, 24.02]
Luo M 2020	35.11	29.3556	201	13.07	7.9259	817	28.8%	22.04 [17.95, 26.13]
Mikami T 2020	70.20	55.2593	806	37.13	24.0000	2014	28.9%	33.07 [29.11, 37.02]
Total (95% CI)			**1125**			**3833**	**100.0%**	**23.61 [15.61, 31.60]**

Heterogeneity: Tau² = 53.44; Chi² = 24.82, df = 4 (P < 0.01); I² = 84%
Test for overall effect: Z = 5.79 (P < 0.01)



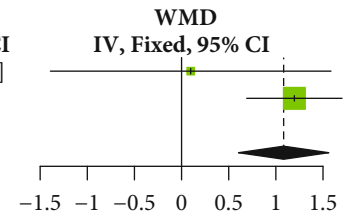
(c) Nonsurvivor versus survivor patients

Figure 7: IL-8 levels in COVID-19 patients. The levels of IL-8 were increased in (a) ICU, (b) severe, and (c) nonsurvivor COVID-19 patients compared to non-ICU, nonsevere, and survivor patients.

Non-severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Zhao Y 2020	4.15	2.6667	53	4.05	2.8222	18	10.4%	0.10 [−1.39, 1.59]
Han H 2020	5.26	1.1481	42	4.06	1.2593	45	89.6%	1.20 [0.69, 1.70]
Total (95% CI)			**95**			**63**	**100.0%**	**1.08 [0.60, 1.56]**

Heterogeneity: Tau² = 0.28; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 4.43 (P < 0.01)

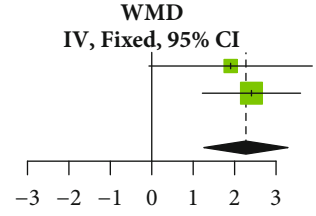


(a) Nonsevere patients versus healthy controls

Severe patients versus healthy controls

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Fixed, 95% CI
Zhao Y 2020	5.95	3.2000	18	4.05	2.8222	18	26.5%	1.90 [−0.07, 3.87]
Han H 2020	6.47	4.4500	60	4.06	1.2593	45	73.5%	2.41 [1.22, 3.59]
Total (95% CI)			**78**			**63**	**100.0%**	**2.27 [1.26, 3.29]**

Heterogeneity: Tau² = 0; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 4.39 (P < 0.01)

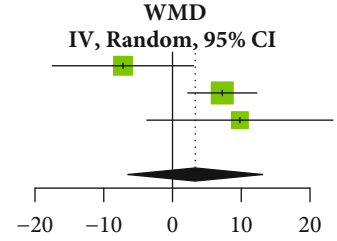


(b) Severe patients versus healthy controls

ICU versus non-ICU patients

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	WMD IV, Random, 95% CI
McElvaney OJ 2020	47.50	17.4000	20	54.70	15.7000	20	31.7%	−7.20 [−17.47, 3.07]
Wang F 2020	13.13	9.4074	14	5.90	1.8519	14	43.1%	7.23 [2.21, 12.26]
Liu SP 2020	26.00	42.8889	41	16.20	24.8889	214	25.2%	9.80 [−3.74, 23.34]
Total (95% CI)			**75**			**248**	**100.0%**	**3.31 [−6.50, 13.11]**

Heterogeneity: Tau² = 51.46; Chi² = 6.66, df = 2 (P = 0.04); I² = 70%
Test for overall effect: Z = 0.66 (P = 0.51)



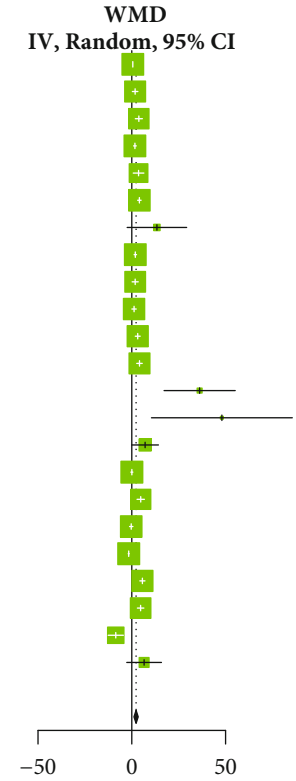
(c) ICU versus non-ICU patients

Figure 8: Continued.

Severe versus non-severe patients

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	WMD IV, Random, 95% CI
Yuan XH 2020	4.80	1.9037	54	4.26	1.4148	53	5.8%	0.54 [−0.09, 1.17]
Lv ZH 2020	8.28	9.3500	239	6.50	4.8400	115	5.4%	1.78 [0.30, 3.26]
Wu YJ 2020	6.39	5.4296	39	2.64	2.4074	32	5.1%	3.76 [1.86, 5.65]
Zou L 2020	7.76	2.3852	52	6.09	1.4593	69	5.8%	1.66 [0.93, 2.40]
Zhu Z 2002	6.89	5.7630	16	3.28	1.7926	111	4.3%	3.61 [0.76, 6.45]
Liu QQ 2020	9.08	6.9700	217	5.03	0.0741	91	5.7%	4.05 [3.12, 4.97]
Kwon JS 2020	17.17	22.7407	8	3.78	4.4300	23	0.5%	13.39 [−2.48, 29.25]
Zeng ZL 2020	7.47	4.5900	224	5.60	1.3333	93	5.8%	1.87 [1.21, 2.53]
Zhao Y 2020	5.95	3.2000	18	4.15	2.6667	53	5.3%	1.81 [0.16, 3.45]
Han H 2020	6.47	4.4500	60	5.26	1.1481	42	5.6%	1.21 [0.03, 2.39]
Yi P 2020	6.97	3.9111	49	3.81	2.7111	51	5.5%	3.16 [1.84, 4.48]
Xu B 2020	9.79	7.5200	107	5.69	1.6741	80	5.4%	4.10 [2.63, 5.57]
Dayarathna S 2020	43.12	27.0074	8	6.95	6.1185	15	0.3%	36.17 [17.20, 55.14]
Dayarathna S 2020	54.47	54.1778	8	6.44	1.0222	16	0.1%	48.03 [10.49, 85.58]
Zhang BC 2020	12.90	14.2963	16	5.80	2.5185	17	1.8%	7.10 [−0.01, 14.21]
Zhang BC 2020	5.23	0.5185	5	5.20	0.8148	27	5.9%	0.03 [−0.52, 0.58]
Zhang BC 2020	10.23	5.2593	34	5.47	1.6296	13	5.0%	4.77 [2.79, 6.74]
Zhang BC 2020	5.50	0.5185	12	5.80	2.1481	24	5.7%	−0.30 [−1.21, 0.61]
Wan SX 2020	4.52	0.4400	21	6.16	1.0750	102	5.9%	−1.64 [−1.92, −1.36]
Tang YT 2020	8.06	5.4400	60	2.41	0.2600	60	5.5%	5.65 [4.27, 7.03]
Chen G 2020	10.77	1.5556	11	6.07	2.3704	10	5.2%	4.70 [2.97, 6.43]
Li XL 2020	2.45	5.4444	56	11.00	24.4444	159	3.3%	−8.55 [−12.61, −4.49]
Jin XH 2020	15.14	28.1185	40	8.57	16.1556	105	1.2%	6.57 [−2.68, 15.81]
Total (95% CI)			**1354**			**1361**	**100.0%**	**2.29 [1.16, 3.41]**

Heterogeneity: $Tau^2 = 5.52$; $Chi^2 = 502.68$, df = 22 ($P < 0.01$); $I^2 = 96\%$
Test for overall effect: $Z = 3.99$ ($P < 0.01$)

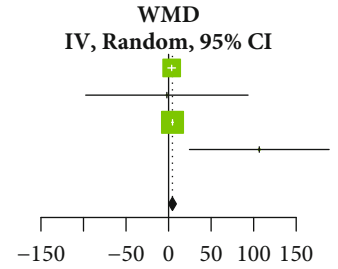


(d) Severe versus nonsevere patients

Non-survivor versus survivor patients

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	WMD IV, Random, 95% CI
Ke CJ 2020	8.69	14.6100	46	5.06	9.9300	148	38.9%	3.63 [−0.88, 8.14]
Gadotti AC 2020	325.00	170.3704	18	327.00	169.6296	38	0.2%	−2.00 [−97.41, 93.41]
Luo M 2020	10.30	7.5630	201	5.68	1.3333	817	60.6%	4.61 [3.56, 5.66]
Hue S 2020	503.70	116.5000	13	397.10	133.1000	25	0.3%	106.60 [24.55, 188.65]
Total (95% CI)			**278**			**1028**	**100.0%**	**4.53 [−0.04, 9.11]**

Heterogeneity: $Tau^2 = 8.71$; $Chi^2 = 6.13$, df = 3 ($P = 0.11$); $I^2 = 51\%$
Test for overall effect: $Z = 1.94$ ($P = 0.052$)



(e) Nonsurvivor versus survivor patients

Figure 8: IL-10 levels in COVID-19 patients. The levels of IL-10 were elevated in (a) nonsevere and (b) severe patients compared to healthy controls, while no significant difference between (c) ICU and non-ICU patients, as well as between (e) nonsurvivor and survivor patients. The levels of IL-10 were elevated in (d) severe patients compared to nonsevere patients.

studies, and pediatric and pregnant COVID-19 patients are excluded in our analysis, and our results may be not applied to them. Additionally, in our meta-analysis, the alterations of serum interleukin (IL-1β, IL-2, IL-4, IL-6, IL-8, and IL-10) levels in COVID-19 patients and healthy subjects were analyzed according to the following groups: (i) COVID-19 patients *vs*. healthy subjects, (ii) severe *vs*. nonsevere patients, (iii) survivor *vs*. nonsurvivor patients, and (iv) ICU *vs*. non-ICU patients. Because no relevant data was reported for the interleukins in some groups, not every kind of interleukin was analyzed according to the four groups, which caused the inconsistency in our results. In the next step, we will further comprehensively analyze the role of interleukins in the development of COVID-19.

Data Availability

The data in the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have declared no potential conflicts of interest in this study.

Authors' Contributions

Concept and design were contributed by Yuanmin Chang and Qinghai You. Acquisition, analysis, or interpretation of data was carried out by Yuanmin Chang and Mengru Bai. Drafting of the manuscript was performed by Yuanmin Chang. Critical revision of the manuscript for important intellectual content was done by all authors. Statistical analysis was carried out by Yuanmin Chang and Mengru Bai. Administrative, technical, or material support was contributed by Qinghai You. Supervision was contributed by Qinghai You.

Supplementary Materials

Supplementary 1. Supplemental Figure 1: the funnel plots concerning IL-2 (A), IL-4 (B), IL-6 (C–E), IL-8 (F, G), and IL-10 (H) in our meta-analysis, and the publication biases were adjusted by the nonparametric trim and fill method.

Supplementary 2. Supplemental Table 1: the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Supplemental Table 2: data extracted from enrolled studies concerning IL-1β in COVID-19 patients. Supplemental Table 3: data extracted from enrolled studies concerning IL-2 in COVID-19 patients and healthy controls. Supplemental Table 4: data extracted from enrolled studies concerning IL-4 in COVID-19 patients and healthy controls. Supplemental Table 5: data extracted from enrolled studies concerning IL-6 in COVID-19 patients and healthy controls. Supplemental Table 6: data extracted from enrolled studies concerning IL-8 in COVID-19 patients. Supplemental Table 7: data extracted from enrolled studies concerning IL-10 in COVID-19 patients and healthy controls. Supplemental Table 8: the Newcastle-Ottawa Scale (NOS) score showed the qualities of included studies.

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