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A systematic review and meta-analysis on blood levels of cytokines/chemokines in COVID-19 cases

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ABSTRACT

We assessed the blood levels of the most important factors such as cytokines/chemokines in Coronavirus disease-2019 (COVID-19). PubMed/Medline and Scopus as two important databases were searched up to March 26, 2020. To analyze the data, we used Review Manager 5.3 software. Out of forty-two records retrieved from two databases, 10 studies were involved in the analysis. Thirty-three cytokines/chemokines were checked. The levels of 27 cytokines/chemokines in COVID-19 patients were higher than the healthy controls, and among 20 cytokines/chemokines; the levels of 10 cytokines/chemokines in severe COVID-19 patients were higher than non-severe COVID-19 patients. Also, out of three cytokines, one had a higher level in the intensive care unit (ICU) patients compared to the non-ICU patients. The findings showed the cytokine storm syndrome in COVID-19 patients, especially in patients with severe disease.

Introduction

In January 2020, severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) extend to various cities in China, and cases with novel Coronavirus disease-19 (nCoV-19) or Coronavirus disease-2019 (COVID-19) have now been confirmed in several countries (1-5). Patients with poor prognostic characteristics at the time of hospitalization often experience significant mortality complications, particularly acute respiratory distress syndrome (ARDS) with various conditions such as multiple organ failure and blood clots (6). Human-to-human transmission is highly correlated with the SARS-CoV-2, and respiratory droplets and human-to-human contact can be the main routes of transmission (7,8). At present, no specific drug is available to treat patients with COVID-19 infection. Hence, there is an immediate need for safe and effective treatment for COVID-19, particularly in severe patients (9). Excessive production of proinflammatory cytokines/chemokines or even hypercytokinemia (cytokine storms) occurs in the Middle East respiratory syndrome-Coronavirus (MERS-CoV)

and SARS-CoV infections (10-12) and is associated with acute lung damage and ARDS development (9,11). Storm cytokines have been described as a systemic inflammatory response to infections and drugs, leading to overactive immune cells and the production of proinflammatory cytokines (13). Recent studies have reported a reduction in the number of peripheral blood lymphocytes and an increase in the level of inflammatory cytokines in COVID-19 patients (14,15). However, it is largely obscure how various subtypes of lymphocytes, as well as the kinetics of inflammatory cytokines in peripheral blood, alter during COVID-19 (16). One research also found that COVID-19 mortality might be due to "cytokine storm syndrome" activated by the virus or fulminant myocarditis (17). Another study (18) reported high morbidity and mortality due to increased levels of interleukin (IL)-6, IL-8, IL-2R, IL-10, and tumor necrosis factor-alpha (TNF-α). The cytokine level may even be used as a prognostic factor for critically ill patients (18). In the study of Takahashi et al. (19), the levels of both IL-8 and IL-18 in the male patients were higher than in female ones; however, a worse prognosis was seen in females with an increased cytokine level. They suggested a bias for gender while interpreting the result. Here, this meta-analysis evaluated the blood levels of cytokines/chemokines in the patients with COVID-19 for better clarification of some aspects of this disease.

Methods

The meta-analysis was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) protocols (20).

Search strategy

Two PubMed/Medline and Scopus databases were comprehensively searched by an author (M.S) to retrieve all relevant references published until March 26, 2020, without restrictions. The searched queries were ("COVID-19" or "nCoV-19" or "Coronavirus disease-19" or "SARS-CoV-2") and ("cytokine*" or "interleukin*" or "interferon*" or "chemokine*"). The citations (all types of studies) correlating with our topic were manually searched, as well.

Eligibility criteria

The inclusion criteria were (1) studies including two separation groups; (2) studies assessing the relationship between blood cytokine levels and COVID-19; (3) the presence of SARS-CoV-2 found by the quantitative polymerase chain reaction method; (4) studies that the data to estimate the mean difference (MD) and 95% confidence interval (CI) in COVID-19 patients and healthy controls.

The exclusion criteria were as (1) studies with insufficient and irrelevant data; (2) conference papers, review articles, book chapters, and meeting abstracts.

The severe type of COVID-19 is defined by the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (21) in the studies as follows: 1. Respiratory distress with a respiratory rate greater than 30 per minute; 2. Oxygen saturation ≤93% in the resting state; 3. Arterial blood oxygen partial pressure (PaO_2)/oxygen concentration (FiO_2) ≤300 mmHg. Additionally, intensive care unit (ICU) patients were the patients who had been admitted to the ICU because they required high-flow nasal cannula or higher-level oxygen support measures to correct the hypoxemia.

Study selection

The titles and abstracts of the retrieved studies were independently checked by two authors (M.R and M.S). Then, both authors selected the relevant articles, while the full-text articles were retrieved by another author (H.N) and he excluded several full-texts.

Data extraction

The data from each study included in the analysis were independently extracted by two authors (M.R and M.S). If there was a discrepancy between the two authors, another author (H.N) helped make the last decision. All the authors endorsed the quality of the articles and reviewed the manuscript.

Statistical Analyses

The crude MD and 95% CI were estimated using Review Manager 5.3 software. Heterogeneity was evaluated across the studies applying both Cochran Q (22) and I^2 metrics (23). Additionally, $P_{heterogeneity}$ or P_h <0.1 and I^2 >50% identified a statistically significant heterogeneity; hence, the analysis of the random-effects model was used to estimate the values of the pooled MD (95% CI). Otherwise, we used the fixed-effects model. The publication bias across the studies with Egger and Begg's tests for the analyses of more than three studies was analyzed by comprehensive meta-analysis version 2.0 software with a $p<0.05$ as statistically significant.

Some studies presented the values of cytokines/chemokines in standard errors and medians (interquartile), which were changed into standard deviation (SD) and mean SD, respectively (24). The blood cytokine/chemokine levels are presented in "pg/mL." The levels of cytokines/chemokines in some studies were estimated based on the graphs by GetData Graph Digitizer 2.26 software. The quality score of each study was performed based on the Newcastle-Ottawa Quality Assessment Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Results

Forty-two records were retrieved from both databases and after removing the duplicate and irrelevant records, seventeen articles met the criteria (Figure 1). Seven full-text articles were excluded for other reasons (one case report, two reviews, and

four articles without healthy control groups). Finally, ten studies (7,16,25-32) were involved in the meta-analysis.

The characteristics of the studies included in the analysis are identified in Table 1. Eight studies (7,16,26-31) compared the cytokine levels in both severe and non-severe COVID-19 patients, two studies (25,29) compared the cytokine levels between non-ICU and ICU patients, and three studies (29,30,32) included healthy control groups. The quality score of each study is shown in Table 1.

The funnel plots are shown in Supplementary Appendix 1 and a summary of the main results is shown in Tables 1, 2, and 3. Table 2 shows the comparison of the levels of cytokines/chemokines in COVID-19 patients versus healthy controls in serum and plasma. The pooled results showed a significant difference between the two groups (COVID-19 patients versus healthy controls) evaluating the levels of IL-1β (MD: 1.02; p<0.00001), IL-1Rα (MD: 692.22; p=0.002), IL-2 (MD: 5.02; p=0.0001), IL-2Rα (MD: 35.84; p=0.02), IL-4 (MD: 1.12; p<0.00001), IL-5 (MD: 5.58; p=0.007), IL-6 (MD: 10.54; p=0.009), IL-7 (MD: 14.21; p<0.0001), IL-8 (MD: 12.27; p=0.008), IL-9 (MD: 28.45; p<0.00001), IL-10 (MD: 9.31; p=0.0003), IL-12 (p70) (MD: 2.65; p=0.0006), IL-13 (MD: 3.32; p<0.00001), IL-15 (MD: 70.15; p=0.01), IL-17 (MD: 1.02; p<0.00001), TNF-α (MD: 18.94; p=0.0002), IFN-γ (MD: 12.42; p=0.0002), IP-10 (MD: 1725.35; p=0.003), G-CSF (MD: 86.33; p=0.0002), MIP-1α (MD: 1.60; p<0.0001), M-CSF (MD: 19.10; p=0.01), CTACK (MD: 325.52; p<0.00001), GM-CSF (MD: 1.22; p<0.001), MCP-1 (MD: 26.88; p=0.003), FGF basic (MD: 10.37; p<0.00001), RANTES (MD: 3010.06; p=0.03), and Eotaxin (MD: 9.57; p=0.02), not for HGF (MD: 546.77; p=0.05), MCP-3 (MD: 3.37; p=0.05), MIG (MD: 636.66; p= 0.05), MIP-1β (MD: 14.42; p=0.08), VEGF (MD: 105.15; p=0.05), and PDGF-BB (MD: 857.47; p=0.26).

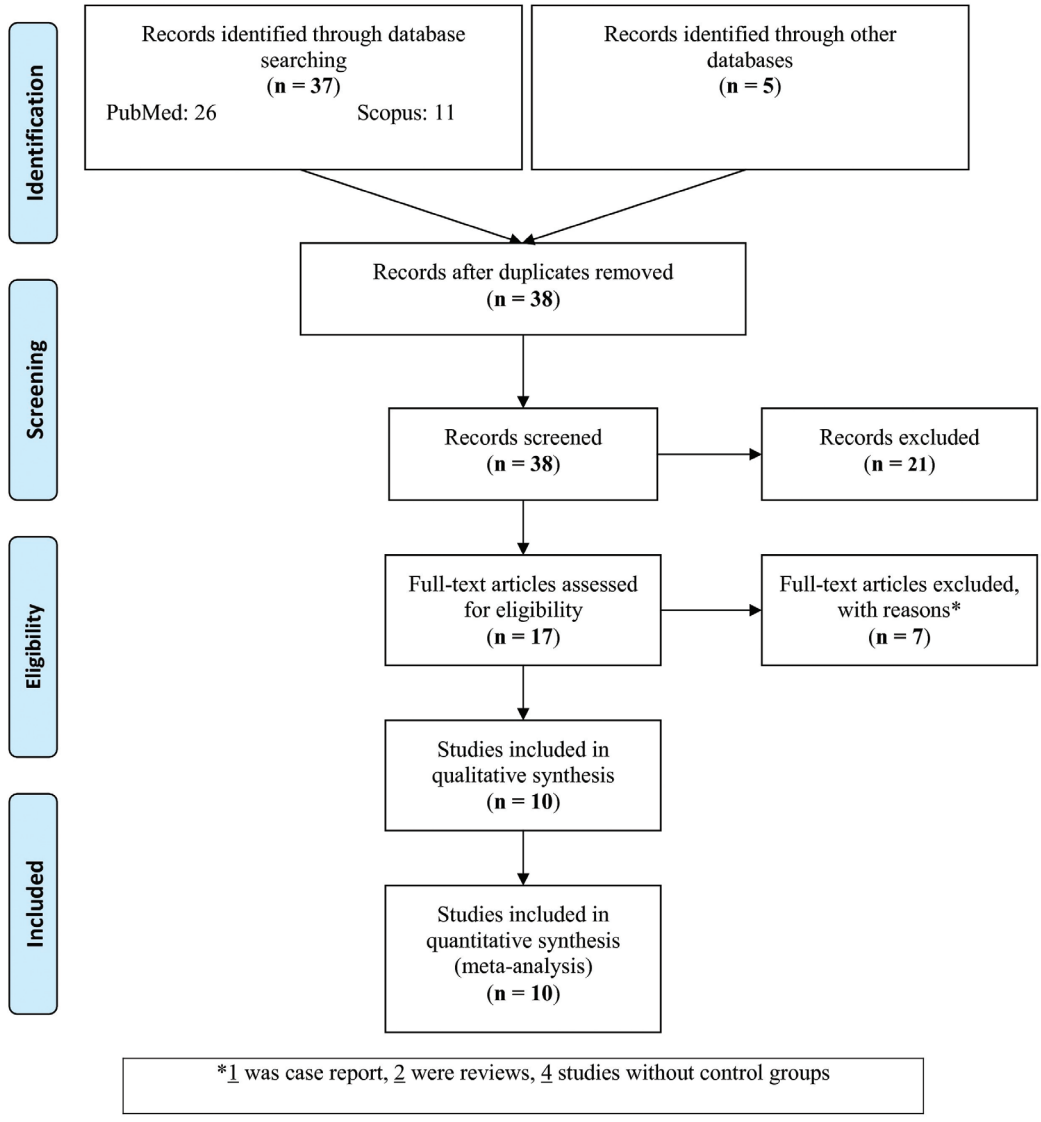

Figure 1. Flowchart of study selection

Table 1. Characteristics of studies included in the meta-analysis (n=10)

Study, year	No of cases	No of controls	Median age of cases, year	Median age of controls, year	Male % of cases	Male % of controls	Quality score	Marker
Cai et al. (25) 2020	240 (no ICU care) & 58 (ICU care)	NA	40 & 64	NA	46.3 & 56.9	NA	6	Il-6
Diao et al. (27) 2020	249 (non-severe) & 20 (severe)	NA	Range: 5-97	NA	NA	NA	6	Il-10, TNF-α, Il-6
Gao et al. (28) 2020	28 (non-severe) & 15 (severe)	NA	43 & 45.2	NA	57 & 60	NA	7	Il-6
Huang et al. (29) 2020	28 (no ICU care) & 13 (ICU care)	4	49 & 49	Adult	68 & 85	NA	6	IL-1b, IL-1RA, IL-2, IL-4, IL-6, IL-7, IL-8, IL-10, IL-17, IFN-γ, TNF-α, PDGF-BB, IP-10, G-CSF, IL-13, IL-9, Eotaxin, VEGF MIP-1β, RANTES, MIP-1α, FGF basic, IL-12 (p70), IL-5, IL-15, MCP-1
Chen et al. (26) 2020	15 (non-severe) & 9 (severe)	NA	56	NA	72	NA	6	IL-1b, IL-2R, IL-6, IL-10, IL-8, TNF-α
Liu et al. (30) 2020	4 (non-severe) & 8 (severe)	8	62.5	28	66.7	50	6	M-CSF, IL-10, IL-17, IL-4, IP-10, IL-7, IL-1RA, G-CSF, IFN-γ, IL-2, PDGF-BB, HGF, MCP-3, MIG, MIP-1α, MIP-1b, TNF-α, IL-8, IL-13, IL-9, Eotaxin, VEGF, RANTES, MIP-1α, FGF basic, IL-12 (p70), IL-5, IL-15, MCP-1
Liu et al. (16) 2020	27 (non-severe) & 13 (severe)	NA	43.2 & 59.7	NA	29.6 & 53.8	NA	6	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ
Qin et al. (31) 2020	166 (non-severe) & 286 (severe)	NA	53 & 61	NA	54.2 & 48.2	NA	7	TNF-α, Il-1β, Il-2R, Il-6, Il-8, Il-10
Wan et al. (7) 2020	45 (non-severe) & 18 (severe) for IL-6, 97 (non-severe) & 21 (severe) for IFN-γ, 102 (non-severe) & 21 (severe) for others	NA	43.0 & 61.3	NA	53.9 & 52.4	NA	6	IL-4, IL-6, IL-10, IL-17, TNF-α, IFN-γ
Yang et al. (32) 2020	19 (non-severe) & 34 (severe)	8	51 & 63.5	NA	47.3 & 64.7	NA	6	FN-γ, IL-1RA, IL-2RA, IL-6, IL-10, IL-18, HGF, MCP-3, MIG, M-CSF, G-CSF, MIG-1a, CTACK, IP-10

NA: Not available, ICU: Intensive care unit, CI: Confidence interval, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha

Table 3 shows the comparison of the blood levels of cytokines/chemokines in severe versus non-severe COVID-19 patients. The pooled results illustrated a significant difference between severe and non-severe COVID-19 patients in IL-1Rα (MD: 1427.24; p=0.008), IL-2R (MD: 504.98; p=0.02), IL-2Rα (MD: 33.14; p<0.00001), IL-6 (MD: 20.52; p<0.00001), IL-8 (MD: 7.27; p<0.01), IL-10 (MD: 2.13; p<0.00001), G-CSF (MD: 80.58; p<0.00001), HGF (MD: 700.67; p=0.005), MCP-3 (MD: 6.48; p<0.00001), and MIG (MD: 1039.43; p=0.0005) levels, not for the IL-1β (MD: 0.15; p=0.84), IL-2 (MD: 2.12; p=0.29), IL-4 (MD: 0.88; p=0.06), IL-17 (MD: 2.50; p=0.33), IFN-γ (MD: 4.66; p=0.09), TNF-α (MD: 0.47; p=0.28), IP-10 (MD: 7991.86; p=0.21), CTACK (MD: 82.97; p=0.42), MIP-1α (MD: 0.82; p=0.54), and M-CSF (MD: 34.62; p=0.18) levels.

The comparison of the blood levels of three cytokines (IL-6, TNF-α, and IL-10) in ICU versus non-ICU patients is shown in Table 4. The pooled results indicated a significant difference between the two mentioned groups just in the TNF-α (MD: 14.46; p=0.004) level, not IL-6 (MD: 12.88; p=0.10) and IL-10 (MD: 4.41; p=0.06) levels.

Table 2. Comparison of blood levels of cytokines/chemokines between COVID-19 patients and healthy controls

Cytokine, pg/mL	No of studies	MD	95% CI		p-value	Chi²	Z	I²	P_h
			Min	Max					
IL-6	3	10.54	2.62	18.47	0.009	25.07	2.61	80%	0.0001
IL-10	3	9.31	4.25	14.37	0.0003	50.65	3.61	90%	<0.00001
TNF-α	2	18.94	8.94	28.95	0.0002	8.46	3.71	65%	0.04
IFN-γ	3	12.42	5.80	19.04	0.0002	37.24	3.68	87%	<0.00001
IL-1b	2	1.02	0.57	1.47	<0.00001	6.70	4.48	55%	0.08
IL-1Rα	3	692.22	257.31	1127.12	0.002	30.98	3.12	84%	<0.00001
IL-2	2	5.02	2.47	7.57	0.0001	9.14	3.86	67%	0.03
IL-4	2	1.12	0.67	1.57	<0.00001	16.99	4.87	82%	0.0007
IL-17	2	4.98	3.00	6.96	<0.00001	4.80	4.94	38%	0.19
IL-8	2	12.27	3.23	21.30	0.008	31.70	2.66	91%	<0.00001
IL-2Rα	2	35.84	4.77	66.91	0.02	36.93	2.26	92%	<0.00001
IP-10	3	1725.35	579.14	2871.57	0.003	45.17	2.95	89%	<0.00001
G-CSF	3	86.33	41.20	131.45	0.0002	26.21	3.75	81%	<0.0001
MIP-1α	3	1.60	0.83	2.38	<0.0001	15.23	4.05	67%	0.009
M-CSF	2	19.10	4.13	34.06	0.01	21.12	2.50	86%	<0.0001
HGF	2	546.77	-10.01	1103.55	0.05	15.59	1.92	81%	0.001
MCP-3	2	3.37	-0.00	6.75	0.05	25.10	1.96	88%	<0.0001
MIG	2	636.66	13.96	1259.37	0.05	16.87	2.00	82%	0.0008
CTACK	2	325.52	186.28	464.75	<0.00001	2.83	4.58	0%	0.42
MIP-1b	2	15.42	-2.11	32.95	0.08	6.26	1.72	52%	0.10
GM-CSF	2	1.22	0.62	1.83	<0.0001	2.20	3.95	0%	0.53
MCP-1	2	26.88	9.07	44.70	0.003	18.39	2.96	84%	0.0004
IL-15	2	70.15	13.96	126.33	0.01	2.71	2.45	0%	0.44
IL-5	2	5.58	1.53	9.63	0.007	0.12	2.70	0%	0.73
IL-12 (p70)	2	2.65	1.14	4.16	0.0006	3.32	3.45	10%	0.34
FGF basic	2	10.37	6.65	14.09	<0.00001	4.52	5.46	34%	0.21
RANTES	2	3010.06	226.48	5793.67	0.03	10.73	2.12	72%	0.01
VEGF	2	105.15	-1.64	211.95	0.05	41.23	1.93	93%	<0.00001
Eotaxin	2	9.57	1.84	17.30	0.02	0.70	2.43	0%	0.87
IL-9	2	28.45	23.50	33.41	<0.00001	1.34	11.25	0%	0.72
IL-13	2	3.32	1.86	4.77	<0.00001	8.04	4.47	63%	0.05
PDGF-BB	2	857.47	-655.68	2406.63	0.26	31.24	1.12	90%	<0.00001
IL-7	2	14.21	7.89	20.52	<0.0001	13.41	4.41	78%	0.004

COVID-19: Coronavirus disease-2019, MD: Mean difference, CI: Confidence interval, P_h: $P_{heterogeneity}$, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, Min: Minimum, Max: Maximum

Both Egger and Begg's tests on the analyses with more than three studies were used (IL-6, IL-10, TNF-α, and IFN-γ levels in severe COVID-19 compared to non-severe COVID-19 patients) (Figure 2). The results didn't show any publication bias across the studies (p>0.05).

Discussion

Studies have shown that cytokines and chemokines can play a significant role in the immunity and immune system of patients with viral infections (9). The nCoV-19 can lead to severe and even fatal respiratory illnesses such as ARDS (14) and COVID-19 treatment depends primarily on the patient's immune system. When the overactive immune system kills the virus, it produces many inflammatory agents, which lead to severe cytokine storms (33). The virus can activate immune cells (such as T-cells, B-cells, macrophages, dendritic cells, neutrophils, and monocytes) and living tissue cells, which produce a large number of inflammatory cytokines (34). This meta-analysis of cytokines reported that the blood levels of most cytokines were higher in the COVID-19 patients than in the healthy controls. Moreover, several cytokines (IL-6, IL-8, G-CSF, IL-10, IL-1Rα, IL-2, HGF, IL-2Rα, MIG, and MCP-3) had higher levels in more severe than non-severe COVID-19 patients. Additionally, the blood levels of TNF-α in the ICU patients were higher than in the non-ICU patients. Finally, generalizations cannot be made for other cytokines.

SARS-CoV-2 is a novel beta-Coronavirus dependent on the Sarbecovirus subgenus of the Coronaviridae family (2). Inflammatory responses due to viral infections play a significant role in the severity of pulmonary pathology (35,36). The virus

Table 3. Comparison of blood levels of cytokines/chemokines between severe COVID-19 and non-severe COVID-19 patients

Cytokine, pg/mL	No of studies	MD	95% CI		p-value	Chi²	Z	I²	P_h
			Min	Max					
IL-6	8	20.52	13.83	27.21	<0.00001	18.61	6.01	62%	0.010
IL-10	6	2.13	1.69	2.57	<0.00001	6.08	9.57	18%	0.30
TNF-α	5	0.47	-0.38	1.32	0.28	11.96	1.08	67%	0.02
IFN-γ	4	4.66	-0.70	10.02	0.09	19.85	1.71	85%	0.0002
IL-1b	3	0.15	-1.31	1.62	0.84	2.16	2.16	54%	0.14
IL-1Rα	2	1427.24	372.97	2481.51	0.008	1.38	2.65	27%	0.24
IL-2	2	2.12	-1.82	6.07	0.29	17.48	1.06	94%	<0.0001
IL-4	3	0.88	-0.05	1.82	0.06	17.77	1.85	89%	0.0001
IL-17	2	2.50	-2.50	7.50	0.33	20.03	0.98	95%	<0.0001
IL-8	3	7.27	1.68	12.87	0.01	6.06	2.55	67%	0.05
IL-2R	2	504.98	44.66	965.31	0.03	138.73	2.15	99%	<0.00001
IL-2Rα	2	33.14	23.49	42.79	<0.00001	0.07	6.37	0%	0.79
IP-10	2	7991.86	-4397.72	20381.45	0.21	4.46	1.26	78%	0.03
G-CSF	2	80.58	45.78	115.38	<0.00001	0.01	4.54	0%	0.94
MIP-1α	2	0.82	-1.79	3.42	0.54	4.95	0.61	80%	0.03
M-CSF	2	34.62	-16.34	85.57	0.18	2.22	1.33	55%	0.14
HGF	2	700.67	210.5	1190.78	0.005	0.00	2.80	0%	0.96
MCP-3	2	6.48	4.13	8.84	<0.00001	1.34	5.39	26%	0.25
MIG	2	1039.43	455.75	16.23.11	0.0005	0.60	3.49	0%	0.44
CTACK	2	82.97	-120.31	286.24	0.42	0.23	0.80	0%	0.63

COVID-19: Coronavirus disease-2019, MD: Mean difference, CI: Confidence interval, P_h: $P_{heterogeneity}$, IL: Interleukin, Min: Minimum, Max: Maximum, TNF-α: Tumor necrosis factor-alpha

Table 4. Comparison of blood levels of cytokines/chemokines in ICU versus non-ICU patients with COVID-19

Cytokine, pg/mL	No of studies	MD	95% CI		p-value	Chi²	Z	I²	P_h
			Min	Max					
IL-6	2	12.88	-2.28	28.04	0.10	1.36	1.67	26%	0.24
IL-10	2	4.41	-0.12	8.94	0.06	0.00	1.91	0%	0.95
TNF-α	2	14.46	4.71	24.21	0.004	0.47	2.91	0%	0.49

MD: Mean difference, CI: Confidence interval, P_h: $P_{heterogeneity}$, IL: Interleukin, COVID-19: Coronavirus disease-2019, Min: Minimum, Max: Maximum, ICU: Intensive care unit, TNF-α: Tumor necrosis factor-alpha

particles extend via the respiratory mucosa and infect other cells, inducing a cytokine storm in the body, triggering many immune responses, and altering peripheral leukocytes and lymphocytes (28), like SARS-CoV-2 (14,31). One study (28) reported that IL-6 levels could be applied to estimate and diagnose the adult COVID-19 severity. SARS-CoV-2 infection increases the secretion of IL-4 and IL-10 and inflammation, which makes a difference with the SARS-CoV infection (37). Due to the high levels of cytokines caused by 2019-nCoV-19 infections, corticosteroids have been continuously applied to remedy patients with severe diseases to get the potential benefits by decreasing inflammatory lung injury (29). One study (30) confirmed that the levels of cytokines could increase in COVID-19 patients because several cytokines/chemokines (IL-1RA, IL-2, IL-4, IL-7, IFN-α2, IFN-γ, IL-10, IL-12, IL-17, IP-10, M-CSF, and G-CSF) were linearly related to lung injury and would be potential biological markers for COVID-19 severity. Studies have shown serum elevated levels of IP-10, MIP-1α, IL-6, IL-8, and MCP1 in the SARS-CoV-infected patients (38,39), and IFN-α2, IFN-γ, IL-10, IL-15, and IL-17 in the plasma levels of the patients with MERS-CoV (40). A study suggested that a subgroup of severe COVID-19 patients have cytokine storm syndrome (41).

The pathophysiology of the above unusual pathogenicity for SARS-CoV or MERS-CoV is not fully understood. Preliminary studies have shown that elevated serum proinflammatory cytokines (e.g., IFN-γ, IP10, MCP1, IL-1β, IL-6, and IL-12) are associated with pulmonary inflammation and extensive lung damage in SARS patients (36). Patients infected with coronavirus had high levels of IL-1β, IP10, IFN-γ, and MCP1, which may lead to the activation of T-helper-1 cell responses. Additionally, patients who required ICU admission had higher concentrations of TNF-α, IP10, G-CSF, MCP1, and MIP-1α, than patients who did not require ICU admission, indicating that cytokine storms were associated with disease severity (29). Lymphocyte subsets play an important role in regulating the body's immune system, with each cell restricting and regulating each other. One study showed that among nCoV-19 pneumonia patients, the reduction in CD4 + T-cells was 52.90% and 95.24% in the mild and severe groups, respectively. The reduction in CD8 + T-cells was 28.40% and 61.90% in the mild and severe groups, respectively, which indicates that T lymphocytes are inhibited in severe patients when the body is resistant to nCoV-19 infection (7).

Although the mechanism of cytokines is largely unknown, efforts to use them or their inhibitors for treating diseases have been successful and acceptable (42,43). Despite their unpleasant side effects, IFN-α and IFN-γ are often used clinically (42,44,45), based on which, IFN-γ is an official drug that is recommended for the diagnosis and treatment of COVID-19-infected pneumonia (46,47). Additionally, one study showed that IL-6 was an early index of the cytokine release syndrome in this pneumonia (48). Therefore, we should consider the potential therapeutic role of extracorporeal cytokine removal in treating COVID-19-associated cytokine storms (49-51) in the future.

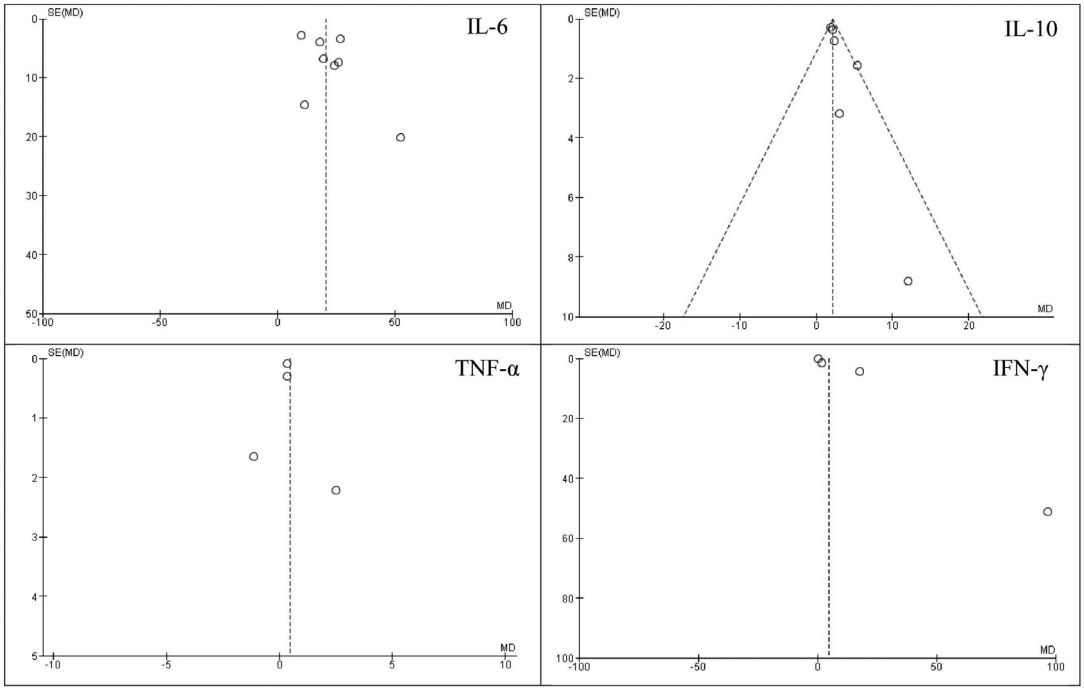

Figure 2. Funnel plots of IL-6, IL-10, TNF-α, and IFN-γ levels in severe COVID-19 compared with non-severe COVID-19 patients
TNF-α: Tumor necrosis factor-alpha, COVID-19: Coronavirus disease-2019, IL: Interleukin

Study Limitations

Limitations of the study were 1) the disease is new and not much research has been done raising concerns of bias across studies, 2) additional analyses were not available (e.g., subgroup and meta-regression analyses), 3) several studies reported their data on the graphs and we had to estimate them based on the software, 4) several studies did not report the mean (±SD) and we had to estimate them based on the formula. The strength of the study was the inclusion of all studies with English and non-English full-texts and preprint studies.

Conclusion

The results confirmed the cytokine storm syndrome in COVID-19 patients, particularly the severe cases. Therefore, the treatment of this syndrome in this disease in the future is recommended as a new treatment to reduce the possible side effects, and studies with more samples and different regions are needed to confirm the results of this meta-analysis. However, generalizations cannot be made for cytokines, which were evaluated in only two studies.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.R., M.S., Design: M.R., M.S., Data Collection or Processing: H.N., F.N., B.S., Analysis or Interpretation: M.R., M.S., Literature Search: M.S., Writing: M.R., H.N., F.N., B.S., M.S.

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