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REVIEW

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Interleukin-6 in Covid-19: A systematic review and meta-analysis

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Summary

Coronaviruses may activate dysregulated host immune responses. As exploratory studies have suggested that interleukin-6 (IL-6) levels are elevated in cases of complicated Covid-19, we undertook a systematic review and meta-analysis to assess the evidence in this field. We systematically searched MEDLINE and EMBASE for studies investigating the immunological response in Covid-19; additional grey literature searches were undertaken. Study selection and data abstraction was undertaken independently by two authors. Meta-analysis was undertaken using random effects models to compute ratios of means with 95% confidence intervals (95%CIs). Eight published studies and two preprints (n = 1798) were eligible for inclusion. Meta-analysis of mean IL-6 concentrations demonstrated 2.9-fold higher levels in patients with complicated Covid-19 compared with patients with noncomplicated disease (six studies; n = 1302; 95%CI, 1.17-7.19; I^2 = 100%). Consistent results were found in sensitivity analyses exclusively restricted to studies comparing patients requiring ICU admission vs no ICU admission (two studies; n = 540; ratio of means = 3.24; 95%CI, 2.54-4.14; $P < .001$; I^2 = 87%). Nine of ten studies were assessed to have at least moderate risk of bias. In patients with Covid-19, IL-6 levels are significantly elevated and associated with adverse clinical outcomes. Inhibition of IL-6 may be a novel target for therapeutics for the management of dysregulated host responses in patients with Covid-19 and high-quality studies of intervention in this field are urgently required.

KEYWORDS

Covid-19, SARS-CoV-2, interleukin, IL6, cytokine storm, Tocilizumab

1 | INTRODUCTION

A novel coronavirus, severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), emerged in December 2019 from Wuhan, China.[1,2] Causing a febrile respiratory illness known as coronavirus disease 2019 (Covid-19), this is the third zoonotic coronavirus to infect humans in the past two decades.[3] Compared to its predecessors, SARS-CoV-2 has demonstrated rapid capacity for dissemination, having infected several million patients worldwide.[4] Such transmission has been fuelled by the high intrinsic reproductive number of 2-2.5,[5-7] burgeoning community transmission,[8-10] and potential occult

Abbreviations: 95%CI, 95% confidence intervals; ARDS, acute respiratory distress syndrome; Covid-19, coronavirus disease 2019; CRS, cytokine release syndrome; EMBASE, Excerpta Medica Database; ICU, intensive care unit; IL2R, interleukin-2 receptor; IL-6, interleukin-6; IQR, interquartile range; IVIg, intravenous immunoglobulin; MEDLINE, Medical Literature Analysis and Retrieval System Online; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systemic Reviews; QUIPS, Quality in Prognostic Studies; RCT, randomized controlled trial; RoM, ratio of means; SARS-CoV-2, severe acute respiratory syndrome - coronavirus 2; SD, standard deviation.

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transmission during the presymptomatic incubation period.[11-13] In China, nearly one-fifth of infected patients experience severe or critical illness,[14] with an overall 2.3% case fatality rate and up to 6.1% of patients experiencing severe complications.[15] Alongside preventative vaccines and antiviral therapies, host-directed therapeutics employing existing immunomodulatory agents must be explored.[16,17]

Coronaviruses have been observed to activate excessive and dysregulated host immune responses which may contribute to the development of acute respiratory distress syndrome (ARDS).[18,19] Autopsy analyses of patients with Covid-19 complicated by ARDS reveal hyperactivation of cytotoxic T-cells, with high concentrations of cytotoxic granules.[20] Reports describing the immunological profile of critically ill patients with Covid-19 suggest hyperactivation of the humoral immune pathway—including interleukin (IL)-6—as a critical mediator for respiratory failure, shock, and multiorgan dysfunction. Given the potential for the development of cytokine release syndrome (CRS) as pathologic underpinning for disease progression of severe Covid-19, characterizing this dysregulation of host immune responses is important as it may act as a target for therapeutics. We therefore designed a systematic review and meta-analysis to assess the evidence describing IL-6 response in patients with Covid-19 to guide patient diagnosis, clarify the immunogenic profile of Covid-19, and inform future trials targeting this immune mediator.

2 | METHODS

2.1 | Design

We undertook a systematic review and meta-analysis investigating IL-6 dysregulation in patients diagnosed with Covid-19. Articles eligible for inclusion were observational cohort, case-control, or randomized controlled trials (RCTs) characterizing serum IL-6 dynamics in adult or pediatric patients diagnosed with Covid-19. This systematic review was undertaken with methodology in accordance with *Cochrane Handbook*,[21] and reporting consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[22] An a priori protocol was designed and registered (PROSPERO identification: CRD42020175879).

2.2 | Search strategy

We designed a high sensitivity search strategy combining free text and keyword search term synonym clusters for Covid-19, combined with clusters for IL-6 or tocilizumab (see Appendix S1 for full search strategies). We then systematically searched for published articles in Ovid MEDLINE and EMBASE and Google Scholar. Further searches were conducted in preprint servers (Biorxiv, Medrxiv, and Chinxiv) employing the keywords "tocilizumab" and "interleukin" to identify potential prepublication manuscripts meeting eligibility criteria. All such searches spanned January 1, 2019 to March 15, 2020.

For additional sensitivity, we then conducted a second, expanded, Ovid MEDLINE and EMBASE database search from January 1, 2020 to March 15, 2020 for all published cohort studies reporting Covid-19 patient characteristics and outcomes alone to ensure all studies reporting data on IL-6 levels in Covid-19 were identified.

No exclusions were made for language, disease severity, or outcomes reported. Citations from MEDLINE and EMBASE were managed with Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) to facilitate removal of duplicates; search results from Google Scholar and the preprint servers were manually parsed for identification of any eligible studies. Reference lists of all included articles were also reviewed for potential eligibility of citations.

2.3 | Study selection and data extraction

Two reviewers (E. A. C. and H. H.) independently undertook two-step selection, with studies screened via titles and abstracts followed by full-text review. Studies were included if they were RCTs, observational cohorts, or case-control in design, describing two or more patients diagnosed with Covid-19, and reported measures of cytokine levels (with a focus on IL-6).

Data extraction was undertaken in duplicate (E. A. C. and H. H.) via standardized data extraction tables. Data were extracted from article text, tables, and graphs (employing figure analysis tools to quantitatively extract data from curves). Data were collected for study design and setting, patient demographics, disease characteristics, levels of immune markers and indicators of systemic inflammation (inflammatory markers and cytokine levels), immunomodulatory agents administered (corticosteroids or intravenous immunoglobulin [IVIg]), and outcomes consistent with complicated infection (hospitalization, intensive care unit (ICU) admission, ARDS, invasive mechanical ventilation, renal replacement therapy, severe disease on clinical scoring tools (such as the Chinese New Coronavirus Pneumonia Prevention and Control Program or any others), or death). Conflicts were resolved by consensus discussion.

2.4 | Statistical analysis

Count data and nominal variables are presented as proportions with percentages while continuous data are presented as means and standard deviations (SDs), or medians and interquartile ranges (IQR) or range. Measures of association relating clinical characteristics or IL-6 levels with downstream clinical outcomes are presented in both unadjusted and adjusted forms, as availability of data permitted.

Results are described and summarized quantitatively and semi-qualitatively; for data deemed adequately homogenous in terms of patient characteristics, interventions, and clinical outcomes, meta-analysis was undertaken using random effects models. For statistical homogeneity, medians and IQRs were converted to means with SDs to maximize the number of studies eligible for meta-analysis.[23] For such continuous data, we computed ratio of means (RoM) for each study and undertook meta-analysis via generic inverse variance methods (DerSimonian and Laird) to produce pooled measures of

association, corresponding 95% confidence intervals (95%CI), and forest plots.[21,24,25] Prespecified subgroup analyses were conducted in regard to individual sub-definitions of complicated disease (as defined by primary studies investigators).

A prespecified alpha of .05 was used for all statistical tests and confidence intervals; statistical heterogeneity was assessed by the I^2 statistic. Data analysis was undertaken utilizing Microsoft Excel version 16.35 (Microsoft, Redmond, United States, 2020) and Review Manager version 5.3.5 (Cochrane Collaboration, Copenhagen, Denmark, 2014).

2.5 | Risk of bias assessment

Two reviewers (E.A.C. and H.H.) independently rated all included studies for risk of bias. The updated Quality in Prognostic Studies (QUIPS) tool was employed for cohort studies associating IL-6 levels with disease severity.[26-28]

3 | RESULTS

Following removal of duplicates, our database search identified 1219 unique citations, of which 112 articles were assessed via full text and eight studies were eligible for inclusion (Figure 1). An additional two articles were identified via preprint server searches. A total of 10 articles were therefore eligible for inclusion, with 10 (n = 1798) contributing to qualitative synthesis and six (n = 1302) undergoing quantitative synthesis (meta-analysis) (Figure 1). The remaining four studies (n = 496) were eligible for inclusion but did not present data in a manner permitting the calculation of RoMs and were therefore not pooled in meta-analysis.

Individual study characteristics and patient demographics are presented in Table 1, and inflammatory markers, therapeutic interventions, and disease complications are presented in Table 2.

Ten cohort studies (n = 1798) described the immunological response to SARS-CoV-2 in patients diagnosed with Covid-19; mean age was 54.8 ± 14.4 and 42% were female. All studies were set in China and all but one exclusively recruited hospital inpatients. Of studies reporting the use of immunomodulatory therapies, corticosteroids were the most commonly administered agents and were received by 32% of patients. In studies reporting survival, mortality was 22% among patients diagnosed with Covid-19 (Tables 1 and 2).

Overall, elevations in IL-6 levels among patients with Covid-19 were identified in all included studies.[29-38] Multiple studies specifically identified higher levels of IL-6 among patients with more severe (complicated) disease.[29,33-36] Descriptions of other inflammatory markers, including IL2R and ferritin, are contained in Appendix S1. A total of six

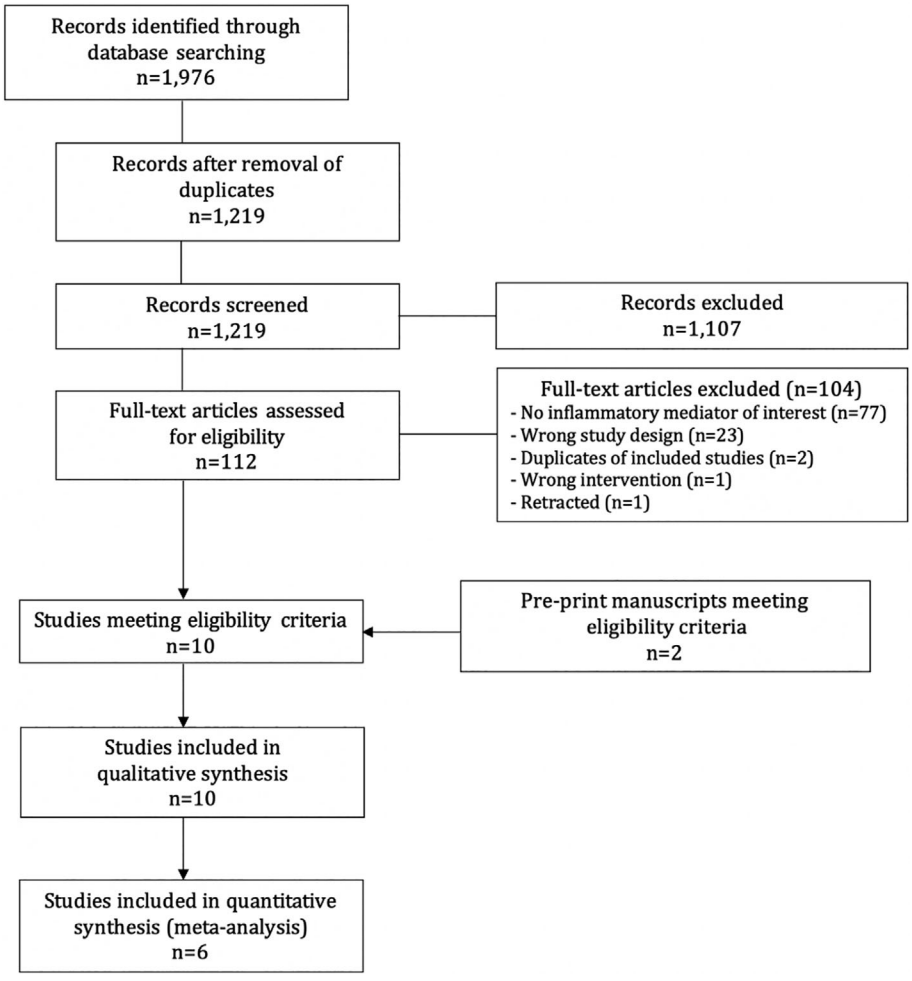

FIGURE 1 Study selection flow

TABLE 1 Methodological and patient characteristics of the studies eligible for inclusion

Study (y)	Location	Setting	Design	No of Participants (n)	Age, y (mean ± SD)	Sex, M/F	Disease severity[a] (n, %)	ICU admission, n (%)	ARDS, n (%)	Invasive mechanical ventilation, n (%)
Chen et al (2020a)[29]	Wuhan, China	Hospital inpatients	Prospective cohort; single center	29 COVID-19 patients	Median 56(range 26-79)	72%/28%	Mild (15; 52%) Severe (9; 31%) Critical (5; 17%)	NR	NR	NR
Chen et al (2020b)[30]	Wuhan, China	Hospital Inpatients	Retrospective cohort; single center	99 COVID-19 patients	55.5 ± 13.1	68%/32%	NR	23 (23%)	17 (17%)	4 (4%)
Diao et al (2020)[36]	Wuhan, China	Hospital inpatients	Retrospective cohort, multicenter	552 COVID-19[b] patients; 40 healthy controls	NR	NR	NR	20 (4%)[b] N = 499	NR	NR
Huang et al (2020a)[32]	Wuhan, China	Hospital inpatients	Prospective cohort; single center	41 COVID-19[b] patients; 4 controls	Median 49(IQR 41-58)	73%/27%	NR	13 (32%)	12 (29%)	4 (10%)
Huang et al (2020b)[31]	Wuhan, China	Hospital inpatients	Retrospective cohort; single center	34 COVID-19 patients	56 ± 17.1	41%/59%	NR	8 (24%)	NR	3 (9%)
Liu et al (2020)[33]	Wuhan, China	Hospital inpatients	Retrospective cohort; single center	80 COVID-19 patients	Median 53 (range 26-86)	43%/57%	Mild (11, 14%) Severe (69, 86%)	3 (4%)	7 (9%)	2 (2.5%)
Qin et al (2020)[34]	Wuhan, China	Hospital inpatients	Retrospective cohort; single center	452 COVID-19 patients	Median 58 (IQR 47-67)	52%/48%	Severe (286, 63%)	NR	NR	NR
Ruan et al (2020)[35]	Wuhan, China	Hospital inpatients	Retrospective cohort; multicenter	150 COVID-19 patients	Died (68 patients): Median 67 (range 15-81) Discharged (82 patients) Median 50 (range 44-81)	68%/32%	NR	41 (27%)	62 (41%)	25 (17%)
Wu et al (2020)[37]	Wuhan, China	Hospital inpatients	Retrospective cohort, multicenter	201 COVID-19 patients	Median 51 (IQR 43-60)	64%/36%	NR	53 (26%)	84 (42%)	6 (3%)
Zhu et al (2020)[38]	Anhui, China	Emergency department, patients under investigation	Retrospective cohort, multicenter	32 COVID-19[b] patients; 84 negative cases	Median 46 (IQR 35-52)	47%/53%	Mild (32, 100%)	NR	NR	NR

[a]Data refer only to patients diagnosed with COVID-19.
[b]As per the Chinese New Coronavirus Pneumonia Prevention and Control Program score.

TABLE 2 Cytokine levels and clinical outcomes in patients with COVID-19

Study (y)	IL-6, pg/mL (mean ± SD)	Lymphocyte cells × 10^9 (mean ± SD)	Ferritin mcg/L (mean ± SD)	CRP, mg/L (mean ± SD)	ESR, mm/h (mean ± SD)	Corticosteroid therapy, n (%)	IVIg, n (%)	Hospitalization, n (%)	Death, n (%)	Renal replacement therapy, n (%)
Chen et al (2020a)[29]	Severe/critical: 72 ± 12 Nonsevere: 34 ± 7	"Decreased" <1.0 (69%)	NR	"Increased" >5 (93%)	NR	NR	NR	29 (100%)	2 (7%)	NR
Chen et al (2020b)[30]	Median 7.9 (IQR 6.1-10.6)	0.9 ± 0.5	808.7 ± 490.7	51.4 ± 41.8	49.9 ± 2 3.4	19 (19%)	27 (27%)	99 (100%)	11 (11%)	9 (9%)
Diao et al (2020)[36]	ICU: 186 ± 283[a] Non-ICU: 51 ± 74[a]	NR	NR	NR	NR	NR	NR	NR	NR	NR
Huang et al (2020a)[32]	ICU: median 6.1 (IQR 1.8-37.7)[a] Non-ICU: median 5 (IQR 0-11.2)	Median 0.8 IQR 0.6-1.1	NR	NR	NR	9 (22%)	NR	41 (100%)	6 (15%)	3 (7%)
Huang et al 2020b[31]	"Increased" (9/9 tested patients)	Decreased (50%)	NR	NR	Increased (59.1%)	21 (62%)	NR	33 (97.1%)	NR	NR
Liu et al (2020)[33]	Severe: median 36.5 (IQR 30.8-42) Nonsevere: median 2.4 (IQR 2.1-2.9)	"Decreased" <1.5 (75%)	690.2 ± 864.3	"Increased" >10 (75%)	40.6 ± 27.2	29 (36%)	36 (45%)	80 (100%)	0 (0%)	0 (0%)
Qin et al (2020)[34]	Severe: median 25.5 (IQR 9.5-54.5) Nonsevere: median 13.3 (IQR 3.9-41.1)	Median 0.9 (IQR 0.6-1.2)	Median 662.4 (IQR 380.9-1311.9)	Median 44.1 (IQR 15.5-93.5)	Median 31.5 IQR 17.0-58.0	NR	NR	452 (100%)	NR	NR
Ruan et al (2020)[35]	8.9 ± 6.7	1.0 ± 1.6	923.9 ± 949.7	76.0 ± 94.0	NR	53 (35%)	NR	150 (100%)	68 (45%)	5 (3%)
Wu et al (2020)[37]	ARDS: median 7.4 (IQR 5.6-10.9) No ARDS: median 6.3 (IQR 5.4-7.8)	Median 0.91 (IQR 0.61-1.29)	Median 594.0 (IQR 315.7-1266.2)	Median 42.4 (IQR 14.2-92.7)	Median 49.3 IQR 40.0-66.9	62 (31%)	NR	201 (100%)	44 (22%)	NR
Zhu et al (2020)[38]	"Increased" in 7/32 (22%)[a]	1.1 ± 0.6[a]	NR	20.7 ± 24.0[a]	42.4 ± 33.6[a]	NR	NR	NR	NR	NR

[a]Data refer to patients with COVID-19.

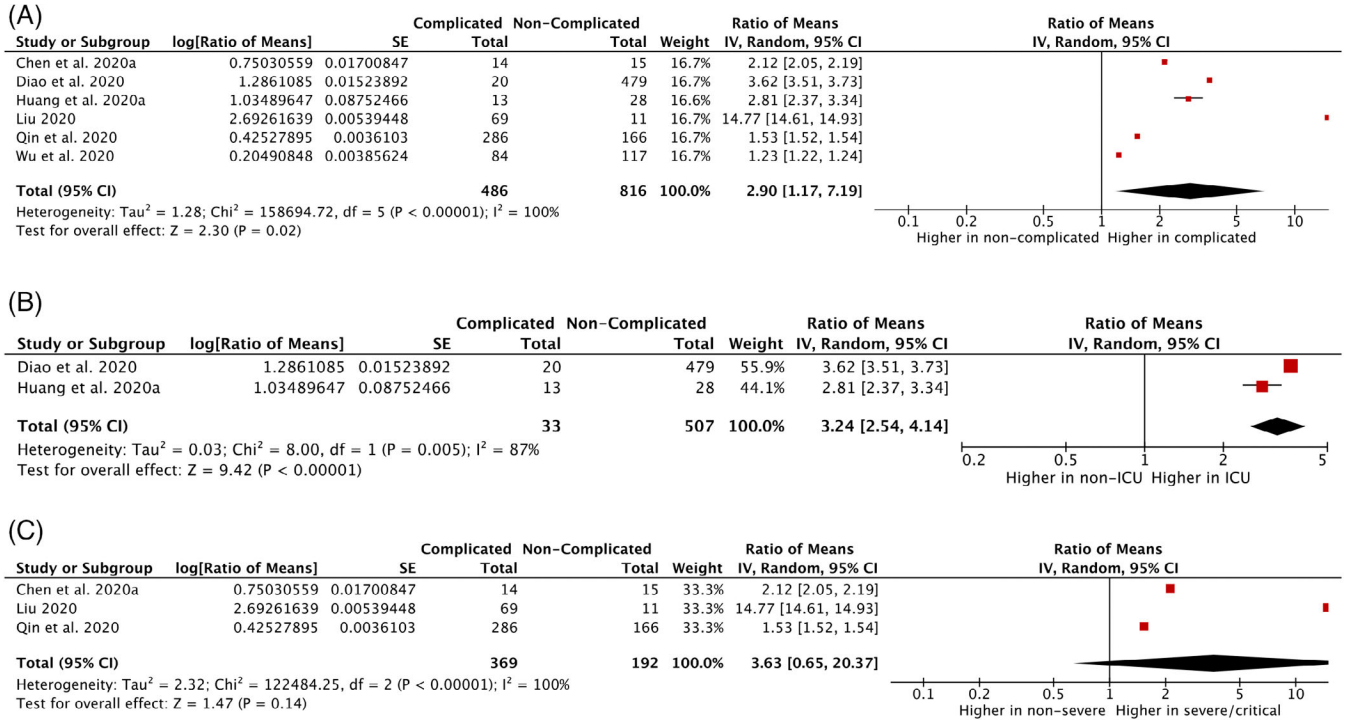

FIGURE 2 Meta-analysis of serum IL-6 levels in COVID-19. A, Patients with complicated COVID-19 vs noncomplicated; B, Patients requiring ICU admission vs not requiring ICU admission; C, Patients with severe or critical COVID-19 vs mild COVID-19

studies (n = 1302) compared IL-6 levels in patients with complicated disease (patients with ARDS, requiring ICU admission, or determined to have either "severe" or "critical" presentations as per the Chinese New Coronavirus Pneumonia Prevention and Control Program score) with noncomplicated disease (none of the above criteria present) and were included in meta-analysis. Compared to patients with non-complicated disease, IL-6 levels in those with complicated Covid-19 were 2.90-fold higher (six studies; n = 1302 patients; 95%CI, 1.17-7.19; $P < .001$; $I^2 = 100\%$; Figure 2, Panel A). Consistent results were found when sensitivity analyses were performed exclusively restricted to studies comparing patients requiring ICU admission vs no ICU admission (two studies; n = 540; RoM = 3.24; 95%CI, 2.54-4.14; $P < .001$; $I^2 = 87\%$; Figure 2, Panel B) but not for the analysis of severe or critical scores vs mild (three studies; n = 561; RoM = 3.63; 95%CI, 0.65-20.37; $P = .14$; $I^2 = 100\%$; Figure 2, Panel C). Statistical heterogeneity was elevated across all analyses and did not significantly improve with the planned sensitivity analyses.

Notably, baseline IL-6 levels positively correlated with bilateral pulmonary involvement ($r = .45$, $P = .001$), and maximum body temperature ($r = .52$, $P = .001$) in the retrospective cohort study by Liu et al[33] Among 30 patients with IL-6 assessment before and after treatment, 26 (87%) patients had significantly reduced IL-6 concordant with improving pulmonary computed tomography. In contrast, among the four patients who experienced progressive clinical deterioration, three (75%) had increasing IL-6 levels.

In the analysis of risk factors for ARDS and death by Wu et al,[37] patients with Covid-19 who progressed to ARDS had significantly increased IL-6 (median 7.39 pg/mL, IQR 5.63-10.89 vs median 6.29 pg/mL, IQR 5.36-7.83; $P = .03$). Further, elevated IL-6 was associated with death. Similarly, Ruan et al[35] identified significantly higher IL-6 levels among patients who die from Covid-19 compared to those who survived (11.4 ± 8.5 pg/mL vs 6.8 ± 3.6 pg/mL, $P < .001$).

3.1 | Risk of bias assessment

Risk of bias was assessed via the QUIPS tool in cohort studies assessing inflammatory response in Covid-19.[26,27] Four studies were determined to be at high risk of bias,[33,35,37,38] five moderate,[29,31,32,34,36] and one low (Figure S1)[30]; this was mostly driven by lack of control for confounding and potential inconsistencies in the measurement of the inflammatory mediators under study.

4 | DISCUSSION

In this systematic review and meta-analysis, we demonstrate that serum levels of IL-6 are significantly elevated in the setting of severe Covid-19 disease. Meta-analysis of the available data indicates that such increased levels are significantly associated with adverse clinical outcomes, including ICU admission, ARDS, and death. Patients with such complicated forms of Covid-19 had nearly threefold higher serum IL-6 levels than those with non-complicated disease.

It is increasingly recognized that a dysregulated host immune response to foreign infectious pathogens is integral to the development of target organ dysfunction and a major contributor to morbidity and mortality. Specifically, the systemic inflammatory response in sepsis has been demonstrated to overlap with that of CRS[39,40]; in patients with Covid-19 complicated by ARDS, such hyperactivation of the humoral immune system with a prominent IL-6 response may suggest that part of the pathogenesis of complicated disease involves a dysregulated and excessive host inflammatory response. This clinical phenotype resembles that of CRS, a condition for which IL-6 receptor inhibition with tocilizumab has clearly demonstrated benefit,[41] and may represent a more severely affected Covid-19 subpopulation, with increased requirements for critical care and worse clinical outcomes.[42]

Given the potential for the development of CRS as a pathologic underpinning for severe Covid-19 infection, studies assessing the potential benefit of host-directed immunomodulatory therapy are urgently needed. Several clinical trials are underway to evaluate the role of biologic inhibitors of key cytokine pathways as a therapy for complicated Covid-19, including trials of IL-6 inhibition with siltuximab, sariliumab, and tocilizumab.[43] While the results of these randomized trials are highly anticipated, the results of initial clinical studies of tocilizumab and siltuximab in severe Covid-19 are promising, with signals of potential for clinical and radiographic improvement.[44,45]

4.1 | Limitations

Although designed and reported in accordance with standardized systematic review methodology[21,22] and employing a highly sensitive search strategy, including the grey literature, this study has important limitations, much of which is inherent to the methodological quality of the included primary studies. All primary studies eligible for inclusion were conducted in China, with several studies recruiting participants from the same centres; while none of the included studies described their data as having been previously published, this remains a theoretical possibility.[46]

We encountered high levels of statistical heterogeneity in our meta-analysis comparing IL-6 levels between patients with complicated and noncomplicated disease; although we performed prespecified sensitivity analyses, these failed to sufficiently explain this heterogeneity. Such residual heterogeneity may have arisen from multiple sources of variability between studies, most prominently due to likely differences in patient characteristics, lack of consecutive enrolment, variable timing of IL-6 measurement, the absence of a set definition of "supportive care", and differences in adjuvant immunomodulatory medications received, such as corticosteroids and IVIg, which may have affected both IL-6 response and patient outcomes.

Most studies included in this review were rated at moderate or high risk of bias, reflecting generally low methodological quality. This was primarily driven by a lack of control for confounding, inconsistencies or lack of clarity of the context in which IL-6 measurements were performed, and potential for selection bias due to lack of consecutive patient enrolment.

5 | CONCLUSIONS

In this systematic review and meta-analysis, we demonstrate that serum levels of IL-6 are significantly elevated in the setting of complicated Covid-19 disease, and increased IL-6 levels to be in turn significantly associated with adverse clinical outcomes. This suggests that the progression of initial SARS-CoV-2 infection to complicated disease may be the consequence of an excessive host immune response and autoimmune injury. These findings support the need for ongoing controlled clinical studies to elucidate the role of immunomodulation, specifically via IL-6 inhibition, in the therapy of severe Covid-19.

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CONFLICT OF INTEREST

Eric A. Coomes is a co-investigator on a clinical trial of favipiravir chemoprophylaxis for COVID-19 outbreaks in long-term care homes. Hourmazd Haghbayan has no actual or potential conflict of interest to declare in relation to this study.

AUTHOR CONTRIBUTIONS

Eric A. Coomes conceived the study hypothesis. Eric A. Coomes and Hourmazd Haghbayan designed the study and undertook the literature search, study selection and data abstraction. Hourmazd Haghbayan analyzed the data. All authors interpreted the data, wrote the manuscript, and edited the manuscript critically for important intellectual content.

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SUPPORTING INFORMATION

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

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