Specific Interleukin-1 Inhibitors, Specific Interleukin-6 Inhibitors, and GM-CSF Blockades for COVID-19 (at the Edge of Sepsis): A Systematic Review

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Sepsis is a syndrome with high mortality, which seriously threatens human health. During the pandemic of coronavirus disease 2019 (COVID-19), some severe and critically ill COVID-19 patients with multiple organ dysfunction developed characteristics typical of sepsis and met the diagnostic criteria for sepsis. Timely detection of cytokine storm and appropriate regulation of inflammatory response may be significant in the prevention and treatment of sepsis. This study evaluated the efficacy and safety of specific interleukin (IL)-1 inhibitors, specific IL-6 inhibitors, and GM-CSF blockades in the treatment of COVID-19 (at the edge of sepsis) patients through systematic review and meta-analysis. Methodology: A literature search was conducted on PubMed, EMBASE, Clinical Key, Cochrane Library, CNKI, and Wanfang Database using proper keywords such as “SARS-CoV-2,” “Corona Virus Disease 2019,” “COVID-19,” “anakinra,” “tocilizumab,” “siltuximab,” “sarilumab,” “mavrilimumab,” “lenzilumab,” and related words for publications released until August 22, 2021. Other available resources were also used to identify relevant articles. The present systematic review was performed based on PRISMA protocol. Results: Based on the inclusion and exclusion criteria, 43 articles were included in the final review. The meta-analysis results showed that tocilizumab could reduce the mortality of patients with COVID-19 (at the edge of sepsis) [randomized controlled trials, RCTs: odds ratio (OR) 0.71, 95%CI: 0.52–0.97, low-certainty evidence; non-RCTs: risk ratio (RR) 0.68, 95%CI: 0.55–0.84, very low-certainty evidence] as was anakinra (non-RCTs: RR 0.47, 95%CI: 0.34–0.66, very low-certainty evidence). Sarilumab might reduce the mortality of patients with COVID-19 (at the edge of sepsis), but there was no statistical significance (OR 0.65, 95%CI: 0.36–1.2, low-certainty evidence). For safety outcomes, whether tocilizumab had an impact on serious adverse events (SAEs) was very uncertain (RCTs: OR 0.87, 95%CI: 0.38–2.0, low-certainty evidence; non-RCTs 1.18, 95%CI: 0.83–1.68, very low-certainty evidence) as was on secondary infections (RCTs: OR 0.71, 95%CI: 0.06–8.75, low-certainty evidence; non-RCTs: RR 1.15, 95%CI: 0.89–1.49, very low-certainty evidence). Conclusions: This systematic review showed that tocilizumab, sarilumab, and anakinra could reduce the mortality of people with COVID-19 (at the edge of sepsis), and tocilizumab did not significantly affect SAEs and secondary infections. The current evidence of the studies on
patients treated with siltuximab, mavrilimumab, and lenzilumab is insufficient. In order to establish evidence with stronger quality, high-quality studies are needed.

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**Keywords**: specific interleukin-1 inhibitors, specific interleukin-6 inhibitors, GM-CSF blockades, coronavirus disease 2019 (COVID-19), SARS-CoV-2, sepsis

1 INTRODUCTION

Sepsis is a life-threatening organ dysfunction syndrome caused by host response imbalance due to an infection or infectious factors. The mortality and treatment expenditure of sepsis are relatively high, and there is no specific drug so far. An article published in *The Lancet* in 2020 pointed out that the number of sepsis patients worldwide reached 48.9 million in 2017, among which 11 million patients died, accounting for one-fifth of the global death toll (Rudd et al., 2020).

During the pandemic of coronavirus disease 2019 (COVID-19), patients with severe and critically ill COVID-19 may develop circulation disorders and severe lung damage. Some patients with multiple organ dysfunction, such as that of the liver and kidney, showed typical characteristics of sepsis and meet the diagnostic criteria for sepsis (Li et al., 2020). According to Sepsis-3, sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The organ dysfunction can be represented by an increase in the Sequential (Sepsis-Related) Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality greater than 10% (Singer et al., 2016). Recent studies have shown that patients with severe and critical diseases may experience immune hyperactivity with increased levels of interleukin (IL)-1, IL-6, granulocyte–monocyte colony-stimulating factor (GM-CSF), interferon-γ-inducible protein 10 (IP-10), tumor necrosis factor-α (TNF-α), and other several inflammatory cytokines and were associated with adverse clinical outcomes (Huang et al., 2020; Qin et al., 2020; Coomes and Haghbayan, 2020; Lucas et al., 2020). Therefore, inhibition of proinflammatory cytokines may be a potential therapeutic strategy in COVID-19 (at the edge of sepsis) patients. This study was the first to screen COVID-19 patients with sepsis or at the edge of sepsis through the SOFA score and systematically reviewed the efficacy and safety of anti-cytokine therapy, such as specific IL-1, IL-6 inhibitors, and anti-GM-CSF in COVID-19 patients with organ dysfunction (SOFA ≥2). This paper could help sepsis treatment strategy researchers to grasp the current status of anti-cytokine therapy for COVID-19 patients (at the edge of sepsis) and provide a new perspective for clinical treatment.

2 METHODOLOGY

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline (Supplementary Material S1) (Moher et al., 2009) and registered with the National Institute for Health Research international prospective register of systematic reviews (PROSPERO registration number: CRD42020226545) (Wang et al., 2020).

2.1 Search Strategy and Selection Criteria

Electronic searches were carried out in PubMed, EMBASE, Clinical Key, Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wanfang Database. The search terms that we used were “SARS-CoV-2,” “corona virus disease 2019,” “COVID-19,” “anakinra,” “tocilizumab,” “siltuximab,” “sarilumab,” “mavrilimumab,” and “lenzilumab” and relevant keywords for publications released until August 22, 2021. The search strategies are available as supplementary data (Supplementary Material S1). Other available resources were also used to identify relevant articles. The language will be limited to Chinese and English. Eligible articles were identified for inclusion by screening the titles, abstracts, and full text. Other relevant studies were manually screened by investigators from the reference list of included studies for further analysis. There was no date limit. Two independent reviewers (YW and KZ) carried out the search in a standardized process, followed with identifying eligible records through the examination of each title, abstract, and full text. Disagreements were resolved by consensus, and unresolved conflicts were decided by a third reviewer (QY).

The studies were selected based on the following inclusion criteria: (1) The patients were diagnosed with SARS-CoV-2 infection and their SOFA score (include mean value, median, and absolute value) ≥2 or, according to the SOFA scoring tool, a certain system index (including mean, median, and absolute value) should be within the range corresponding to the system score ≥2—for example, PaO₂/FiO₂ ratio (P/F) (including absolute value, mean value, or median value) was less than 300 mmHg (Singer et al., 2016). A SpO₂/FiO₂ ratio (S/F) of 315 corresponded with a P/F ratio of 300 mmHg [S/F = 64 + 0.84*(P/F)] (Rice et al., 2007). In this review, we defined such COVID-19 patients to be at the edge of sepsis. (2) The intervention of interest was a specific IL-1 inhibitor (anakinra), specific IL-6 inhibitors (tocilizumab, siltuximab, and sarilumab), GM-CSF blockades (mavrilimumab and lenzilumab) with or without standard of care (or treatment), and glucocorticoids. Comparator treatments included placebo, standard of care (or treatment), glucocorticoids, or no intervention; studies with no comparator group were also included. (3) Randomized clinical trials (RCTs), cohort studies, case–control studies, case series, case reports, clinical guidelines, protocols for clinical trials, and any other gray literatures will be included. The studies will not be limited in terms of country. The exclusion criteria were as follows: (1) The patients were not diagnosed as COVID-19; (2) The SOFA score (absolute value,
mean value, or median value) of the patients was less than 2 or did not reach 2 on any of the system indicators; (3) Data on SOFA score or certain indicators in the SOFA scoring tool for the patients studied were not available in the study text, additional materials, or any other relevant resources; and (4) Studies without an available full text or whose data were incomplete or unavailable, posters, commentaries, letters, opinion articles, and in vitro studies were excluded. The defined primary outcome was all-cause mortality at 28–30 days. The safety outcomes included serious adverse events (SAEs) and (serious) secondary infection. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.0 (National Institutes of Health, 2017).

2.2 Data Extraction and Quality (Risk of Bias) Assessment

Two independent reviewers (YW and KZ) extracted data from the eligible studies, and a third one (QY) validated it. The following information will be extracted: year of publication, authors, country, study type, sample size, participant demographics, time of administration, intervention characteristics (name of agent, dose, and route), concomitant medications, survival outcome, treatment-related adverse events, and conclusions of the authors.

The included studies were assessed in terms of potential bias by two reviewers (RD and RL) independently. The third researcher (XL) was consulted for resolving any difference of opinion. The Quality Assessment for Case Series of the National Institute for Health and Care Excellence will be used to evaluate the quality of the case reports (series). The total score is 8 points, in which a score of 4–8 is high quality, and a score less than 4 is low quality. The methodological quality for cohort and case–control studies was assessed based on the Newcastle–Ottawa Scale (NOS) (NOS, 2020). The total score is 9 points, in which scores of 0–3, 4–6, and 7–9 are respectively considered as low, moderate, and high quality. The methodological quality of RCTs was assessed based on the “Risk of Bias” 2.0 tool (Sterne et al., 2019). Each checklist item was judged as “low,” “moderate,” “serious,” and “critical.” The quality of evidence was assessed by using the “Grading of Recommendations Assessment Development and Evaluation (GRADE)” tool (Granholm et al., 2019). The quality of evidence of each outcome is classified as “high,” “moderate,” “low,” or “very low.”

2.3 Data Synthesis and Analysis

The Review Manager version 5.4.1 software was used for analyses. One reviewer (YW) would have to enter the data into the software, and another reviewer (M.L) would have to check the data for accuracy. For dichotomous outcomes, the number of events and total number of participants in the two groups were recorded. The different types of studies were analyzed separately, such as non-RCTs (cohorts and case–control studies) and RCTs. The risk ratio (RR) and odds ratio (OR) with 95% confidence intervals (CIs) were respectively assessed for non-RCTs and RCTs. The risk ratio (RR) and odds ratio (OR) with 95% confidence intervals (CIs) were respectively assessed for non-RCTs and RCTs. Fixed-effects model was used if the result of the Q test was not significant ($p > 0.1$) and $I^2 < 50\%$. Chi-square test, with a significance level at $p \leq 0.1$, was used to assess the heterogeneity of treatment effects between trials. The $I^2$ statistic was used to
### TABLE 1 | Characteristics of the included studies.

| Study | Country | Study type | P | SORF score or indicators, median (OR) | Laboratory variables, median (OR)-days | Intervention group | Control group | Time of administration, median (OR)-days | Dosage | Usage | Concomitant medications | Effective outcomes | Safety outcomes | Authors' conclusion |
|-------|---------|------------|---|---------------------------------------|----------------------------------------|-----------------|-----------|------------------------------------------|--------|--------|------------------------|-----------------|---------------|----------------------|
| Suhardjito et al. (2020) | Indonesia | RCT, single-site open label | 128 | 77 M:69 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 12 (0-11) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| REMAP-CAP Investigators et al. (2020) | United Kingdom, Australia, Canada, New Zealand, France | RCT, multicentre open label | 865 | 629 M:493 F | 85 (56) | TCB + standard of care | Standard of care | Days from hospital admission to emollient (OR): 12 (0-28) | TCB: 8 mg/kg given over 24 h to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| Campile et al. (2021) | Italy | MC, retrospective cohort | 230 | 94 M:136 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 11 (7-14) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| Marceloni et al. (2021) | Italy | SC, retrospective, case-control study | 79 | 64 M:48 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 11 (7-14) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| Fisher et al. (2021) | United States | RCT, single-site open label | 115 | 60 M:55 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 7 (4-11) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| Comportin et al. (2021) | Italy | SC, retrospective cohort | 86 | 64 M:22 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 11 (7-14) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients |
| Vajpayee Gulati et al. (2021) | United States | SC, retrospective cohort study | 43 | 16 M:27 F | 85 (56) | TCB + standard of care | Standard of care | Days from symptom onset to randomization, median (OR): 11 (7-14) | A dose of 8 mg/kg up to a maximum of 660 mg, followed by a second dose after 12 h | Intensive care | No reduction in mortality associated with the risk of infection | TCB was not associated with the risk of infection, bleeding, or thrombosis | TCB did not affect the 30-day mortality in severe respiratory impairment patients | (Continued on following page)
Administration of TCB might decrease in ICU mortality of critical COVID-19 patients with severe hypoxemic respiratory failure.

Fewer deaths in ICU death rate in HCQ (63), critically ill COVID-19 azithromycin (69), and remdesivir (9), DXMS.

TCB Non-TCB Median (range):
- A single 400 mg dose

In the cohort, administration of TCB was associated with a lower mortality in spite of higher superinfection occurrence.

### TABLE 1 (Continued) Characteristics of the included studies.

| Study | Country | Study type | P | Multivariable Cox regression model | Effective outcomes | Safety outcomes | Authors’ conclusion |
|-------|---------|------------|---|-----------------------------------|-------------------|----------------|-------------------|
| Rajendram et al. (2021) | United States | Retrospective observational cohort | 164, 103 | M:61 F | ICU mortality was lower in the TCB group, with more patients treated with TCB showed a high mortality as well as those with low IL-6 treated with TCB treated patients, both in the overall population and among the subgroup of patients requiring MV. Early TCB treatment might improve the regeneratin (P/F) in patients with high IL-6. Patients with high IL-6 not treated with TCB showed a high mortality as well as those with low IL-6 treated with TCB. | There was no difference in the rates of superinfection occurrence. There was no difference in the rates of superinfection occurrence. | Administration of TCB might decrease in ICU mortality of critical COVID-19 patients with severe hypoxemic respiratory failure. TCB use was associated with significant decrease in ICU death rate in critically ill COVID-19 patients with severe hypoxemic respiratory failure. |
| Huang et al. (2021) United States SC, retrospective observational cohort | 96, 64 | M:52 F | CRP, median (range): TCB 122.3 (96–154), control 136.8(108–192); SOFA score, median (range): TCB 4 (0–14), control 6 (2–17) | A single 400 mg dose | Intensive DB (67), COPD (48), HTN (98), DB (53), Intravenous Comorbidities (27), CA (24) | Secondary Infections were not different between the two groups and were predominantly related to invasive devices, such as urinary and central vein catheters. | Administration of TCB was associated with fewer deaths compared to non-treatment despite predominantly being used in patients with more advanced respiratory disease. |
| Gabon-Román et al. (2021) Spain | SC, retrospective observational study | 146, 97 | M:49 F | Baseline IL-6 more than 30 pg/ml predicts IMV requirement. | Secondary Infections were not different between TCB and comparator patients. In the multivariable Cox regression model for mortality at 30 days, administration of TCB was not associated with decreased mortality. | Relevant SAEs were not observed in TCB-treated patients. | Baseline IL-6 more than 30 pg/ml predicts MV requirement in patients with COVID-19 and contributes to the establishment of an adequate indication for the treatment of TCB. |
| Shafi et al. (2021) | United States | Retrospective cohort | 130, 93 | M:37 F | A Kaplan-Meier survival curve demonstrated no difference in survival between TCB and comparator patients. | Positive blood cultures was not statistically significant between the groups. | No difference in survival was observed in critical patients treated with TCB. |
| Sorensen et al. (2021) | United States SC, observational controlled cohort | 154, 102 | M:62 F | In IPW-adjusted models, TCB was associated with a lower mortality in spite of higher superinfection occurrence and contribution to the development of secondary infections. There was no difference in the rates of superinfection occurrence. | In the cohort, administration of TCB was associated with a lower mortality in spite of higher superinfection occurrence. | TCB was associated with an increased proportion of patients with superinfections, but there was no difference in the 28-day case fatality rate between the two groups. | No difference in survival was observed in critical patients treated with TCB. |
TABLE 1 (Continued) Characteristics of the included studies.

| Study                          | Country       | Study type               | P    | SORA score or indications, median (IQR) | Laboratory values, median (IQR) | Intervention group | Control group | Time of administration, median (IQR)-days | Dosage Usage | Concomitant medical condition(s) | Concomitant medications | Effective outcomes | Safety outcomes | Authors’ conclusions |
|-------------------------------|---------------|--------------------------|------|----------------------------------------|---------------------------------|---------------------|--------------|------------------------------------------|---------------|-----------------------------|----------------------|------------------|-----------------|-------------------|
| Breckonhart et al. (2021)     | United States | Multicenter, retrospective cohort | 627; 366 | M:171 F | SORA score: TCB (7) (5-10); control 6 (p=15) | -- | Steroid + TCB | Steroid | A total of 90% of patients received 480 mg as a single dose | Intravenous | HTN without complications (515) | DB without complications (25) | Antiretroviral, immune globulins, HCQ, methylprednisolone, DHE, hydroxychloroquine, prophylaxis. | The combination group (TCB) had improved 28-day mortality compared with the steroid-only group without increasing the risk of infection. | The combination group had improved 28-day mortality compared with the steroid-only group without increasing the risk of infection. |
| Corominas et al. (2021)       | Spain         | Single-center observational study | 104; 72 | M:20 F | P/F, mean (SD): 201.3 (78.1) mmHg | IL-6 pg/ml, mean (SD): 171.6 (40.2-210.7) | CRP- mg/L, mean (SD): 198.4 (161.5) | TCB | -- | If 77.5 kg a single dose of 600 mg, less than 77.5 kg a single dose of 480 mg | -- | HTN, diabetes, obesity, CVD, DB | -- | HCQ | The overall mortality rate was 5.85%. Mortality in hospitalized non-TCB treated patients was 10%. There was no significant difference in adverse clinical outcome risk in patients treated with IL-6 or IL-1 inhibition relative to patients who did not receive interleukin inhibitors. | The overall mortality rate was 5.85%. Mortality in hospitalized non-TCB treated patients was 10%. There was no significant difference in adverse clinical outcome risk in patients treated with IL-6 or IL-1 inhibition relative to patients who did not receive interleukin inhibitors. |
| Cavalli et al. (2021)         | Italy         | Cohort study             | 302; 301 | M:91 F | P/F ≤ 300 mmHg | CRP- mg/L: 129 (100-171) | Anakinra, tocilizumab, sarilumab | No interleukin inhibitors | None | Anakinra: 5 mg/kg/dose intravenous daily dose, TCB: 200 mg a single dose | Intravenous | CAD (15); history of neutropenia (9); DB (7) | -- | HCQ, glucocorticoid | There was no difference in adverse clinical outcome risk in patients treated with IL-6 or IL-1 inhibition relative to patients who did not receive interleukin inhibitors. | IL-1 inhibition was associated with a significant reduction of mortality in COVID-19 patients. IL-6 and IL-1 inhibition were effective in patients with low interleukin inflammatory concentrations. |
| Abe et al. (2020)             | Japan         | Case reports             | 2; 1 M T F | PLT-<100*10^3/L | PT: IL-6 pg/ml: 416.1, P2: IL-6 pg/ml: 90.6 | TCB | Days from symptom onset to TCB: application: P1: 8 days later; P2: 4 days later | Intravenous | DB, KD | PT: paroxysmal atrial fibrillation; P2: paroxysmal atrial fibrillation, immunoglobulin | -- | -- | -- | -- | Anticoagulant therapy might be effective for severe COVID-19 in end-stage renal disease patients. | -- |
| Patel et al. (2020)           | United States | Case reports | 1; 1 F | PLT<100*10^3/L | IL-6 pg/ml: 34; CRP- mg/L: 8.3 | TCB | Days from symptom onset to TCB: application: 12 | Intravenous | Severe thrombocytopenia | HCQ, remdesivir, immunoglobulin, methylprednisolone Discharged | -- | -- | -- | -- | Treatment with cytokine-directed agents such as TCB could be considered in critically ill patients. | -- |
| Mady et al. (2020)            | Saudi Arabia  | A case series            | 61; 54 | M:7 F | Scr, Cr, median (IQR): 1.18 (0.45-3.18) | CRP- mg/L: 31.7 (565-486) | TCB | -- | 8 mg/kg (two consecutive intravenous infusions) 12 h apart | Intravenous | More than one comorbidity (%): 38 (26%) | LyP or rituximab Administration of TCB did not affect the mortality of COVID-19 patients. No SAEs were reported. Treatment was not associated with increased risk of severe complications. | Administration of TCB did not affect the mortality of COVID-19 patients. No SAEs were reported. Treatment was not associated with increased risk of severe complications. | TCB could be an adjunct salivary therapy in rapidly evolving COVID-19 and associated critical illness. |
| Bonardo et al. (2021)         | Italy         | Case reports             | 1; M | PT: 266 mmHg | CRP- mg/L: 240 | TCB | 4th day of admission | Intravenous | Hypogammaglobulinemia, paraproteinemia, AF, CRD | HCQ, LyP | -- | -- | -- | Considering the increasing use of TCB in COVID-19 patients, this case example further studies evaluating the possible association of tuberculin skin test and the risk of clinical outcomes would be informative. | Considering the increasing use of TCB in COVID-19 patients, this case example further studies evaluating the possible association of tuberculin skin test and the risk of clinical outcomes would be informative. | (Continued on following page) |
TABLE 1 | (Continued) Characteristics of the included studies.

| Study | Country | Study type | P | SOPA score or indicators, median (OR) | Laboratory values, median (OR) | Intervention group | Control group | Time of administration, median (OR)-days | Dosage | Usage | Concomitant medication(s) | Effective outcomes | Safety outcomes | Authors’ conclusion |
|-------|---------|------------|---|--------------------------------------|-------------------------------|-----------------------|--------------|-----------------------------------------|--------|-------|------------------------------|-----------------|-----------------|------------------|
| Morillas et al. (2021) | United States | Case reports | 6; 2M/4F | Pt: HIV; THR (300 mg) | CRP-mg/L: 193; IL-6-pg/ml: 5.7 | TCB | – | – | – | – | – | – |
| Castelli et al. (2021) | Italy | Case reports | 1; M | Pt: 150 mmHg Lpv/Rtv; | Prednisone 8 mg/kg, 800 mg TCB | – | – | 2nd day of admission | 6 mg/kg, 160 mg | Intensive | – | – | Lp/Rt/Rt, HCG | Discharged | – |
| Al-Kaf et al. (2021) | Kingdom of Saudi Arabia | Case reports | 1; M | Pt: IL-6-pg/ml: 130; P2:IL-6-pg/ml: 13 | TCB | – | – | 5th day of admission | – | – | – | – | – | – |
| Eroglu et al. (2021) | Turkey | Case reports | 1; M | Pt: HIV infection, DB, | – | TCB | – | 8th day of admission | TCB 400 mg was infused on day 2 | Intensive | – | – | FA/IN, corticosteroids | Discharged | – |
| Kataoka et al. (2021) | Japan | Case reports | 1; M | Pt: IL-6-pg/ml: 154; | TCB | – | – | – | – | – | – | – | – | – |
| Kishaba et al. (2021) | Japan | Case reports | 1; M | Pt: IL-6-pg/ml: 154; | TCB | – | – | On the day of admission | 480 mg (0 mg/kg/day) | Intensive | – | – | FA/IN, methylprednisolone | Discharged | – |
| Leelapunthakul et al. (2021) | Thailand | Case reports | 2; 1 M:1 F | Pt: IL-6-pg/ml: 228; | TCB | – | – | – | – | – | – | – | – | – |
| McKelvy et al. (2021) | United States | Case series | 16; M:12 | Pt: IL-6-pg/ml: 154; | TCB | – | – | – | – | – | – | – | – | – |

(Continued on following page)
### TABLE 1 | (Continued) Characteristics of the included studies.

| Study                  | Country               | Study type | P | SOFA score or indicators, median (IQR) | Laboratory values, median (IQR) | Intervention | Control group | Time of administration, median (IQR)-days | Dosage | Usage | Concomitant medication(s) | Effective outcomes | Safety outcomes | Authors’ conclusion |
|------------------------|-----------------------|------------|---|----------------------------------------|---------------------------------|--------------|---------------|------------------------------------------|--------|-------|----------------------------|-------------------|-----------------|---------------------|
| Noutil et al. (2021)   | France                | Case reports | 1; M | SOFA score: 13 | 10-12 | TCB | On day 7 of the illness | 400 mg/dose | – | – | HCO, prednisolone | Discharged | – | A single dose of 400 mg of TCB was effective and well tolerated |
| Ladnia et al. (2021)  | United States         | Case series | 2; 2 M | P1: P/RF 17 mmHg; P2: 116 mmHg | P1: IL-6 pg/mL: 45; P2: IL-6 pg/mL: 34; P1: CRP: 71; P2: CRP: 71 | TCB | First hospital day | 400 mg/dose | – | – | P1: G6, D6, HTN, dyspnea, kidney and heart transplant; P2: chronic hepatitis B complicated by hepatitis cellular carcinoma in situ post orthotopic liver transplant, HTN, DB | Discharged | – | TCB appears to hold promise for critical COVID-19 patients who require MV when given early after intubation |
| Marcheglia et al. (2021) | Brazil                | Case report | 1; M | P/RF 87 mmHg | 25.3 (IQR) | TCB | – | 400 mg/dose for 2 days | Intensive | Intensive | DM3S | Discharged | – | No adverse events |
| Thrommesen et al. (2021) | Thailand              | Case report | 1; M | P/RF 226 mmHg | IL-6 pg/mL: 17.1 (IQR) | TCB | 6th hospital day | 8 mg/h/dose | – | – | Kidney transportation, HTN, dysplasia, and post transplant DB | Discharged | – | For this COVID-19 patient with kidney transplant, biopass together with deceased immunosuppression and IL-6 inhibitor antibody provides favorable outcomes. Further intervention may be provided by IL-6 and monitoring. |
| Lisuen et al. (2021)  | ArgentinaBrazil, Canada, Chile, France, Germany, Israel, Japan, Russia, and Spain | MC RCT | 416; 261 | M: 155 F: 210 | SpO2/RGR median (IQR): 237 (IQR: 973.6–682.2) | TCR | Time from diagnosis to baseline | 230 mg, 400 mg | Intravenous | Intensive | HTN/111, DB/110, CA/90, HTN/99, IL-6/11, IL-8/22, IL-10/22 | Discharged | – | The results of this study did not show the efficacy of sarilumab in patients admitted to the hospital with COVID-19 and missing supplemental oxygen |
| Deol et al. (2020)    | Italy                 | SC open-label cohort study | 56; 44 | M: 12 F: 32 | P/RF 200 mmHg | 116 (131-170); creatinine mg/dL: 1.375 (IQR: 0.25-0.25) | Sarilumab + standard care | Duration of symptoms before enrollment (days) | 7 (0-11) | 400 mg | Intensive | HTN/111, DB/110, CA/90, HTN/99, IL-6/11, IL-8/22, IL-10/22 | Discharged | – | The results of this study did not show the efficacy of sarilumab in patients admitted to the hospital with COVID-19 and missing supplemental oxygen |
| Arnold et al. (2020)  | Italy                 | SC observational cohort | 53; 47 | M: 10 F: 43 | P/RF 200 mmHg | 162 (130-235); creatinine mg/dL: 1.175 (IQR: 0.25-0.25) | Sarilumab + standard care | No control group | – | 400 mg, 1 to 2 doses | Intensive | Luprem, LPS/RPG | Discharged | Sarilumab appears to be safe |

(Continued on following page)
Early administration of anakinra guided by suPAR shows 2.78 times better improvement of overall clinical status in COVID-19 patients compared to standard of care group. Bozzi et al. (2020) Italy SC, retrospective observational cohort 129; 96 M:24 F 1,555 (1,239–1,867) Time from symptom onset to start of study drug (days) median (Q1–Q3) 9 (7–11) 100 mg daily, 7–10 days Subcutaneous COX-2, mean (SD) 2.2 (1.6) DB (94), HCT (0), ICH (10), COPD (24), GAD (41), ANA (3) Remdesivir, DXMS Anakinra 
combined with standard of care group compared to placebo (combined with standard of care group). 
The 28-day mortality protected from severe disease or death; the 28-day mortality decreased in anakinra-treated patients compared to controls. 
Remdesivir, DXMS Anakinra combined with standard of care group. Compared to placebo (combined with standard of care group). 
The incidence of treatment-related SAEs through day 28 was lower among anakinra-treated patients compared to controls. 
Ferritin-mcg/L: 50.6 (25.3–99.7); IL-6, mean (SD)-pg/ml: 16.8 (7.0–39.8); CRP, mean (SD)-mg/L: 15.2 (10.8–24.9); 
Methylprednisolone maybe an effective therapy in COVID-19 patients with infections were observed. 
Mortality rate was significantly lower between anakinra-treated patients and comparators progress into ARDS associated with COVID-19. 
Early administration of anakinra guided by suPAR showed better improvement of overall clinical status in moderate and severe COVID-19 patients compared to controls. 
The mortality rate was 77.6% in controls and 32.7% in anakinra-treated patients. 
No significant difference observed in the rate of infectious-related adverse events between groups. 
Administration of anakinra combined with methylprednisolone may be an effective therapy in COVID-19 patients with respiratory failure and hyperinflammation, also on MV.

### TABLE 1 | (Continued) Characteristics of the included studies.

| Study | Country | Study type | Patients | Study design | SOFA score or indicators median (QR) | Laboratory values, median (QR) | Intervention group | Control group | Time of administration, median (QR)-days | Dosage | Usage | Concomitant medication | Concomitant medical condition | Effective outcomes | Safety outcomes | Conclusions |
|-------|---------|------------|----------|-------------|--------------------------------------|--------------------------------|------------------------|---------------|---------------------------------------|---------|-------|------------------------|-----------------------------|----------------------|-----------------|------------|
| Kyriazopoulou et al. (2021a) | Greece | MC, cohort | 260; 165 M:90 F | 25 (1); PR (1) | SORPA score: 2 | 29 (10–41) | CKD | Anakinra | SOC | Days from onset of symptoms to start of treatment | 100 mg once daily for 10 days | Subcutaneous | COX-2, mean (SD) 3.2 (1.6) | DB (10), GAD (10), ANA (3), ICH (10), COPD (24) | Remdesivir, DXMS Anakinra combined with standard of care | The rate of SAEs was lower among anakinra-treated patients. | The other factors that enhanced the administration of anakinra in the situation of viremia could also be sorted as no response to full-dose antiviral drugs, antiviral side effects, or no success to antiviral treatment. | Daily soluble urokinase plasminogen activator receptor guided anakinra dominated lower respiratory failure and reduced the pro-inflammatory balance. |
| Enderle et al. (2021) | Turkey | SC, retrospective case review | 11; 12 M:6 F | SOFA score, median (QR): 3 | Anakinra | 0 mg | Duration of COVID-19 symptoms before anakinra | Day 10 after admission | 100 mg intramuscularly followed by 100 mg subcutaneously | Intensive and subcutaneous | Lpx/Rx, HCQ Treatment was well tolerated. | The mortality rate was 77.6%. 1 patient was receiving low-flow oxygen supply. 3 patients no longer needed oxygen supply, and 10 patients were discharged. | Discharged | This critical COVID-19 patient was successfully treated with IL-1 receptor antagonist. |
| Filicori et al. (2020) | Italy | Case report | 1; M | P:16; meningi – | Anakinra | Day 10 after admission | 200 mg intramuscularly | Intensive and subcutaneous | – | – | – | – | This critical COVID-19 patient was successfully treated with IL-1 receptor antagonist. | (Continued on following page)
### TABLE 1 | (Continued) Characteristics of the included studies.

| Study | Country | Study type | P | SOFA score or indicators, median (IQR) | Laboratory values, median (IQR) | Intervention group | Control group | Time of administration, median (IQR)-days | Dosage | Usage | Concomitant medications(n) | Concomitant medications(s) | Effective outcomes | Safety outcomes | Authors’ conclusion |
|-------|---------|------------|---|----------------------------------------|---------------------------------|-----------------------------|----------------|---------------------------------------------|--------|-------|-----------------------------|---------------------------|-----------------|----------------|---------------------|
| Franzetti et al. (2020) | Italy | Case report | 1; M | P/F: 50 mmHg – | | Anakinra | Day 7 after admission | 100 mg/6 h | Subcutaneous | – | Lpv/Rtv, remdesivir | By day 16, a substantial improvement in the respiratory function of the patient was also noticed, with SAPD levels of 92% while on Venturi mask.
| Cremer et al. (2021) | United States | MC, RCT, double-blind | 40; 26 | M: 14 F | Baseline SOFA score, median (IQR): 2 (1–3); baseline P/F-mmHg: 137 (88–192) | CRP-mg/dl: 13.1 (9.8–18.8); ferritin-µg/ml: 1,040 (486–1,860) | Mavrilimumab | Placebo | Time from symptom onset to hospitalization: 7 (4–10) | A single dose of 6 mg/kg | Intravenous | Antibiotics, convalescent plasma, corticosteroids, other immunosuppressive agents | At 14 days, 12 patients in the mavrilimumab group were alive and off supplemental oxygen therapy compared with 9 patients in the placebo group. Treatment-related deaths were not observed.
| De Luca et al. (2021) | Italy | SC, prospective cohort | 32; 29 | M: 10 F | Baseline SOFA score, median (IQR): 112 (107–117); control 122 (117–123) | CRP-mg/L: 18.6 (10.5–26.3); ferritin-µg/L: 1,953 (1,040–2,071) | Mavrilimumab + standard of care | Standard of care | Fever duration (days): mavrilimumab 11 (10–12), control 7 (4–12) | A single dose of 6 mg/kg | Intravenous | – | During the 28-day follow-up, 7 patients in the control group died, and no patient in the mavrilimumab group died. At day 28, 17 patients in the control group showed clinical improvement and all patients in the mavrilimumab group. Fever resolution was faster in mavrilimumab recipients versus controls.

**Legend:**
- MC, multi-center; SC, single-center; F, female; M, male; IL-6, interleukin-6; CRP, C-reactive protein; ALT, alanine aminotransferase; INR, international normalized ratio; PLT, platelet; AF, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DB, diabetes; CKD, chronic kidney disease; HL, hyperlipidemia; CVI, cardiovascular impairment; CVD, cardiovascular disease; HTN, hypertension; IFI, hepatic impairment; HF, heart failure; CA, cancer; CLD, chronic lung disease; CCD, chronic cardiac disease; CPD, chronic pulmonary disease; AMN, active malignant neoplasm; NIV, noninvasive ventilation; MV, mechanical ventilation; CI, confidence interval; TCB, tocilizumab; CP, cumulative percentage; SAE, serious adverse events; AE, adverse events; HCO, hydroxychloroquine; Lpv/Rtv, lopinavir/ritonavir; IFN, interferon; HR, hazard ratio; OR, odds ratios; P/F, PaO2/FiO2; SOT/CTTR, solid organ and composite tissue transplant recipients; CCI, Charlson Comorbidity Index; suPAR, soluble urokinase plasminogen activator receptor;
quantify possible heterogeneity (75–100% considerable heterogeneity). We would explore potential causes through sensitivity and subgroup analyses if heterogeneity had been above 80%. We would not have conducted a meta-analysis if we had not found a reason for heterogeneity. If we could not perform a meta-analysis, we had planned to comment on the results from all studies.

3 RESULTS

3.1 Search Results
Because of insufficient evidence available from RCTs, we also included cohort studies, case-control studies, and case reports (series). The search of the electronic databases on Aug 22, 2021 yielded a total of 5,118 studies. Following the elimination of duplicates and screening of titles and abstracts, we evaluated 244 articles in full text. Among these, we found 43 eligible articles (5 RCTs, 16 cohort studies, 2 case-control studies, and 20 case reports) (Figure 1) (Salvarani et al., 2021; REMAP-CAP Investigators et al., 2021; Canziani et al., 2020; Menzella et al., 2020; Fisher et al., 2021; Campochiaro et al., 2020; Vazquez Guillamet et al., 2021; Rajendram et al., 2021; Huang et al., 2021; Galván-Román et al., 2021; Saffo et al., 2021; Somers et al., 2021; Brosnahan et al., 2021; Corominas et al., 2021; Cavalli et al., 2021; Abe et al., 2021; Patel et al., 2020; Mady et al., 2020; Bernardo et al., 2020; Morillas et al., 2020; Cascella et al., 2020; Al-Kaf et al., 2021; Ergolu et al., 2021; Kataoka et al., 2021; Kishaba et al., 2021; Leelayuwatanakul et al., 2021; McKenzie et al., 2021; Nourié et al., 2021; Ladna et al., 2021; Senegaglia et al., 2021; Thammathiwat et al., 2021; Leszure et al., 2021; Della-Torre et al., 2020; Gremese et al., 2020; Kyriazopoulou et al., 2021a; Bozzi et al., 2021; Franzetti et al., 2021; Kyriazopoulou et al., 2021b; Erden et al., 2021; Filocamo et al., 2020; Franzetti et al., 2020; Cremer et al., 2021; De Luca et al., 2020). All studies were published in peer-reviewed journals.

In the process of full-text review, there were four articles for which we failed to obtain the full texts. The four studies were related to tocilizumab. Two studies did not report the efficacy and safety of tocilizumab (Garg et al., 2020; Kashin et al., 2020). The other two studies were case reports, in which one patient developed tuberculosis reactivation during treatment and the other patient had a secondary infection. The authors of the two case reports suggested that patients might be at a high risk for secondary infection after receiving tocilizumab or tocilizumab combined with glucocorticoid. They suggested that clinicians should use tocilizumab with caution and screen for latent tuberculosis before medication (Mazankova et al., 2020; Moideen et al., 2020).

3.2 Risk of Bias Assessment
The risk of bias of the RCTs was low to moderate, respectively. The results are shown in Supplementary Figure S1 (Supplementary Material S2, Appendix p1). Some studies reported only one outcome, and we assessed the risk of bias for the results—for instance, bias in the measurement of outcomes was not available for safety for the study of Brosnahan et al. (2021) because they did not report it. For mortality outcomes, the methodological quality of 16 cohorts was moderate to high, and those of 2 case-control studies were moderate. For safety outcomes, the methodological quality of 14 cohorts was low to high, and those of 2 case-control studies were low to moderate (NOS assessment results are shown in Supplementary Material S2, Appendix p2–40). The methodological quality evaluation results of the included case reports (series) showed that the quality was low to moderate (the results of quality are shown in Supplementary Material S2, Appendix, p41–42).

3.3 Characteristics of Patients
The 43 studies included were identified and critically evaluated, which included a total of 4,951 patients with confirmed SARS-CoV-2 infection, of whom 2,243 received mechanical ventilation. Only 11 studies reported the SOFA score of enrolled patients, of which 4 studies reported SOFA scores greater than or equal to 6 (tocilizumab), 3 studies reported scores between 4 and 5 (tocilizumab), and 4 studies reported scores between 2 and 3 (for anakinra, 1 for mavrilimumab). The remaining 32 articles reported the respiratory status (including P/F or S/F) and platelet of patients, of which 5 studies included patients with P/F less than or equal to 100 mmHg and of which 13 studies reported patients with P/F between 100 and 200 mmHg.

Most patients received standard of care (or standard of treatment) based on local treatment guidelines. However, the medication regimens of the standard of care were different, mainly including antiviral drugs, antibiotics, glucocorticoids, and other symptomatic drugs. Anti-cytokine agents were mainly used by intravenous injection and, in a few studies, by subcutaneous administration. In addition, there is still no consensus on the dosage of anti-cytokine agents for such patients until now. In the included articles, the dosage of most patients was as follows: tocilizumab, 8 mg/kg/dose and up to a maximum of 800 mg; sarilumab, 400 mg/dose with 1 to 2 doses; anakinra 100 mg/dose 1–4 times a day; and mavrilimumab 6 mg/kg/dose. The characteristics of the included studies are presented in Table 1.

3.4 Results of the Meta-analysis
We cannot conduct a quantitative analysis of anakinra, sarilumab, and mavrilimumab for some outcomes, owing to differences in outcomes reported, study design, and limited study numbers. Especially for mavrilimumab, only one RCT and one cohort met the inclusion criteria. If we could not perform a meta-analysis, we commented on the results from all included studies.

3.4.1 Mortality Outcome (All-Cause Mortality at Days 28–30)

Tocilizumab
Among the 14 controlled studies, one RCT and 6 cohorts neither reported a difference for mortality at days 28–30 between the tocilizumab and control groups. Compared to the control group, the results of RCTs showed that the use of tocilizumab for
patients with COVID-19 (at the edge of sepsis) might decrease the mortality rate (OR 0.71, 95%CI: 0.52--0.97, \(I^2 = 0\)%), and there was a significant difference between the two groups (Figure 2A). The non-RCTs showed a similar result (RR 0.68, 95%CI: 0.55--0.84, \(I^2 = 45\)%), and there was statistical significance (Figure 2B).

**Sarilumab**

For sarilumab, of the studies that met the inclusion criteria, only two RCTs (one of the RCTs studied tocilizumab and sarilumab) and two non-RCTs provided data on mortality outcome. Among the two non-RCTs, one cohort did not set up a control group. Compared to the control group, the results of RCTs showed that
the use of sarilumab for patients with COVID-19 (at the edge of sepsis) might reduce the mortality rate (OR 0.65, 95%CI: 0.36–1.2, $I^2 = 8\%$), but there was no significant difference between the two groups (Figure 3). However, due to the lack of research, data synthesis for outcomes of non-RCTs was not conducted.

**Anakinra**

For anakinra, of the studies that met the inclusion criteria, 1 RCT and 4 non-RCTs provided data on mortality outcome. Due to the insufficiency of RCTs, we only quantitatively synthesized the results of non-RCTs. Compared to the control group, the results of non-RCTs showed that the use of anakinra for patients with COVID-19 (at the edge of sepsis) might reduce the mortality rate (RR 0.47, 95%CI: 0.34–0.66, $I^2 = 0\%$), and there was statistical significance (Figure 4).

**Mavrilimumab**

The only RCT, published in 2021, explored outcomes in 21 patients who received mavrilimumab and 19 patients who received placebo. The median (IQR) baseline SOFA score of enrolled patients was 2 (2 to 3). The study reported no significant association with the proportion of patients alive and off oxygen therapy at day 14. The other cohort, published in 2020, explored outcomes in 12 patients who received mavrilimumab and 26 patients who received standard of care. The median (IQR) P/F ratio of the mavrilimumab and control group was 196 (167–215) and 217 (138–258) mmHg, respectively. The study reported that

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**TABLE 2 | Adverse events (AEs) summarized from controlled studies.**

| Author | Immunomodulator | AEs (percentages) |
|--------|----------------|------------------|
| Salvarani et al. (2021) | Tocilizumab | Control group: 2 severe infections; treatment group: 1 upper gastrointestinal tract bleeding. The most common adverse events were increased alanine aminotransferase level and decreased neutrophil count (2021) |
| REMAP-CAP Investigators et al. (2021) | Tocilizumab, sarilumab | Treatment group: 1 secondary bacterial infection, 5 bleeding events, 2 cardiac events, 1 deterioration in vision. Control group: 4 bleeding events, 7 thromboses |
| Canziani et al. (2020) | Tocilizumab | Thrombosis: treatment group (19%), control group (17%). Bleeding: treatment group (17%), control group (13%). Infection: treatment group (31%), control group (39) |
| Fisher et al. (2021) | Tocilizumab | No observed increased risk of secondary infection within 14 days of treatment with tocilizumab |
| Campochiaro et al. (2020) | Tocilizumab | Pulmonary thrombosis: treatment group (6%), control group (9%). Raised ALT, AST level: treatment group (15%), control group (18%). Neutropenia: treatment group (16%), control group (8) |
| Vazquez Guillame et al. (2021) | Tocilizumab | Culture-negative sepsis: treatment group (41.7%), control group (19.4) |
| Rajendram et al. (2021) | Tocilizumab | Secondary infection: treatment group (25.6%), control group (25.6%) |
| Huang et al. (2021) | Tocilizumab | Secondary infection: treatment group (31%), control group (17%) |
| Saffo et al. (2021) | Tocilizumab | Bleeding: treatment group (24.1%), control group (14.5%). Blood stream infection: treatment group (7.4%), control group (8.2%). Pulmonary infection (endotracheal aspirates/spumum): treatment group (25.9%), control group (30.3%) |
| Somers et al. (2021) | Tocilizumab | Superinfection: treatment group (54%), control group (26%). Bloodstream infection: treatment group (14%), control group (9%). Pneumonia: treatment group (45%), control group (20%) |
| Brosnahan et al. (2021) | Tocilizumab | Positive blood culture: combination group (steroid + tocilizumab) (11.6%), steroid group (12.7%). Positive Fungitell test: combination group (6.9%), steroid group (10.4%). Positive T2Candida panels: combination group (6.4%), steroids group (6.9%). Cytomegalovirus viral loads elevated: combination group (3.5%), steroids group 4.6% |
| Lesure et al. (2021) | Sarilumab | Serious infection: treatment group (12%), control group (12%). ALT increase: treatment group (31%), control group (26%). Pulmonary infection (endotracheal aspirates/spumum): treatment group (27.7%), control group (31.5%) |
| Delia-Torre et al. (2020) | Sarilumab | Infections: treatment group (21%), control group (18%). Neutropenia: treatment group (14%), control group (7%). Increase in liver enzymes: treatment group (14%), control group (0). Thrombocytopenia: treatment group (7%), control group (7%) |
| Kyriazopoulou et al. (2021a) | Anakinra | Infections and infestations: treatment group (8.4%), control group (15.9%). Anemia: treatment group (14.3%), control group (19.6%). Increase of liver function tests: treatment group (35.8%), control group (33.3%). Hyperglycemia: treatment group (36.5%), control group (40.2%). Hypotension: treatment group (7.9%), control group (12.2%). Hyponatremia: treatment group (11.4%), control group (9%) |
| Bozzi et al. (2021) | Anakinra | Treatment group: grade ≥3 GGT increase (27.7%), anemia (24.6%), ALT increase (6.2%), granulocytopenia (1.5%). Control group: a comparable proportion of these AEs |
| Franzetti et al. (2021) | Anakinra | Bloodstream infections: treatment group (16%), control group (7.1%). Urinary tract infections: treatment group (3.5%), control group (1.8%). Pneumonia infections: treatment group (7.1%), control group (7.1%) |
| Kyriazopoulou et al. (2021b) | Anakinra | Electrolyte abnormalities: treatment group (26.9%), control group (31.5%). Elevated liver function tests: treatment group (30.8%), control group (39.2%). Gastrointestinal disturbances: treatment group (11.5%), control group (6.9%). Anemia: treatment group (16.9%), control group (20%) |
| Cremer et al. (2021) | Mavrilimumab | Bacterial pneumonia: treatment group (10%), control group (5%). SAEs: treatment group (24%), control group (21%). Circulatory shock: treatment group (10%); control group (5%). Acute kidney injury: treatment group (19%), control group (16%). ALT ≥3ULN: treatment group (24%), control group (16%). AST ≥3ULN: treatment group (29%), control group (21%) |
| De Luca et al. (2020) | Mavrilimumab | Infectious complications: treatment group (3), control group (12%) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; ULN, upper limit of normal.
mavrilimumab was associated with a reduced mortality rate and improved clinical outcomes. The benefits of mavrilimumab therapy for those patients remained uncertain, given the insufficient controlled studies and the small sample size.

3.4.2 Safety Outcomes
Treatment-related adverse events (TRAEs) were reported in the majority of research and typically included neutropenia, secondary infections, increase in liver enzymes, and thromboembolism (Table 2). Due to the insufficient studies of safety outcome, we only conducted a quantitative synthesis for tocilizumab.

Tocilizumab
Both 2 RCTs reported SAEs and secondary infections; 4 of 11 non-RCTs reported SAEs and 10 reported secondary infections. Tocilizumab was associated with less SAEs (OR 0.87, 95%CI: 0.38–2.00, \( I^2 = 0 \)) and lower rates of secondary infections (OR 0.71, 95%CI: 0.06–8.75, \( I^2 = 42 \)) compared with the control groups, which both did not reach significance in RCTs (Figures 5A,B). For non-RCTs, tocilizumab was associated with slightly more SAEs (RR 1.18, 95%CI: 0.83–1.68, \( I^2 = 0 \)) and secondary infections (RR 1.15, 95%CI: 0.89–1.49, \( I^2 = 49 \)) compared with the control arm, but there was no statistical significance (Figures 6A,B).

Other Anti-cytokine Agents
The included RCTs reported that the incidence of treatment-emergent SAEs through day 28 was higher in the placebo and standard-of-care group (21.2%) compared to the anakinra and standard-of-care group (16.5%). The non-serious TRAEs were similar in both treatment groups (Kyriazopoulou et al., 2021a). Only two cohorts reported secondary infection outcomes, and none reported SAEs. Both Franzetti M et al. and Bozzi G et al. reported that the rate of adverse events related to infection (or bloodstream infections) was similar between groups—for example, 26.8% occurred in the anakinra group and 16.1% in the control group (Bozzi et al., 2021; Franzetti et al., 2021). Among these infectious events, 9/56 developed bloodstream infections in the anakinra group and 4/56 in the control group (Franzetti et al., 2021). Meanwhile, they all suggested that special attention should be paid to possible infective reactivations or bacterial sepsis due to anakinra. In studies with a comparator arm exploring outcomes from patients who received mavrilimumab or sarilumab, the frequency of TRAEs was similar in both treatment and comparator groups.

3.5 Quality of Evidence
For mortality outcomes, the quality of evidence of tocilizumab for COVID-19 (at the edge of sepsis) was of low and very low quality for RCTs and non-RCTs, respectively. Meanwhile, the quality of evidence of sarilumab and anakinra for COVID-19 (at the edge of sepsis) was of low and very low quality, respectively. As for the SAEs and secondary infections of tocilizumab for COVID-19 (at the edge of sepsis), the quality of evidence was all low for RCTs and very low for non-RCTs, respectively. The results are shown in Supplementary Table S8 (Supplementary Material S2, Appendix p43–45).

4 DISCUSSION
In terms of etiology, sepsis can be classified as bacterial sepsis, fungal sepsis, and viral sepsis based on different pathogens. Sepsis patients with a SOFA score of 2 or more in a general hospital population with presumed infection had an increased risk of death by 2–25 times compared to patients with a SOFA score of less than 2 (Singer et al., 2016; Seymour et al., 2016). The population included in this study was COVID-19 patients with SOFA score ≥2, who were already in the state of sepsis or were...
about to deteriorate into sepsis, and these patients urgently needed appropriate, safe, and effective treatment. In this study, we evaluated the efficacy and safety of tocilizumab, sarilumab, siltuximab, anakinra, mavrilimumab, and lenzilumab to provide relevant clinical evidence and research ideas for treatment.

4.1 Anti-cytokine Therapy

The local inflammatory response caused by an infection can promote the replacement of damaged tissues by new tissues and play a role in weakening the damage that has occurred, but when excessive inflammation occurs, it may cause systemic inflammatory response syndrome (SIRS) and lead to sepsis. Therefore, timely detection of cytokine storms and proper regulation of inflammatory response may be of great significance to the prevention of sepsis. The “Expert Consensus on Early Prevention and Blocking of Sepsis in China” recommended that when infected patients experience significant increases in cytokines or inflammatory imbalances, the inflammation should be adjusted as soon as possible using glucocorticoids, nonsteroidal anti-inflammatory drugs, traditional Chinese medicine preparations, antibodies targeting inflammatory mediators, etc. (Emergency medicine branch of CPAM et al., 2020). Many studies showed that the factors mainly involved in SIRS and compensatory anti-inflammatory response syndrome include TNF-α, IL-1, IL-6, etc. The Expert Consensus suggested that, for patients with high-risk sepsis infection, cytokine monitoring should be carried out regularly (2–4 h repetition) to find suspected sepsis patients in time. At present, the cytokine commonly detected in hospitals is IL-6. As a cytokine, IL-6 mainly stimulates the proliferation and differentiation of cells involved in immune response and plays an important role in the anti-infection immune response (Emergency Medicine Branch of CPAM et al., 2020).

IL-6 inhibitors include tocilizumab, sarilumab and siltuximab. Tocilizumab and sarilumab were approved for rheumatoid arthritis, and siltuximab was approved for Castleman’s disease. The IL-1 receptor antagonist (anakinra) is a cornerstone treatment for hyperinflammatory conditions such as Still’s disease. Some studies showed that cytokine-directed agents such as IL-6 and IL-1 inhibitors might be effective in the treatment of cytokine storm syndromes, including macrophage activation syndrome and cytokine release syndrome (La Rosée et al., 2019). The GM-CSF blockade included mavrilimumab and lenzilumab, which is designed to prevent and treat cytokine storm (De Luca et al., 2020; Aroldi et al., 2019).

This systematic review identified and summarized RCTs, non-RCTs, and case reports (series) to evaluate the effect and safety of tocilizumab, sarilumab, siltuximab, anakinra, mavrilimumab, and lenzilumab. The meta-analysis results showed that tocilizumab might reduce the mortality of patients with COVID-19 (at the edge of sepsis) (RCTs: OR: 0.71, 95%CI: 0.52–0.97, low-certainty evidence; non-RCTs: RR: 0.68, 95%CI: 0.55–0.84, very low-certainty evidence) as was anakinra (non-RCTs: RR: 0.47, 95%CI: 0.34–0.66, very low-certainty evidence). Sarilumab might reduce the mortality of patients with COVID-19 (at the edge of sepsis), but there was no statistical significance (OR: 0.65, 95%CI: 0.36–1.2, low-certainty evidence). For safety outcomes, whether tocilizumab had an impact on SAEs was very uncertain (RCTs: OR: 0.87,
95%CI: 0.38–2.0, low-certainty evidence; non-RCTs: OR: 1.18, 95%CI: 0.83–1.68, very low-certainty evidence) as was on secondary infections (RCTs: OR: 0.71, 95%CI: 0.06–8.75, low-certainty evidence; non-RCTs: RR: 1.15, 95%CI: 0.89–1.49, very low-certainty evidence).

### 4.2 Special Population

At present, there are still few large-scale randomized controlled prospective studies on COVID-19 (at the edge of sepsis). The experiences of case or case series still have a certain reference significance for clinical treatment, especially for the individualized treatment of special populations, such as critically ill children, immunocompromised individuals, and elderly patients with a variety of chronic diseases. Patel PA et al. reported a case of severe pediatric COVID-19 presenting with respiratory failure and severe thrombocytopenia. On day 7, because of continued fever and elevated inflammatory markers, remdesivir and tocilizumab were given. On the next day, she had significant clinical improvement, so the treatment with cytokine-directed agents may be considered in critically ill patients (Patel et al., 2020).

Patients with impaired immune function are more at risk in case of adverse outcomes. Leelayuwatanaku N et al. reported two patients (P/F < 300 mmHg) with human immunodeficiency virus (HIV) infection and multiple myeloma relapse, respectively. After tocilizumab, hemoperfusion, and immunoglobulin comprehensive treatment, their P/F levels increased significantly, and they survived to discharge (Leelayuwatanaku et al., 2021). In addition, Kataoka H et al. reported an 85-year-old patient with Sjögren’s syndrome, whose P/F decreased to 100 mmHg. After receiving a single dose of tocilizumab, the symptoms improved. This patient represents a supplementary case confirming the safety and efficacy of tocilizumab for elderly COVID-19 patients with autoimmune diseases. It is also suggested that combination therapy may be a promising treatment for severe COVID-19 in immunocompromised hosts (Kataoka et al., 2021).

The experience of COVID-19 patients with solid organ and composite tissue transplantation has not been reported in detail before. Morillas JA et al. reported 5 patients with COVID-19 (P/F < 300 mmHg) who received kidney transplantation, lung transplantation, face transplantation, and liver transplantation, respectively. These patients also had chronic diseases, such as heart diseases, bladder cancer, rheumatic heart disease, etc. Their C-reactive protein (CRP) levels decreased significantly within a few days after the application of tocilizumab. The findings showed that tocilizumab could be used without major direct toxicity in solid organ and composite tissue transfer recipients early after initiation of mechanical exploitation due to COVID-19, regardless of the type of organ transferred. However, the authors suggested that the diagnosis and side effects need to be further studied (Morillas et al., 2020). Ladna M et al. and Thammathiwat T et al. shared the treatment experiences of transplant patients, respectively. One patient who received a kidney and heart transplant in February 2020 had a relatively poor clinical condition with a P/F level of 117 mmHg. On day1, he was given a dose of 400 mg of tocilizumab, broad-spectrum antibiotics, and hydroxychloroquine, and transplant immunosuppression with tacrolimus was continued. After 11 days of treatment, he was discharged without supplemental oxygen requirement (Ladna et al., 2021; Thammathiwat et al., 2021).

In addition to tocilizumab treatment cases, there are few case reports on IL-1 receptor antagonist. Filocamo G et al. and Franzetti M et al. in Italy treated two severe patients (P/F <200 mmHg) with IL-1 receptor antagonist anakinra. These studies suggested that, in the cytokine storm occurring during severe COVID-19 pneumonia, the high tolerability, short half-life, and immunomodulatory profile of anakinra may be useful. IL-1 inhibition may represent a safe and promising strategy to reduce inflammation, thus preventing multi-organ dysfunction (Filocamo et al., 2020; Franzetti et al., 2020).

### 4.3 Limitation

First, the lack of RCTs limited our analyses. Some included studies were case reports or series and had no proper control groups. Meanwhile, some articles of which the full texts or data were not accessible and those in languages other than Chinese and English were excluded from the analysis. This might have led to overlooking some critical findings or observations. In addition, in this study, the SOFA score or related indicators of some patients included in the study were median or mean, so not all patients were septic patients, but the results of this population also reflected a trend problem because some patients might be or would be in a state of sepsis. Thirdly, we found that most patients use antiviral drugs, glucocorticoids, immunoglobulins, plasma, broad-spectrum antibiotics, and other drugs at the same time. We cannot rule out the impact of these drugs on the disease.

### 5 CONCLUSION

The results of this systematic review showed that tocilizumab, sarilumab, and anakinra might reduce the mortality of people with COVID-19 (at the edge of sepsis), and tocilizumab did not significantly affect SAEs and secondary infections. However, given the limited clinical researches and low-quality evidence, this conclusion needs more clinical evidence to be verified. In addition, so far, there is still no unified opinion on the timing, dosage, usage, and applicable population of these drugs all over the world, which also adds to the uncertainty of the conclusion of this study.

### DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

### AUTHOR CONTRIBUTIONS

YW and KZ contributed equally to this work. YW, KZ, and QY conceived and designed the study protocol. YW and KZ executed
SUPPLEMENTARY MATERIAL

The supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.804250/full#supplementary-material
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