Elevated Levels of Pleiotropic Interleukin-6 (IL-6) and Interleukin-10 (IL-10) are Critically Involved With the Severity and Mortality of COVID-19: An Updated Longitudinal Meta-Analysis and Systematic Review on 147 Studies

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ABSTRACT

OBJECTIVES: Disruption in the natural immune reaction due to SARS-CoV-2 infection can initiate a potent cytokine storm among COVID-19 patients. An elevated level of IL-6 and IL-10 during a hyperinflammatory state plays a vital role in increasing the risk of severity and mortality. In this study, we aimed to evaluate the potential of circulating IL-6 and IL-10 levels as biomarkers for detecting the severity and mortality of COVID-19.

METHODS: This study was conducted according to the Cochrane Handbook and PRISMA guidelines. Authorized databases were searched to extract suitable studies using specific search terms. RevMan 5.4 was applied for performing the meta-analysis. Mean differences in IL-6 and IL-10 levels were calculated among COVID-19 patients via a random-effects model. NOS scoring, publication bias and sensitivity analyses were checked to ensure study quality.

RESULTS: A total of 147 studies were selected, with 31 909 COVID-19 patients under investigation. In the severity analysis, the mean concentration of IL-6 was significantly higher in the severe COVID-19 cases than in the non-severe cases (MD: 19.98; $P < .001$; 95% CI: 17.56, 22.40). Similar result was observed for IL-10 mean concentration in severe COVID-19 cases (MD: 1.35; $P < .001$; 95% CI: 0.90, 1.80). In terms of mortality analysis, circulating IL-6 showed sharp elevation in the deceased patients (MD: 42.11; $P < .001$; 95% CI: 36.86, 47.36). IL-10 mean concentration was higher in the dead patients than in the survived patients (MD: 4.79; $P < .001$; 95% CI: 2.83, 6.75). Publication bias was not found except for comparing IL-6 levels with disease severity. Sensitivity analysis also reported no significant deviation from the pooled outcomes.

CONCLUSIONS: Elevated levels of circulating IL-6 and IL-10 signifies worsening of COVID-19. To monitor the progression of SARS-CoV-2 infection, IL-6 and IL-10 should be considered as potential biomarkers for severity and mortality detection in COVID-19.

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Introduction

Novel coronavirus disease (COVID-19) prevalence was first commenced in 2019 by a highly variating virus "SARS-CoV-2" (severe acute respiratory syndrome coronavirus 2) infection. The infection spread rapidly, turning into a worldwide pandemic that caused nearly 5.6 million death in the last 2 years.[1-3] A number of diagnostic and treatment approaches have been approved in the fight against COVID-19, although a concrete predictor of disease progression is yet to reveal.[4,5] The highly unpredictable nature of this current pandemic has made it difficult to detect the severity of the condition in time. It is crucial to establish a reliable diagnostic marker to follow the pattern of disease development and to halt the process from getting severe, even fatal. Moreover, identifying sensitive and specific biomarkers would create an opportunity to promote stronger preventive and therapeutic strategies.[6-8]

The key negative prognostic factor of SARS-CoV-2 infection pathophysiology is cytokine storm, a hyperinflammatory process of cytokine releasing that causes acute systemic reactions. This specific immune reactive condition drives the disease state toward acute respiratory distress syndrome (ARDS). Inflammatory cytokines, more specifically interleukins, are found to be the main mediators involved in the cytokine storm development.[9] Although rapid innate immune system reaction following SARS-CoV-2 infection is the first-line defense against COVID-19, excessively active immune reaction generates severe

complications. During SARS-CoV-2 infection, irreversibly critical damage occurs in the pulmonary system and lung tissues by higher plasma concentrations of circulating interleukins.[9,10] Among the multifunctional proinflammatory cytokines, interleukin-6 (IL-6) and interleukin-10 (IL-10) are suspected to be strongly involved in the COVID-19 related cytokine storm for their potential roles in acute phase immune reactions.[11-13]

IL-6, an inflammatory mediator with pleiotropic nature, is highly produced during the initial stage of inflammation and rapidly activates multiple acute phases of inflammatory reactants. In COVID-19 patients, IL-6 is produced in response to antigens from several immune cell types, and a number of clinical investigative studies have reported that serum level of circulating IL-6 was critically higher among the COVID-19 patients from severe to the critical stage.[11,14-16] Another cross-sectional study stated evidence that serum levels of IL-6 above 24.3 pg/ml might be associated with severe pneumonia in COVID-19 patients.[17] IL-10 exerts powerful anti-inflammatory actions that control severe host immune responses toward antigens by preventing multiple functions of T-cells and neutral killer (NK) cells. Again, dysregulation in IL-10 concentration may influence the immune response and severity of SARS-CoV-2 infected patients.[18] In this context, the serum level of IL-10 also showed significant elevation in severe and critical cases of COVID-19, commensurate with IL-6 serum level. Several studies showed evidence that both IL-6 and IL-10 are positively related to the severity and mortality of COVID-19.[8,19-21] According to this evidence, alteration in the normal level of circulating IL-6 and IL-10 can act as potential biomarkers for COVID-19.[13]

Although some previous meta-analyses attempted to evaluate the link between circulating IL-6 and IL-10 levels with severity and mortality of COVID-19, they recommended further investigation with a larger sample size to validate their findings. For this reason, we conducted this updated systematic review and meta-analysis with available literature to reveal the correlation between IL-6 and IL-10 elevation with COVID-19 and the effectiveness of testing serum IL-6 and IL-10 levels as clinical biomarkers.

Methods

The recommendations narrated in the Cochrane Handbook[22] and PRISMA (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines[23] were followed to conduct this systematic review and meta-analysis. The study is also registered in INPLASY (http://inplasy.com/), and the registration number is INPLASY202240046.

Literature searching strategy

The international scientific authorized databases such as Google Scholar, PubMed, Embase, CNKI, Cochrane Library, and Web of science were used as primary sources to identify and collect the eligible literature. Additional secondary databases were also comprehensively searched to extract more related studies. The specific search terms used for this study were: "COVID-19" OR "SARS-Cov-2"; "interleukin-6 " OR "IL-6"; and "interleukin-10" OR "IL-10." The search strategy for each database is enlisted in Supplemental Table 1. All the included literature was selected from December 2019 to December 2021 time period.

Study selection

Two authors individually screened titles and abstracts of the studies from different databases to avoid bias and shortlisted articles with eligibility potentials. The unrelated articles were eliminated from the list after full-text inspection based on the inclusion and exclusion criteria. Any difference of opinions among the authors was resolved via a logical argument with the assistance of the third researcher. The study selection process is outlined in Figure 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) clinical studies, case-control investigations or cohort studies; (2) articles representing severity and mortality in COVID-19 patients; (3) articles providing information on IL-6 and IL-10 level among mild-to-severe COVID-19 patients; (4) articles reporting IL-6 and IL-10 level in the COVID-19 survivors and deceased patients.

Critically ill patients, patients with severe dyspnea, critically low oxygen level, patients under mechanical ventilation, or admitted to the intensive care unit (ICU) were considered severe conditions of COVID-19.

Exclusion criteria: (1) meta-analysis, review articles, letters, or comments; (2) articles written in languages other than English or Chinese; (3) incomplete information required in this meta-analysis; (4) unavailability of full texts.

Quality assessment

The Newcastle-Ottawa Scale (NOS) can determine the quality range of studies by rating them from 0 to 10 stars based on some specific features (Available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.). Articles that scored ⩾6 were considered high-quality ones. All the studies included in this meta-analysis were assessed with NOS for quality evaluation by 2 reviewers independently. Studies that scored less than 6 stars were excluded to maintain the quality range for the present analysis.

Data extraction

Data collection from the enlisted articles was conducted by 2 researchers. Basic information like author name, study period,

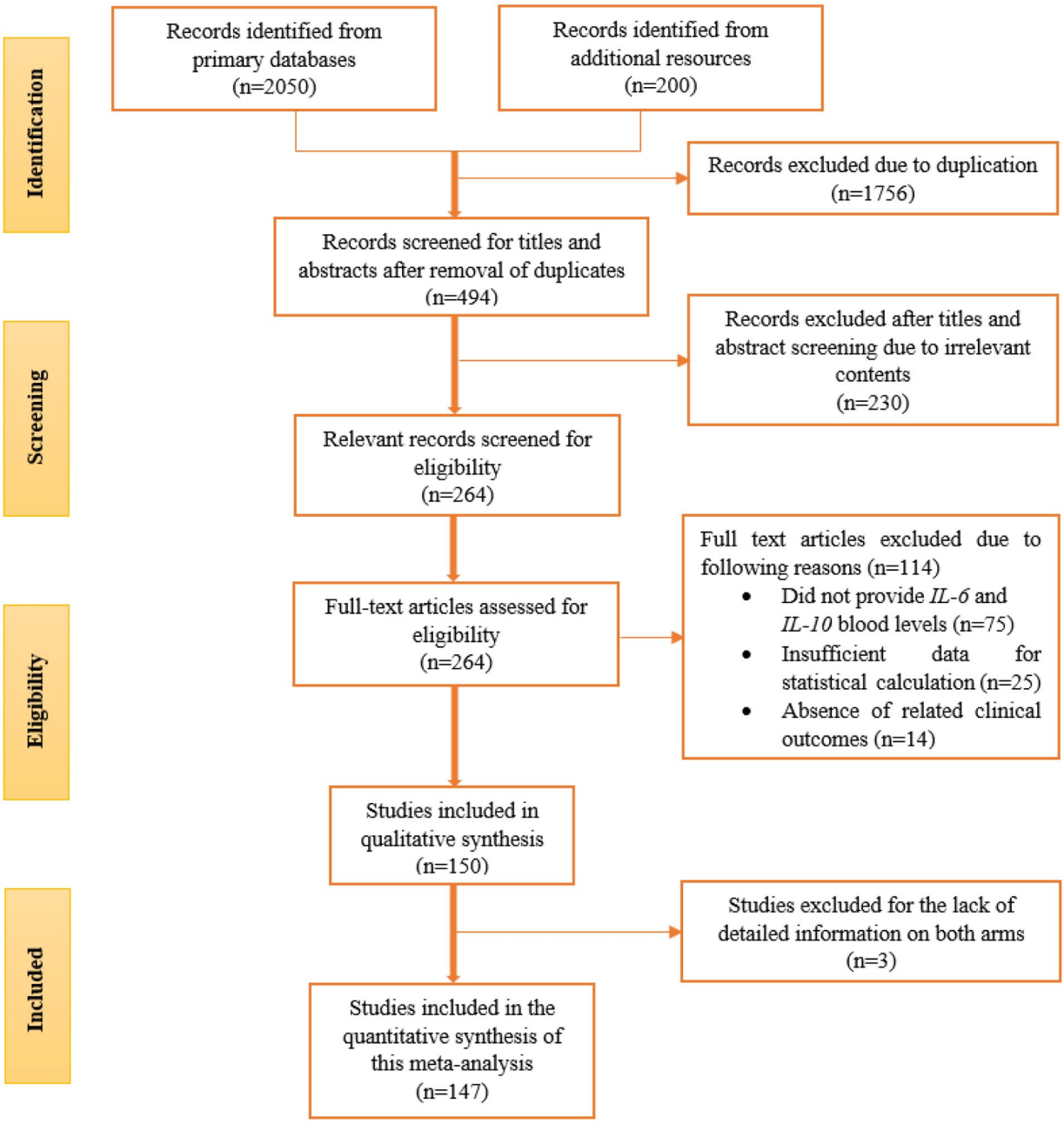

Figure 1. Study flow chart representing the selection process of eligible studies.

study location, ethnicity, settings, study design, number of COVID-19 patients, age, mild state, severe to a critical state, number of deceased patients, IL-6, and IL-10 concentrations in patients were extracted.

Publication bias assessment

The risk of publication bias was determined by using Review Manager (RevMan 5.4) software for systematic review and meta-analysis. Egger regression test and Begg & Mazumdar test were performed to detect the presence of publication bias. Both the tests were used to verify the significance level of bias among the studies. The presence of asymmetry in the funnel plots also indicates a significant presence of publication bias.

Statistical analysis

The statistical analysis was performed by comparing the concentration level of both IL-6 and IL-10 among the COVID-19 patients according to the disease severity. Patients with mild symptoms or at the recovery stage were considered as the control population and patients with severe or critical conditions were termed as an experimental population. A secondary analysis was also conducted among the survived patients and deceased patients. The control arm showed the IL-6 and IL-10 concentrations among the survived patients, and the experimental arm showed peak concentration (last diagnostic count) levels among the dead patients. The name of the software used to carry out this meta-analysis was RevMan 5.4 from the

Cochrane Collaboration, 2020. The unit of concentration measured as pg/ml. We used mean concentration with standard deviation for numerical presentation. The numerical data (mean and SD) was estimated using a validated equation. Estimation of the outcome was pooled as the mean difference with 95% CIs (confidence interval). Two analysis models were used for statistical calculation—the fixed-effects model and the random-effects model. In case of significant heterogeneity (chi-square $I^2 \geq 50$ and $P < .10$), DerSimonian-Laird random-effects model was applied and, in the absence of the heterogeneity fixed-effects model (Mantel-Haenszel) was applied (chi-square $I^2 = 50$ and $P > .10$). To evaluate the credibility of the results acquired from this study, we performed sensitivity analysis by omitting the studies one by one with the application of RevMan 5.4.

Results

Study selection

We conducted this meta-analysis on overall 31 909 COVID-19 patients from 147 studies.[2,4-7,9-18,24-154] Among the recruited patients, 3137 were deceased, and the rest, 28 772 patients, showed mild to severe disease symptoms. The age range of the patients was between 6.25 ± 4.31 and 85.83 ± 7.61 years. All the studies had hospital-based settings; patients under investigation were admitted to the hospitals. No patients under self-quarantine or without hospital admission were included in the study. The recruited studies followed various designs, such as retrospective cohort, prospective cohort, observational cohort, single centered or multicentered cohort, case-control cohort, retrospective observational, prospective observational, prognostic cohort, retrospective longitudinal, non-randomized, cross-sectional observational, and clinical studies. From 147 studies, 107 studies reported IL-6 and IL-10 concentrations in COVID-19 patients and their association with disease severity. On the other hand, 49 studies reported an association of IL-6 and IL-10 serum levels with mortality in COVID-19 patients. Cytokine levels were measured using different biochemical assays—Enzyme-linked immunosorbent assay (ELISA); Electro-chemiluminescent immunoassay (ECLIA); Chemiluminescent immunoassay (CLIA); Online hemodiafiltration (OLHDF), Flow cytometry, Bio plex multiplex immunoassay, Automated immunoassay multiplex array system, and Enzyme-immune assay. The basic information is outlined in Table 1.

Association of IL-6 with the severity and mortality of COVID-19

We assessed 107 studies to verify fluctuation in serum IL-6 concentration among COVID-19 patients in response to disease severity. Comparatively, elderly patients showed severe to critical symptoms than younger patients, according to selected studies. The mean difference in serum IL-6 level was 19.98 higher in the severe patients than in the mild category patients. IL-6 level showed significant elevation in the severe COVID-19 cases (MD: 19.98; $P < .001$; 95% CI: 17.56, 22.40).

To evaluate the impact of IL-6 level on the mortality of COVID-19 patients, 49 studies of 147 included studies were assessed. The result showed that deceased COVID-19 patients had 42.11 times higher mean concentration than survived patients. IL-6 level was significantly increased in the dead patients (MD: 42.11; $P < .001$; 95% CI: 36.86, 47.36), and the fluctuation was highly noticeable (Table 2, Figures 2 and 3).

Association of IL-10 with the severity and mortality of COVID-19

Fifty-two studies were assessed to identify fluctuation in serum IL-10 concentration according to disease severity among COVID-19 patients. The mean difference in serum IL-10 level was 1.35 between severe and mild COVID-19 patients. IL-10 level showed significantly high concentration in the severe COVID-19 cases (MD: 1.35; $P < .001$; 95% CI: 0.90, 1.80).

To evaluate the impact of elevated IL-10 level on the mortality of COVID-19 patients, 12 studies of 147 included studies were assessed. The outcome showed that dead COVID-19 patients had an increased IL-10 to a mean concentration of 4.79 than survived patients. IL-10 level was significantly increased in the deceased patients (MD: 4.79; $P < .001$; 95% CI: 2.83, 6.75), and the fluctuation indicated that IL-10 might be associated with mortality in COVID-19 (Table 2, Figures 2 and 3).

Sensitivity analysis and publication bias

No visual asymmetry was observed during analyzing funnel plots indicating the absence of publication bias (Figure 4). Egger's regression test showed a significant outcome in IL-6 versus COVID-19 severity model ($P = .005$). Other analyses did not show any significant publication bias (IL-6 vs COVID-19 mortality: $P = .652$; IL-10 vs COVID-19 severity: $P = .091$; IL-10 vs COVID-19 mortality: $P = .669$). Begg-Mazumdar's test also showed similar results (IL-6 vs COVID-19 severity: $P = .023$; IL-6 vs COVID-19 mortality: $P = .730$; IL-10 vs COVID-19 severity: $P = .455$; IL-10 vs COVID-19 mortality: $P = 1.00$). The results are shown in Table 2. Sensitivity analysis was performed by excluding the studies one by one to verify the stability of the final outcome. The final outcome was stable, and none of the studies interfered with the core results (not shown).

Discussion

The wave of COVID-19 is still ongoing, with full rhythm failing a number of attempts to control this pandemic situation. Most of the COVID-19 cases remain mild, and patients get their recovery from the fully active natural immune system, but 14% of patients face severe symptoms that lead to

Table 1. Baseline characteristics of the investigative studies reporting blood levels of IL-6 and IL-10 in COVID-19 patients.[2,4-7,9-18,24-154].

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Bergantini et al[2]	Caucasian	Italy	HB	Monocentric retrospective	24	Mild: 62.2 ± 15.6 Severe: 65.2 ± 8	Mild: 14 Severe: 10	NA	ECLIA	IL-6	7
Burian et al[24]	Caucasian	Germany	HB	Retrospective cohort	37	61.5 ± 17	Mild: 25 Severe: 12	NA	Biochemical assay	IL-6	7
Cai et al[25]	Asian	China	HB	Retrospective	298	47.17 ± 20.86	Mild: 240 Severe: 58	NA	Biochemical assay	IL-6	8
Chang et al[26]	Asian	China	HB	Retrospective	150	NA	Mild: 93 Severe: 57	NA	Biochemical assay	IL-6	8
Chen et al[4]	Asian	China	HB	Retrospective cohort	660	52.33 ± 25.26	NA	Dead: 82 Survivors: 578	Biochemical assay	IL-6	8
Chen et al[27]	Asian	China	HB	Retrospective	21	57 ± 11.93	Mild: 10 Severe: 11	NA	CLIA	IL-6, IL-10	8
Chen et al[28]	Asian	China	HB	Retrospective	172	64	NA	Dead: 87 Survivors: 85	Biochemical assay	IL-6	7
Chen et al[29]	Asian	China	HB	Retrospective	29	NA	Mild: 15 Severe: 14	NA	ELISA	IL-6, IL-10	8
Chen et al[30]	Asian	China	HB	Retrospective observational	94	52.75 ± 16.09	Mild: 69 Severe: 25	NA	CLIA	IL-6, IL-10	9
Chen et al[31]	Asian	China	HB	Retrospective cohort	548	56 ± 14.5	Mild: 345 Severe: 203	Dead: 103 Survivors: 445	Biochemical assay	IL-6	8
Chen et al[5]	Asian	China	HB	Retrospective cohort	274	58.67 ± 19.38	NA	Dead: 113 Survivors: 161	Biochemical assay	IL-6, IL-10	7
Chen et al[32]	Asian	China	HB	Retrospective	55	55 ± 54.05	NA	Dead: 19 Survivors: 36	Biochemical assay	IL-6	6
Chen et al[9]	Asian	China	HB	Retrospective	48	64.6 ± 18.1	Mild: 21 Severe: 27	NA	Biochemical assay	IL-6	6
Chen et al[11]	Asian	China	HB	Retrospective	1453	NA	Mild: 962 Severe: 491	NA	ELISA	IL-6	8
Chi et al[10]	Asian	China	HB	Retrospective cohort	70	Mild : 42 ± 10.98 Severe: 43.24 ± 14.76	Mild: 4 Severe: 66	NA	Multiplex biometric immunoassay	IL-6, IL-10	8

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Crespo et al[33]	Caucasian	Spain	HB	Prospective cohort	16	73.6 ± 4.7	NA	Dead: 8 Survivors: 8	Biochemical assay	IL-6	6
De La Flor et al[34]	Caucasian	Spain	HB	Observational retrospective	10	73.5 ± 9.46	NA	Dead: 3 Survivors: 7	OLHDF	IL-6	7
D'Alto et al[35]	Caucasian	Italy	HB	Prospective	94	Dead: 68 ± 12 Survivors: 62 ± 13	NA	Dead: 25 Survivors: 69	Biochemical assay	IL-6	7
Ding et al[6]	Asian	China	HB	Prognostic	104	62.82 ± 14.77	Mild: 50 Severe: 54	Dead: 16 Survivors: 88	Biochemical assay	IL-6	7
Ding et al[36]	Asian	China	HB	Retrospective	32	Mild: 54.9 ± 11.3 Severe: 61.3 ± 17.9 Critical: 73.5 ± 12.3	Mild: 11 Severe: 21	NA	CLIA	IL-6	8
El-Shabrawy et al[14]	African	Egypt	HB	Prognostic cohort	116	Mild : 44.67 ± 42.13 Severe: 54.17 ± 54.97	Mild: 99 Severe: 17	NA	ELISA	IL-6	8
Fan et al[37]	Asian	China	HB	Retrospective	73	58.36 ± 14.31	NA	Dead: 47 Survivors: 26	Biochemical assay	IL-6	7
Fan et al[38]	Asian	China	HB	Retrospective observational	101	65.46 ± 9.74	NA	Dead: 101 Survivors: 0	Biochemical assay	IL-6	8
Fan et al[39]	Asian	China	HB	Retrospective longitudinal	21	62.5 ± 12.6	NA	Dead: 4 Survivors: 17	Biochemical assay	IL-6	6
Fei et al[40]	Asian	China	HB	Retrospective	72	Mild: 55.7 ± 11.9 Severe: 64 ± 16.8	Mild: 52 Severe: 20	NA	ELISA	IL-6	7
Fei et al[41]	Asian	China	HB	Retrospective cohort	191	56.33 ± 15.69	NA	Dead: 54 Survivors: 137	Biochemical assay	IL-6	7
Feng et al[7]	Asian	China	HB	Single-centered, prospective, and observational	114	63.96 ± 13.41	Mild: 94 Severe: 20	NA	Biomarkers assay	IL-6, IL-10	7
Gadotti et al[12]	Caucasian	Brazil	HB	Prospective cohort	56	60.33 ± 19.78	NA	Dead: 18 Survivors: 38	ELISA	IL-6, IL-10	8
Gan et al[42]	Asian	China	HB	Retrospective case-control	95	65.67 ± 15.06	NA	Dead: 39 Survivors: 56	Biochemical assay	IL-6, IL-10	7
Gao et al[43]	Asian	China	HB	Retrospective	43	43.74 ± 12.12	Mild: 28 Severe: 15	NA	ECLIA	IL-6	8

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Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Gil-Etayo et al[44]	Caucasian	Spain	HB	Prospective observational	34	58.08 ± 23.79	NA	Dead: 6 Survivors: 28	Flow cytometry	IL-6	8
Guirao et al[15]	Caucasian	Spain	HB	Retrospective cohort	50	Mild: 56.2 ± 2.85 Moderate: 65.7 ± 2.05 Severe: 64.5 ± 2.26	Mild: 10 Severe: 40	Dead: 14 Survivor s: 36	ECLIA	IL-6	9
Guner et al[45]	Caucasian	Turkey	HB	Retrospective cohort	222	50.6 ± 16.5	Mild: 172 Severe: 50	NA	Biochemical assay	IL-6	8
Han et al[13]	Asian	China	HB	Retrospective cohort	102	Mild: 58.3 ± 12.6 Severe: 59.3 ± 14.4 Critical:65.1 ± 14.4	Mild: 42 Severe: 60	NA	Flow cytometry	IL-6, IL-10	9
Yang et al[46]	Asian	China	HB	Single-centered, retrospective, and observational	94	Dead: 75.8 ± 12.9 Survivors: 65.8 ± 10.2	NA	Dead: 13 Survivors: 81	Biochemical assay	IL-6, IL-10	9
Henry et al[18]	Caucasian	USA	HB	Prospective observational	52	52 ± 20.59	Mild: 36 Severe: 16	NA	ELISA	IL-6, IL-10	9
He et al[47]	Asian	China	HB	Retrospective	204	48.33 ± 20.91	Mild: 135 Severe: 69	NA	Biochemical assay	IL-6, IL-10	7
He et al[48]	Asian	China	HB	Single-center retrospective	93	47.9 ± 13.2	Mild: 60 Severe: 33	NA	Biochemical assay	IL-6, IL-10	7
Herold et al[16]	Caucasian	UK	HB	Prospective cohort	89	54.33 ± 49.74	Mild: 57 Severe: 32	NA	ELISA	IL-6	8
Holt et al[49]	Caucasian	USA	HB	Retrospective cohort	62	Dead: 74.16 ± 11.4 Survivors: 60.3 ± 12.5	NA	Dead: 19 Survivors: 43	Biochemical assay	IL-6	6
Hu et al[50]	Asian	China	HB	Retrospective cohort	76	50.47 ± 3.10	Mild: 63 Severe: 13	NA	Multiplex biometric immunoassay	IL-6	6
Huang et al[51]	Asian	China	HB	Retrospective	64	47.8 ± 18.5	Mild: 43 Severe: 21	Dead: 4 Survivors: 27	Biochemical assay	IL-6, IL-10	6
Huang et al[52]	Asian	China	HB	Single-center retrospective	218	62.33 ± 13.43	Mild: 116 Severe: 102	NA	ELISA, CLIA	IL-6	7
Huang et al[53]	Asian	China	HB	Retrospective	83	62 ± 12.31	Mild: 21 Severe: 62	NA	Biochemical assay	IL-6	6
Jain et al[54]	Asian	India	HB	Prospective observational	154	Mild: 42.34 ± 6.41 Severe: 51.41 ± 9.12	Mild: 91 Severe: 63	NA	ELISA	IL-6	7

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Ke et al[55]	Asian	China	HB	Single-centered, retrospective case-control	194	63.08 ± 12.88	NA	Dead: 46 Survivors: 148	Flow cytometry	IL-6, IL-10	7
Keske et al[56]	Caucasian	Turkey	HB	Retrospective	43	61.67 ± 51.39	NA	Dead: 6 Survivors: 37	Biochemical assay	IL-6	6
Kumar et al[57]	Asian	India	HB	Clinical study	386	Dead: 63.4 ± 14 Survivors: 48.1 ± 16.3	NA	Dead: 16 Survivors: 370	CLIA	IL-6	8
Laguna-Goya et al[58]	Caucasian	Spain	HB	Prospective cohort	454	52 ± 11.9	NA	Dead: 33 Survivors: 421	Flow cytometry	IL-6	9
Li et al[59]	Asian	China	HB	Retrospective	476	61.33 ± 14.09	NA	Dead: 183 Survivors: 293	Biochemical assay	IL-6, IL-10	7
Li et al[60]	Asian	China	HB	Retrospective cohort	102	57.33 ± 18.8	NA	Dead: 15 Survivors: 87	Biochemical assay	IL-6, IL-10	6
Li et al[61]	Asian	China	HB	Retrospective	1449	55 ± 17.81	NA	Dead: 122 Survivors: 1327	Biochemical assay	IL-6, IL-10	6
Li et al[62]	Asian	China	HB	Single-center, retrospective	215	Mild: 42.67 ± 14.96 Severe: 49.5 ± 39.57	Mild: 159 Severe: 56	NA	Flow cytometry	IL-6, IL-10	7
Liu et al[63]	Asian	China	HB	Multicenter, Retrospective cohort	2044	61 ± 14.09	Mild: 1087 Severe: 957	NA	CLIA	IL-6, IL-10	8
Liu et al[64]	Asian	China	HB	Retrospective	50	54 ± 20.86	Mild: 24 Severe: 26	NA	Biochemical assay	IL-6, IL-10	6
Liu et al[65]	Asian	China	HB	Single-center, retrospective	51	43.33 ± 12.97	Mild: 44 Severe: 7	NA	Biochemical assay	IL-6	6
Liu et al[66]	Asian	China	HB	Retrospective cohort	255	60 ± 50.7	Mild: 214 Severe: 41	NA	Biochemical assay	IL-6, IL-10	7
Liu et al[67]	Asian	China	HB	Retrospective cohort	80	55 ± 43.3	Mild: 11 Severe: 69	NA	ELISA	IL-6, IL-10	8
Liu et al[68]	Asian	China	HB	Retrospective cohort	124	NA	Mild: 37 Severe: 87	NA	Biochemical assay	IL-6	7
Liu et al[70]	Asian	China	HB	Retrospective cohort	101	62.33 ± 17.3	Mild: 47 Severe: 54	NA	Biochemical assay	IL-6, IL-10	7

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Liu et al[71]	Asian	China	HB	Retrospective	76	47 ± 45.36	Mild: 30 Severe: 46	NA	Biochemical assay	IL-6, IL-10	6
Liu et al[72]	Asian	China	HB	Single-center, retrospective	67	Mild: 46 ± 22.79 Severe: 64.77 ± 11.79 Critical: 64 ± 11.21	Mild: 10 Severe: 57	NA	Flow cytometry	IL-6, IL-10	6
Luo et al[73]	Asian	China	HB	Multicenter, Retrospective	1018	59.67 ± 14.85	NA	Dead: 201 Survivors: 817	CLIA	IL-6, IL-10	9
Lu et al[74]	Asian	China	HB	Single-center, retrospective	121	6.25 ± 4.31	Mild: 101 Severe: 20	NA	Flow cytometry	IL-6, IL-10	9
Lv et al[75]	Asian	China	HB	Retrospective cohort	354	58.33 ± 49.87	Mild: 115 Severe: 239	NA	Biochemical assay	IL-6, IL-10	7
Ma et al[76]	Asian	China	HB	Single-center, retrospective	37	63.67 ± 8.48	Mild: 17 Severe: 20	NA	Biochemical assay	IL-6	6
Ma et al[77]	Asian	China	HB	Retrospective cohort	84	50.93 ± 15.24	Mild: 64 Severe: 20	NA	Flow cytometry	IL-6	7
Maeda et al[78]	Caucasian	USA	HB	Single-center retrospective cohort	224	63 ± 17	Mild: 167 Severe: 57	NA	Biochemical assay	IL-6	8
Mandel et al[79]	Caucasian	Israel	HB	Prospective non-randomized cohort	71	62 ± 13.8	NA	Dead: 12 Survivors: 59	ELISA	IL-6	8
McElvaney et al[80]	Caucasian	Ireland	HB	Retrospective	40	55.5 ± 17.7	Mild: 20 Severe: 20	NA	ELISA	IL-6, IL-10	8
Merza et al[81]	Caucasian	Iraq	HB	Retrospective	56	Mild: 35.7 Severe: 51.75	Mild: 41 Severe: 15	NA	ELISA	IL-6, IL-10	8
Mikami et al[82]	Caucasian	USA	HB	Multicenter Retrospective cohort	6493	58 ± 21.5	Mild: 2785 Severe: 3708	Dead: 806 Survivors: 2014	Biochemical assay	IL-6	7
Mo et al[83]	Asian	China	HB	Single-center, retrospective	155	54 ± 17.96	Mild: 70 Severe: 85	NA	Biochemical assay	IL-6	6
Morisson et al[84]	Caucasian	USA	HB	Retrospective observational cohort	81	64.33 ± 9.81	NA	Dead: 35 Survivors: 46	Biochemical assay	IL-6	6

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Myhre et al[85]	Caucasian	Norway	HB	Prospective observational	123	Dead: 64.3 ± 10.7 Survivors: 57.8 ± 16.3	NA	Dead: 35 Survivors: 88	ECLIA	IL-6	7
Nie et al[86]	Asian	China	HB	Retrospective	97	43 ± 22.58	Mild: 72 Severe: 25	NA	Biochemical assay	IL-6, IL-10	6
Pandolfi et al[87]	Caucasian	Italy	HB	Prospective cohort	33	Mild: 62.67 ± 8.05 Severe: 58 ± 11.33	Mild: 5 Severe: 28	NA	ELISA	IL-6	8
Qin et al[88]	Asian	China	HB	Single-center, retrospective	452	57.33 ± 14.87	Mild: 166 Severe: 286	NA	Flow cytometry	IL-6, IL-10	8
Quartuccio et al[89]	Caucasian	Italy	HB	Retrospective	24	Dead: 68.8 ± 9.4 Survivors: 65.8 ± 8.2	NA	Dead: 6 Survivors: 18	ECLIA	IL-6	7
Quiroga et al[90]	Caucasian	Spain	HB	Single-centered, prospective, and observational	16	72 ± 15	NA	Dead: 4 Survivor s: 12	Enzyme-immune assay	IL-6	7
Rastrelli et al[91]	Caucasian	Italy	HB	Retrospective cohort	31	Mild: 61.5 ± 9.14 Severe: 62.83 ± 48.15 Dead: 73 ± 27.85	Mild: 21 Severe: 10	NA	ECLIA	IL-6	8
Ruan et al[92]	Asian	China	HB	Multicenter Retrospective cohort	150	Dead: 54.33 ± 49.99 Survivors: 58.3 ± 27.9	NA	Dead: 68 Survivors: 82	Biochemical assay	IL-6	6
Sabaka et al[93]	Caucasian	Slovakia	HB	Retrospective	45	Mild: 80.33 ± 10.98 Severe: 85.83 ± 7.61	Mild: 26 Severe: 19	NA	ECLIA	IL-6	8
Sarfaraz et al[94]	Asian	Pakistan	HB	Prospective cohort	170	Dead: 61 ± 12.57 Survivors: 53 ± 13	NA	Dead: 67 Survivors: 103	Biochemical assay	IL-6	6
Sarhan et al[95]	African	Egypt	HB	Retrospective	203	58.67 ± 23.89	Mild: 26 Severe: 19	NA	ELISA	IL-6	8
Shi et al[96]	Asian	China	HB	Multicenter Retrospective cohort	Zhao et al[148]	50.58 ± 10.67	Mild: 119 Severe: 29	NA	Biochemical assay	IL-6, IL-10	9
Shi et al[97]	Asian	China	HB	Retrospective	87	56.67 ± 49.75	Mild: 51 Severe: 36	NA	Biochemical assay	IL-6	6
Shi et al[98]	Asian	China	HB	Prospective observational	45	Mild: 40.23 ± 12.61 Severe: 59.35 ± 18.07 Critical: 66.9 ± 17.01	Mild: 13 Severe: 32	NA	Biochemical assay	IL-6, IL-10	7

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Simioli et al[99]	Caucasian	Italy	HB	Single-center case-control	29	64 ± 22.5	Mild: 11 Severe: 18	NA	Biochemical assay	IL-6	7
Song et al[100]	Asian	China	HB	Retrospective	73	Mild: 48 ± 17.1 Severe: 55.93 ± 12.51	Mild: 31 Severe: 42	NA	Biochemical assay	IL-6, IL-10	6
Song et al[101]	Asian	China	HB	Single-center, retrospective cohort	1172	59 ± 14.84	Mild: 881 Severe: 291	NA	Biochemical assay	IL-6, IL-10	7
Song et al[102]	Asian	China	HB	Cross sectional observational	41	40.83 ± 12.68	Mild: 29 Severe: 12	NA	Flow cytometry	IL-6	8
Sun et al[103]	Asian	China	HB	Retrospective	244	Dead: 72 ± 9 Survivors: 67.67 ± 6	NA	Dead: 121 Survivors: 123	Biochemical assay	IL-6	7
Sun et al[104]	Asian	China	HB	Prospective observational cohort	99	Mild: 52 ± 15.28 Severe: 70.83 ± 14.88	Mild: 49 Severe: 50	NA	Biochemical assay	IL-6, IL-10	7
Sun et al[105]	Asian	China	HB	Prospective cohort	63	45 ± 62.21	Mild: 44 Severe: 19	NA	Biochemical assay	IL-6	6
Taha et al[106]	African	Egypt	HB	Observational cohort	85	54 ± 17.35	Mild: 46 Severe: 39	Dead: 21 Survivors: 64	ELISA	IL-6	8
Tang et al[107]	Asian	China	HB	Prospective	120	58 ± 15.76	Mild: 60 Severe: 60	NA	Flow cytometry	IL-6, IL-10	9
Tian et al[108]	Asian	China	HB	Multicenter, retrospective, cohort	751	63.33 ± 8.91	Mild: 84 Severe: 148	NA	CLIA	IL-6, IL-10	9
Toniati et al[109]	Caucasian	Italy	HB	Single-centered, prospective	100	63.33 ± 10.53	Mild: 77 Severe: 23	NA	Biochemical assay	IL-6	6
Tu et al[110]	Asian	China	HB	Single-center, retrospective cohort	174	Dead: 71.33 ± 12.58 Survivors: 50 ± 18.71	NA	Dead: 25 Survivors: 149	Biochemical assay	IL-6	7
Vultaggio et al[17]	Caucasian	Italy	HB	Retrospective observational cohort	208	65.7 ± 15	Mild: 145 Severe: 63	NA	ELISA	IL-6	8
Wan et al[111]	Asian	China	HB	Prospective	66	Mild: 43.05 ± 13.12 Severe: 61.29 ± 15.55	Mild: 45 Severe: 21	NA	Flow cytometry	IL-6, IL-10	8

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Wang et al[112]	Asian	China	HB	Retrospective	28	68.6 ± 9	Mild: 14 Severe: 14	NA	Biochemical assay	IL-6, IL-10	6
Wang et al[113]	Asian	China	HB	Multicenter, retrospective	165	45.67 ± 11.97	Mild: 115 Severe: 50	NA	Biochemical assay	IL-6	7
Wang et al[114]	Asian	China	HB	Retrospective	339	70 ± 8.19	NA	Dead: 65 Survivors: 274	Biochemical assay	IL-6	6
Wang et al[115]	Asian	China	HB	Single-center, retrospective, descriptive	125	38.76 ± 13.799	Mild: 100 Severe: 25	NA	Biochemical assay	IL-6	6
Wang et al[116]	Asian	China	HB	Retrospective case-control	43	Mild: 43.05 ± 13.12 Severe: 61.29 ± 15.55	Mild: 35 Severe: 8	NA	Flow cytometry	IL-6. IL-10	8
Wang et al[117]	Asian	China	HB	Retrospective cohort	43	46.33 ± 20.44	Mild: 36 Severe: 7	NA	Biochemical assay	IL-6, IL-10	7
Wang et al[118]	Asian	China	HB	Retrospective	59	67.4 ± 11.3	NA	Dead: 41 Survivors: 18	CLIA	IL-6, IL-10	6
Webb et al[119]	Caucasian	USA	HB	Prospective observational cohort	72	55.67 ± 18.62	Mild: 5 Severe: 67	NA	Biochemical assay	IL-6	6
Wei et al[120]	Asian	China	HB	Retrospective	252	64.8 ± 13.3	Mild: 131 Severe: 98	NA	CLIA	IL-6, IL-10	9
Wu et al[121]	Asian	China	HB	Retrospective cohort	201	51.33 ± 12.69	Mild: 117 Severe: 84	Dead: 44 Survivor s: 40	Biochemical assay	IL-6	6
Wu et al[122]	Asian	China	HB	Single-center, retrospective cohort	Zhao et al[148]	75 ± 78.61	Mild: 60 Severe: 88	NA	Biochemical assay	IL-6, IL-10	6
Wu et al[123]	Asian	China	HB	Retrospective	71	57 ± 21.19	Mild: 32 Severe: 39	NA	Flow cytometry	IL-6, IL-10	8
Xiao et al[124]	Asian	China	HB	Retrospective	143	NA	Mild: 107 Severe: 36	NA	Biochemical assay	IL-6	6
Xie et al[125]	Asian	China	HB	Retrospective	29	64.1 ± 14.95	Mild: 22 Severe: 7	NA	Biochemical assay	IL-6	7
Xu et al[126]	Asian	China	HB	Single-centered, retrospective observational	187	60.5 ± 16.81	Mild: 80 Severe: 107	Dead: 28 Survivors: 117	Biochemical assay	IL-6, IL-10	7

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Xu et al[127]	Asian	China	HB	Multicenter Retrospective observational	324	63.2 ± 14.5	Mild: 177 Severe: 147	NA	Biochemical assay	IL-6	8
Xu et al[128]	Asian	China	HB	Retrospective	155	Mild: 39.84 ± 15.09 Severe: 50.97 ± 13.55	Mild: 125 Severe: 30	NA	Biochemical assay	IL-6	6
Xu et al[69]	Asian	China	HB	Single-center, retrospective cohort	88	57.11 ± 15.39	Mild: 47 Severe: 41	NA	Biochemical assay	IL-6	6
Xu et al[129]	Asian	China	HB	Multicenter Retrospective	69	56.33 ± 19.69	Mild: 44 Severe: 25	NA	Flow cytometry	IL-6	9
Yan et al[130]	Asian	China	HB	Single-centered, retrospective observational	48	69.4 ± 9.9	NA	Dead: 39 Survivors: 9	Biochemical assay	IL-6	6
Yang et al[131]	Asian	China	HB	Single-center, retrospective	93	46.4 ± 17.6	Mild: 69 Severe: 24	NA	Flow cytometry	IL-6, IL-10	8
Yang et al[132]	Asian	China	HB	Retrospective	76	NA	Mild: 42 Severe: 34	NA	Biochemical assay	IL-6, IL-10	6
Yang et al[133]	Asian	China	HB	Retrospective observational	55	44 ± 15.23	Mild: 21 Severe: 34	NA	Biochemical assay	IL-6	6
Yang et al[134]	Asian	China	HB	Retrospective case-control	45	32 ± 29.87	Mild: 23 Severe: 22	NA	Flow cytometry	IL-6	8
Yuan et al[135]	Asian	China	HB	Retrospective	189	60.33 ± 14.94	Mild: 102 Severe: 87	NA	Biochemical assay	IL-6	6
Yuan et al[136]	Asian	China	HB	Retrospective	117	64.67 ± 10.51	Mild: 53 Severe: 54	NA	Biochemical assay	IL-6, IL-10	6
Zeng et al[137]	Asian	China	HB	Retrospective	49	Mild: 46 ± 19 Severe: 60 ± 16 Critical: 68 ± 20	Mild: 28 Severe: 21	NA	Biochemical assay	IL-6, IL-10	6
Zeng et al[138]	Asian	China	HB	Retrospective	317	61 ± 14.15	Mild: 93 Severe: 224	NA	CLIA	IL-6, IL-10	8
Zhang et al[139]	Asian	China	HB	Retrospective	222	61 ± 12.69	Mild: 81 Severe: 67	NA	Automated immunoassay multiplex array system	IL-6, IL-10	8
Zhang et al[140]	Asian	China	HB	Retrospective	82	72.5 ± 11.32	NA	Dead: 82 Survivors: 0	Automated immunoassay multiplex array system	IL-6	8

(Continued)

Table 1. (Continued)

STUDY (REFERENCE)	ETHNICITY	LOCATION	SETTING	DESIGN	NO. OF PARTICIPANTS	AGE (MEAN ± SD)	DISEASE SEVERITY	MORTALITY	CYTOKINE ASSAY	BIOMARKER STUDY	NOS RATING
Zhang et al[141]	Asian	China	HB	Retrospective case-series	98	63.9 ± 1.4	NA	Dead: 36 Survivors: 62	Biochemical assay	IL-6	7
Zhang et al[142]	Asian	China	HB	Retrospective	43	Mild: 44.4 ± 15.9 Severe: 61.9 ± 9.4	Mild: 29 Severe: 14	NA	ELISA	IL-6, IL-10	8
Zhang et al[143]	Asian	China	HB	Single-center, retrospective	111	42.33 ± 18.78	Mild: 93 Severe: 18	Dead: 18 Survivors: 93	Biochemical assay	IL-6, IL-10	7
Zhang et al[144]	Asian	China	HB	Retrospective	134	60.78 ± 12.98	Mild: 33 Severe: 101	Dead: 101 Survivors: 33	Biochemical assay	IL-6	6
Zhang et al[145]	Asian	China	HB	Single-center retrospective observational	74	63.33 ± 12.10	Mild: 47 Severe: 27	NA	Biochemical assay	IL-6	7
Zhang et al[146]	Asian	China	HB	Retrospective	38	Dead: 37.7 ± 8.2 Survivors: 35.8 ± 4.1	NA	Dead: 18 Survivors: 20	Biochemical assay	IL-6	6
Zhang et al[147]	Asian	China	HB	Retrospective	326	51.33 ± 54.36	Mild: 28 Severe: 293	NA	Flow cytometry	IL-6	8
Zhao et al[149]	Asian	China	HB	Single-center, retrospective	172	64.33 ± 10.47	Mild: 112 Severe: 60	NA	Biochemical assay	IL-6, IL-10	7
Zhao et al[150]	Asian	China	HB	Prospective	71	49.33 ± 19.67	Mild: 53 Severe: 18	NA	Bio plex multiplex immunoassay	IL-6, IL-10	8
Zheng et al[150]	Asian	China	HB	Single-center, Retrospective cohort	96	54.7 ± 15.43	Mild: 22 Severe: 74	NA	Biochemical assay	IL-6, IL-10	7
Zheng et al[151]	Asian	China	HB	Retrospective	34	66.67 ± 13.93	Mild: 19 Severe: 15	NA	ELISA	IL-6, IL-10	8
Zhou et al[41]	Asian	China	HB	Multicenter, retrospective, cohort	191	56.33 ± 15.69	NA	Dead: 54 Survivors: 137	Biochemical assay	IL-6	7
Zhou et al[152]	Asian	China	HB	Single-center, retrospective	21	66.10 ± 13.94	Mild: 8 Severe: 13	NA	Automatic biochemical analyzer	IL-6	9
Zhu et al[153]	Asian	China	HB	Retrospective	127	50.90 ± 15.26	Mild: 111 Severe: 16	NA	Flow cytometry	IL-6, IL-10	8
Zou et al[154]	Asian	China	HB	Retrospective	121	63.83 ± 12.38	Mild: 69 Severe: 52	Dead: 14 Survivors: 107	Biochemical assay	IL-6, IL-10	7

Abbreviations: CLIA, chemiluminescent immunoassay; ECLIA, electro-chemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; HB, hospital based; NA, not available; NOS, Newcastle Ottawa Scale; OLHDF, online hemodiafiltration.

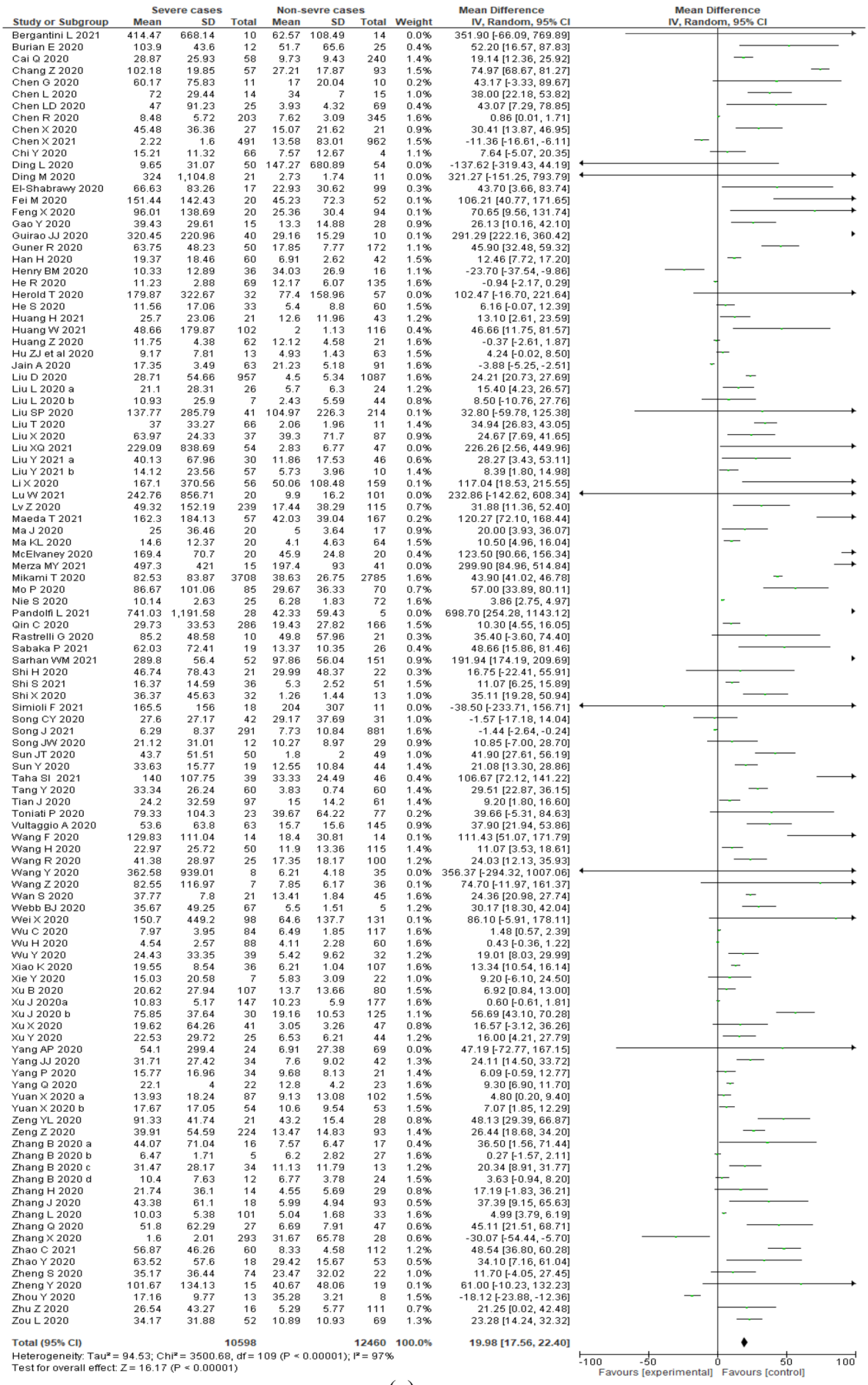
Table 2. Effect of elevated IL-6 and IL-10 levels on disease severity and mortality in COVID-19 patients.

INTERLEUKIN	COVARIATES	TEST OF ASSOCIATION			TEST OF HETEROGENEITY			PUBLICATION BIAS (*P*-VALUE)	
		MEAN DIFFERENCE	95% CI	*P*-VALUE	MODEL	*P*-VALUE	I^2 (%)	EGGER'S TEST	BEGG-MAZUMDAR'S TEST
IL-6	Severity	19.98	17.56, 22.40	<.001	Random	<.001	97	0.005	0.023
	Mortality	42.11	36.86, 47.36	<.001	Random	<.001	98	0.718	0.716
IL-10	Severity	1.35	0.90, 1.80	<.001	Random	<.001	91	0.091	0.455
	Mortality	4.79	2.83, 6.75	<.001	Random	<.001	81	0.669	1.00

ARDS, septic shock and multiple organ failure.[13] The ultimate outcome of severe SARS-CoV-2 infection becomes life-threatening, which is undeniable. Moreover, the rate of survival is minimal in severe to critical cases. The burden of emergency COVID-19 cases is uprising drastically worldwide. SARS-CoV-2 infection has become a threat to human race, and researchers are still struggling to improve this overwhelming situation. Early detection of the severe stage of infection could cease the disease progression toward the critical stage. Checkpoint of severity will also reduce the risk of mortality from COVID-19.[8]

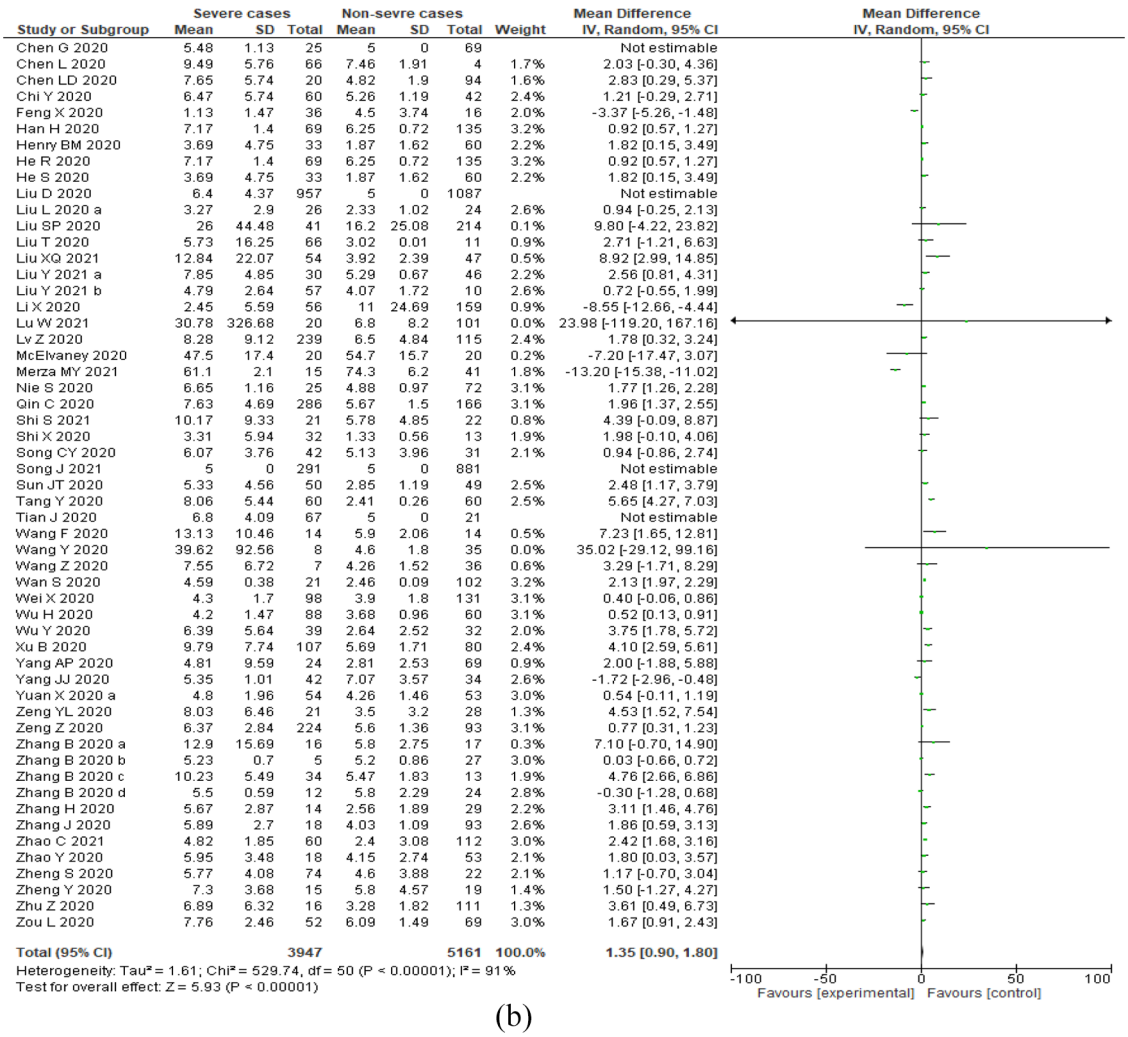
In our study, we have accumulated a number of evidence suggesting that cytokine storms developed during SARS-CoV-2 infection intensify the damage rapidly. Elderly patients, children, or patients with a previous disease condition with a weak immunity system mostly show a severe immune reaction. Anti-inflammatory treatments could not instantly reduce the sharp elevation of cytokines in the human body. As a result, the consequences of acute tissue damage and critical lung inflammation become challenging to control.[155] IL-6 and IL-10 show a significant elevation in COVID-19 patients with mild conditions, and the concentration sharply increases manyfold when the condition gets worsens. These 2 biomarkers should be observed as a primary prognostic indicator in COVID-19 patients to understand the disease state.[155,156]

Efficient immune activity is essential in the fight against any infection, although overproduction and unnecessary activation of active immune cells may cause much more irreversible damage than the actual infection. In COVID-19 cases, cytokine storm in the risk population reduces the lung capacity by flooding lung surfaces with inflammatory cells. The oversensitive immune activity becomes ineffective and fills the air sacks of the lungs with fluid limiting their oxygen uptake ratio, which leads to inevitable deaths.[157-159] IL-6 and IL-10 are major pleiotropic interleukins involved in potent inflammatory reactions observed in human body during any infection. Among these 2 cytokines, IL-6 helps to conduct acute phase immune reactions by recruiting immune cells in the infected area. But the excess level of IL-6 is responsible for anaphylactic shock or cytokine storm. This phenomenon will cause additional damage rather than wiping out infectious agents. On the other hand, IL-10 is responsible for maintaining homeostatic balance in the immune system by exerting anti-inflammatory actions. Human immune system can control or inhibit severe inflammation itself when the body starts healing by a homeostatic mechanism. Both IL-6 and IL-10 are closely involved in COVID-19 pathogenesis.[160-162] IL-6 is one of the critical inflammatory mediators in patients severely suffering from COVID-19. The level of IL-6 is elevated in these subjects and has been considered an important choice for COVID-19 targeting. Therapeutic agents (eg, sarilumab, tocilizumab) that suppress the IL-6



(a)

Figure 2. *(Continued)*



(b)

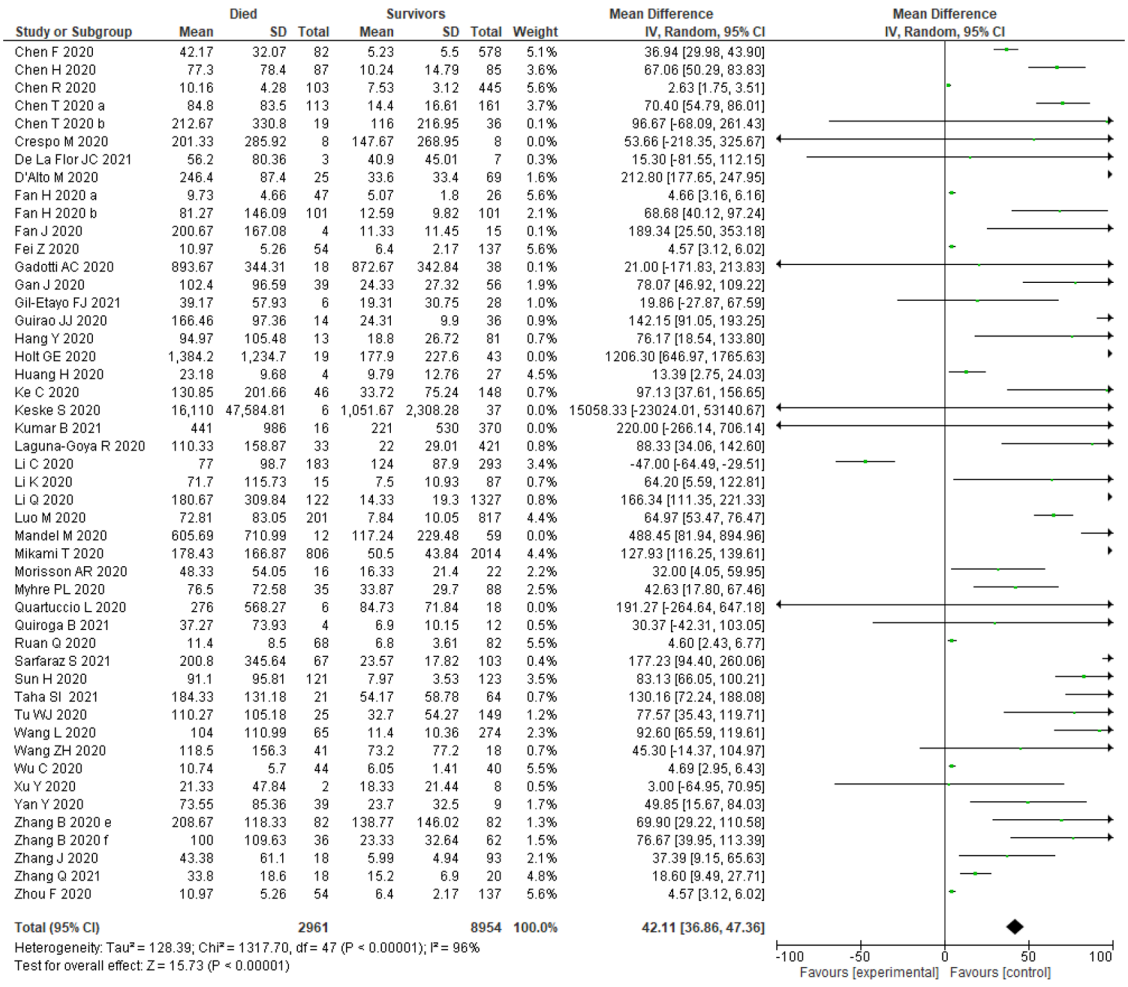
Figure 2. Forest plots showing IL-6 and IL-10 levels in COVID-19 patients based on disease severity index: (a) IL-6 levels in severe and non-severe COVID-19 cases and (b) IL-10 levels in severe and non-severe COVID-19 cases.

signaling mechanism have been reported to be effective against COVID-19.[163-165]

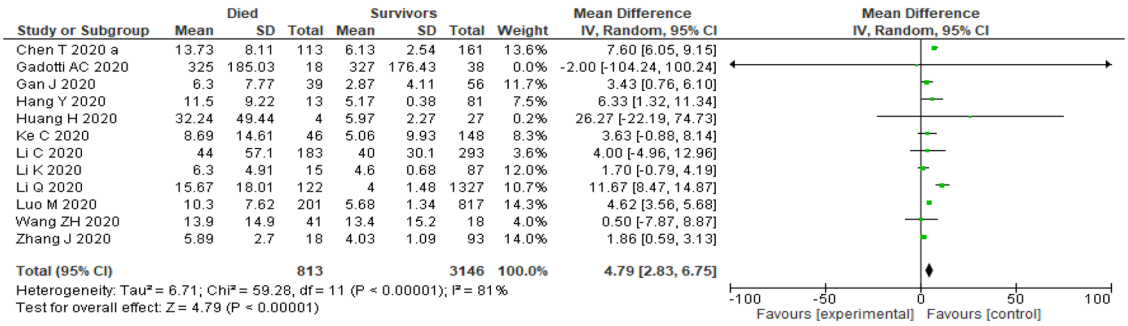
Many studies attempted to find out immune-inflammatory predictors for disease severity in COVID-19. A recent systematic review and meta-analysis that included 19 studies with 3115 participants found that IL-6 and IL-10 level was higher in the severe COVID-19 cases than in the non-severe cases.[166] Another study performed on 24 articles with 6212 participants recommended both IL-6 and IL-10 as potential biomarkers for COVID-19 severity and mortality.[155] Bao et al[167] reported that severe patients had increased levels of IL-6 (1.93-fold) and IL-10 (1.55-fold) serum concentration in a study involving 35 articles (5912 patients). Zawawi et al[168] showed that both the interleukins are associated with the severity of COVID-19 in their recent meta-analysis. In another network meta-analysis with 71 eligible studies involving 8647 patients, a rise in the IL-6 and IL-10 count was observed with worsening of the COVID-19 infection.[169] Other studies with a limited sample size also conducted a similar assessment and reported similar findings.[8,19-21] The evidence from these studies was sub-optimal and significant heterogeneity was observed due to the limited sample size. To create valid evidence that sharp elevation in IL-6 and IL-10 levels should be considered as a checkpoint of COVID-19 severity and mortality, we carried out this large-scale updated meta-analysis.

The findings from our present meta-analysis revealed that the mean IL-6 and IL-10 serum level was significantly higher in the COVID-19 patients. Severe category patients faced a sharp increase in the serum level compared to non-severe category patients. A similar result was also observed in the case of mortality. The deceased patients showed abnormally high serum concentrations of IL-6 and IL-10 than the survived patients. Moreover, the concentration of serum interleukins in the dead patients was significantly higher than the severe cases of COVID-19.

The current meta-analysis had some drawbacks that should be mentioned. Most of the included studies were retrospective cohort studies with smaller sample sizes. As the number of studies was huge, some detailed and basic information



(a)



(b)

Figure 3. Forest plots showing IL-6 and IL-10 levels in COVID-19 patients based on mortality index: (a) IL-6 levels in dead and survivors COVID-19 cases and (b) IL-10 levels in dead and survivors COVID-19 cases.

like—sex, treatment, duration of infection, smoking habit, and body mass index (BMI) could not be added to the meta-analysis. The presence of heterogeneity was another limitation of the study. The heterogeneity may be due to the different ethnic groups, sample size variation, different interventions to treat the symptoms of COVID-19 and variation in the inclusion and exclusion criteria for mild and severe groups selection. In spite of the limitations, our study is methodologically strong. According to our understanding, this is the most comprehensive and updated systematic review and meta-analysis on the association between circulating levels of IL-6 and IL-10 and the severity and mortality of COVID-19.

Conclusion

In summary, this investigative meta-analysis confirmed that sharp elevation in serum IL-6 and IL-10 worsens COVID-19 clinical outcomes. IL-6 and IL-10 are associated with the severity and mortality of COVID-19. The circulating level of both interleukins can act as potential biomarkers for the disease severity and mortality in SARS-CoV-2 infected patients.

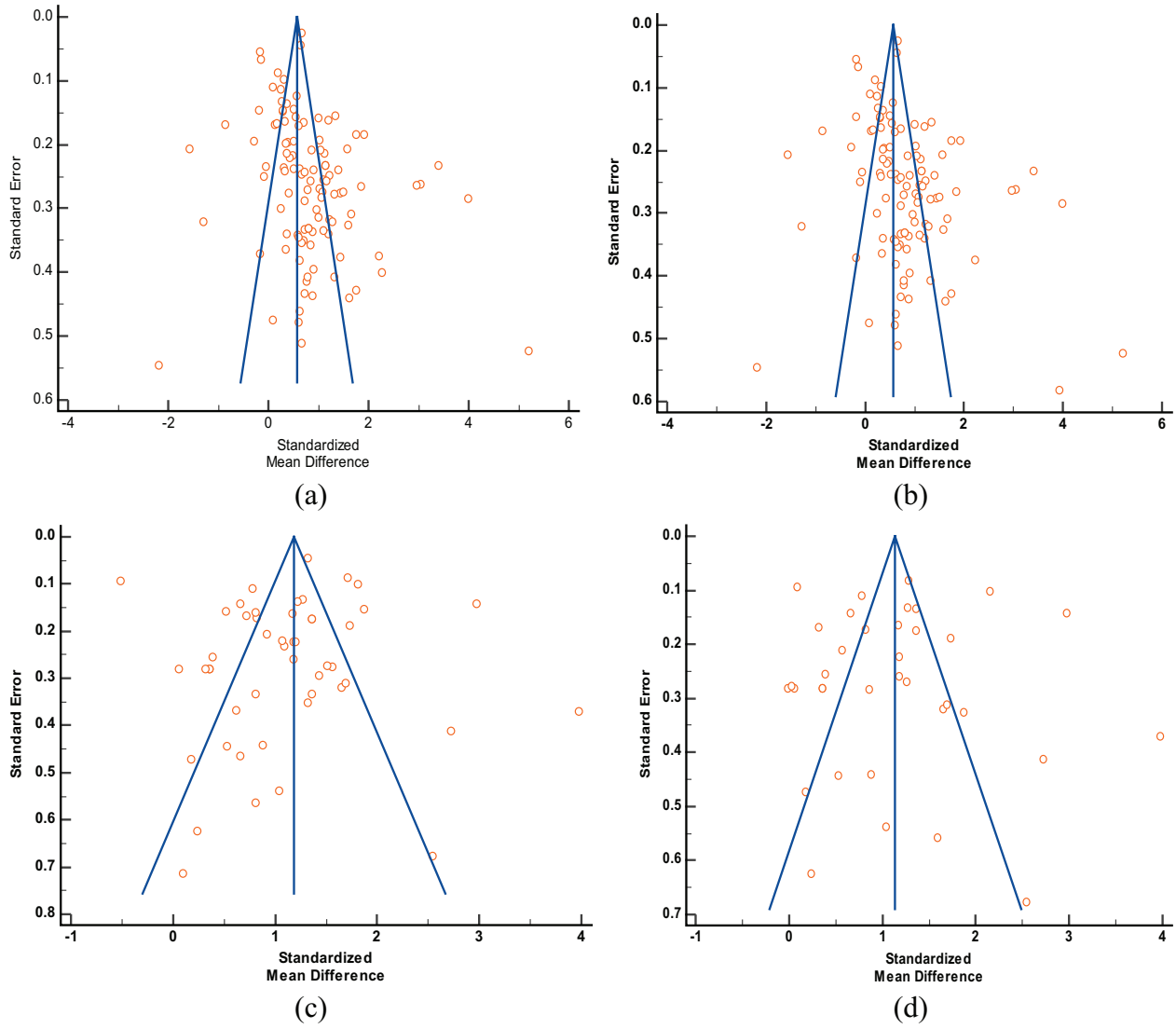


Figure 4. Funnel plots for publication bias analysis in different meta-analysis models: (a) IL-6 and severity of COVID-19, (b) IL-10 and severity of COVID-19, (c) IL-6 and mortality of COVID-19, and (d) IL-10 and mortality of COVID-19.

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Author Contributions

MSI conceptualized this meta-analysis; SJ and MAA wrote the primary draft; MSI carried out the statistical analyses; MSI critically reviewed and revised the manuscript; Before submission, all authors read and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during the present meta-analysis are available from the corresponding author on reasonable request.

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Supplemental Material

Supplemental material for this article is available online.

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