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A meta-analysis of the efficacy and safety of immunomodulators in the treatment of severe COVID-19

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Abstract

Objective: To evaluate the efficacy and adverse events of immunomodulators in the treatment of severe coronavirus disease 2019 (COVID-19).

Methods: A literature search for the meta-analysis was performed using PubMed, The Cochrane Library, Embase, Wanfang Data, CNKI, and Web of Science to identify randomized controlled trials assessing the outcomes of patients treated with corticosteroids alone and/or interleukin-6 receptor antagonists for COVID-19. The risk of bias was assessed using the Cochrane method. The protocol was registered with PROSPERO (registry number: CRD42022356904).

Results: Compared with patients receiving standard of care, patients treated with corticosteroids alone had an increased risk of 14-day in-hospital death, whereas those treated with interleukin-6 receptor antagonists alone or in combination with corticosteroids had a lower risk of 14-day in-hospital death. Corticosteroid therapy alone was associated with increased risk of several adverse events, including intensive care unit admission and non-invasive ventilation, whereas interleukin-6 receptor antagonists alone or in combination with corticosteroids were not linked to adverse effects.

Conclusions: The findings supported the safety and efficacy of interleukin-6 receptor antagonists, either alone or together with corticosteroids, in patients with severe COVID-19; evidence supporting the efficacy and safety of corticosteroids monotherapy is lacking.

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Introduction

Since its initial detection in 2019, coronavirus disease 2019 (COVID-19) spread rapidly and became a global pandemic. COVID-19 is an acute infectious pneumonia caused by severe acute respiratory syndrome coronavirus 2, and it is primarily transmitted through respiratory routes. The disease has a long incubation period (1–14 days), is highly contagious, and has universal susceptibility among populations. Clinically, COVID-19 is often characterized by fever, cough, and fatigue, with a minority of patients experiencing symptoms such as sputum production, sore throat, and diarrhea.[1,2] Populations in heavily polluted areas often experience higher COVID-19 mortality because of the rapid spread of the virus under such conditions. Air pollutants can interact with pathogens, potentially causing mutations and increased resistance, transmissibility, and infectivity.[3] Although human-to-human transmission is the major route, viral shedding into wastewater and the environment is a growing concern, especially in areas with poor sanitation and wastewater treatment. The effects of weather and air pollution effects on viral transmission have also been described, with airborne spread deemed critical.[4] Corticosteroids have been widely used in the treatment of COVID-19. On July 6, 2021, the World Health Organization (WHO) updated its guidelines for COVID-19 treatment to include interleukin (IL)-6 receptor antagonists. However, IL-6 receptor inhibitors displayed mixed results in trials, with some studies reporting improved outcomes and reduced mortality with others findings no effect.[5] WHO stated that IL-6 receptor antagonists can save the lives of severe and critically ill patients with COVID-19, especially when used in conjunction with corticosteroids. On March 14, 2022, China's National Health Commission released the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Ninth Edition)," which officially proposed the use of corticosteroids and IL-6 receptor antagonists for the immunomodulatory treatment of COVID-19 and indicated that this combination could be attempted in severe and critically ill patients with elevated IL-6 levels. Therefore, the use of corticosteroids and IL-6 receptor antagonists in COVID-19 has greatly piqued the interest of researchers. Corticosteroids do not directly inhibit COVID-19 replication, as their main actions are to suppress inflammation and immune responses.[6] IL-6 is a pleiotropic cytokine with both anti-inflammatory and pro-inflammatory effects. In COVID-19 pneumonia, IL-6 stimulates the secretion of IL-1Ra, IL-17, and IL-10, ultimately leading to the cytokine storm, excessive immune responses in the body, worsening conditions, and potentially death. IL-6 receptor antagonists counteract and block the IL-6 signal transduction pathway, reducing its effects. Several studies revealed that corticosteroids and IL-6 receptor antagonists can improve patient outcomes and increase the survival rate of patients requiring oxygen. A randomized controlled trial demonstrated that the anti-IL-6 drug clazakizumab significantly improved 28-day ventilator-free survival, 28- and 60-day

overall survival, and clinical outcomes in hospitalized patients with COVID-19 and severe inflammation.[7] Another prospective study reported that a course of high-dose methylprednisolone followed by tocilizumab might accelerate respiratory recovery, reduce in-hospital mortality, and decrease the likelihood of invasive mechanical ventilation in patients with COVID-19-related cytokine storm syndrome.[8] In addition, studies have focused on the obvious side effects of this combination, and recent research described adverse events such as increased blood sugar levels, liver and kidney dysfunction, shock, infection, and pulmonary embolism. For example, the randomized controlled trials (RCTs) by Jeronimo[9] and Villar[10] both reported increased blood sugar levels in patients treated with corticosteroid and IL-6 receptor antagonists, and prospective controlled studies by Salama[11] and Declercq[12] both described increased rates of shock. Thus, the available data regarding the effectiveness and safety of corticosteroids and IL-6 receptor antagonists in treating severe COVID-19 are inconsistent. Therefore, we pooled the latest research evidence and conducted a systematic review and meta-analysis to assess the effectiveness and safety of corticosteroids and IL-6 receptor antagonists in patients with severe COVID-19.

Methods

Sample and data sources

The literature search for the meta-analysis used PubMed, The Cochrane Library, Embase, Wanfang database, CNKI, and Web of Science to identify RCTs comparing the outcomes of patients with COVID-19 who received corticosteroids and/or interleukin-6 receptor antagonists. The flowchart of the screening procedure is presented in Figure 1. The primary outcome indicators for the studies included the risk of death in hospitalized patients (7-, 14- and 28-day in-hospital mortality), and the secondary outcomes included the need for mechanical ventilation, number of intensive care unit (ICU) admissions, and adverse events (*e.g.*, glycemia, liver and kidney insufficiency, shock, pulmonary embolism). A summary of the study literature characteristics is presented in Supplementary Table 1. The protocol was registered with PROSPERO (registry number: CRD42022356904). The work has been reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Assessing the methodological quality of systematic reviews guidelines.[13]

Inclusion and exclusion criteria

The inclusion criteria encompassed critically ill patients diagnosed with COVID-19, with interventions focusing on the use of IL-6 receptor antagonists such as sarilumab and tocilizumab and corticosteroids including dexamethasone, methylprednisolone, and hydrocortisone. The comparisons involved four distinct groups: patients receiving only corticosteroids, those receiving IL-6 receptor antagonists alone, patients receiving the combination of corticosteroids and IL-6 receptor antagonists, and those receiving standard-of-care treatment (controls). Meanwhile, studies lacking raw data and findings, non-comparative studies, meta-analyses, duplicate publications, and research that did not report results of interest or focused on non-severe COVID-19 were excluded to ensure that the study focused on high-quality, relevant data for critical patient populations.

Measures of variables

Quality evaluation. Two authors independently evaluated the quality of the included studies using the Cochrane Risk of Bias Assessment Tool to assess the risk of systematic errors in individual trials, with six items incorporated: bias in the random

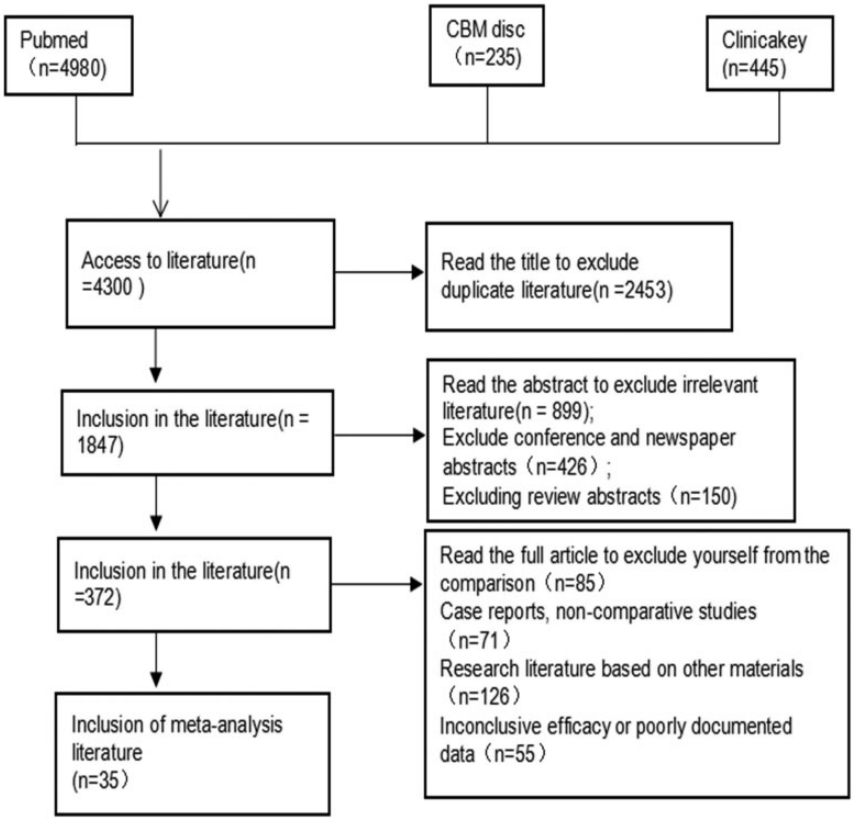

Figure 1. The flowchart of the screening procedure.

allocation method, bias in allocation concealment, bias in blinding, bias in data integrity, bias with or without selective reporting, and other sources of risk of bias. The quality of the studies was evaluated as high risk if one or more of the studies were assessed as high risk, low risk if there were no high-risk factors, and unknown risk if the risk of bias was unclear. Heterogeneity in the primary studies was assessed using Cochran's Q-test and the I^2 index. The results of quality evaluation are presented in Figure 2(a)–(b).

Data extraction. Two independent investigators reviewed the study titles and abstracts to identify those meeting the inclusion and exclusion criteria, and detailed analysis and data extraction were performed by two investigators with 98% agreement, with disagreements resolved by a third investigator. We extracted the following data from each selected study: name, year of the study, age of participants, study title, study area, study type, number of intervention groups (hormone group, IL-6 receptor antagonist group, combination group), the number of control patients, the specific name and dosage of the drug, the main outcome indicators, the number of deaths, the number of ICU admissions, and the number of adverse events

Data analysis procedure

Statistical analysis. The associations of the interventions with mortality and adverse

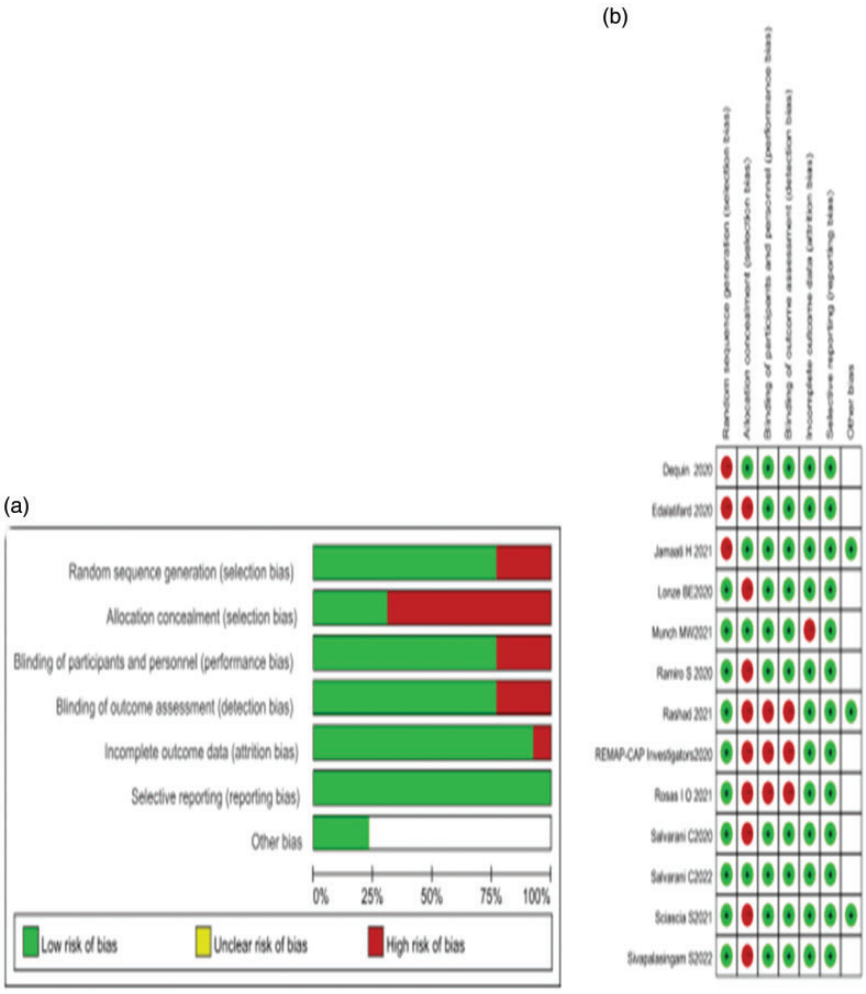

Figure 2. The quality evaluation tables. (a) Summary of risk bias assessment and (b) risk of bias assessment.

events were quantified as the odds ratio (OR) or relative risk (RR), both together with the 95% confidence interval (CI). Cochrane's I^2 test was performed to assess heterogeneity between studies. In the absence of significant heterogeneity between studies ($I^2 \leq 50\%$), we used a fixed-effects model; otherwise ($I^2 > 50\%$), we used a random-effects model. Statistical significance was denoted by $P < 0.05$. When the number of studies included in the meta-analysis was ≥ 10, publication bias was visually determined using funnel plots.

Results

In total, 6668 articles were identified. After excluding duplicates, reviewing abstracts, and full texts, 35 studies with a total of 9836 participants were finally included in the meta-analysis.

COVID-19 treated with corticosteroids alone

Compared with the findings in the control group, corticosteroid treatment alone was

associated with a higher risk of 28-day death (RR = 1.37, 95% CI = 1.22–1.54; Figure 3). However, the funnel plot for the 28-day risk of death had poor symmetry (Figure 4), indicating potential publication bias. In addition, patients treated with corticosteroids has an increased risk of 14-day in-hospital death (RR = 1.25, 95% CI = 1.11–1.41; Figure 3(b)). The funnel plot for the risk of in-hospital was poorly symmetrical (Figure 5), suggesting potential publication bias.

During hospitalization, treatment with corticosteroids was linked to an increased risk of ICU admission (RR = 1.36, 95% CI = 1.18–1.56; (Figure 3(c)) and an increased

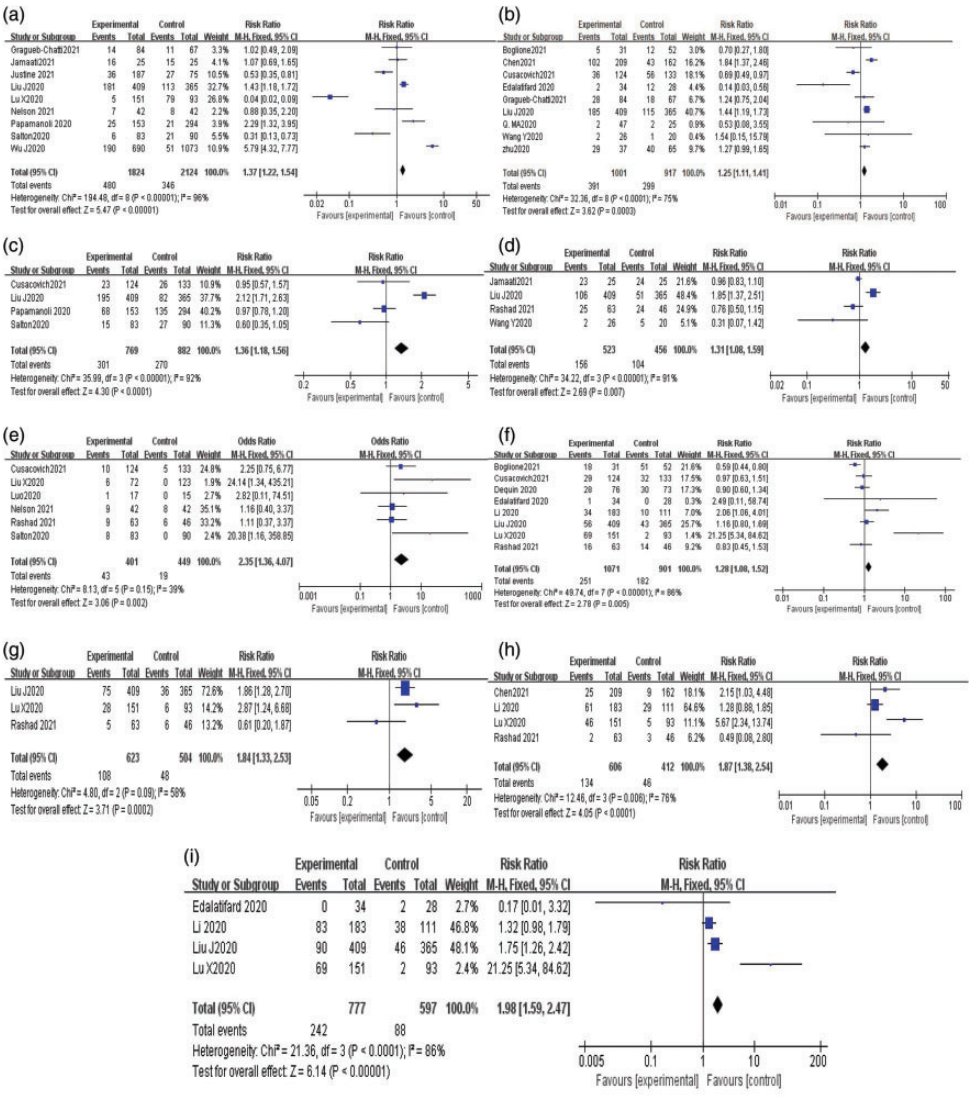

Figure 3. Outcomes of coronavirus disease 2019 treated with corticosteroids alone. M-H, Mantel–Haenszel; CI, confidence interval.

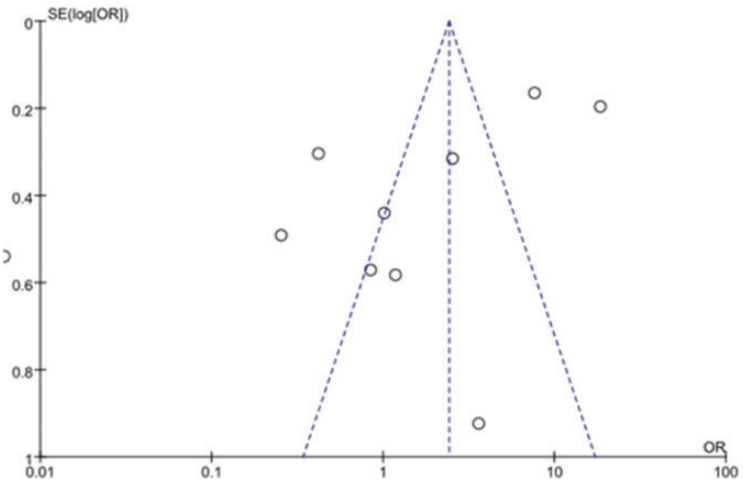

Figure 4. Funnel plot of 28-day mortality risk.

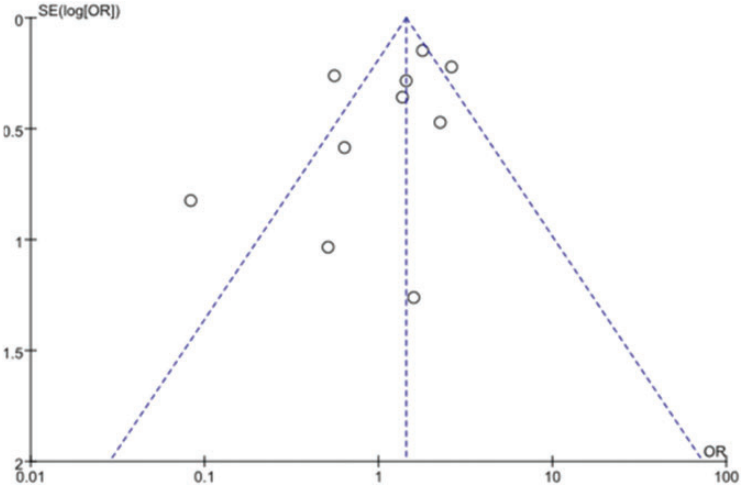

Figure 5. Funnel plot of the risk of in-hospital death.

risk of non-invasive ventilation (RR = 1.31, 95% CI = 1.08–1.59; Figure 3(d)). Concerning adverse events, corticosteroids increased the risk of glycemia (OR = 2.35, 95% CI = 1.36–4.07; Figure 3(e)), secondary infection (RR = 1.28, 95% CI = 1.08–1.52; Figure 3(f)), hepatic enzyme elevation (RR = 1.84, 95% CI = 1.33–2.53; Figure 3 (g)), renal insufficiency (RR = 1.87, 95% CI = 1.38–2.54; Figure 3(h)), and shock (RR = 1.98, 95% CI = 1.59–2.47; Figure 3(i)).

Treatment of COVID-19 with IL-6 receptor antagonists alone

Compared with the findings in the control group, treatment with IL-6 receptor antagonists alone in patients with severe COVID-19 was associated with a lower risk of 14-day mortality (OR = 0.42, 95% CI = 0.20–0.89; Figure 6(j)). However, there was no reduction in the risk of 28-day mortality (RR = 0.82, 95% CI = 0.62–1.09;

Figure 6(k)). IL-6 receptor antagonist therapy was not associated with an increased risk of secondary infection (RR = 1.13, 95% CI = 0.92–1.38; Figure 6(l))) or hepatic insufficiency (OR = 1.12, 95% CI = 0.51–2.43; Figure 6(m)).

Treatment of COVID-19 with corticosteroids in combination with IL-6 receptor antagonists

The combination of corticosteroids and IL-6 receptor antagonists was associated with a lower risk of in-hospital death than standard-of-care therapy (RR = 0.50, 95% CI = 0.38–0.65; Figure 7(n)). No evidence of adverse events was found.

Discussion

This is the first meta-analysis to evaluate the efficacy and safety of immunomodulators in the treatment of COVID-19 since the release of the ninth edition of the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia in 2022. The present study analyzed treatment outcomes for patients with severe COVID-19 receiving

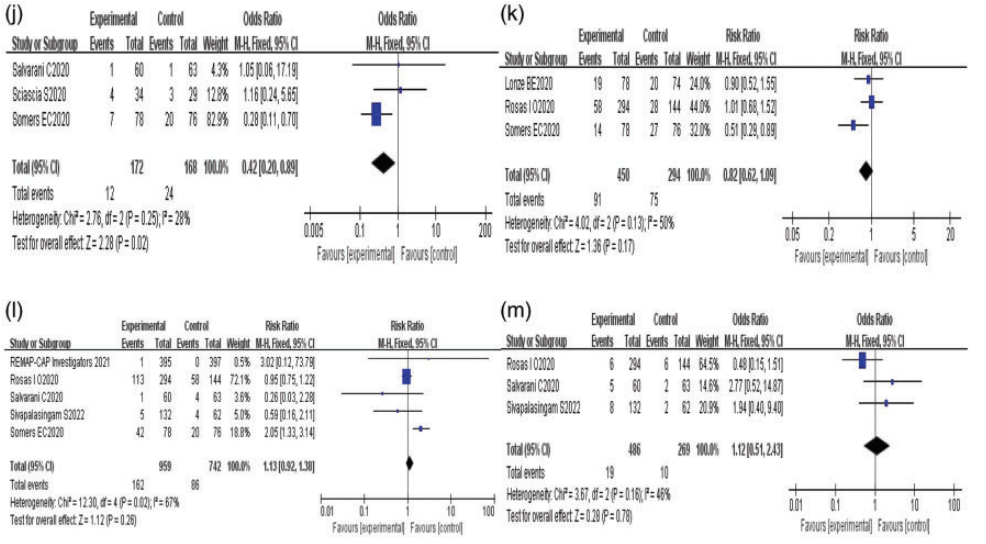

Figure 6. Outcomes of coronavirus disease 2019 treated with interleukin-6 receptor antagonists alone. M-H, Mantel–Haenszel; CI, confidence interval.

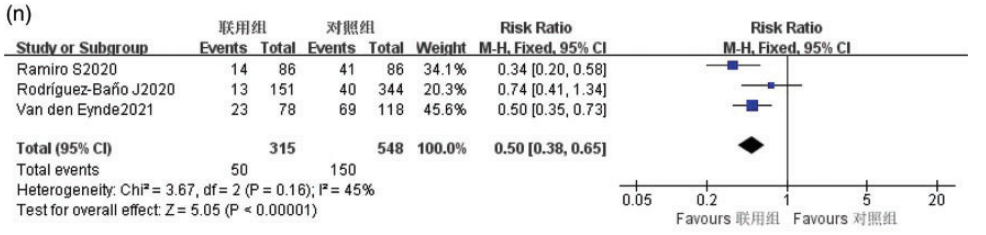

Figure 7. Outcomes of coronavirus disease 2019 treated with corticosteroids in combination with interleukin-6 receptor antagonists. M-H, Mantel–Haenszel; CI, confidence interval.

corticosteroids alone, IL-6 receptor antagonists alone, or the combination of both drug classes. The study primarily assessed the risk of death, the need for mechanical ventilation, ICU admissions, and adverse events.

The analysis indicated that corticosteroid treatment alone significantly increased the risk of in-hospital death among patients with severe COVID-19. The publication bias, as indicated by the asymmetry in funnel plots, suggests the need for caution in interpreting these results because of the potential selective reporting of studies that recorded significant outcomes. The increased risk of ICU admission and the need for non-invasive ventilation further underline the severity of the disease in patients treated with corticosteroids alone. Additionally, corticosteroids were linked to a higher risk of adverse events, including glycemia, secondary infections, hepatic enzyme elevation, renal insufficiency, and shock. Although corticosteroids displayed no benefit in past coronavirus outbreaks, they were associated with reduced mortality in hospitalized patients with COVID-19 requiring oxygen or ventilation.[4]

By contrast, IL-6 receptor antagonists alone were associated with a promising reduction in the 14-day risk of death compared with that in the control group. However, this effect did not persist at 28 days, as no significant reduction in the risk of death was observed. IL-6 receptor antagonists also did not increase the risk of secondary infections or hepatic insufficiency, representing a favorable outcome compared with corticosteroid treatment. The combination of corticosteroids and IL-6 receptor antagonists also significantly reduced the risk of death in hospitalized patients. This finding is particularly noteworthy because it suggests that the synergistic effect of the drugs could improve patient outcomes. Importantly, no evidence of increased adverse events was found for this combination treatment, making it a potentially safer and more effective option. COVID-19 acute respiratory distress syndrome (ARDS) has varying responses to steroids, leading to distinct clinical outcomes. Contrary to expectations, "cytokine storms" are less common in severe COVID-19, and pro-inflammatory marker levels are lower in severe COVID than in non-COVID-19 ARDS, casting doubt on the universal efficacy of immunomodulatory treatments for patients with severe COVID-19.[14]

In our study, IL-6 receptor antagonists displayed a beneficial effect in reducing the intermediate risk of death in patients with severe COVID-19. This finding might be related to their mechanism of action. Respiratory failure in patients with severe COVID-19 is generally characterized by high serum IL-6 concentrations.[15] IL-6 activates cells and induces the secretion of pro-inflammatory cytokines through two signaling pathways: 1) IL-6 binds to membrane-bound receptors and induces signaling through gp130 and 2) IL-6 binds to soluble receptors and produces signal transduction through gp130 on the membrane.[16] Excessive IL-6 signaling can lead to several biological effects. IL-6 might also be associated with tissue and vascular endothelial cell damage, leading to platelet aggregation and angiotensin II-induced microvascular dysfunction. Prior studies illustrated that cytokine release syndrome caused by COVID-19 can be blocked by IL-6 receptor antagonist therapy. Tocilizumab, the most widely used anti-IL-6 drug, binds to soluble and membrane-bound IL-6 receptor and inhibits IL-6-mediated cis-and trans-signaling,[17] thereby inhibiting and blocking the effect of IL-6. An RCT reported that treatment with tocilizumab and thalidomide led to improve outcomes, including improved survival, in ICU-admitted critically ill patients with COVID-19 receiving organ support.[18] In addition, we found no significant

difference in adverse event rates between IL-6 receptor antagonist treatment and the standard of care, highlighting the safety of these drugs.

A multicenter observational study reported that the early administration of long-term low-dose methylprednisolone therapy was associated with significant reductions in the risk of death and ventilator dependency in patients with severe COVID-19 pneumonia.[19] Ruiz-Antorán *et al.*[20] revealed that survival rates in critically ill patients with COVID-19 who received tocilizumab as a standard treatment were higher than those in patients who did not receive tocilizumab, and the benefits appeared to be greater when tocilizumab was administered with steroids. In our study, the combination of IL-6 receptor antagonists and corticosteroids was found to reduce the risk of in-hospital death in patients with COVID-19. However, because of the lack of a survival benefit of corticosteroids alone and their poor safety, we considered that the observed benefit was primarily attributable to IL-6 receptor antagonists. Langarizadehma *et al.*[21,22] stated that corticosteroids can cause a variety of medium- and long-term adverse reactions, including increased insulin resistance, increased risks of bacterial infections, and repeated infection. We also briefly examined the results of the adverse effects induced by glucocorticoids in this study. First, concerning blood glucose, as an important insulin receptor antagonist in the body, glucocorticoids can induce insulin resistance, interfere with the uptake and utilization of glucose by skeletal muscle cells, inhibit the intracellular transport of glucose in adipose tissues, and affect insulin sensitivity by regulating the levels of adipocytokines such as leptin and resistin. Akter *et al.*[23] noted that corticosteroids could cause damage through multiple pathways, including tissue insulin resistance, decreased peripheral glucose uptake in muscles and adipose tissues, increased gluconeogenesis attributable to the activation of genes involved in carbohydrate liver metabolism, and the inhibition of pancreatic β-cell production and insulin secretion. In the case of secondary infection, corticosteroids exert immunosuppressive effects mainly by inhibiting the activity of the key transcription regulatory factors of pro-inflammatory genes and reducing lymphocyte counts. Systemic corticosteroid treatment might adversely affect the congenital and adaptive immune responses and impair the ability of neutrophils to migrate to the infected site.[24] Exposure to systemic corticosteroids could represent a risk factor for bacterial and cytomegalovirus infection in patients with severe COVID-19. Regarding hepatic insufficiency, corticosteroids are often used empirically for severe forms of hepatic impairment. However, their transient immunosuppression leads to immune reconstitution, awakening an autoimmune-like response in a susceptible host that can increase the risk of autoimmune hepatitis in susceptible patients. The results of a retrospective study by Li *et al.*[25] revealed that exacerbations of ARDS-induced pulmonary fibrosis can occur in patients treated with corticosteroids. Hepatic fibrosis has a protective effect in the short term, but a long-term fibrotic reaction will lead to permanent liver injury.[26] Concerning renal insufficiency, the hypoxic state caused by pulmonary lesions in patients with COVID-19 can lead to renal hypoxia injury because of the inflammatory exudation of pulmonary alveoli in patients with ARDS and the inhibition of the smooth exchange of oxygen in the air into the blood, leading to renal oxygen supply insufficiency and further renal impairment. ARDS occurs in the patients with the most critical forms of COVID-19.[27] In shock, the cytokine storm is the basis of the immunopathology of severe COVID-19. The cytokine profile observed in patients with COVID-19 establishes a

pro-inflammatory feedback loop, triggering cytokine storms that circulate and cause local tissue damage as well as systemic effects, such as septic shock, multiple-organ failure, and blood phagocytosis of reticuloendothelial organs.[28] The aforementioned mechanisms and conclusions might explain the increased risk of death and adverse events of patients with severe COVID-19 who received corticosteroids. Corticosteroids have poor safety profiles in patients with COVID-19, and blood glucose, liver and kidney function, and other indicators should be closely monitored during their use. Clinicians treating patients with weakened immune systems must recognize that the scientific evidence supporting the use of immunomodulators in this group is scarce. Consequently, making clinical decisions to optimize care for these patients is challenging, and it could require a personalized assessment of risks and benefits to guide treatment.[29] A significant number of COVID-19-related deaths were observed among nonwhite individuals (54.8% of all deaths, $P < 0.001$), patients with incomes below the median (67.5% of all deaths, $P < 0.001$), individuals with education levels below high school (25.6% of all deaths, $p < 0.001$), and veterans (19.5%, $P < 0.001$).[30]

One limitation of this analysis was that the effect of treatment on long-term prognosis was not clarified. The differences in the types and doses of glucocorticoids and IL-6 receptor antagonists used in the treatment of COVID-19 pneumonia might have affected the results of the study, and no study has precisely compared the changes in patients under different drug types and doses. Second, our study did not provide an individualized treatment plan according to the severity of the disease, and there is no unified standard for the definition and boundary of critical illness. More studies are needed to clarify the differences in efficacy and safety among the treatment plans. Third, although most of the included studies were published in high-impact journals and they were cited multiple times, some study characteristics carried potential risks of bias. Finally, our funnel plots identified publication bias in the literature. High-quality RCTs are needed before the combination treatment can be implemented globally.

Conclusion

The data provide valuable insights into the complex landscape of COVID-19 treatment options. Although corticosteroids alone appear to increase risks, IL-6 antagonists alone displayed promise in reducing short-term mortality. The combination of both drug classes offered the most promising results, suggesting a potential new standard of care for hospitalized patients with COVID-19. Further research is warranted to fully understand and leverage these findings in the ongoing fight against this pandemic disease.

Author contributions

Xuegui Ju: Concept/design, Data analysis/interpretation, drafting of the article, Critical revision of the article, Approval of the article, Statistics, Funding, Data collection.
Jiayao Li: Concept/design, Data analysis, drafting of the article, Critical revision of the article, Approval of the article.
Haonan Huang: Concept/design, Data analysis, drafting of the article, Critical revision of the article, Approval of the article.
Yidan Qing: Concept/design, Data analysis, drafting of the article, Critical revision of the article, Approval of the article.
Bhushan Sandeep: Concept/design, Data analysis/interpretation, drafting of the article, Critical revision of the article, Approval of the article, Statistics, Funding, Data collection.

Availability of data and materials

Not applicable, please contact author for data requests.

Declaration of conflicting interest

The authors declare that they have no competing interests.

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Supplementary material

Supplemental material for this article is available online.

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