CoLab Network

Tocilizumab for the Treatment of Hospitalized Patients With COVID-19

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Key Messages

Tocilizumab is administered to hospitalized patients with COVID-19.

Tocilizumab may be efficacious in reducing the length of hospitalization and the progression to the combined end point of mechanical ventilation or death. The other reported outcomes remain inconclusive. These findings are based on 12 randomized control trials.

The safety of tocilizumab remains unclear. Few studies report the effect of tocilizumab treatment on death and the incidence of serious adverse events.

Administration of tocilizumab and a patient population matching the characteristics of those in the RECOVERY and REMAP-CAP (2 of the largest and best-run) trials may yield the best outcomes. The use of tocilizumab in these trials can be applied to develop practice standards that align with current clinical recommendations.

Evidence is lacking for patients with compromised immune systems, comorbidities, and concomitant bacterial infections.

The studies lack similarity in their study populations, treatment characteristics (ex., COVID-19 severity, medication taken in addition to the study treatments, and time of medication administration relating to the clinical course of infection), and the usual care used among trial sites.

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Stakeholders:
One clinician with content expertise provided comments on this report.

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Abbreviations

ARDS	acute respiratory distress syndrome
CrI	credible interval
CI	confidence interval
COVID–19	coronavirus 2019
ECMO	extracorporeal membrane oxygenation
FiO_2	fraction of inspired oxygen
HR	hazard ratio
ICU	intensive care unit
IMV	invasive mechanical ventilation
MV	mechanical ventilation
NIV	non-invasive ventilation
NR	not reported
OR	odds ratio
PaO_2	partial pressure of oxygen
PCR	polymerase chain reaction
RCT	randomized control trial
SAE	serious adverse events
TCZ	tocilizumab
UC	usual care
WHO-CPS	World Health Organization Clinical Progression Scale

Introduction and Rationale

Background and Rationale

Several drug treatments for coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are approved for use in Canada, including nirmatrelvir-ritonavir (Paxlovid), remdesivir (Veklury), and tocilizumab (Actemra). Tocilizumab (TCZ) is administered as an IV solution to hospitalized adults receiving corticosteroids and supplemental oxygen, mechanical ventilation (MV), or extracorporeal membrane oxygenation (ECMO). This medication is indicated for several rheumatological diseases including rheumatoid arthritis and cytokine release syndrome and received an expanded indication for COVID-19 in October 2022. TCZ is a humanized monoclonal antibody against the interleukin-6 (IL-6) receptor. IL-6 is one of the inflammatory markers released when the immune system triggers a cytokine storm, for instance, when a patient has a severe COVID-19 infection that requires hospitalization. The activation of the IL-6 receptor leads to an inflammatory response, including severe acute respiratory distress syndrome (ARDS).

Currently, the federal government carries out the procurement and allocation of this medication, as well as the other 2 COVID-19 treatments, through the Public Health Agency of Canada (PHAC). PHAC is interested in determining whether a provincial and territorial distribution method is beneficial based on new and postmarketing evidence released since the publication of the first CADTH report,[1] in March 2021, on tocilizumab use in COVID-19 treatment. The goal of such reallocation is the equitable distribution and access to these therapies within the Canadian health care system.

Rationale
PHAC currently sources and distributes COVID-19 drugs for Canada's health care systems. Gathering postmarket evidence on their safety and efficacy is important to help determine fair access in the future.

Objectives

The objectives of this rapid systematic review are to determine the state of evidence on the efficacy and safety of TCZ for hospitalized patients and which populations of patients are most likely to benefit from treatment with TCZ.

Policy Questions

This rapid systematic review will address the following policy questions:

1. What new evidence on the efficacy and safety of TCZ is available since the publication of the CADTH report?
2. Which patients are most likely to benefit from treatment with TCZ?

Research Questions

This rapid systematic review will address the cited policy questions by exploring the following research questions:

1. What is the efficacy of TCZ in patients with COVID-19?
2. What is the safety of TCZ in patients with COVID-19?
3. What are the characteristics of patients (e.g., comorbidities) associated with improved outcomes in the treatment of COVID-19 with TCZ?
4. What are the characteristics of patients (e.g., comorbidities) associated with risk of adverse outcomes when treated with TCZ?

Methods

A rapid systemic review was undertaken as opposed to a meta-analysis as there is a limited amount of literature that is within the eligibility criteria (12 studies) and between the studies, there is too much heterogeneity in each study population to make a reliable analysis.

Literature Search Methods

Methods:
We used a rapid systematic review approach, looking at randomized controlled trials and controlled clinical trials. We selected studies for inclusion using criteria from the PICOS framework.

An information specialist developed and conducted a literature search for clinical studies using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist. The complete search strategy is presented in (Appendix 1).

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. The Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparator, and study design (PICOS) framework and research questions. The main search concepts were tocilizumab and COVID-19. The US National Institutes of Health's clinicaltrials.gov trials registry was also searched.

CADTH-developed search filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Retrieval was not limited by publication date but was limited to the English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on May 1, 2023. Regular alerts updated the database literature searches until June 19.

Eligibility Criteria

Studies that met the PICOS criteria were selected for inclusion. Studies were not included or excluded on the basis of reported outcomes. (Table 1) describes the inclusion criteria.

Table 1

Selection Criteria

Criteria	Description
Population	Hospitalized adult patients with COVID-19.
Intervention	Tocilizumab with usual care
Comparators	• Remdesivir • Sarilumab • Dexamethasone • Usual care • Placebo
Outcomes	Efficacy and safety
Study design	Completed phase II/III randomized control trials (or higher)

Population and Subgroups

The population of interest is hospitalized adult patients with a COVID-19 infection. There is also an interest in subgroups such as immunocompromised patients, patients with comorbidities, and patients with concomitant bacterial infections (regardless of source, including superimposed bacterial pneumonia).

Intervention and Comparators

The intervention of interest is TCZ with usual care (UC) administered in a hospital setting. UC is defined as the use of steroids, antibiotics, diuretics, oseltamivir, and bronchodilators (SABA/SAC), but is not limited to these options. The comparators are remdesivir, sarilumab, dexamethasone, UC alone, and placebo.

Outcomes Definition

The outcomes of interest are efficacy and safety. Efficacy outcomes include ICU admission, initiation/discontinuation of MV, invasive mechanical ventilation (IMV or ECMO/venovenous (VV)-ECMO) or high-flow oxygen (HFO)/noninvasive positive pressure ventilation (NIPPV) (i.e., bilevel positive airway pressure (BiPAP)), initiation/discontinuation of intubation or re-intubation, need for vasopressors, and duration of hospitalization, ICU stay, or ventilation. Safety outcomes include death, serious adverse events (SAE) (as defined by each study), development of ARDS, development of cytokine storm, and superimposed bacterial pneumonia.

Study Designs

Phase II/III or higher randomized controlled trials (RCTs) that meet the previously defined population, intervention, comparator, and outcome criteria.

Study Selection Process

Two reviewers (MT, JR) independently applied the eligibility criteria to each title and abstract identified in the literature search to determine which met inclusion criteria. Full-texts from citations identified as potentially eligible were obtained. The eligibility criteria were then applied to full-text studies by the same reviewers, independently, and a final decision about eligibility was made. Conflicts were resolved by discussion and consensus. The reviewers were not blinded to study authors or centre of publication prior to study selection.

Quality Assessment

Risk of bias was assessed using Cochrane's Risk of Bias assessment tool (version 1.0) for the following domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, and selective reporting bias.[2] Classes of outcomes (efficacy and safety) were assessed separately for blinding and completeness of outcome

data. We graded each domain as having high, low, or unclear risk of bias among all included studies. Additional details were sought from supporting literature (e.g., published protocol and/or supplementary material) should the information not be explicitly documented in the text of the main study. Risk of bias assessments were performed by one reviewer and verified by a second reviewer. Disagreements were resolved by consensus (MT, TA).

Data Extraction

Data extraction, using the Covidence Data Extraction 2.0 form, was conducted once full-text screening was completed by 2 reviewers. Two reviewers (JR, LW) independently extracted data using a piloted data abstraction form. Any disagreements were resolved by consensus. The key data extracted to follow the research questions were objective, study characteristics, patient characteristics (age, sex, race, comorbidities, immunocompromised, concomitant bacterial infections, days of hospital admission or symptom onset to randomization, ventilation, ICU, and other hospital information), and any relevant efficacy and safety outcomes.

Data Analyses and Synthesis

A descriptive summary of the study selection process, eligibility criteria, and study and patient characteristics is presented for each of the included RCTs that reported at least one outcome of interest. Using the data extracted from the RCTs, the outcome of interest was compared among the other studies reporting the same outcome and analyzed to determine whether TCZ had a statistically significant impact on the outcome in comparison to its comparator. The efficacy outcomes analyzed were clinical status, hospital discharge, duration of hospitalization, ICU admission, ICU duration and discharge, initiation of IMV or death, incidence of IMV, ventilation or supplementary oxygen discontinuation, and duration of ventilation or supplementary oxygen. The safety outcomes analyzed were mortality and death and incidence of SAE.

Results of Clinical Evaluation

Selection of Primary Studies

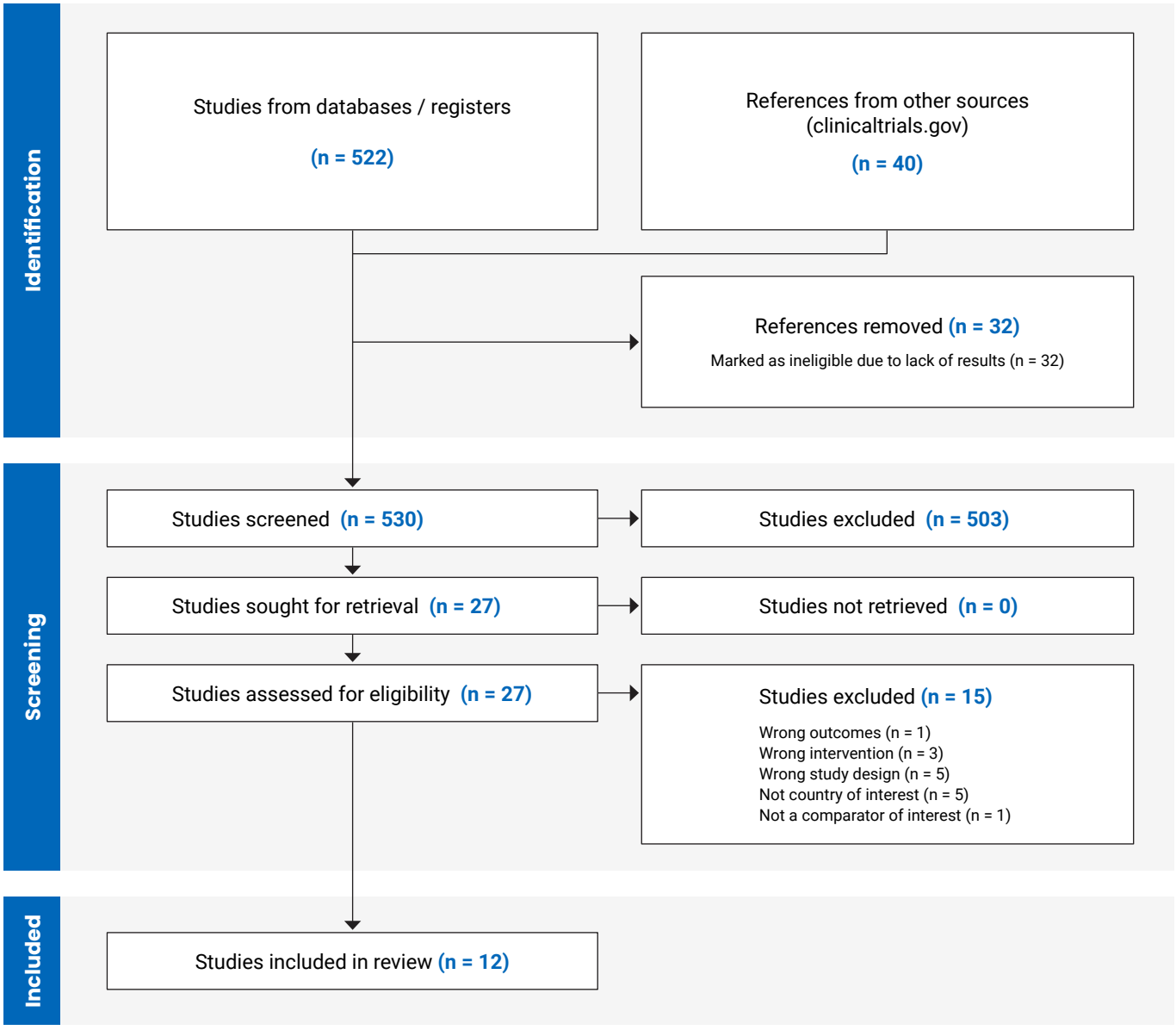
The results of the literature search yielded 522 studies (refer to Figure 1 for PRISMA flow chart). Following the initial screening process, 27 studies were sought for retrieval and assessed for eligibility. Following full-text screening, 12 studies were deemed eligible for inclusion and, subsequently, underwent data extraction. A total of 15 studies were excluded due to the studies reporting outcomes that were not of interest (1 study), interventions not of interest (3 studies), studies that were not RCTs (5 studies), not in a country of interest (5 studies), and not with a comparator of interest (1 study).

The clinicaltrials.gov trials registry search yielded 40 clinical trials. Of the 40 trials, 8 had results. The 8 were screened by one reviewer (JR). Of the 8 that were screened: one was a non-randomized study, 6 were duplicates (4 were included in the final analysis), and one did not use TCZ as treatment.

Included Studies:
Twelve studies are included in the final analysis, 7 of which were included in the initial CADTH report done in March 2021.

Figure 1

PRISMA Flow chart of Selected Studies



Study and Patient Characteristics

A total of 12 studies have been extracted, seven[3-9] of which were also reported on in the initial CADTH report.[1] The study characteristics of design, location, size, and intervention are reported in Table 2. Patient characteristics as well as efficacy and safety end points of each study can be found in Table 3.

Table 2

Study Characteristics of Included RCTs (12 studies)

Study	Study Design	Recruitment Period	Location, # of centres	Total sample size, randomization	Intervention dose and frequency	Intervention comparator	Intervention treatment follow–up duration
RECOVERY[3]	Phase II and III, MC, OL, platform, Investigator-initiated	April 2020 to January 2021	UK 131	4,116 1:1	TCZ 400 mg to 800 mg IV • 800mg if weight > 90kg • 600 mg if weight > 65 and ≤ 90 kg • 400 mg if weight > 40 and ≤ 65 kg • 8 mg/kg if weight ≤ 40 kg • And UC • Once; additional dose 12-24 hrs later if condition not improved (% of patients receiving second dose NR)	UC: including steroids	IV fusion over 60 minutes 24 hours post-randomization, 28 days follow-up
Broman et al. 2022 (COVIDSTORM)[4]	Single centre, OL, prospective	August 2020 to June 2021	Finland 1	86 2:1	TCZ IV • 400 mg for <60 kg • 600 mg for 60-90 kg • 800 mg for >90 kg And UC Once	UC: glucorticoids, SC low-molecular-weight heparin	IV fusion over 60 minutes 1 hour immediately post-randomization, 28 days follow -up

Study	Study Design	Recruitment Period	Location, # of centres	Total sample size, randomization	Intervention dose and frequency	Intervention comparator	Intervention treatment follow–up duration
Declercq et al. 2021 (COV-AID)[5]	Phase III, MC, OL, Prospective, (2x2 factorial design)	April 2020 to December 2020	Belgium 16	342 114 TCZ arm, 113 Siltuximab arm 1:1:1	TCZ 8mg/kg (maximum 800 mg) IV And UC Once	UC: corticosteroids, dexamethasone, Hydroxychloroquine	Administered on day 1, 28 days follow-up
Gordon et al. 2021 (REMAP-CAP)[6]	Phase IV, MC, OL, multifactorial adaptive platform, non-blinded	March 2020 - ongoing	13 however, 6 countries specific to immune modulation therapy: UK, the Netherlands, Australia, New Zealand, Ireland, Kingdom of Saudi Arabia 113	865 353 TCZ arm, 48 Sarilumab arm 1:1	TCZ 8 mg/kg (max 800 mg) IV And UC Once; repeat 12 to 24 hrs later at discretion of clinician (29% received a second dose)	1. UC: glucocorticoids, remdesivir 2. Sarilumab	IV fusion over 60 minutes and within 24 hours of starting organ support in ICU, 21 days follow-up
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7]	MC, OL	March 2020 to April 2020	France 12	92 1:1	TCZ 8mg/kg IV And UC Once; 400 mg on day 3 recommended and left to physician discretion if oxygen requirement was not decreased by > 50%	UC: corticosteroids, Antibiotics antivirals, vasopressor support, anticoagulants	Administered on day 1, 90 days follow-up

Study	Study Design	Recruitment Period	Location, # of centres	Total sample size, randomization	Intervention dose and frequency	Intervention comparator	Intervention treatment follow–up duration
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8]	MC, OL, bayesian	March 2020 to April 2020	France 9	130 1:1	TCZ 8mg/kg IV And UC Once; 400 mg on day 3 recommended and left to physician discretion if oxygen requirement was not decreased by > 50%	UC: corticosteroids antibiotics, antivirals, vasopressors, anticoagulants	Administered on day 1, 28 days follow-up
Rosas et al. 2021 (COVACTA)[9]	Phase III, MC, DB, PB	April 2020 to May 2020	US, UK, Canada, Italy, Denmark, Netherlands, Spain, France, Germany 62	438 2:1	TCZ 8 mg/kg (max. 800 mg) IV And UC Once; second dose 8 to 24 hrs later if patient did not improve or worsened (25% received)	Placebo plus UC according to local practice: glucocorticoids antivirals, convalescent plasma, supportive care	Administered on day 1, 28 days follow-up
Rosas et al. 2022 (COVACTA)[10]							Administered on day 1, 60 days follow-up (28 days for time to clinical improvement and duration of supplemental oxygen)
Rutgers et al. 2022[11]	Phase II, OL prospective,	February 2020 to January 2021	Netherlands 11	354 1:1	TCZ 8mg/kg (maximum 800 mg) IV And UC Once; twice if hypoxia not resolved	UC: All permitted including dexamethasone, hydroxychloroquine, remdesivir	Administered within 1-2 days of hospitalization, 30 days follow-up
Salama et al. 2021 (EMPACTA)[12]	Phase III, MC, DB, PB	NR	US, Brazil, Kenya, Mexico, Peru, South Africa 61	377 2:1	TCZ 8 mg/kg (max. 800 mg) IV And UC Once; second dose 8 to 24 hrs later if patient did not improve or worsened	Placebo plus UC: glucocorticoids, antivirals, Supportive care	IV fusion over 60 minutes on day 1 of randomization, 28 days (efficacy analysis) 60 days total follow-up (safety)

Study	Study Design	Recruitment Period	Location, # of centres	Total sample size, randomization	Intervention dose and frequency	Intervention comparator	Intervention treatment follow–up duration
Salvarani et al. 2021[13]	Phase II MC, OL	March 2020 to June 2020	Italy 24	126 1:1	TCZ 8 mg/kg (max. 800 mg) IV And UC Twice, doses 12 hrs apart	UC: Supportive care, all drugs allowed except IL-1 blockers, Jak inhibitors, TNF inhibitors	IV fusion over 60 minutes on day 1 of randomization, 30 days follow-up
Stone et al. 2020[14]	Phase III, MC, DB, PC	April 2020 to June 2020	US 7	243 2:1	TCZ 8 mg/kg (max. 800 mg) IV And UC Once, within 3 hours of obtaining consent	Placebo and UC: glucorticoids, remdesivir, antivirals, hydroxychloroquine	IV fusion over 60 minutes on day 1 of randomization, 28 days follow-up (29 days for discontinuation of supplemental oxygen)

DB = double-blind; ICU= intensive care unit; MC = multicentre; NR = not reported; OL= open-label; PC = placebo controlled; SC = Subcutaneous; TCZ = tocilizumab; TNF = Tumour Necrosis Factor; UC = usual care.

Study Design, Location, Randomization, and Sample Size

Key Point:
All of the included studies are randomized controlled trials of phase II/III or higher.

All 12 studies are RCTs of phase II/III or higher. With the exception of COVIDSTORM,[4] all trials were conducted at multiple centres. While 4 trials are multinational, only the COVACTA[9,10] studies had testing centres within Canada. The trials' sample sizes varied: 2 had fewer than 100 participants,[4,7] one had over 800 participants,[6] and one had over 4,000 participants.[3] The rest of the trials were conducted with 100 to 500 participants.[5,8–14]

Six studies[3,6–8,11,13] randomized their participants in a 1:1 ratio. REMAP-CAP also included a sarilumab arm, but it did not have many participants compared to the other 2 arms (48).[6] Five studies[4,9,10,12,14] conducted 2:1 randomization with the comparator of UC. CoV-AID's randomization of 1:1:1 is unique because of its third arm, siltuximab, whose baseline and efficacy data were combined with that of TCZ.[5]

Of note for inclusion, while CoV-AID reported their efficacy outcomes as IL-6 antagonists treatment effects, their safety outcomes were stratified by drug and are discussed in this report. Additionally, the COVACTA trial, that examined the same patient cohort at 2 different time points, produced 2 published papers. The 2021 study examined the cohort at 28 days postrandomization, while the 2022 study at 60 days post-randomization[9,10] This contrasts with the 2 CORIMUNO trials which reported on 2 separate patient cohorts.[7,8]

Intervention, Comparator, and Follow Up

Summary:
Primary intervention: 8mg/kg of tocilizumab via IV infusion in 10 of 12 studies. Common comparator: usual care in all 12 studies. Timing: intervention given on day 1, with 9 studies providing a second dose if no improvement.

For ten[5–14] of the 12 studies, TCZ was administration of via IV infusion at a dose of 8mg/kg along with the UC of the site. RECOVERY[3] and COVIDSTORM[4] utilized a predetermined dosage between 400 mg to 800 mg that was then administered to the patients based on their body weight range. Six studies[3,6,9,10,12,13] administered an additional dose within 24 hours of the first if there was no clinical improvement, Rutgers et al.[11] administered an additional dose 8 hours after the first if hypoxia was not resolved, and the CORIMUNO-19 trials[7,8] administered an additional fixed dose of 400 mg on day 3 if the oxygen requirement had not decreased by more than 50%.

All studies reported UC as a comparator but COVACTA,[9,10] EMPACTA,[12] and Stone et al.[14] had placebos with UC. All studies reported corticosteroids as part of their UC; Rutgers et al.[11] and COV-AID[5] reported using dexamethasone specifically. Nine studies[6–14] included antivirals in their standard care, with Rutgers et al.[11] and REMAP-CAP[6] reporting use of remdesivir specifically. Otherwise, UC ranged among the trials: COVIDSTORM[4] included heparin, COV-AID[5] and Rutgers et al.[11] included hydroxychloroquine, COVACTA 2021[9] included convalescent plasma, the CORIMUNO studies[7,8] included antibiotics, vasopressors, and anticoagulants, and Salvarani et al.[13] allowed the use of any drug except IL-1 blockers, Jak inhibitors, and tumour necrosis factor inhibitors.[7,8] Six studies[3–5,7–9,12] had follow-up durations of 28 days. REMAP-CAP[6] had a follow-up duration of 21 days, Rutgers et al.,[11] Salavarani et al,[13] and Stone et al.[14] of 30 days, and COVACTA 2022[10] and EMPACTA[12] of 60 days.

Inclusion and Exclusion Criteria

All studies were conducted with populations of hospitalized adults defined as 18 years of age and older, except for Stone et al.[14] which included patients 19 to 85 years old. Five studies[3,4,9,10,12] reported hypoxia, with some indicating hypoxemia defined as blood oxygen saturation below a specific threshold, in their inclusion criteria. EMPACTA[12] excluded those who were receiving MV or positive/bilevel airway pressure. COV-AID[5] also reported hypoxia as an inclusion criterion but measured it with the ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) and excluded those who had been on MV for more than 24 hours.

The other 6 studies[5–8,11,14] did not include hypoxia or hypoxemia in their inclusion criteria but did report ventilation criteria as such. Three[7,11,14] of these reported supplemental oxygen as an inclusion criterion: Stone et al.[14] excluding those receiving greater than 10 L/min and TOCI-2[7] excluding those receiving noninvasive ventilation (NIV) or HFO. Two studies[8,13] reported respiratory failure as an inclusion criterion: TOCI-1[8] including those on NIV, MV, and HFO but Salvarani et al.[13] excluding those receiving NIV, IMV, and patients wanting to avoid future intubation. REMAP-CAP[6] reported receipt of respiratory organ

Inclusion and Exclusion:
Of the studies, 6 studies included hypoxia – low oxygen content in the blood – in their inclusion criteria. The other 6 studies did not include hypoxia but reported on ventilation criteria.

support, via IMV, NIV, or HFO, as an inclusion criterion. The specific values or ranges required by each of these studies for their respective inclusion criteria can be found in Table 3.

Six studies[3–5,11,13,14] also listed systemic inflammation or cytokine release syndrome, evidenced by laboratory values, as part of their inclusion criteria. C-reactive protein (CRP) was the most included value, required by all 6 except Rutgers et al.,[11] followed by ferritin which was required by four[4,5,11,14] of these studies. The specific laboratory value thresholds defining inclusion criteria for each of these studies can be found in Table 3.

Only one study[6] had a population of ICU patients exclusively, specifically patients who had been in the ICU less than 24 hours. Salvarani et al.[13] excluded ICU patients, while the Rutgers et al.[11] inclusion criteria specified patients admitted to the general ward. Otherwise, the remaining 9 studies[3–5,7–10,12,14] did not include admission to the ICU within their criteria. Notably, the CORIMUNO-19 trials[7,8] had originally included ICU admission within the exclusion criteria of TOCI-1[8] and the inclusion criteria of TOCI-2,[7] but this was later amended such that patients were assigned to the TOCI-1 or TOCI-2 trials based on World Health Organization Clinical Progression Scale (WHO-CPS) scores (Table 4; Appendix 2 Table 22) among the other inclusion criteria.

EMPACTA[12] also reported a unique inclusion criterion of patients at high risk and those in a minority position.

Active infection other than COVID-19 was a common exclusion criterion for all studies except 3.[6,13,14] Six studies[4–6,9,10,12] also excluded patients if it was determined that death was imminent. TOCI-1[8] excluded patients with a do not resuscitate order and Rutgers et al.[11] did not report any exclusion criteria.

Comorbidities

All studies reported a variety of comorbidities, except for Rutgers et al.[11] which only reported the total proportion of patients with comorbidities (Appendix 2, Table 19). Diabetes was the most consistently reported comorbidity (11 studies)[3–10,12–14], its prevalence ranging from 17% to 42% of patients among the TCZ arm (with a median of 30.5%) and 14% to 43% patients among the comparator arm (with a median of 32.5%). The 11 studies reporting specific comorbidities also reported on various cardiovascular conditions, including hypertension and chronic cardiac disease. Ten studies reported on a variety of respiratory conditions whether COPD (4 studies),[4,12–14] asthma (5 studies),[4,7,8,12,14] or chronic lung disease (5 studies).[3,7–10] Other commonly reported comorbidities included kidney impairment/chronic kidney disease (CKD) (6 studies),[3,5–8,14] hepatic impairment (4 studies),[3,6,9,10] and obesity (5 studies).[4,9,10,12,13] Overall, the proportion of patients with a particular or total number of comorbidities were equal between the TCZ and comparator arms of all trials. Moreover, for specific comorbidities where proportions were not equal, there was no overall trend of one treatment arm exhibiting a greater frequency of comorbidities than the other.

Comorbidities:
The number of patients with comorbidities was the same between those receiving tocilizumab and those receiving the comparator in all studies. Diabetes was the most consistently reported comorbidity.

COVID-19 Diagnosis and Severity

All studies included patients with a confirmed COVID-19 diagnosis, with RECOVERY[3] and REMAP-CAP[6] also including patients clinically suspected of COVID-19. The most common confirmation method was a polymerase chain reaction (PCR) test, a standard for all studies except RECOVERY,[3] COV-AID,[5] and REMAP-CAP.[6] Other confirmation methods included laboratory values,[3,5] chest CT scan,[7–10] radiographic imaging,[12] bilateral chest infiltrates,[9,10] and serum IgM antibody assays.[14]

One study reported outcomes in a population with moderate-severe COVID-19,[8] two[6,7] reported outcomes in a critically ill COVID-19 population, and eight[3–5,9–12,14] reported outcomes in a population with severe COVID-19. Salvarani et al.[13] did not report COVID-19 severity but excluded ICU and MV patients.

Key Point:
All included studies had patients with a confirmed COVID-19 diagnosis with RECOVERY and REMAP-CAP, including patients with clinically suspected COVID-19 infection.

Table 3

Study Patient Characteristics of the Included RCTs (12 studies)

Study	Inclusion criteria	Exclusion criteria	COVID-19 confirmation, COVID-19 severity	End points efficacy	End points safety
RECOVERY[3]	• Hospitalized adults • Hypoxia[a] • Evidence of systemic inflammation[a] • No medical history that puts patient at risk if they participate	• Hypersensitivity to TCZ • Active TB, bacterial, fungal, viral, or other infection (besides COVID-19) • TCZ definitely indicated or contraindicated by physician	Clinically suspected or laboratory-confirmed Severe (hypoxia and inflammation)	• Time till hospital discharge • Hospital discharge • IMV or death • Receipt of non-invasive, invasive, or either ventilation • Cessation of IMV	• Mortality • SAE
Broman et al. 2022 (COVIDSTORM)[4]	• Hospitalized adults 18+ • Hypoxemia[a] • Increase in at least 2 of 4 inflammatory markers lab value beyond specified values[a]	• Previous severe allergic reaction to monoclonal antibody therapy • Concurrent infection (confirmed or probable) other than COVID-19 • Imminent and inevitable progression to death within 24 hours, irrespective of provision of treatments • Long-term immunomodulatory drugs, including corticosteroids equivalent to >15 mg/d of methylprednisolone • Pregnant or breastfeeding • Participating in other clinical drug trials • Neutrophil, platelet count, ALT values beyond specified threshold[a]	PCR positive Severe TCZ NEWS: median 6 (range: 1 to 2), mean 5.9 (SD 2.4) UC NEWS: median 6 (range 1 to 9), mean 6 (SD 2)	• Clinical status at day 28 assessed using a seven-category ordinal scale • Oxygen supplementation • Hospital discharge • Duration of hospitalization • ICU admission • Duration of ICU stay • Initiation of IMV • Duration of ventilation	• Death • SAE

Study	Inclusion criteria	Exclusion criteria	COVID-19 confirmation, COVID-19 severity	End points efficacy	End points safety
Declercq et al. 2021 (COV-AID)[5]	• Hospitalized adults ≥18 years • Symptoms between 6 and 16 days • Hypoxia[a] • Signs of a CRS as determined by lab values[a]	• MV for > 24 h at randomization • Clinical frailty score > 3 before SARS-CoV-2 infection • Unlikelihood to survive beyond 48 h based on clinical assessment • An active coinfection defined on clinical grounds (positive blood or sputum cultures) • Thrombocytopenia or neutropenia • History of bowel perforation or diverticulitis; or high dose systemic steroid or immunosuppressive drug use for a COVID-19 unrelated disorder	Laboratory-proven diagnosis Severe	• None reported for TCZ alone	• Death • SAE
Gordon et al. 2021 (REMAP-CAP)[6]	• Critically ill patients ≥18 years • Admitted to ICU • Receiving respiratory (IMV or NIV, high-flow nasal cannula if the flow rate > 30 L/min and the fraction of inspired oxygen was > 0.4) or cardiovascular (intravenous infusion of any vasopressor or inotrope) organ support	• Death is imminent • Known or suspected pregnancy • Hypersensitivity • Prior participation in REMAP-CAP within 90 days • More than 24 hours has elapsed since ICU admission • Platelet, ALT, AST values[a]	Clinically suspected or microbiological confirmation Critical, severe	• Clinical status • Time to ICU discharge • Hospital discharge • Organ support-free days including respiratory-support free days • MV or death	• Death • 90-day survival • SAE

Study	Inclusion criteria	Exclusion criteria	COVID-19 confirmation, COVID-19 severity	End points efficacy	End points safety
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7]	• Hospitalized patients ≥18 years • Critical pneumonia defined as WHO-CPS score≥6 • Respiratory failure and requiring HFO or NIV or MV	• Hypersensitivity to TCZ • Pregnancy • Current documented bacterial infection • ANC, PLT laboratory results out of range[a] • DNR order	rRT-PCR and/or CT scan, Critical	• Clinical status • Extubation or removal of NIV • Ventilation free days • Oxygen supply independency • Hospital discharge • ICU discharge	• Death • Overall survival • SAE
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8]	• WHO-CPS score 5 • Receiving at least 3L·min^{-1} O2 but without NIV or High flow	• Known hypersensitivity to TCZ • Pregnancy • Current documented bacterial infection • ANC, PLT laboratory results out of range[a]	rRT-PCR and/or typical chest CT scan Moderate or severe	• Clinical status • MV or death • NIV, HFO, MV, or death • ICU admission • Oxygen supply independency • Hospital discharge	• Death • SAE
Rosas et al. 2021 (COVACTA)[9] **Rosas et al. 2022 (COVACTA)**[10]	• Hospitalized patients ≥18 years • Blood oxygen saturation ≤ 93% or partial pressure of oxygen or fraction of inspired oxygen < 300 mm Hg	• Death is imminent within 24 hours • Active TB, bacterial, fungal, or viral infection other than SARS-CoV-2	PCR, bilateral chest infiltrates on chest radiography or CT Severe TCZ NEWS2 score: mean 7.1 (SD: 3.0) UC NEWS2 score: mean 7.0 (SD 3.0)	• Clinical status and failure • ICU admission • ICU duration • Hospital discharge • Ventilation incidence • Ventilation-free days	• Death • SA
				• Hospital discharge • Clinical improvement • Duration of supplemental oxygen	• Death • SAE

Study	Inclusion criteria	Exclusion criteria	COVID-19 confirmation, COVID-19 severity	End points efficacy	End points safety
Rutgers et al. 2022[11]	• Hospitalized adults ≥18 years • Admitted to the general ward • Need of supplemental oxygen • Have at least one of the specified signs compatible with hyperinflammation[a]	• NR	Nasopharyngeal swab PCR Severe	• ICU admission • Duration of hospital stay • Duration of ICU stay • MV • Duration of ventilation • MV or death	• Mortality • SAE
Salama et al. 2021 (EMPACTA)[12]	• Hospitalized patients 1≥18 years • Blood oxygen saturation < 94% while breathing ambient air, • High risk and minority patients	• Death is imminent and inevitable within 24 hours • Receiving continuous positive airway pressure, bilevel positive airway pressure, or mechanical ventilation • Active TB • Suspected active Bacterial, fungal, or viral infection other than SARS-CoV-2 and well controlled HIV • Patients with coexisting conditions that preclude safe participation in the trial	PCR, radiographic imaging Severe	• MV or death • Hospital discharge • Clinical status or failure	• Death • SAE

Study	Inclusion criteria	Exclusion criteria	COVID-19 confirmation, COVID-19 severity	End points efficacy	End points safety
Salvarani et al. 2021[13]	• Hospitalized adults ≥18 years • Acute respiratory failure with a partial pressure of arterial oxygen to fraction of inspired oxygen ratio between 200 mm Hg and 300 mm Hg • An inflammatory phenotype[a]	• ICU admission • Known hypersensitivity to TCZ • Any condition preventing future admission to ICU (advanced age with multiple comorbidities, expressed will to avoid future intubation etc.) • IMV or NIV	PCR Severity NR	• ICU admission • Clinical worsening • Hospital discharge	• Death • SAE
Stone et al. 2020[14]	• 19 to 85 years old • 2 of the following signs: fever (body temperature > 38°C) within 72 hours before enrolment, pulmonary infiltrates, or a need for supplemental oxygen to maintain an oxygen saturation > 92% • One of the specified laboratory parameter indicating inflammation[a]	• Supplemental oxygen > 10 L/min • Recent history of treatment with biologic drugs or small molecule immunosuppressive therapy • Receiving other immunosuppressive therapy that placed them at higher risk for an infection • Diverticulitis	Nasopharyngeal swab PCR, serum IgM antibody assay Severe	• MV or death • MV • Discontinuation of supplemental oxygen • Clinical worsening and improvement • Hospital discharge • Hospitalization duration • Duration of receipt of supplemental oxygen or MV • Admission to ICU or death	• Death • SAE

ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; CRS = cytokine release syndrome; CT = computed tomographic; DNR = do not resuscitate; HFO= high-flow oxygen; ICU= intensive care unit; IMV= invasive mechanical ventilation; MV= mechanical ventilation; NEWS = National Early Warning Score; NIV= non-invasive ventilation; NR = not reported; PCR= polymerase chain reaction; PLT = platelet count; SAE= serious adverse event; SD = standard deviation TB = tuberculosis; WHO-CPS = World Health Organization Clinical Progression Scale.

[a] Additional definition/laboratory range in Appendix 2 Table 20.

Quality Assessment

We assessed the risk of bias of each included study using the Cochrane Risk of Bias assessment tool across 5 domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of outcome data, and selective reporting.[2] Results of the risk of bias summary are shown in Table 4.

Risk of Bias Assessment: Overall, all 12 studies are at a low risk of bias, with some lack of clarity on risk across a few of the domains.

Risk of bias was found to be low for sequence generation and allocation concealment among all included studies.[3–14] Eight studies[3–8,11,13] were conducted as open-label trials, the remaining 4 studies[9,10,12,14] were conducted as placebo-controlled, double-blinded trials. Blinding of participants, personnel, and outcome assessors was judged to be of low risk of bias for efficacy and safety outcomes among 2 of the open-label trials as they included protections to blind all other parties involved in the studies with the exception of patients and clinical staff.[3,6] Blinding of participants, personnel, and outcome assessors for efficacy and safety outcomes was judged to be unclear risk of bias in all remaining studies that were open-label design as details on blinding outcome assessors and other parties were not explicitly described. It was unclear if personnel such as outcome assessors or statisticians were blinded in these studies.[4,5,7,8,11] Among the 4 double-blinded trials, risk of bias for blinding of participants, personnel, and outcome assessors was found to be low for efficacy and safety outcomes.[9,10,12,14]

The outcome data were found to be low risk of bias for efficacy outcomes among 10 of the included studies.[3–8,11–14] Two COVACTA studies by Rosas et al. were assessed to have unclear risk of bias for efficacy outcomes as it was unclear how discontinued trial participants contributed data to the primary end point.[9,10] The outcome data were judged to be of low risk of bias for safety outcomes among all included studies. Lastly, selective outcome reporting was judged to be of low risk of bias across all included studies.[3–14]

Table 4

Risk of Bias Assessment

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel (Efficacy Outcomes)	Blinding of Participants and Personnel (Safety Outcomes)	Incomplete Outcome Data (Efficacy Outcomes)	Incomplete Outcome Data (Safety Outcomes)	Selective Reporting
RECOVERY[3]	Low	Low	Low	Low	Low	Low	Low
Broman et al. 2022 (COVIDSTORM)[4]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Declercq et al. 2021 (COV-AID)[5]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Gordon et al. 2021 (REMAP-CAP)[6]	Low	Low	Low	Low	Low	Low	Low
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Rosas et al. 2021 (COVACTA)[9]	Low	Low	Low	Low	Unclear[a]	Low	Low
Rosas et al. 2022 (COVACTA)[10]	Low	Low	Low	Low	Unclear[a]	Low	Low
Rutgers et al. 2022[11]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Salama et al. 2021 (EMPACTA)[12]	Low	Low	Low	Low	Low	Low	Low
Salvarani et al. 2021[13]	Low	Low	Unclear[a]	Unclear[a]	Low	Low	Low
Stone et al. 2020[14]	Low	Low	Low	Low	Low	Low	Low

[a] Unclear is defined as having insufficient information to make a fair assessment.

Summary of Results

Efficacy

The most commonly reported efficacy outcome was clinical status including clinical improvement or failure (9 studies)[4,6–10,12–14] which studies defined using the WHO scale,[6] WHO-CPS,[7,8] 7-category ordinal scale,[4,7,12,14] National Early Warning Signs 2 (NEWS2),[10] or their own definition of clinical status.[13] The second most commonly reported outcome was hospital discharge (7 studies)[3,4,7,8,10,13,14] and duration of hospitalization (7 studies).[3,4,6,9,11,12,14] Studies also reported on ICU admission (5 studies),[4,8,9,11,13] ICU discharge and duration (5 studies),[4,6,7,9,11] MV or death (6 studies),[3,6,8,11,12,14] incidence of IMV (5 studies),[3,4,9,11,14] ventilation or supplementary oxygen discontinuation (6 studies),[3,6–9,14] and duration of ventilation or supplementary oxygen (4 studies).[4,10,11,14] Three studies reported outcomes unique to their studies including organ-support free days (1 study),[6] NIV, HFO, MV, or death (1 study),[8] and ICU or death (1 study).[14] CoV-AID did not report any efficacy outcomes for TCZ alone and hence the study is excluded from all efficacy-related outcomes.[5]

Clinical Status, Improvement, or Failure

There appeared to be mixed findings regarding the impact of TCZ on clinical status, improvement, or failure (Table 5).

Findings Suggest:
Tocilizumab has variable efficacy related to clinical status, including clinical improvement or failure.

Clinical Status (5 studies)

Five studies reported clinical status.[4,6–9] Of these, COVIDSTORM[4] and REMAP-CAP[6] reported statistically significant results and TOCI-1,[8] TOCI-2,[7] and COVACTA 2021[9] reported nonstatistically significant results. On the 7-category ordinal scale, COVIDSTORM[4] reported clinical status at day 28 to be statistically significantly better in the TCZ group (P = 0.037). REMAP-CAP[6] used the WHO scale to determine clinical status at day 14 and found statistically significant improvement for the TCZ group (median adjusted OR 1.41 [95% CI, 1.18 to 1.70]) and sarilumab (median adjusted OR: 1.86 [1.22 to 2.91]). TOCI-1[8] and TOCI-2[7] used the WHO-CPS scale to determine clinical status at day 4, 7, and 14. Both studies found nonstatistically significant results. Similarly, COVACTA 2021[9] used the 7-category

ordinal scale at day 14 and 28 and found the odds ratio to be nonstatistically significant (OR 1.19 [95% CI, 0.81 to 1.76], P = 0.31).

Clinical Improvement (5 studies)

Studies reported clinical improvement (2 studies)[4,9,10,12,14] or median time to clinical improvement in days (3 studies)[4,9,10,12,14]. TOCI-2[7] assessed clinical improvement as a decrease in WHO-CPS scale of at least one point by day 4, and reported no statistically significant change in this measure at this time point (median posterior absolute risk difference with 90% credible interval: 1.7% [−13.6 to 17.1]). Stone et al.[14] defined clinical improvement as an increase in score by at least 2-points. on the ordinal scale (hazard ratio [HR] 1.06 [0.80 to 1.41]), and results were not statistically significant. The other 3 studies report median time to clinical improvement. Of these, only COVACTA 2022[10] found TCZ beneficial in reducing median time to clinical improvement on the NEWS2 scale (cox proportional HR 1.45 [95% CI,1.01 to 2.08], P = 0.044). COVACTA 2021[9] and EMPACTA,[12] both of which used the 7-category ordinal scale, did not find a statistically significant difference between the TCZ group and their respective comparators.

Clinical failure (3 studies)

Clinical failure, or worsening, was assessed in three[9,12,14] studies with one[12] reporting median time to clinical failure at day 28 in days. EMPACTA,[12] found a statistically significant reduction in median time to clinical failure in study participants receiving TCZ (HR 0.55, 95% 0.33 to 0.93). Clinical failure, which COVACTA 2021[9] defined as death, withdrawal from trial, transfer to ICU or initiation of IMV at day 28, was statistically significantly reduced in the treatment group (HR 0.61 [95% CI , 0.40 to 0.94]). Stone et al.[14] reported contrary results for clinical worsening on the 7-category ordinal scale at day 14 and 28 (HR 1.11 [0.59 to 2.10] P = 0.73). Worsening, in Stone et al.,[14] was defined as an increase in score on the ordinal clinical improvement scale by at least 1 point among patients receiving supplemental oxygen at baseline or at least 2 points among those not receiving supplemental oxygen at baseline.

Table 5

Efficacy Outcome: Clinical Status, Improvement, or Failure (9 studies)

Study	Outcome	Scale	TCZ	Comparator	Treatment effect	Statistically significant
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Clinical status at day 28	7-category ordinal scale[a]	NA	UC: NA	P = 0.037	Yes
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Clinical status at day 14	WHO (0 to 8)	NR	UC: NR	TCZ Median adjusted OR: 1.41 (95% CI, 1.18 to 1.70) Sarilumab Median adjusted OR: 1.86 (95% CI, 1.22 to 2.91)	Yes
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	No improvement on day 4	WHO-CPS (0 to 10)[b]	N = 35 (71%)	UC: N = 30 (70%)	Median posterior absolute risk difference with 90% CI, 1.7% (−13.6–17.1%)	No
	Clinical status at day 4, 7, and 14	WHO-CPS (0 to 10)[b]	Median at day 4: 7 (IQR: 7–8) Median at day 7: 7 (IQR: 5–8) Median at day 14: 7 (IQR: 5–8)	UC: Median at day 4: 8 (IQR: 7–8) Median at day 7: 8 (IQR: 7–8) Median at day 14: 7 (IQR: 5–9)	Day 4: OR 0.85 (95% CI, 0.39–1.82) Day 7: OR 0.69 (95% CI, 0.32–1.47) Day 14: OR 0.68 (95% CI, 0.32–1.43)	No

Study	Outcome	Scale	TCZ	Comparator	Treatment effect	Statistically significant
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	WHO-CPS score >5 on day 4	WHO-CPS (0 to 10)[b]	N = 12 of 63 (19%)	UC: N = 19 of 67 (28%)	Median posterior absolute risk difference −9% (95% CrI, −23.3 to 5.5)	No
	Clinical status at day 4, 7, and 14	WHO-CPS (0 to 10)[b]	Median at day 4: 5 (IQR: 5 to 5) Median at day 7: 5 (IQR: 5 to 5) Median at day 14: 2 (IQR: 2 to 5)	UC: Median (IQR) at day 4: 5 (5 to 6) Median (IQR) at day 7: 5 (5 to 6) Median (IQR) at day 14: 4 (2 to 7)	Day 4: OR 0.60 (95% CI, 0.27 to 1.28) Day 7: OR 0.86 (95% CI, 0.43 to 1.71) Day 14: OR 0.76 (95% CI, 0.40 to 1.42)	No
Rosas et al. 2021 (COVACTA)[9] N = 438	Clinical status at day 14 and 28	7-category ordinal scale[a]	Median (IQR) at day 14: 3.0 (2.0 to 4.0) Median (IQR) at day 28:1.0 (1.0 to 1.0)	Placebo + UC: Median at day 14: 4.0 (IQR: 3.0 to 5.0) Median at day 28: 20 (IQR: 1.0 to 4.0)	Day 14: Difference −1.0 (95% CI, −2.0 to 0.5) Day 28: Difference −1.0 (95% CI, −2.5 to 0.0) OR 1.19 (95% CI, 0.81 to 1.76)	No
	Median time until improvement, days	7-category ordinal scale[a]	14.0 (IQR: 12.0 to 17.0)	Placebo + UC: 18.0 (IQR: 15.0 to 28.0)	HR: 1.26 (95% CI, 0.97 to 1.64)	No
	Clinical failure among patients not receiving MV at randomization[a]	7-category ordinal scale[a]	N = 53 of 183 (29.0%)	Placebo + UC: N = 38 of 90 (42.2%)	HR: 0.61 (95% CI, 0.40 to 0.94)	Yes
Rosas et al. 2022 (COVACTA)[10] N = 438	Clinical improvement at day 28 (NEWS2 ≤2 for 24 h)	NEWS2[c]	N = 103 (35.0%)	Placebo + UC: N = 41 (28.5%)	NR	NR
	Median time to clinical improvement at 28 days	NEWS2[c]	NR	Placebo + UC: NR	HR : 1.45 (95% CI, 1.01 to 2.08),	Yes

Study	Outcome	Scale	TCZ	Comparator	Treatment effect	Statistically significant
Salama et al. 2021 (EMPACTA)[12] N = 377	Median time until improvement by day 28, days	7-category ordinal scale[a]	6.0 (IQR: 6.0 to 7.0)	Placebo + UC: 7.0 (IQR: 6.0 to 9.0)	HR: 1.15 (95% CI, 0.90 to 1.48)	No
	Median time to clinical failure by day 28, days	7-category ordinal scale[a]	NR	Placebo + UC: NR	HR: 0.55 (95% CI, 0.33 to 0.93)	Yes
Salvarani et al. 2021[13] N = 126	Clinical worsening at 14 days	Occurrence of 1 of the following events, whichever occurred first: • Admission to ICU with MV • Death from any cause • PaO2/FIO2 ratio less than 150 mmHg in 1 of the scheduled arterial blood gas measurements or in an emergency measurement, confirmed within 4 hours by a second examination	N = 17 (28.3%)	UC:N = 17 (27%)	Rate ratio: 1.05 (95% CI, 0.59 to 1.86)	No

Study	Outcome	Scale	TCZ	Comparator	Treatment effect	Statistically significant
Stone et al. 2020[14] N = 243	Clinical worsening at day 14 and 28	7-category ordinal scale[a]	Day 14: 18.0% (95% CI, 12.9 to 24.9) Day 28: 19.3% (95% CI, 4.0 to 26.2)	Placebo + UC: Day 14: 14.9% (95% CI, 8.7 to 24.7) Day 28: 17.4% (95% CI, 10.7 to 27.7)	HR: 1.11 (95% CI, 0.59 to 2.10)	No
	Clinical improvement at day 14 and 28	7-category ordinal scale[a]	Day 14: 86.3% (95% CI, 80.6 to 91.1) Day 28: 91.3% (95% CI, 86.3 to 95.1)	Placebo + UC: Day 14: 81.5% (95% CI, 72.4 to 89) Day 28: 88.9% (95% CI, 81 to 94.5)	HR: 1.06 (95% CI, 0.80 to 1.41)	No

CI = confidence interval; CrI = credible interval; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; MV = mechanical ventilation; NA = not applicable; NEWS = National Early Warning Score; NR= not reported; NA= not applicable, OR = odds ratio; UC= usual care; WHO-CPS = World Health Organization Clinical Progression Scale.

[a] 7-category ordinal scale: 1 = discharged or ready for discharge; 2 = in non–ICU hospital ward, not requiring supplemental oxygen; 3 = in non–ICU hospital ward, requiring supplemental oxygen; 4 = in ICU or non–ICU hospital ward, requiring NIV or HFO; 5 = in ICU, requiring intubation and MV; 6 = in ICU, requiring ECMO or MV and additional organ support; 7 = death.

[b] Additional information in Appendix 2 Table 22.

[c] Additional information in Appendix 2 Table 22.

Hospital Discharge and Hospitalization Duration

Only 2[3,8] of the 7 studies[3,4,7,8,10,13,14] reporting on the number of hospital discharges found statistically significant results, both of which examined discharges at day 28 (Table 6). TOCI-2[7] looked at discharges at day 90 and found TCZ did not statistically significantly increase the number of hospital discharges compared to UC (HR 1.28 [95% CI, 0.80 to 2.03]). Salvarani et al.[13] and Stone et al.[14] looked at discharge outcomes at days 14 and 30 and days 14 and 28, respectively, and also did not find a statistically significant difference between treatment and comparator groups (UC and placebo and UC, respectively).

Results for duration of hospitalization were split, with 3 studies[4,6,9] reporting a statistically significant decrease in duration and three[11,12,14] finding no difference between TCZ and comparator groups (Table 7). REMAP-CAP[6] also reported results for sarilumab, which was found to be statistically significant (median adjusted HR 1.51 [95% CI, 1.17 to 2.40]).

Findings Suggest:
Tocilizumab may be effective in reducing the length of hospitalization but may have variable efficacy in reducing the number of hospital discharges.

Table 6

Efficacy Outcome: Hospital Discharge (7 studies)

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically Significant
RECOVERY[3] N = 4,116	Discharge at day 28	N = 1,150 (57%)	UC: N = 1,044 (50%)	RR: 1.22 (95% CI, 1.12 to 1.33)	Yes
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Discharge at day 28	93% (53 of 57)	UC: 86% (25 of 29)	NR	NR
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	Discharges at day 14, 28, and 90	Day 14: N = 13 of 49 26% (95% CI, 15 to 40) Day 28: N = 29 of 49 59% (95% CI, 44 to 72) Day 90: N = 34 of 49 69% (95% CI, 53 to 80)	UC: Day 14: N = 7 of 43 16% (95% CI, 7 to 29) Day 28: N = 21 of 43 49% (95% CI, 33 to 63) Day 90: N = 28 of 43 60% (95% CI, 74 to 77)	Day 28: HR 1.44 (95% CI, 0.20 to 2.52) Day 90: HR 1.28 (95% CI, 0.80 to 2.03)	No
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	Discharge at day 28	N = 52 of 63 CIF 83% (95% CI, 70 to 90)	UC: N = 49 of 67 CIF 73% (95% CI, 61 to 82)	HR: 1.52 (95% CI, 1.02 to 2.27)	Yes
Rosas et al. 2022 (COVACTA)[10] N = 438	Discharge at day 60	N = 197 (67.0%)	Placebo + UC: N = 92 (63.9%)	NR	NR
Salvarani et al. 2021[13] N = 126	Discharges at day 14 and 30	Day 14: N = 34 (56.7%) Day 30: N = 54 (90%)	UC: Day 14: n = 36 (57.1%) Day 30: n = 58 (92.1%)	Day 14: RR 0.99 (95% CI, 0.73 to 1.35) Day 30: RR 0.98 (95% CI, 0.87 to 1.09)	No
Stone et al. 2020[14] N = 243	Discharge at day 14 and 28	At day 14: 86.3% (95% CI, 80.6 to 91.1) At day 28: 91.3% (95% CI, 86.3 to 95.0)	Placebo + UC: At day 14: 81.5% (95% CI, 72.4 to 89.0) At day 28: 88.9% (95% CI, 81.0 to 94.5)	HR: 1.08 (95% CI, 0.81 to 1.43)	No

CI = confidence interval; CIF = cumulative incidence function; HR = hazard ratio; NR = not reported; RR = risk ratio; UC = usual care.

Table 7

Efficacy Outcome: Duration of Hospitalization (7 studies)

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
RECOVERY[3] N = 4116	Median time to discharge, days	19	UC: >28	NR	NR
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Median duration of hospitalization, days	9 (IQR: 7 to 12)	UC: 12 (IQR 9 to 15)	P = 0.014	Yes
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Time to hospital discharge	NR	UC: NR	TCZ Median adjusted HR 1.41 (95% CI, 1.18 to 1.70) Sarilumab Median adjusted HR 1.60 (95% CI, 1.17 to 2.40)	Yes
Rosas et al. 2021 (COVACTA)[9] N = 438	Median time to discharge, days	20.0 (95% CI, 17.0 to 27.0)	Placebo + UC: 28.0 (95% CI, 20.0 to NE)	HR: 1.35 (95% CI, 1.02 to 1.79)	Yes
Rutgers et al. 2022[11] N = 354	Median duration of hospitalization, days	9 (IQR: 6 to 15)	UC: 9 (IQR: 6 to 14)	P = 0.80	No
Salama et al. 2021 (EMPACTA)[12] N = 377	Median time to discharge or readiness for discharge by day 28, days	6.0 (95% CI, 6.0 to 7.0)	Placebo + UC: 7.5 (95% CI, 7.0 to 9.0)	HR: 1.16 (95% CI, 0.91 to 1.48)	No
Stone et al. 2020[14] N = 243	Median time to discharge, days	6.0 (95% CI, 4.0 to 7.0)	Placebo + UC: 6.0 (95% CI, 5.0 to 6.0)	NR	No

CI = confidence interval; HR= hazard ratio; IQR= interquartile range; NE= not evaluable; NR = not reported; RR = risk ratio; UC= usual care.

ICU Admission, Discharge, and Duration

ICU admission was reported in 5 studies[4,8,9,11,13] (Table 8). Three[4,11,13] reported a nonstatistically significant difference between treatment and UC while 2 studies[8,9] reported statistically significantly less ICU admissions when patients were treated with TCZ than when treated with UC or UC and placebo.

Findings Suggest:
Tocilizumab has variable efficacy in reducing the number of ICU admissions, ICU discharges, and the time to ICU discharge.

Table 9 reports outcomes of ICU discharge and duration. TOCI-2[7] found no statistically significant difference in the number of patients discharged from ICU at days 28, and 90 (day 28: HR 1.28 [95% CI, 0.73 to 2.24]; day 90: HR 1.15 [95% CI, 0.73 to 1.81]).

Of the 4 studies[4,6,9,11] reporting median duration of ICU or time to ICU discharge, two[6,11] reported a statistically significantly reduced ICU stay and the other 2 studies[4,9] reported a nonstatistically significant difference. Additionally, REMAP-CAP[6] found sarilumab to be equally effective in statistically significantly decreasing time to ICU discharge (median adjusted HR 1.51 [95% CI, 1.17 to 2.40]). Stone et al. reported an outcome of admission to ICU or death (15.9% vs. 15.8% in TCZ vs. placebo), which was not significant (RR 0.97; 95% CI, 0.50 to 1.88).[14]

Table 8

Efficacy Outcome: ICU Admission (5 studies)

Study	Outcome	TCZ	Comparator	Statistically significant
Broman et al. (COVIDSTORM)[4] N = 86	N = 4 of 50 (8.0%)	UC: N = 4 of 25 (16.0%)	P = 0.43	No
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	N = 11 of 60 (18%)	UC: N = 22 of 64 (36%)	Risk difference: 18% (95% CI, 0.4 to 31)	Yes
Rosas et al. 2021 (COVACTA)[9] N = 438	N = 27 of 127 (21.3%)	Placebo + UC: N = 23 of 64 (35.9%)	Weighted difference: −14.8 (95% CI, −28.6 to −1.0)	Yes

Study	Outcome	TCZ	Comparator	Statistically significant
Rutgers et al. 2022[11] N = 354	N = 29 (17%)	UC: N = 31 (17%)	P = 0.89	No
Salvarani et al. 2021[13] N = 126	Day 14: N = 6 (10.0%) Day 30: N = 6 (10.0%)	UC: Day 14: N = 5 (7.9%) Day 30: N = 5 (7.9%)	Day 14 and 30: Rate ratio (95% CI, 1.26 0.41 to 3.91)	No

CI = confidence interval; UC= usual care.

Table 9

Efficacy Outcome: ICU Discharge and Duration (5 studies)

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
Broman et al. (COVIDSTORM)[4] N = 86	Median duration of ICU, days	6 (IQR: 4 to 12) n = 11 (19.3%)	UC: 5 (IQR: 3.5 to 24) n = 8 (27.6%)	P = 0.54	No
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Time to ICU discharge	NR	UC: NR	TCZ: Median adjusted HR 1.42 (95% CI, 1.18 to 1.70) Sarilumab: Median adjusted HR 1.64 (95% CI, 1.21 to 2.45)	Yes
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	Discharges at day 14, 28 and 90	Day 14: N = 16 of 40 40% (95% CI, 25 to 55) Day 28: N = 29 of 40 72% (95% CI, 55 to 84) Day 90: N = 33 of 40 84% (95% CI, 66 to 93)	UC: Day 14: N = 16 of 37 43% (95% CI, 27 to 58) Day 28: N = 22 of 37 60% (95% CI, 42 to 74) Day 90: N = 30 of 37 83% (95% CI, 63 to 93)	Day 28: HR 1.28 (95% CI, 0.73 to 2.24) Day 90: HR 1.15 (95% CI, 0.73 to 1.81)	No
Rosas et al. 2021 (COVACTA)[9] N = 438	Median duration of ICU, days	9.8 (IQR: 7.0 to 15.7)	Placebo + UC: 15.5 (IQR: 8.7 to 25.5)	Difference −5.8 (95% CI, −15.0 to 2.9)	No
Rutgers et al. 2022[11] N = 354	Median duration of ICU, days	9 (IQR :5 to 14)	UC: 14 (IQR: 9 to 28)	P = 0.014	Yes

CI = confidence interval; HR= hazard ratio; NR = not reported; UC= usual care.

MV or Death

Six studies[3,6,8,11,12,14] reported the combined outcome of MV or death (Table 10). TOCI-1[8] and Stone et al.[14] found the combined outcome of MV or death to be not statistically significant between the TCZ and comparator groups (UC in TOCI-1 and placebo + UC in Stone et al.) at days 14 and days 14 and 28, respectively. The other 4 studies[3,6,11,12] found statistically significant results of TCZ reducing the incidence of the combined outcome of MV or death.

REMAP-CAP[6] reported the cumulative incidence of intubation, ECMO, or death for both TCZ and sarilumab. TOCI-1[8] reported the cumulative incidence of 1 of the following outcomes: NIV, HFO, MV, or death (difference −12, 95% CI, −28 to 4), which was not statistically significant between TCZ and UC.

Findings Suggest:
Tocilizumab may be effective in reducing the progression to the combined end point of mechanical ventilation or death.

Table 10

Efficacy Outcome: MV or death (6 studies)

Study	Outcome	TCZ	Comparator	Statistically significant
RECOVERY[3a] N = 4,116	N = 619 of 1,754 (35%)	UC: N = 754 of 1,800 (42%)	RR: 0.84 (95% CI, 0.77 to 0.92)	Yes
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	N = 100 of 242 (41.3%)	UC: N = 144 of 273 (52.7%) Sarilumab: N = 13 of 37 (35.1%)	TCZ: Median adjusted OR: 1.69 (95% CI, 1.17 to 2.42) Sarilumab Median adjusted OR: 1.74 (95% CI, 1.01 to 3.14)	Yes
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	At day 14: N = 11 (17%, 95% CI, 8 to 26)	UC: At day 14: N = 18 27% (95% CI, 15 to 37)	Posterior median HR: 0.58 (90% CrI: 0.30-1.09) Difference (95% CI, −9 (−24 to 5)	No
Rutgers et al. 2022[11] N = 354	N = 36 (21%, 95% CI, 16 to 28)	UC: N = 55, 31% (95% CI, 24 to 38)	HR = 0.65 (95% CI, 0.42 to 0.98)	Yes

Study	Outcome	TCZ	Comparator	Statistically significant
Salama et al. 2021 (EMPACTA)[12] N = 377	12.0% (95% CI, 8.5 to 16.9)	Placebo + UC: 19.3% (95% CI, 13.3 to 27.4)	HR: 0.56 (95% CI, 0.33 to 0.97)	Yes
Stone et al. 2020[14] N = 243	At day 14: 9.9% (95% CI, 6.2 to 15.7) At day 28: 10.6% (95% CI, 6.7 to 16.6)	Placebo + UC: At day 14: 10.0% (95% CI, 5.1 to 18.9) At day 28: 12.5% (95% CI, 6.9 to 22.0)	HR: 0.83 (95% CI, 0.38 to 1.81) Adjusted HR: 0.66 (95% CI, 0.28 to 1.52)	No

CI = confidence interval; CrI = credible interval; HR = hazard ratio; OR = odds ratio; RR = risk ratio; UC = usual care.

[a] Analyses include only those on no ventilator support or noninvasive ventilation at second randomization. Combined output of IMV or death.

Incidence of IMV and Discontinuation of Ventilation or Supplementary Oxygen

Five studies[3,4,9,11,14] reported incidence of IMV (Table 11). Only one[3] reported incidence of IMV to be statistically significantly different among the treatment and comparator groups (RR [95% CI], 0.79 [0.69 to 0.92] P = 0.0019). COVIDSTORM.,[4] COVACTA 2021,[9] Rutgers et al.,[11] and Stone et al.[14] did not find incidence to be significantly less in the TCZ group in comparison to UC or to placebo with UC.

Discontinuation of ventilation or supplementary oxygen was reported by 6 studies[3,6–9,14] (Table 12). Only 1[6] reported respiratory-support free days to be statistically significantly greater among participants in the TCZ group (median adjusted OR: 1.73 [1.31 to 2.27]) and found similarly statistically significant results for sarilumab (median adjusted OR: 1.94 [1.27 to 3.32]). The other 5 studies[3,7–9,14] found no statistically significant difference amongst the TCZ and comparator groups for outcomes of successful cessation of IMV, mean number of ventilator-free days at day 28, oxygen supply independence at day 14, 28, and 90, or extubating or removal of NIV or HFO for more than 48 hours by day 14.

Findings Suggest:
Tocilizumab is not effective in reducing the progression to invasive mechanical ventilation, or stopping ventilation or supplementary oxygen.

Table 11

Efficacy Outcome: Incidence of IMV (5 studies)

Study	TCZ	Comparator	Treatment effect	Statistically significant
RECOVERY[3] N = 4·116	N = 265 of 1,754 (15%)	UC: N = 343 of 1,800 (19%)	RR: 0·79 (95% CI, 0·69 to 0·92) P = 0.0019	Yes
Broman et al. 2022 (COVIDSTORM)[4] N = 86	N = 5 of 57 (8.8%)	UC: N = 3 of 28 (10.7%)	P = 1.0	No
Rosas et al. 2021 (COVACTA)[9] N = 438	N = 51 of 183 (27.9%)	Placebo + UC: N = 33 of 90 (36.7%)	Weighted difference −8.9% (95% CI, −20.7 to 3.0)	No
Rutgers et al. 2022[11] N = 354	N = 18 (10%)	UC: N = 27 (15%)	P = 0.18	No
Stone et al. 2020[14] N = 243	At day 14: 6.8% (95% CI, 3.6 to 11.4) At day 28: 6.8% (95% CI, 3.6 to 11.4)	UC: At day 14:10.0% (95% CI, 4.6 to 17.7) At day 28:10.0% (95% CI, 4.6 to 17.7)	HR 0.65 (95% CI, 0.26 to 1.62)	No

CI = confidence interval; HR= hazard ratio; RR; risk ratio; UC= usual care.

Table 12

Efficacy Outcome: Ventilation or Supplementary Oxygen Discontinuation (6 studies)

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
RECOVERY[3] N = 4·116	Successful cessation of IMV (subsidiary)	N = 95 of 268 (35%)	N = 98 of 294 (33%)	RR: 1·08 (95% CI, 0·81 to 1·43) P = 0.60	No
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Respiratory support-free days	Median: 9.5 (IQR: −1, 16)	UC: Median: 0 (IQR: −1, 14) Sarilumab: Median: 11.5 (IQR: 0,16)	TCZ: Median adjusted OR: 1.73 (95% CI, 1.31 to 2.27) Sarilumab: Median adjusted OR: 1.94 (95% CI, 1.27 to 3.32)	Yes
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	Mean number of ventilator-free days at day 28	12.8 (SD 10.7)	UC: 10.3 (SD 11.1)	Mean difference −2.5 (95% CI, −6.9 to 1.7)	No
	Oxygen supply independency on day 14, 28, and 90	Day 14: N =13 of 49 CIF 26% (95% CI, 15 to 40) Day 28: N = 29 of 49 CIF 59% (95% CI, 44 to 72) Day 90: N = 34 of 49 CIF 69% (95% CI, 53 to 80)	UC: Day 14: N = 7 of 43 CIF 16% (95% CI 7 to 29) Day 28: N = 21 of 43 CIF 49% (95% CI, 33 to 63) Day 90: N = 28 of 43 CIF 64% (95% CI, 47 to 77)	Day 28: HR 1.44 (95% CI, 0.82 to 2.52) Day 90: HR 1.28 (95% CI, 0.80 to 2.03)	No
	Extubation or removal of NIV or HFO >48 hrs at day 14	47% (95% CI, 32 to 60)	UC: 42% (95% CI, 27 to 56)	HR 1.19 (95% CI, 0.71 to 2.04)	No
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	Oxygen supply independency on day 28	N = 55 of 63 89% (95% CI, 78 to 95)	UC: N = 50 of 67 75% (95% CI, 62 to 83)	HR 1.41 (95% CI, 0.98 to 2.01)	No
Rosas et al. 2021 (COVACTA)[9] N = 438	Median number of ventilator-free days at day 28	22.0 (IQR: 18.0 to 28.0)	Placebo + UC: 16.5 (IQR: 11.0 to 26.0)	Difference 5.5 (95% CI, −2.8 to 13.0)	No
Stone et al. 2020[14] N = 243	Discontinuation of supplemental oxygen among patients receiving at baseline, % patients	At day 14: 75.4% (95% CI, 67.9 to 82.2) At day 28: 82.6% (95% CI, 75.9 to 88.4)	UC: At day 14: 78.8% (95% CI, 68.3 to 87.7) At day 28: 84.9% (95% CI, 75.2 to 92.2)	HR 0.94 (95% CI, 0.67 to 1.30)	No

CI = confidence interval; CIF= cumulative incidence function; HR= hazard ratio; IQR= interquartile range; IMV= invasive

mechanical ventilation; OR= odds ratio; RR; risk ratio; UC= usual care.

Duration of Ventilation or Supplementary Oxygen

Four studies[4,10,11,14] reported duration (median number of days) of ventilation or supplementary oxygen outcomes (Table 13). Two studies[10,11] found supplemental oxygen and MV duration, respectively, to be significantly decreased in the treatment group (P = 0.0048; P = 0.0036). In contrast, COVIDSTORM4 reported TCZ to be ineffective at reducing the duration of ventilation for intubated patients (P = 0.042).

Findings Suggest:
Tocilizumab has variable efficacy in reducing the duration of ventilation or supplementary oxygen.

Table 13

Efficacy Outcome: Duration of Ventilation or Supplementary Oxygen (4 studies)

Study	Ventilation or supplemental oxygen	TCZ, median days (IQR)	Comparator, median days (IQR)	Treatment effect	Statistically significant
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Ventilation for intubated patients	11 (10 to 19)	UC: 20.5 (10 to 29.5)	P = 0.42	No
Rosas et al. 2021 (COVACTA)[9] N = 438	Supplemental oxygen	26.5 (19.0 to 28.0)	Placebo + UC: 28.0 (26.0 to 28.0)	Difference: -1.5 days (95% CI, −9.0 to 0.5)	Yes
Rutgers et al. 2022[11] N = 354	MV	10 (7 to 12)	UC: 15 (9 to 26)	P = 0.036	Yes
Stone et al. 2020[14] N = 243	Supplementary oxygen	4.0 (1.8 to 11.6)	Placebo + UC: 3.9 (1.1 to 9.2)	NR	NR
	MV	15.0 (12.6 to NR)	Placebo + UC: 27.9 (16.3 to NR)	NR	NR

CI = confidence interval; MV= mechanical ventilation; NR= not reported; UC= usual care.

Safety

Findings Suggest:
The safety of tocilizumab is variable in terms of death and the occurrence of serious adverse events.

All studies reported safety and death outcomes, but most were not adequately powered or did not report statistical significance for safety outcomes. Of the 12, none of the studies reported withdrawal due to adverse events (AEs), but rather, if a withdrawal was reported, it was due to death. There were mixed results regarding the safety of TCZ in terms of death and mortality outcomes (Table 14). Two[3,6] of the 12 studies found death or mortality rates to differ significantly among the TCZ and comparator groups (UC in RECOVERY and UC and sarilumab in REMAP-CAP). Additionally, REMAP-CAP[6] found sarilumab comparable to TCZ for its impact on mortality (median adjusted HR: 1.82 [1.22 to 3.38]). Eight studies[7–14] did not find the treatment effective at reducing death or mortality. Notably, COVACTA 2022[10] reported time to death by day 60 for specific and total number of comorbidities, such as those with hepatic impairment. Those results were also not statistically significantly different between the treatment and the placebo plus UC groups (N = 232 vs. N = 124, HR 1.05 [95% CI, 0.69 to 1.59]). No studies focused on mortality or death in patients who were immunocompromised. One study[10] analyzed mortality outcomes with respect to comorbidities, finding that TCZ statistically significantly improved 60-day mortality outcomes for patients with hepatic impairment.

SAE was reported by 11 studies (Table 15). Nine studies[3,5,6,9–14] provided definitions for SAEs: seven[3,5,6,9,10,12,14] of these defined an SAE as: "an event that is fatal, life threatening, results in (or may result in) disability that is long-lasting and significant, or results in a birth defect or congenital anomaly." With the exception of REMAP-CAP,[6] they all also added that an SAE could be "a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)." As for the other 2 studies, Rutgers et al.[11] defined SAE as AEs of severity grade 4 or more and Salvarani et al.[13] defined their AEs according to the Common Terminology Criteria for Adverse Events, version 5.0.

Of the 11 studies reporting SAEs, only two[6,7,11] reported the treatment effect. One[7] reported a statistically significant decrease of SAE in the TCZ group (P = 0.020) while the other[11] did not find a statistically significant result (P = 0.45). REMAP-CAP reported SAE not as events, but as the number of patients with 1 or more SAE for TCZ and sarilumab.[6] Neither treatment effects were statistically significant. ARDS was reported in 2 studies,[7,8] with one[8] reporting a statistically significant difference of ARDS among the treatment and comparator group (P = 0.03). Bacterial pneumonia was also reported in 2 studies.[8,12]

Table 14

Safety Outcome: Death and Mortality (12 studies)

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
RECOVERY[3] N = 4116	28–day mortality	N = 621 (31%)	UC: N = 729 (35%)	RR: 0.85 (95% CI, 0.76 to 0.94) P = 0.0028	Yes
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Death at day 28	N = 1 (1.8%)	UC: N = 0	NR	NR
Declercq et al. 2021 (COV-AID)[5] N = 342	Death at day 28	N = 10 (12%)	UC: N = 9 (12%)	NR	NR
	Death caused by COVID-19	N = 7 (9%)	UC: N = 5 (7%)	NR	NR
	Estimated mortality at day 28 and 90, % patients	Day 28: 11% (95% CI, 6 to 20) Day 90: 12% (95% CI, 7 to 22)	UC: Day 28: 10% (95% CI, 5 to 20) Day 90: 13% (955 CI, 7 to 23)	NR	NR

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Death	N = 98 of 350 (28%)	UC: N = 142 of 397 (36%) Sarilumab: N = 10 of 45 (22%)	TCZ: Median adjusted OR 1.64 (95% CI, 1.14 to 2.35) Sarilumab: Median adjusted OR 2.01 (95% CI, 1.18 to 4.71)	Yes
	Probability of 90-day survival	NR	UC: NR Sarilumab: NR	TCZ: Median Adjusted HR 1.59 (95% CI, 1.24 to 2.05) Sarilumab: Median adjusted HR: 1.82 (95% CI, 1.22 to 3.38)	Yes
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	Death at day 90	N = 12 (24%)	UC: N = 13 (30%)	Adjusted HR 0.67 (95% CI 0.30 to 1.49)	No
	Overall survival % patients	Day 14: 90% (95% CI, 82 to 99) Day 28: 84% (95% CI, 74 to 95) Day 90: 76% (95% CI, 64 to 89)	UC: Day 14: 79% (95% CI, 68 to 92) Day 28: 77% (95% CI, 65 to 90) Day 90: 70% (95% CI, 57 to 85)	Day 14: HR 0.37 (95% CI, 0.12 to 1.15) Day 28: HR 0.56 (95% CI, 0.22 to 1.46) Day 90: HR 0.67 (95% CI, 0.30 to 1.49)	No
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	Overall Survival at day 14 and 28	Day 14: 89% (95% CI, 81 to 97) Day 28: 89% (95% CI, 81 to 97)	UC: Day 14: 91% (95% CI, 84 to 98) Day 28: 88% (95% CI, 80 to 96)	Day 28: adjusted HR, 0.92 (95% CI, 0.33 to 2.53)	No
	Death	Day 14: N = 7 Day 28: N = 7	UC: Day 14: N = 6 Day 28: N = 8	NR	NR
Rosas et al. 2021 (COVACTA)[9] N = 438	Death at day 28	N = 58 (19.7%)	Placebo + UC: N = 28 (19.4%)	Weighted difference 0.3 (95% CI, −7.6 to 8.2)	No
	Death caused by COVID-19	N = 39 (13.2%)	Placebo + UC: N = 18 (12.6%)	NR	NR

Study	Outcome	TCZ	Comparator	Treatment effect	Statistically significant
Rosas et al. 2022 (COVACTA)[10] N = 438	Death at day 60	N = 72 of 294 patients (24.5%)	Placebo + UC: N = 36 of 144 patients (25.0%)	Weighted difference: −0.5% (95% CI, −9.1 to 8.0) Percent difference: −0.8 (95% CI, −9.7, 7.5)	No
	Time to death by day 60 for subjects with comorbidities	N = 232	Placebo + UC: N = 124	HR 1.05 (95% CI, 0.69, 1.59)	No
Rutgers et al. 2022[11] N = 354	30–day mortality	N = 21, 12% (95% CI, 8 to 18)	UC: N = 34, 19% (95% CI, 14 to 26)	HR: 0.62 (90% CI, 0.39 to 0.98; 95% CI, 0.36 to 1.07) P = 0.086	No
Salama et al. 2021 (EMPACTA)[12] N = 377	Death at day 28	N = 26 (10.4%, 95% CI, 7.2 to 14.9)	Placebo + UC: N = 11 (8.6%, 95% CI, 4.9 to 14.7)	Weighted difference: 2.0 (95% CI, −5.2 to 7.8)	No
	Death at day 60 (safety population)	N = 29 (11.6%)	Placebo + UC: N = 15 (11.8%)	NR	No
Salvarani et al. 2021[13] N = 126	Death at day 14 and 30	Day 14: N = 1 (1.7%) Day 30: N = 2 (3.3%)	UC: Day 14: N = 1 (1.6%) Day 30: N = 1 (1.6%)	Day 14: Rate ratio 1.05 (95% CI, 0.07 to 16.4) Day 28: Rate ratio 2.10 (95% CI, 0.20 to 22.6)	No
Stone et al. 2020[14] N = 243	Death at day 14 and 28	At day 14: 4.4% (95% CI, 2.1 to 8.9) At day 28: N = 9, 5.6% (95% CI, 3.0 to 10.5)	Placebo + UC: At day 14: 1.3% (95% CI, 0.2 to 8.7) At day 28: N = 3, 3.8% (95% CI, 1.2 to 11.3)	HR 1.52 (95% CI, 0.41 to 5.61)	No
	Death in safety population	N = 9 (5.6%)	Placebo + UC: N = 4 (4.9%)	P = 0.81	No

CI = confidence interval; HR= hazard ratio; NR= not reported; RR; risk ratio; UC= usual care.

Table 15

Safety Outcome: Number of SAE Events (11 studies)

Study	TCZ	Comparator	P value	Statistically significant
RECOVERY[3] N = 4116	N = 3	UC: N = 0	NR	NR
Broman et al. 2022 (COVIDSTORM)[4] N = 86	N = 1	UC: N = 1	NR	NR
Declercq et al. 2021 (COV-AID)[5] N = 342	N = 5 (6%)	UC: N = 6 (8%)	NR	NR
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	N = 93	UC: N = 55	P = 0.020	Yes
	ARDS: N = 13 Cause of death: ARDS: N = 7	UC: ARDS: N = 15 Cause of death: ARDS: N = 7	NR	NR
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	N = 26	UC: N = 57	NR	NR
	ARDS: N = 9 Cause of death: ARDS: N = 7	UC: ARDS: N = 19 Cause of death: ARDS: N = 9	P = 0.03	Yes
Rosas et al. 2021 (COVACTA)[9] N = 438	N = 183	Placebo + UC: N = 117	NR	NR
Rosas et al. 2022 (COVACTA)[10] N = 438	N = 192	Placebo + UC: N = 122	NR	NR
	Bacterial pneumonia: N = 6 (2.0%)	Placebo + UC: Bacterial pneumonia: N = 2 (1.4%)	NR	NR
Rutgers et al. 2022[11] N = 354	N = 45 (26%)	UC: N = 53 (29%)	P = 0.45	No

Study	TCZ	Comparator	P value	Statistically significant
Salama et al. 2021 (EMPACTA)[12] N = 377	N = 38 (15.2%)	Placebo + UC: N = 25 (19.7%)	NR	NR
	Bacterial pneumonia: N = 0	Placebo + UC: Bacterial pneumonia: N = 2	NR	NR
Salvarani et al. 2021[13] N = 126	N = 1 (1.7%)	UC: N = 2 (2.3%)	NR	NR
Stone et al. 2020[14] N = 243	N = 36	Placebo + UC: N = 38	NR	NR

ARDS = acute respiratory distress syndrome; NR = not reported.

Efficacy Outcomes Significance Reporting

Table 16 provides a summary of the efficacy outcomes reported in each study and whether a statistically significant effect was found.

Table 16

Summary of Efficacy by Reported Outcome and Statistical Significance of Corresponding Effects (11 studies)

Study	Status			Hospitalization		ICU		Ventilation			
	Clinical status	Clinical improvement	Clinical failure	Hospital discharge	Duration of hospitalization	ICU admission	ICU duration and discharge	MV or death	Incidence of IMV	Discontinuation of ventilation or supplementary oxygen	Duration of ventilation or supplementary oxygen
RECOVERY[3] N = 4,116	NR	NR	NR	Yes	NR	NR	NR	Yes	Yes	No	NR
Broman et al. 2022 (COVIDSTORM)[4] N = 86	Yes	NR	NR	NR	Yes	No	No	NR	No	NR	No
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Yes	NR	NR	NR	Yes	NR	Yes	Yes	NR	Yes	NR
Hermine et al. 2022 (CORIMUNO-19: TOCI-2)[7] N = 92	No	No	NR	No	NR	NR	No	NR	NR	No	NR

Study	Status			Hospitalization		ICU		Ventilation			
	Clinical status	Clinical improvement	Clinical failure	Hospital discharge	Duration of hospitalization	ICU admission	ICU duration and discharge	MV or death	Incidence of IMV	Discontinuation of ventilation or supplementary oxygen	Duration of ventilation or supplementary oxygen
Hermine et al. 2021 (CORIMUNO-19: TOCI-1)[8] N = 130	No	NR	NR	Yes	NR	No	NR	No	NR	No	NR
Rosas et al. 2021 (COVACTA)[9] N = 438	NR	No	Yes	No	Yes	No	No	NR	No	No	NR
Rosas et al. 2022 (COVACTA)[10] N = 438	NR	Yes	NR	NR	NR	NR	NR	NR	NR	NR	Yes
Rutgers et al. 2022[11] N = 354	NR	NR	NR	NR	No	No	Yes	Yes	No	NR	Yes
Salama et al. 2021 (EMPACTA)[12] N = 377	NR	No	Yes	NR	No	NR	NR	Yes	NR	NR	NR
Salvarani et al. 2021[13] N = 126	NR	NR	NR	No	NR	No	NR	NR	NR	NR	NR
Stone et al. 2020[14] N = 243	NR	No	No	No	No	NR	NR	No	No	No	NR

NR = not reported.

Discussion

Summary of Evidence

Efficacy

Efficacy:
Tocilizumab may improve the length of hospitalization and mechanical ventilation or death but, the other reported outcomes remain inconclusive. Notably, it appears to be more efficacious than usual care.

The analysis of the 12 studies demonstrates mixed results, suggesting that TCZ is of variable efficacy, likely driven by the heterogeneity in study designs and patient populations. While TCZ does appear to significantly improve duration of hospitalization and MV or death (with at least half of the studies reporting statistically significant results), the findings for the other reported outcome effects remain inconclusive. Importantly, TCZ appears to be more efficacious than UC and there are signals toward clinically positive outcomes albeit with uncertainty in whom it works best for. These findings are similar to those found in the initial CADTH report published in 2021, which found the evidence for efficacy to be unclear.[1]

Of the 6 studies[4,6,9,11,12,14] that statistically assessed duration of hospitalization, three[4,6,9] demonstrated that TCZ significantly improved the outcome: 2 of which were REMAP-CAP[6] and COVACTA 2021.[9] Importantly, there was significant variation inpatient populations in terms of disease severity and prognosis. Similarly, of the 6 studies[3,6,8,11,12,14] reporting on outcomes of MV or death, four[3,6,11,12] found that TCZ statistically significantly improved the outcome, of which 2 were RECOVERY[3] and REMAP-CAP.[6] The initial CADTH report[1] found 4 of the 5 studies to demonstrate a beneficial effect of TCZ on the combined end point of MV or death, which aligns with our findings. Published literature on these outcomes shows similar findings to our report.

A recent meta-analysis containing 6 RCTs (which are included in this report) found TCZ treatment to be associated with a statistically significant reduction in MV or death (RR: 0.83 [95% CI, 0.74 to 0.92], I2 = 0, tau2 = 0).[15] Another meta-analysis also found statistically significant results for the outcome of MV or death when pooling 8 RCTs (RR = 0.81, 95% CI, 0.72 to 0.90, P < 0.001) and for time to

hospital discharge using 5 RCTs (HR = 1.30, 95% CI, 1.16 to 1.45, P < 0.001).[16] The RECOVERY[3], REMAP-CAP,[6] and COVACTA 2021[9] trials found that TCZ statistically significantly improved a number of outcomes. Namely, RECOVERY3 found that TCZ improved time to hospital discharge, MV or death, and IMV outcomes; REMAP-CAP[6] reported significant results for clinical status, duration of hospitalization, ICU discharge, MV or death, and ventilation or supplementary oxygen discontinuation; and COVACTA 2021[9] found statistically significant improvements in clinical failure and duration of hospitalization with TCZ. Interestingly, these findings from both REMAP-CAP[6] and RECOVERY[3] studies may be attributable to over 80% of the study patients receiving corticosteroids and being administered TCZ early in the course of infection (2 days of hospitalization for RECOVERY[3] and less than 24 hours in ICU for REMAP-CAP[6]) (Table 9). Additionally, both studies recruited patients with either clinically suspected, or laboratory confirmed COVID-19. REMAP-CAP[6] and COVACTA 2021[9] both excluded patients whose death was imminent, which may have influenced the significant clinical status and failure outcomes. The RECOVERY[3] trial did not include patients with medical histories that would put them at substantial risk should they participate, and the REMAP-CAP[6] study was the only one that included patients solely from the ICU.

It is important to note that the COVACTA trials examine the same patient cohort at different time points, providing insight into the treatment's longer-term effects and a more comprehensive understanding of its efficacy and safety. This is in contrast to the CURMINO trials that report on 2 separate patient cohorts. This limits the generalizability of the study's findings but offers differing insights.

In examining clinical status, improvement, and failure, it was challenging to conclude if TCZ is beneficial in improving clinical status and decreasing clinical failure, as this outcome was not consistently measured across studies. Although 5 [4,6,9,10,12] of the 9 [4,6–10,12–14] studies found statistically significant results supporting the efficacy of TCZ treatment, these findings may not be

representative of broader TCZ efficacy across all clinically relevant efficacy outcomes. As for the other efficacy outcomes, little evidence was provided that TCZ decreased incidence of IMV or increased the discontinuation of ventilation or supplementary oxygen with the exception of the REMAP-CAP[6] and RECOVERY[3] trials. Interestingly, TOCI-2,[7] which focused on a critically ill/ICU patient population, found contrary results to that of the RECOVERY[3] and REMAP-CAP[6] trials which included similar patient populations. This may be attributed to the lack of treatment combination with dexamethasone (DEX). Hermine et al.[7,8] conducted an additional study[17] to tackle the question of whether TCZ plus DEX versus DEX alone was efficacious and safe. Their results found no statistically significant difference when treating patients with moderate-to-severe COVID-19. However, more trials are warranted, and future studies should consider adding a third arm to compare TCZ alone to TCZ plus DEX and DEX.

Safety

Safety:
The safety of tocilizumab remains unclear as few studies reported on important safety outcomes, aside from mortality.

The 2 safety outcomes we report on are mortality and SAE. Through our analysis of the 12 studies, it remains to be seen whether TCZ significantly improves mortality outcomes for patients with COVID-19. Of the 10 studies[3,6–14] reporting statistical significance of their mortality results, only two[3,6] found TCZ to be significant in improving mortality[3,6] and 90-day survival[3,6] outcomes. These significant results may be attributed to concomitant corticosteroid treatment, early administration of treatment in clinical progression, and inclusion of clinically suspected, but not confirmed, COVID-19 patients. Only one study[10] analyzed mortality outcomes with respect to comorbidities, finding that TCZ statistically significantly improved 60-day mortality outcomes for patients with hepatic impairment. TCZ and placebo with UC were otherwise comparable in their mortality outcomes for all other comorbidities.

As for the SAE, only 3 studies[6,7,11] reported the statistical significance of their results. Of those that did, one[7] found that TCZ statistically significantly decreased the number of SAE when compared to its comparator and the other[8] that TCZ significantly reduced ARDS incidence when compared to its comparator. Due to the limited data

on the studies' statistical significance, it is difficult to determine what patient or treatment characteristics may lead TCZ to be more beneficial in reducing ARDS and SAE incidence when compared to UC or UC and placebo. Thus, no conclusions can be drawn on TCZ's effect on the incidence of SAE.

Meta-analyses have been conducted to find the association between TCZ and safety outcomes. Two meta-analyses[18,19] have found 28-day or 30-day mortality to differ based on the type of study or severity of COVID-19. Peng et al. pooled a summary RR for all-cause mortality and found TCZ to be 0.89 (95% CI, 0.82 to 0.96, P = 0.003).[18] However, when only peer-reviewed studies and double-blinded RCTs were analyzed, there was no longer a statistically significant association between TCZ treatment and all-cause mortality. Similarly, Yu et al. determined that TCZ showed differing effects on all-cause 28-day mortality according to the severity of COVID-19.[19] Only groups classified as moderate-to-severe were less likely to experience an SAE from TCZ treatment (RR 0.89, 95% CI, 0.81 to 0.96, I2 0%, 4 studies). COV-AID,[5] RECOVERY[3], and COVACTA 2021[9] were among the 4 studies included in Yu et al.'s[19] analysis. A similar meta-analysis including 6 studies[6,8,9,12–14] in this report found TCZ to statistically significantly decrease all-cause mortality (RR 0.89, 95% CI, 0.81 to 0.98, P = 0.03, I2 0%).20 Meanwhile, Yu et al.[19] and Peng et al.[18] found mixed results for associations between TCZ and the number of SAE. While Peng et al.[18] found no association, Yu et al.[19] found TCZ effective in decreasing the number of SAE in comparison to each study's comparator (RR 0.83, 95% CI, 0.71 to 0.97). The mixed results found in meta-analyses align with our findings and are likely due to the heterogenous nature of disease severity, concomitant medication and UC, in addition to the timing of TCZ administration in the clinical course of the infection. This report did not conduct a meta-analysis as the level of heterogeneity in the study design and populations was too great to allow for reliable analyses.

When considering the use of TCZ in hospitalized adult patients, the current clinical recommendations and evidence support mirroring

Key Point:
The current clinical recommendations and reported evidence support mirroring the RECOVERY and REMAP-CAP trials for tocilizumab treatment in hospitalized adults with COVID-19 infection.

RECOVERY[3] and REMAP-CAP.[6] These trials were methodologically strong, with RECOVERY having a large sample size (4,116 patients) and REMAP-CAP considering sarilumab, another IL-6 antagonist. Table 17 summarizes these studies' use of TCZ, which can be applied to develop practice standards in line with current clinical recommendations.[21,22]

Table 17

Summary of RECOVERY and REMAP-CAP studies

Study	Patient characteristics	Methods	Treatment	Other therapies
RECOVERY[3] N = 4,116	Hospitalized adult patients with clinically suspected or confirmed COVID-19 infection Hypoxia (oxygen saturation <92% on air or requiring oxygen) and have systemic inflammation (CRP ≥75 mg/L)	Administered within 24 hours of recruitment Additional dose 12-24 hours later if condition not improved	TCZ dose stratified by weight • 800mg if weight > 90kg • 600 mg if weight > 65 and ≤ 90 kg • 400 mg if weight > 40 and ≤ 65 kg • 8 mg/kg if weight ≤ 40 kg	Treatment in combination with a system corticosteroids (> 80% of population using dexamethasone)
Gordon et al. 2021 (REMAP-CAP)[6] N = 865	Critically ill hospitalized patients with clinically suspected or confirmed COVID-19 infection	Administered within 24 hours of ICU admission Additional dose 12-24 hours later at discretion of clinician	TZC: 8 mg/kg (max 800 mg)	Treatment in combination with glucocorticoids (>80%)

Strengths and Limitations of the Systematic Review

Strengths

Our review has several strengths. Firstly, specific outcomes of importance were reported and compared among the studies. This allowed for a greater and more thorough understanding of the impact of TCZ treatment on specific outcomes. For specific outcomes, we also leveraged previously completed systematic reviews to support our findings and ensure the robustness of our methods. We were also able to focus on multiple research questions regarding efficacy, safety, and the population characteristics for which TCZ could be a

Strengths:
This review reported on the specific outcomes of interest across the 12 studies, which all had a low risk of bias and focused on answering similar questions.

viable treatment option. Secondly, the extracted trials included in this report were all focused on answering similar questions, allowing for a robust and comprehensive report. The risk of bias shows most studies to have low risk, allowing for confidence in the studies in comparison to the true effect. Lastly, the included trials were conducted in higher income countries; this provides the benefit of the studies being comparable to the Canadian system and resource level.

Limitations

There are several limitations to our review. Firstly, each study population was heterogeneous. Study population characteristics differed in confirmed COVID-19 status, ICU or general ward admission, ventilation, comorbidities, and high risk or minority status. Additionally, the administration of treatment was heterogeneous: the timing of TCZ treatment in the clinical course of the disease, the provision of a second dose to study participants that did not show improvement, and the dosing of TCZ was not standardized among trials. This may have led studies to conclude significant results in some studies and not others. Secondly, because many of the studies are international, there is a lack of standardized UC across trial sites and countries. UC was heterogeneous across all the studies, with varying drugs and proportions of study participants receiving drugs. Thirdly, 8 out of the 12 studies were open-label trials, which potentially induces biases and limits the generalizability of reported efficacy and safety outcomes. However, for many drug trials conducted in hospitals, this is an unavoidable limitation and the outcomes that are quantitative and objectively measured are likely less susceptible to these biases. Fourthly, there is potential for bias in the assessment of outcomes when using CRP levels as an indicator of treatment group designation. This could potentially reveal which patients were in the treatment group. Lastly, most studies that reported safety outcomes were underpowered, which may have resulted in studies unable to detect a true difference in the various outcomes and the risk of type II error. This may be due to safety outcomes not being the primary focus of the studies.

Limitations:
Key limitations of the studies included in this review are the heterogeneity in the study populations and treatment characteristics and usual care not being standardized across the studies.

Conclusions and Implications for Decision- or Policy-Making

This report summarized the findings of RCTs on the clinical efficacy and safety of TCZ for hospitalized adults with COVID-19 as compared to UC[3–8,11,13] or placebo with UC.[9,10,12,14] For the outcomes of interest, TCZ did not appear to consistently be more efficacious than UC or placebo with UC as evidenced by the mixed results. Two outcomes, duration of hospitalization and combined outcome of progression to MV or death, presented with more studies favouring TCZ but this conclusion may be due to studies skewing results and the heterogeneity of the studies. Overall TCZ was found to be generally safe, but few studies reported on important safety outcomes, and most were likely underpowered to do a true assessment of safety. It is worth noting that both the RECOVERY and REMAP-CAP trials implemented early treatment initiation strategies with concurrent use of systemic corticosteroids/glucocorticoids that allowed their studies to show favouring results. This observation corresponds with the recommendation put forth by the Infectious Disease Society of America.[22] The populations of these trials would benefit the most from TCZ. Our analysis shows little to no evidence on the impact of TCZ in patients who are immunocompromised, with comorbidities, and concomitant bacterial infections leaving a gap in the current knowledge and important areas for future work.

Overall, we found that the evidence highlights that TCZ is likely safe and efficacious in some hospitalized patients with COVID-19, with patients mirroring those in the RECOVERY and REMAP-CAP trials benefiting the greatest. Although these trials are overall strong methodologically, further evidence is required to better understand how to best use TCZ to treat the patients that may benefit most. Finally, as is commonly seen, there are some populations excluded from all trials whose inclusion is warranted in further investigations.

Implications:
Tocilizumab is likely safe and efficacious in some hospitalized patients with COVID-19. Patients mirroring those in the RECOVERY and REMAP-CAP trials would likely benefit the most.

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Clinical Review

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Theresa Aves supported analysis of data, writing, and editing.

Mina Tadrous screened studies, supported writing report, and contributed to methodology/style of report and editing.

Research Information Services

Carolyn Spry designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and appendix, managed referencing of the report and provided final approval to the version of the report submitted for publication.

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Conflicts of Interest

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Green Shield Canada: Data Analytics (2021)

Emily Reynen disclosed the following:

LifeArc Charities UK: Co-investigator (member) for Nebulized Furosemide for Pulmonary Inflammation in intubated, mechanically ventilated patients with COVID-19—a phase II/phase III study

TELUS Health Solutions Inc.: Provided a comprehensive health technology assessment (HTA) report and a drug formulary listing recommendation for TELUS Health formularies (member).

Ontario Committee to Evaluate Drugs: Committee member (member).

No other conflicts of interest were declared.

For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.

Appendix 1: Literature Search Strategy

Clinical Literature Search

Overview

Interface: Ovid

Databases

- MEDLINE All (1946-present)
- Embase (1974-present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 1, 2023

Alerts: Bi-weekly search updates until June 19.

Search filters applied: randomized controlled trials; controlled clinical trials

Limits

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 18

Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1 (RHPM-1 or RG-1569 or RG1569 or R-1569 or R1569 or BAT-1806 or BAT1806 or I031V2H011 or MSB11456 or MSB-11456 or tocilizumab* or atlizumab* or RO-4877533 or RO4877533 or Actemra* or roactemra* or lusinex*).ti,ab,kf,hw,rn,nm. 33724

2 exp Covid-19/ or SARS-CoV-2/ 591399

3 (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/) 49541

4 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARS-COV2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px. 766544

5 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot. 191700

6 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot. 32458

7 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot. 1035

8 or/2-7 810986

9 1 and 8 10600

10 9 use medall 2002

11 *tocilizumab/ 5813

12 (RHPM-1 or RG-1569 or RG1569 or R-1569 or R1569 or BAT-1806 or BAT1806 or MSB11456 or MSB-11456 or tocilizumab* or atlizumab* or RO-4877533 or RO4877533 or Actemra* or roactemra* or lusinex*).ti,ab,kf,dq. 20028

13 11 or 12 20233

14 exp Coronavirus disease 2019/ 573486

15 sars-related coronavirus/ or SARS coronavirus/ 14973

16 (coronavirinae/ or betacoronavirus/ or coronavirus infection/) and (epidemic/ or pandemic/) 48839

17 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,hw,ot. 780022

18 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,hw,ot. 458947

19 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot. 32458

20 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot. 1035
21 or/14-20 820008
22 13 and 21 5103
23 22 use oemezd3254
24 23 not (conference abstract or conference review).pt. 2310
25 10 or 24 4312
26 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. 687142
27 Randomized Controlled Trial/ 1373785
28 exp Randomized Controlled Trials as Topic/ 424519
29 "Randomized Controlled Trial (topic)"/ 258768
30 Controlled Clinical Trial/ 564430
31 exp Controlled Clinical Trials as Topic/ 439892
32 "Controlled Clinical Trial (topic)"/ 13560
33 Randomization/ 206025
34 Random Allocation/ 202156
35 Double-Blind Method/ 359975
36 Double Blind Procedure/ 209818
37 Double-Blind Studies/ 342394
38 Single-Blind Method/ 82187
39 Single Blind Procedure/ 51584
40 Single-Blind Studies/ 84252
41 Placebos/ 381404
42 Placebo/ 402195
43 Control Groups/ 112889
44 Control Group/ 112889
45 (random* or sham or placebo*).ti,ab,hw,kf. 4333591
46 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 627093
47 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf. 3697
48 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf. 2931414
49 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf. 124024
50 allocated.ti,ab,hw. 191670

51 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. 130800
52 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. 30180
53 (pragmatic study or pragmatic studies).ti,ab,hw,kf. 1496
54 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. 16292
55 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. 31221
56 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf. 161047
57 or/26-56 6327652
58 25 and 57 955
59 remove duplicates from 58 546
60 limit 59 to (english or french) 527

MEDLINE results: 381, Embase results: 146

Clinical Trials Registries

ClinicalTrials.gov

Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials.

Search results: 40 Studies found for: tocilizumab | "COVID-19" | Completed Studies

Appendix 2: Supplemental Tables

Table 19

Comorbidities of Patients of the Included RCTs (12 studies)

Study	Comorbidity	TCZ	Comparators
RECOVERY[3]	Diabetes	569 (28%)	600 (29%)
	Heart Disease	435 (22%)	497 (24%)
	Chronic Lung disease	473 (23%)	484 (23%)
	Tuberculosis	3 (<1%)	5 (<1%)
	HIV	7 (<1%)	8 (<1%)
	Severe liver disease	14 (1%)	10 (<1%)
	Severe kidney impairment	118 (6%)	99 (5%)
	Any of the above	1100 (54%)	1163 (56%)
Broman et al. 2022 (COVIDSTORM)[4]	Diabetes	15 (26.3%)	6 (20.7%)
	Chronic heart failure	4 (7.0%)	1 (3.5%)
	Hypertension	22 (38.6%)	10 (34.5%)
	Atherosclerosis	7 (12.3%)	2 (6.9%)
	COPD	2 (3.5%)	1 (3.5%)
	Asthma	9 (15.8%)	3 (10.3%)
	Obstructive sleep apnoea	9 (15.8%)	8 (27.6%)
	Malignancy (treated or untreated	6 (10.5%)	4 (13.8%)
	Obesity	34 (60.7%)	20 (69.0%)
	≥1 diagnosis	47 (82.5%)	24 (82.7%)
Declercq et al. 2021 (COV-AID)[5]	Diabetes	59 (26%)	36 (31%)
	CVD	46 (20%)	24 (21%)
	Arterial Hypertension	115 (51%)	46 (40%)
	CKD	25 (11%)	12 (10%)

Study	Comorbidity	TCZ	Comparators
Gordon et al. 2021 (REMAP-CAP)[6]	Diabetes	123 of 349 (35.2%)	150 of 401 (37.4%)
	Severe CVD	34 of 339 (10.0%)	47 of 395 (11.9%)
	Respiratory disease	82 of 349 (23.5)	98 of 401 (24.4)
	Kidney disease	30 of 312 (9.6)	43 of 372 (11.6)
	Liver cirrhosis/failure	2 of 339 (0.6)	1 of 395 (0.3)
	Immunosuppressive disease	8 of 348 (2.3)	14 of 401 (3.5)
Hermine et al. 2021 (CORIMUNO-19: TOCI-2)[7]	Diabetes	20 (41%)	12 (29%)
	Chronic cardiac disease	14 (29%)	13 (32%)
	Chronic pulmonary disease (not asthmas)	3 (6%)	4 (10%)
	Asthma	3 (6%)	2 (5%)
	CKD (Stage 1-3) or dialysis	3 (6%)	3 (7%)
	Active malignant neoplasm	1 (2%)	1 (2%)
Hermine et al. 2022 (CORIMUNO-19: TOCI-1)[8]	Diabetes	20 of 61 (33%)	23 of 67 (34%)
	Chronic cardiac disease	20 of 61 (33%)	20 of 67 (30%)
	Chronic pulmonary disease (not asthmas)	3 of 61 (5%)	3 of 67 (5%)
	Asthma	5 of 61 (8%)	3 of 67 (5%)
	CKD (Stage 1-3) or dialysis	5 of 61 (8%)	13 of 67 (19%)
	Active malignant neoplasm	4 of 61 (7%)	5 of 67 (8%)
Rosas et al. 2021 (COVACTA)[9]	Diabetes	105 (35.7%)	62 (43.1%)
	Cardiovascular impairment	105 (35.7%)	35 (24.3%)
Rosas 2022. (COVACTA)[10]	Hypertension	178 (60.5%)	94 (65.3%)
	Chronic lung disease	49 (16.7%)	22 (15.3%)
	Hepatic impairment	6 (2.0%)	2 (1.4%)
	Obesity	63 (21.4%)	27 (18.8%)
	>1 diagnosis	231 (78.6%)	124 (86.1%)

Study	Comorbidity	TCZ	Comparators
Rutgers et al. 2022[11]	Total number (e.g., malignancies, autoimmune disease, transplant)	127 (73%)	136 (76%)
Salama et al. 2021 (EMPACTA)[12]	Diabetes	105 (42.0%)	48 (37.8%)
	Myocardial infarction	4 (1.6%)	3 (2.4%)
	Atrial fibrillation	6 (2.4%)	6 (4.7%)
	Hypertension	119 (47.6%)	63 (49.6%)
	COPD	12 (4.8%)	5 (3.9%)
	Asthma	27 (10.8%)	16 (12.6%)
	Hyperlipidemia	70 (28.0%)	34 (26.8%)
	Stroke	8 (3.2%)	3 (2.4%)
	Obesity	54 (21.6%)	38 (29.9%)
	≥1 comorbidity	191 (76.4%)	96 (75.6%)
Salvarani et al. 2021[13]	Diabetes	10 (16.7%)	9 (13.6%)
	Hypertension	27 (45.0%)	29 (43.9%)
	COPD	2 (3.3%)	2 (3.0%)
	Obesity	16 (28.1%)	22 (36.1%)
Stone et al. 2020[14]	Diabetes	45 (28%)	30 (37%)
	Heart failure	17 (11%)	7 (9%)
	History of myocardial infarction	15 (9%)	6 (7%)
	Hypertension	80 (50%)	38 (46%)
	COPD	15 (9%)	7 (9%)
	Asthma	15 (9%)	7 (9%)
	CKD	29 (18%)	13 (16%)
	History of Cancer	22 (14%)	8 (10%)
	Current Smoker	7 (4%)	0
	Former Smoker	46 (29%)	26 (32%)

COPD = chronic obstructive pulmonary disorder, CVD = cardiovascular disease, CKD = chronic kidney disease.

Table 20

Laboratory Values of Inclusion Criteria (12 studies)

Study	Inclusion criteria	Exclusion criteria
RECOVERY[3]	• Hypoxia (oxygen saturation < 92% on air, or requiring oxygen therapy) • Evidence of systemic inflammation (CRP ≥ 75 mg/L)	NA

Broman et al. 2022 (COVIDSTORM)[4]	• Hypoxemia: Peripheral oxygen saturation ≤93% on ambient air or respiratory rate >30/min
	• At least 2 of 4:
	  • IL-6 >11.8 ng/L (2xULN)
	  • Ferritin >300 mg/L in women or > 800 mg/L in men (2 x ULN)
	  • D-dimer >1.5 mg/L
	  • C-reactive protein>40 mg/L
		• ANC < 1.0 x 109/L
		• Platelet count < 50x109/L
		• ALT > 350 IU/L in women or > 500 IU/L in men (10 x UNL)

Declercq et al. 2021 (COV-AID)[5]	• Hypoxia: a ratio PaO2 to FiO2 (P:F ratio) of < 350 mm Hg on room air or < 280 mm Hg on supplemental oxygen and bilateral pulmonary infiltrates • A single ferritin concentration measurement of > 2,000 mcg/L at inclusion when they immediately required high-flow oxygen or MV, or a ferritin concentration of > 1,000 mcg/L, which had been increasing over the previous 24 h, or lymphopenia below 800/mL with 2 of the following criteria: • An increasing ferritin concentration of > 700 mcg/L • An increasing lactate dehydrogenase concentration of more than 300 international units (IU)/L • An increasing CRP concentration of > 70 mg/L • An increasing D-dimers concentration of > 1,000 ng/mL. If the patient had 3 of the previous criteria at hospital admission with lymphopenia of < 800/µL, there was no need to document an increase over 24 h	• Thrombocytopenia of < 50,000 per ¼L or neutropenia of < 1,500 per ¼L
Gordon et al. 2021 (REMAP-CAP)[6]	NA	• Baseline platelet count < 50 x 109/L • Baseline ALT or AST > 5 ULN

Hermine et al. 2021 (CORIMUNO-19: TOCI-2)[7]	NA	• Laboratory results out of range the ranges detailed below:
		  • ANC 1.0 ×109/L or less
		  • platelets less 50 G/L

Hermine et al. 2022 (CORIMUNO-19: TOCI-1)[8]	NA	• Laboratory results out of range the ranges detailed below: • ANC 1.0 ×109/L or less • platelets less 50 G/L

Study	Inclusion criteria	Exclusion criteria
Rutgers et al. 2022[11]	Have at least one of the following signs compatible with hyperinflammation: 1. need for supplemental oxygen (inspired by the ASTCT consensus grade 2 for CRS, generally matching a saturation < 94%) 2. and/or ferritin >2000ug/L or a doubling of serum ferritin in 20-48 hrs	NA
Salvarani et al. 2021[13]	An inflammatory phenotype defined by • a temperature > 38°C during the last 2 days or serum CRP ≥ 10 mg/dL • CRP level increased to at least twice the admission measurement	NA
Stone et al. 2020[14]	• One of the following laboratory parameters: CRP level 50 mg/L • Ferritin level 500 ng/L • D-dimer level 1,000 ng/L • Lactate dehydrogenase level > 250 U/L	NA

ALT = alanine transaminase; ANC = absolute neutrophil count; AST = aspartate transaminase; ASTCT = American Society for Transplantation and Cellular Therapy; CRP = c-reactive protein; CRS= cytokine release syndrome; FiO2 = fraction of inspired oxygen; MV = mechanical ventilation; NA = not applicable; PaO2 = partial pressure of oxygen.

Table 21

Medications Administered in UC (12 studies)

Study	Medication	TCZ	Comparators
RECOVERY[3]	Corticosteroids	1462 (74%)	1568 (77%)
	Antivirals • Lopinavir-ritonavir • Remdesivir	48 (2%) 533 (27%)	56 (3%) 600 (29%)
	Azithromycin or other macrolide	663 (34%)	657 (32%)
	Hydroxychloroquine	42 (2%)	36 (2%)
	REGN-COV2	164 (8%)	162 (8%)
Broman et al. 2022 (COVIDSTORM)[4]	Glucocorticoid treatment at randomization	52 (91%)	29 (100%)

Study	Medication	TCZ	Comparators
Declercq et al. 2021 (COV-AID)[5]	Antibiotics	103 (45%)	55 (48%)
	Remdesivir	11 (5%)	6 (5%)
	Hydroxychloroquine	25 (11%)	15 (13%)
	Glucocorticoids	141 (62%)	72 (63%)
Gordon et al. 2021 (REMAP-CAP)[6]	Corticosteroids	50 (14.2%)	52 (12.9%)
	Covid-19 Antiviral	169 (47.9%)	217 (54.0%)
	Covid-19 Immunoglobulin	175 (49.6%)	202 (50.3%)
	Therapeutic Anticoagulation	119 (33.7%)	146 (36.3%)
	Macrolide	24 (6.8%)	27 (6.7%)
	Vitamin C	0	0
	Antiplatelet	7 (2.0%)	4 (1.0%)
	Statins Therapy	13 (3.7%)	13 (3.2%)
	Corticosteroids within 48 hours of randomization[b]	252 of 272 (92.7%)	293 of 312 (93.9%)
	Remdesivir within 48 hours of randomization[b]	10 of 341 (31.4%)	133 of 389 (34.2%)
Hermine et al. 2021 (CORIMUNO-19: TOCI-2)[7]	Anticoagulants	34 (69%)	29 (67%)
	Antibiotics • Azithromycin	46 (94%) • 5 (10%)	38 (88%) • 8 (19%)
	Hydroxychloroquine	10 (20%)	6 (14%)
	Antiviral drugs • Lopinavir/Ritonavir • Osteltamivir	8 (16%) • 5 (10%) • 3 (6%)	4 (9%) • 2 (5%) • 2 (5%)
	Immuno-modulators	0	1 (2%)
	Corticosteroids • Dexamethasone	20 (41%) • 3 (6%)	17 (40%) • 1 (2%)

Study	Medication	TCZ		Comparators	
Hermine et al. 2022 (CORIMUNO-19: TOCI-1)[8]		Before Randomization	After Randomization	Before Randomization	After Randomization
	Anticoagulants	35 (56%)	39 (62%)	33 (49%)	38 (57%)
	Azithromycin	13 (21%)	10 (16%)	13 (19%)	10 (15%)
	Hydroxychloroquine	4 (6%)	5 (8%)	7 (10%)	8 (2%)
	Antiviral drugs • Lopinavir/Ritonavir • Lopinavir • Remdesivir • Osteltamivir	6 (10%) • 5 (8%) • 1 (2%) • 0 • 0	1 (2%) • 1 (2%) • 0 • 0 • 0	12 (18%) • 11 (16%) • 0 • 0 • 1 (1.5%)	4 (6%) • 3 (4%) • 0 • 1 (1.5%) • 0
	Immuno-modulators	0	1 (2%)	0	4 (6%)
	Corticosteroids • Dexamethasone	10 (16%) • 4 (6%)	19 (30%) • 9 (14%)	12 (18%) • 5 (7%)	37 (55%) • 19 (28%)
Rosas et al. 2021[9], 2022[10] (COVACTA)	Glucocorticoids	57 (19.4%)		41 (28.5%)	
	Antiviral drugs	71 (24.1%)		42 (29.2%)	
Rutgers et al. 2022[11]	Dexamethasone	151 (87%)		162 (90%)	
	Hydroxychloroquine	1 (1%)		4 (2%)	
	Remdesivir	36 (21%)		29 (16%)	
Salama et al. 2021 (EMPACTA)[12]	Systemic Corticosteroids • Dexamethasone	200 (80.3%) • 138 (55.4%)		112 (87.5%) • 86 (67.2%)	
	Antiviral • Remdesivir	196 (78.7%) • 131 (52.6%)		101 (78.9%) • 75 (58.6%)	
Salvarani et al. 2021[13]	Hydroxychloroquine	53 (88.3%)		62 (93.9%)	
	Low-molecular-weight heparin	41 (68.3%)		40 (60.6%)	
	Antiretrovirals	21 (35.0%)		31 (47.0%)	
	Azithromycin	10 (16.7%)		16 (24.2%)	
Stone et al. 2020[14]	Remdesivir	53 (33%)		24 (29%)	
	Hydroxychloroquine	6 (4%)		3 (4%)	
	Glucorticoids	18 (11%)		5 (6%)	

[a] Concomitant medication at day of randomization.
[b] Added on as part of UC, available to all domains above.

The World Health Organization Clinical Progress Scale (WHO-CPS) is used to measure a patient's infectious disease severity across a range from 0 (not infected) to 10 (dead).

Table 22

WHO Clinical Progression Scale

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalized: moderate disease	Hospitalized; no oxygen therapy	4
	Hospitalized; oxygen by mask or nasal prongs	5
Hospitalized: severe disease	Hospitalized; oxygen by NIV of HFO	6
	Intubation and MV, pO_2 /FiO_2 ≥150 or SpO_2 /FiO_2 ≥200	7
	MV pO_2 /FiO_2 <150(S pO_2 /FiO_2 <200) or vasopressors	8
	MV pO_2 /FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

ECMO = extracorporeal membrane oxygenation; FiO_2 = fraction of inspired oxygen; HFO= high-flow oxygen; MV = mechanical ventilation; NIV = noninvasive ventilation; pO_2 = partial pressure of oxygen; RNA = ribonucleic acid; SpO_2 = saturation of peripheral oxygen.

Source: Reprinted from Lancet Infectious Diseases. 2020 Aug; 20(8):e192-197, Marshall et al. A minimal common outcome measure set for COVID-19 clinical research. Copyright 2020, with permission from Elsevier. https://www.sciencedirect.com/journal/the-lancet-infectious-diseases

The National Early Warning Score (NEWS 2) is a scale used to determine the degree of illness of a patient and prompts critical care intervention.

Table 23

National Early Warning Score

Indicators	3	2	1	0	1	2	3
Respiration rate	≤ 8	—	9-11	12-20	—	—	—
SpO_2 scale 1	≤ 91	92-93	94-95	≥96	—	—	—
SpO_2 scale 2	≤ 83	84-85	86-87	88-92 or ≥ 93 on air	93-94 on oxygen	95-96 on oxygen	≥97 on oxygen
Air (no machine) or oxygen	Oxygen	Oxygen	Oxygen	Air	—	—	—
Systolic blood pressure	≤90	91-100	101-110	111-219	—	—	—
Pulse	≤40	—	41-50	51-90	91-110	111-130	≥ 131
Consciousness	Alert	Alert	Alert	Alert	Alert	Alert	CVPU
Temperature	≤ 35.0	—	35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	—
Score				**Clinical Risk**			
Aggregate score 0-4				Low clinical risk			
Score of 3 in any individual parameter				Low-medium clinical risk			
Aggregate score of 5-6				Medium clinical risk			
Aggregate score ≥7				High clinical risk			

Source: Zhang et al. The prognostic accuracy of National Early Warning Score 2 on predicting clinical deterioration for patients with COVID-19: a systematic review and meta-analysis. *Front Med*. 2021;8:699880. Copyright 2021 The authors. Reprinted in accordance with Creative Commons Attribution License CC BY.