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ORIGINAL RESEARCH

Therapeutic Impact of Tocilizumab in the Setting of Severe COVID-19; an Updated and Comprehensive Review on Current Evidence

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Abstract: **Introduction:** The COVID-19 pandemic caused by SARS-CoV-2 has been the major health concern in 2019 globally. Considering the severity and phase of the disease, various pharmacotherapy schedules were proposed. Here, we set out to provide close-up insights on the clinical utility of Tocilizumab (TCZ), a biologic monoclonal antibody in this regard. **Methods:** In this comprehensive review, various databases, including Scopus, PubMed Central, Medline, Embase, Google Scholar, and preprint publishers (med/bioRxiv) were searched until January 30, 2024, according to the keywords and search criteria. **Results:** Besides the pros and cons, compelling evidence purported the safety and efficacy of TCZ and indicated that it exhibits great potential to reduce short-term and all-cause (28-30-day) mortality. TCZ significantly drops the adverse events if administered in the right time course (in the inflammatory phase) during critical/severe COVID-19 pneumonia. Despite contradictory results, the benefits of TCZ appear significant, especially in combination with add-on therapies, such as corticosteroids. Although the safety of TCZ is acceptable, solid data is lacking as to its benefits during pregnancy. There are limited data on TCZ combination therapies, such as hemoperfusion, intravenous immunoglobulin (IVIG), simple O2 therapy, vasopressor support, convalescent plasma therapy, and even in vaccinated patients and COVID-19 reinfection, especially in elderly persons. In addition, the impact of TCZ therapy on the long-lasting COVID-19 is unclear. **Conclusion:** Personalized medicine based on individual characteristics and pertinent clinical conditions must be considered in the clinicians' decision-making policy. Finally, to mitigate the risk-to-benefit ratio of TCZ, a treatment algorithm, based on available literature and updated national institute of health (NIH) and Infectious Diseases Society of America (IDSA) guidelines, is also proposed.

Keywords: Treatment outcome; COVID-19; SARS-CoV-2; Algorithms; COVID-19 drug treatment; Tocilizumab

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1. Introduction

During the coronavirus disease (COVID-19) pandemic, from December 2019 to May 2023, a highly contagious respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had spread worldwide (1). The evolution of SARS-CoV-2 variants resulted in significant public health concerns with a high rate of morbidity and mortality worldwide (2) and a likelihood of reinfection and relapse (3).

Despite available vaccines and emergency use authorization (EUA), pharmacological therapy was still essential for managing COVID-19, particularly in patients hospitalized due to a critical form of the disease. However, currently, effective and optimum therapeutic protocols should be globally considered in facing upcoming SARS-CoV-2 variants of concern (VOCs) (4).

Since the COVID-19 pandemic, the world health organization (WHO) has issued numerous interim guidelines consecutively updated according to the latest clinical reports. As a result, the recent paradigm of COVID-19 therapy has been predominately modified. Among the multiple proposed medications, antiviral agents (e.g., Remdesivir and favipiravir as broad-spectrum RNA polymerase inhibitors by mimicking purine RNA constituents), Protease inhibitors (such as a combination of lopinavir and ritonavir), corticosteroids (e.g.,

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Dexamethasone and methylprednisolone), anti-interleukin-6 (IL-6) monoclonal antibodies (Tocilizumab, Sarilumab), anti-IL-1 (anakinra), and Interferon (INF)- 1b and 1a modulators, have indicated substantial clinical efficacy in viral and inflammatory phases, respectively (5-9).

Calling attention, the dynamic levels of IL-6 are distinct between patients with mild and severe COVID-19 (10). In this respect, the inhibition of IL-6 function via receptor antagonizing and direct blocking could be considered a target of therapeutic strategy, particularly in severe cases and critically ill patients (11, 12).

Tocilizumab (TCZ), as a biological agent, is defined as a recombinant humanized immunoglobulin G1k (IgG1k) subclass monoclonal antibody (mAb), specifically antagonizing the IL-6 receptor, both IL-6 soluble receptor (sIL-6R) and membrane receptor (mIL-6R). This function of TCZ is mediated in either JAK-STAT or MAPK/NF-kB-IL-6 pathway-dependent manner to quench the pro-inflammatory effects of IL-6 (13, 14).

Conventionally, TCZ is utilized as a main therapeutic option for idiopathic and rheumatoid arthritis (RA), as well as off-label use in systemic sclerosis (15, 16). Because of its long half-life (8-30 days), TCZ can also exert a good safety profile for the treatment of giant cell arteritis (GCA) and systemic juvenile idiopathic arthritis (sJIA) (17), which has later been considered to mitigate the cytokine release syndrome (CRS) (18). The CRS mainly refers to excessive immune responses and subsequent release of pro-inflammatory mediators, chemokines, and cytokines, observed during inflammatory diseases (19). Moreover, inflammation plays a crucial role in the severity of COVID-19, and the majority of COVID-19 hospitalized patients with evidence of acute respiratory distress syndrome (ARDS) had CRS (20-23). Importantly, patients who developed COVID-19-related CRS could be candidates for off-label use of TCZ with promising suppressive potential against the CRS phenomenon (24, 25).

In addition, it has been postulated that overwhelming inflammation stimuli may decrease the level of cytochrome p450 (CYP450) enzyme expression (26). On the other hand, IL-6 receptor blocking yielded by TCZ administration retrieves the CYP450 activity and simultaneously induces the metabolism of substrates. This raises the risk of immunosuppression and thus could be considered in patients with immunodeficiency conditions. In Figure 1, the TCZ-related mechanism of action in favor of COVID-19-derived CRS has been depicted. Albeit, a better understanding of the appropriate dosage of TCZ in COVID-19 patients is imperative, the heterogeneity of inclusion criteria, clinical consequences, and follow-up duration in previous literature make it challenging to draw practical and applicable conclusions, across the entire spectrum of TCZ indication in hospitalized patients. In this article, we delved deeper into tracking the TCZ territory in the clinical setting during the COVID-19 pandemic and reviewed the available evidence regarding the TCZ safety and efficacy in in-hospital COVID-19 patients, regardless of age, gender, race, and location, to answer critical questions listed below:

Is TCZ-based treatment effective for both short and long-term mortalities?

Is the intensive care unit (ICU) length of stay and mortality rate affected by the timely administration of TCZ?

Is there any synergistic effect of TCZ combination therapy with other non-pharmacologic interventions (such as O2 therapy, hemoperfusion, convalescence plasma, intravenous immunoglobulin (IVIG)?

Can a superior effect be observed with TCZ treatment following vasopressor support in patients admitted to the ICU?

Can an additive effect also be observed with TCZ treatment following corticosteroids and/or antiviral drug therapy?

Could TCZ administration be considered in vaccinated populations with severe COVID-19 reinfection?

Furthermore, we evaluated the composite outcomes across different subgroups with a special focus on pregnant women, the time course of drug administration (early or late phase), safety, and benefits of the combination therapy with other inflammatory agents e.g., corticosteroids. Finally, an algorithm was designed for TCZ therapy based on multiple systematic reviews and meta-analyses, accompanied by updated guidelines.

2. Methods

2.1. Search strategy

In this comprehensive review, various databases, including Scopus, PubMed Central, MEDLINE, EMBASE, Google Scholar, and preprint servers (medRxiv and bioRxiv) were searched up to 30th January 2024, according to the listed keywords resulting from Medical Subject Headings (MeSH), as follows:

"coronavirus disease 2019" OR "2019 novel coronavirus infection" OR "2019 ncov disease" OR "covid" OR "covid 19" OR "covid 19 induced pneumonia" OR "covid 2019" OR "covid 10" OR "covid 19" OR "covid 19 induced pneumonia" OR "covid 19 pneumonia" OR "covid19" OR "sars coronavirus 2 infection" OR "sars coronavirus 2 pneumonia" OR "sars cov 2 disease" OR "sars cov 2 infection" OR "sars cov 2 pneumonia" OR "sars cov2 disease" OR "sars cov2 infection" OR "sarscov2 disease" OR "sarscov2 infection" OR "wuhan coronavirus disease" OR "wuhan coronavirus infection"

AND

"tocilizumab" OR "actemnitio ra" OR "actemra 200" OR "atlizumab" OR "bat 1806" OR "bat1806" OR "lusinex" OR "msb 11456" OR "msb11456" OR "r 1569" OR "r1569" OR "rg 1569" OR "rg1569" OR "ro 4877533" OR "ro4877533" OR "roactemra" OR "tocilizumab"

AND

"systematic review" OR "review systematic" OR "systematic review" OR "review" OR "analysis, meta" OR "meta-analysis"

The publication date was not limited and recent 'cited by' or associated publications were also surveyed. All types of

review articles that were clinically and scientifically relevant to the scope of this article, including narrative review, systematic review, systematic review and meta-analysis, living systematic review and meta-analysis, network meta-analysis, Umbrella review(s), and case reports with literature review were also included, reviewed and cited.

In terms of the PICO of this study, all patients with severe forms of COVID-19 were defined as the study population. The therapeutic intervention was TCZ administration, which was further compared with anti-inflammatory medications, antivirals, and other mAbs with similar structures, if available. Finally, the rate of mortality, ICU admission, mechanical ventilation (MV) requirement, length of hospital stay, and adverse events such as secondary infection were also evaluated as the study outcomes.

2.2. Study selection and quality assessment

The initial electronic search yielded 1135 records. After review by two authors, 341 duplicated articles, and seven ineligible reports, titles, and abstracts were excluded in the initial screening via the Endnote software (ver. 21.0). The two reviewers (AR and FM) independently agreed to exclude 567 records because of irrelevancy. Out of 149 studies with relevant scope, 62 review articles, i.e., systematic reviews with/without meta-analyses, and an umbrella review were included (n=63). The study selection algorithm was brought into the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 2). Two reviewers independently evaluated publications containing quantitative data for methodological validity using the Joanna Briggs Institute (JBI) critical appraisal tool for systematic review and meta-analysis. Any disagreements between the reviewers were resolved through discussion or by involving a third reviewer.

2.3. Eligibility criteria

All review articles (with or without meta-analysis) on hospitalized COVID-19 patients and TCZ treatment, with at least one endpoint (primary/secondary) were included. As exclusion criteria, all case-control, cross-sectional, and cohort studies, as well as clinical trials were excluded from this assessment.

2.4. Primary and secondary outcomes

The primary outcomes were any improvement in the rate of mortality (short-term, 28-day, and all-cause mortalities), mechanical ventilation (MV) requirement, need for intubation, length of hospital stay, and ICU transfer. Moreover, superimposed/secondary infection and organ failure (as adverse events), neutropenia, indication in pregnancy, the synergistic potential of combination therapies besides the adjuvant therapeutic strategy, consisting of O2 therapy, receiving vasopressors, IVIG, Hemoperfusion (27), and vaccines (regardless of platform applied for vaccine synthesis) were also evaluated in comparison with the standard of care (SOC). The final data were carefully entered into the data extraction table by two authors, independently (AR and STT).

2.5. Data extraction

Using Microsoft Office Excel pre-formatted forms (version 2016), the extraction tables were categorized into seven and nine headings, respectively, including 1) basic study specifications (the first co-author's name, year of publication, review type, tools used for assessment of risk of bias, applied methodology, the tools and/or models for analysis). 2) Baseline characteristics (total number of participants, TCZ dosage, and disease severity). 3) Clinical endpoints, including mortality rate (short-term, and in hospital after 14 days, 28-30 days, and all-cause mortality), discharge rate, ICU transfer, invasive/non-invasive MV, and possible adverse effects, i.e., secondary infection, neutropenia, and combination therapy, in details. The extraction was performed from either the main text or tables of published articles (Tables 1 and 2).

2.6. Dose consideration

The National Institutes of Health (NIH) Guideline recommended a single intravenous (IV) dose of TCZ (400-800 mg, and an initial dose of 8 mg/kg weight-based dose). However, the criteria in the case of the initial dose, the need for a second dose, the optimal number of doses, and the treatment time course varied across the studies and mainly relied on the clinician's decision according to the patient's condition. For instance, in some studies, the participants were randomized to receive SOC only or SOC+ TCZ, IV, at a dose of 400–800 mg (adjusted according to body weight), and a second dose of TCZ was given 12–24 h after the initial dose if clinical improvement was not found (28). Of note, the RCT-TCZ-COVID-19 trial also indicated that the early administration of TCZ could not alleviate the risk of disease progression in patients with PaO2/FiO2 between 200-300 mmHg due to lower IL-6 serum levels, and in those with fever or c-reactive protein (CRP) ≥ 10 mg/dL (mild inflammation) (29).

According to the available evidence, TCZ is applicable in patients with CRP ≥ 75 mg/dL (hyper-inflammation) along with higher levels of IL-6 (Ĩ00 pg/ml) (30).

3. Findings and discussion

Characteristics of included studies

The selected studies were divided into three quality categories based on their scores: a total score exceeding 80% was considered high quality, a score between 60% and 80% was deemed medium quality, and a score below 60% was classified as low quality. Meanwhile, the quality of 72.8%, 18.2%, and 9% of the included studies in Tables 1 and 2 were high, medium, and low, respectively (Supplementary table I).

3.1. Survival rate

The strategies for the assessments of TCZ effectiveness on the survival rate were inconsistent in the available literature. The

results of subgroup analysis i.e., unadjusted, adjusted, performed on the randomized clinical trials (RCTs) and observational studies were also controversial. For example, it has been clarified that TCZ efficacy on 28-30 all-cause mortality rate in non-severe patients was significant, while no mortality benefit was achieved in critically ill patients (31). Another study indicates that TCZ resulted in a significantly lower risk of all-cause mortality in RCTs (p = 0.03), but not in cohorts (32). However, TCZ therapy was not associated with reduced short-term mortality in RCT studies (33). In contrast, a meta-analysis revealed that TCZ is associated with a great decrease in mortality rate in both severe and critically ill patients according to the data analysis of observational studies but not RCTs (34).

Although most of the meta-analyses have provided positive signals in reducing either short-term (14-day) (35) and 28-30-day all-cause/overall mortality incidents (36-39) if administered at the right time (40), a network meta-analysis indicates that TCZ was not clinically effective in reducing 28–30-day mortality in COVID-19 patients (41), which was in line with a living systematic review (42). At the same time, others have reported that TCZ has the potential to reduce the mortality rate in both observational and RCT studies (11% and 31%, respectively) in comparison with the control group (43). However, some studies did not report which type of mortality (long-term or short-term, in-hospital, or all-cause mortality) has been assessed (44, 45). Another point is that the method used for data analysis could affect the obtained results. For example, in adjusted estimates, TCZ is effective in reducing mortality rate (hazard ratio (HR): 0.50, 95% confidence interval (CI): 0.38–0.64, $p < 0.001$ vs. odds ratio (OR): 0.74, [95% CI: 0.55–1.01, p = 0.057]) (46).

Together, timely administered TCZ appears to be effective for the reduction of mortality rate in patients with severe COVID-19. However, due to the heterogeneity, the meta-analysis reported somewhat controversial results in either different types of studies (RCTs vs. Cohorts) or following adjusted/non-adjusted analysis.

3.2. Mechanical ventilation (MV)

3.1.1. Non-invasive MV

Noticeably, there is a direct link between CRS, especially elevated IL-6 serum level, and the need for mechanical ventilation. The eligibility criteria of RECOVERY and REMAPCAP trials provided evidence that TCZ would be more practical in hospitalized patients with systemic inflammation requiring oxygen or in those receiving MV within the last 24 hours (47). As a composite endpoint, among patients who received TCZ, a substantially lower proportion of patients required non-invasive/invasive MV or died within two weeks (48).

In this regard, a living systematic review and meta-analysis was also designed to evaluate the effect of TCZ on MV requirement as well as survival rate. The extracted cumulative moderate-certainty evidence showed that of five RCTs, four studies with 771 patients declared that TCZ has the potential to reduce the risk of MV based on a pooled risk ratio (49). In contrast, the meta-analysis conducted in the same year (2021), revealed no differences (14.75% vs. 19.55%) (44). Differences in the results of the two studies may be related to either different methods applied for analysis or the number of included studies [using the Mantele–Haenszel methods and fixed effect model for analysis of four RCTs vs. using a random-effects model for fifteen studies (including case-control, RCT, and cohorts)]. A meta-analysis of the first eight months of the pandemic on 15,000 patients with COVID-19-induced pneumonia also reported that TCZ failed to prevent MV requirement based on unadjusted estimation (46). In the meta-analysis conducted by Jiang et al., the results of both overall and subgroup analyses (considering ethnicity, drug dose, disease severity, study type, and size) also showed that there is no significant association between TCZ and estimated risk of MV (50).

Even so, an umbrella review that included fifty eligible meta-analyses, revealed that based on pooled estimates of eight retrospective studies and seven RCTs with 5792 COVID-19 patients, TCZ reduced the risk of MV by up to 23% compared with the SOC group. However, this improvement was not significantly associated with a reduced risk of ICU admission (51). Moreover, the risk difference (RD) is considered a crucial measurement. They reported that in the TCZ group, the NNT for MV is 9.1 in patients with severe COVID-19 (37). Besides, the positive feedback of TCZ to avert MV in a patient with progressive respiratory distress with no further therapeutic response to SOC (including Hydroxychloroquine, azithromycin, and zinc), who was ultimately downgraded from the ICU, underscored the significance of early consecutive monitoring of IL-6 serum levels and other acute phases reactants, such as ferritin, D-dimer, and C-reactive protein (CRP), in optimal clinical decision-making in the management of potentially ill patients with severe and critical COVID-19 (52).

In a living meta-analysis, the need for MV was evaluated at two time points (14 and 28 days). According to the results of the analysis, TCZ exerted benefits regarding the risk of MV, while it did not result in a significant difference regarding the ventilator-free days at 28 days when compared with the control arm. In addition, in two trials ventilator-free days at 28 days were reported without significant difference between TCZ and control arm [(median 22, 95% CI: 18.0–28.0) vs. (median 16.5, 95% CI: 11.0–26.0), p = 0.32 and RR: 1.36 95% CI: 0.733–2.55)], respectively (31). To explain these non-significant differences, it can most likely be attributed to baseline characteristics such as disease severity, which was more critical in the TCZ group (39).

3.1.2. Invasive MV/Intubation

Regarding the invasive MV (IMV), highlighting the importance of the individual's assessment for TCZ therapy (34). However, TCZ failed to show benefits in the rate of IMV according to thirteen studies with 1703 patients (53).

Furthermore, the percentage of TCZ efficacy in the analysis

of both primary and secondary endpoints revealed that TCZ is associated with a 19% reduction of IMV/need for intubation based on RCTs (nine studies), which was in line with another study that highlighted the reduction of intubation risk in patients who received TCZ (n=1612, p = 0.04) (45). However, in the observational studies (n=43) TCZ could not exert a significant improvement. Albeit, it should be taken into account that the heterogeneity in observational studies was high when compared with the RCTs (I^2 = 70.2%), and the sample size was rather small (54).

3.1.3. Simple oxygen support

Beyond the IMV/non-IMV, accumulating data support the fact that TCZ improved oxygenation (high-flow oxygen requirement) in COVID-19 patients who underwent oxygen support for better disease management, especially in the inflammatory phase with substantially raised inflammatory markers (55). Consistent with this, Bayesian Reanalysis performed on a meta-analysis demonstrated that the group that received simple oxygen only (defined as oxygen flow rate 15 L/min provided by face mask or nasal cannula) was associated with a probability of a significant clinical benefit from TCZ with the posterior probability of any favorable association (56). A case series with a literature review also indicated that TCZ+ high-flow nasal cannula oxygenation exerted beneficial effects following anti-viral therapy in critically ill patients, with remarkable improvement in respiratory rates and arterial blood gas parameters (57).

Overall, regarding the MV requirement, two domains of behavior emerged following TCZ infusion: (i) reduction in the need for MV and (ii) no superiority of TCZ compared to SOC regarding MV requirement. Also, in the case of ventilator-free days at 28 days and IMV, data was controversial. Yet, the results of the multiple meta-analyses and case reports underscore the beneficial effects of TCZ in combination with simple O2 therapy.

3.2.1 ICU Admission/Transfer

The ICU transfer or ICU length of stay is usually categorized as a secondary/surrogate endpoint in the setting of severe/critical COVID-19. According to the data analysis extracted from the meta-analysis, considering the high level of heterogeneity, TCZ exerted no effect on the risk of ICU admission and the outcome was similar between the TCZ and control groups based on pooled risk ratio (RR) in four independent studies, as follows:

a. 1.40 (95% CI: 0.64–3.06; P = 0.4; I^2 = 88%) (53)

b. 0.98 (95% CI: 0.36–2.66; P = 0.99; I^2 = 89.4%) (45)

c. 1.51 (95% CI: 0.33–6.78; I^2 = 86%) (39)

d. RR of the composite endpoints of ICU admission + IMV = 1.08, 95% CI: 0.85–1.38, 95% PI: 0.67–1.73) (54)

e. RD: 0.003, 95% CI: -0.14–0.14, p = 1.00, I^2 = 90.7% (37)

The analysis of the first eight months of pandemic (n=15000 patients with COVID-19 pneumonia) also emphasized that although unadjusted estimates failed to show a benefit on survival and ICU admission, adjusted estimates interestingly reported a significant reduction in both mortality and ICU admission rates [hazard ratio (HR) 0.50 (95% CI: 0.38–0.64), p < 0.001, and OR 0.16 (95% CI: 0.06–0.43), p < 0.001, respectively] (46). Taken together, TCZ, at least in part, indicated no substantial effectiveness on the ICU admission of inpatients, similar to SOC treatment. However, the majority of the studies claimed possible TCZ benefits in the setting of ICU admission, and mentioned the positive effects of the drug, especially in reducing the ICU mortality rate.

In Figure 3, the clinical benefits of TCZ therapy following hospitalization are schematically illustrated in individuals with severe COVID-19 infection.

3.3. Length of hospital stay (LOS)/ Duration of hospitalization

According to the results of a meta-analysis, it has been delineated that the TCZ group has a potential effect (but not certainly) on LOS when compared with the SOC or placebo counterpart [weighted mean difference (WMD) 1.96 days, 95% CI: 4.24 to 0.33] (58). Another meta-analysis determined the TCZ effect on LOS according to the clinical study type. In parallel with similar results, the pooled standardized mean differences (SMDs) was 0.10 in the RCTs/cohorts, while the mean ± SD LOS was shorter for the TCZ in comparison with SOC, which was not significant (10.82 ± 5.18 vs. 16.56 ± 11.13 days; p = 0.23) (45). Optimal TCZ therapeutic implications in the severe and critical COVID-19 were assessed on LOS, which was adjusted based on CRP level. Surprisingly, the authors noted that TCZ increased the LOS when the CRP value was lower than 100 mg/L (36), highlighting the importance of CRP levels for the right TCZ administration. In addition, the results of a meta-analysis unveiled a non-significant reduction in the LOS following TCZ therapy in both RCTs and observational studies considering a high level of heterogeneity (I^2 = 99.0% and 97.5%, respectively) (54). Per available data, the benefits of TCZ on LOS are insufficiently established. However, TCZ could be more effective than SOC in this regard. Moreover, there is a direct association between serum levels of CRP and TCZ potential on LOS as a therapeutic endpoint.

3.4. TCZ safety profile (Pharmacovigilance)

3.4.1. Adverse Events (AEs)

There is inadequate data to support the TCZ administration as a precipitating factor in deriving COVID-19-induced adverse events risk (59).

Following TCZ administration, thrombocytopenia, neutropenia, pruritus, and elevated liver enzymes (hepatotoxicity) could be observed in COVID-19 patients (25, 60, 61). Moreover, TCZ is contraindicated in immunosuppressed patients with alanine transaminase (ALT) five times higher than the upper limit normal, neutrophil count less than 500 cells/L, and platelet count less than 50 000 cells/L, as well as in those at high risk for gastrointestinal perforation and other serious infections (Figure 4) (62). Notably, Severino et al. reported that the cumulative incidence of AEs caused by

TCZ was 69.6% (95% CI: 63.5-76.6). Noteworthy, a rise in ALT and aspartate aminotransferase (AST), as well as the development of particular infections (reactivation of latent tuberculosis) were the most reported AEs, suggesting monitoring blood count, liver function tests, and ruling out infection before TCZ administration (63, 64). Recently, a pharmacovigilance study was performed on TCZ-induced AEs with a special focus on designated medical events per the FDA Adverse Event Reporting System (65). Statistically significant reporting odds ratios (RORs) were recorded for 13 designated medical events (DMEs), with drug-induced liver injury (n= 91), pancreatitis (n= 151), and pulmonary fibrosis (n= 222) as unpredictable AEs (65).

3.4.1.1. Neutropenia

As mentioned above, the serious AEs observed upon the TCZ treatments are rare and mostly indicated through case reports and case series. For example, some rare AEs, such as bilateral retinopathy were previously reported following TCZ administration in patients suffering from RA (66). Neutropenia can be also considered one of the most frequent hematologic AEs (32). During the early phase of the safety and efficacy assessments, an individual with COVID-19-induced ARDS benefited from TCZ treatment; however, the development of severe prolonged neutropenia occurred following the administration of TCZ (67).

Another case report represented severe neutropenia (absolute neutrophil count (ANC) = 300 cells/μl), and leukopenia as catastrophic events derived by acute COVID-19 in a Nepalese male; however, the cautious treatment with TCZ + granulocytes-colony stimulating factor (G-CSF, Filgrastim) with acceptable safety led to patient recovery and even reversed the neutropenia level in blood profile (68). In this respect, the effect of some risk factors (i.e., genetic, race, and ethnicity variety) should be taken into account in determining the likelihood of secondary infection incidents. In this line, Avni et al. also showed that the neutropenia incident (ANC < 500-1000 cells/μl) was significantly higher in the group that received TCZ (31). Of note, African American patients are more likely to have lower ANC than other ethnicities without increased risk of infection (in 66.7% ANC is less than 2000 cells/μl), which is associated with the Duffy-null phenotype (lack of the Duffy antigen expression on the red blood cells) (69). Following acute neutropenia derived from TCZ treatment, severe prolonged neutropenia was observed in another COVID-19 patient of African American ethnicity (for at least 4 weeks, neutropenia after TCZ: 0.52 × 109/L vs. neutrophilia before receiving TCZ 9.8 × 109/L) (70). However, data is lacking to determine unequivocally whether or not neutropenia is the most concerning AE attributed to TCZ therapy in the general population.

3.4.1.2. Organ failure

In non-COVID-19 patients, the previous data indicated the possible impacts of TCZ on the cardiovascular system, including the shortening of the QT interval, hypertension, and hypercholesterolemia. Furthermore, drug-drug interactions have been also reported with some antiarrhythmics, antiplatelet drugs, anticoagulants, statins, and beta-blockers (71, 72). Calling attention, among medications defined in the COVID-19 treatment protocols, TCZ has been introduced as a safe agent in combination with antipsychotic drugs, most likely due to the retrieval effect on CYP450 enzyme activity with a special effect on the increase of CYP3A4 substrate metabolism, which was down-regulated following COVID-19 hyper-inflammatory responses (73). Given that multi-organ failure is thought to be one of the complications associated with the cytokine storm (74, 75), the benefits of TCZ in dropping the risk of multi-organ failure in patients with severe COVID-19 drew clinicians' attention.

3.4.2. Secondary infections

Available evidence indicated that the secondary infections among patients with severe COVID-19 and in those who need IMV are mainly caused by multiple organisms (Pseudomonas aeruginosa, Escherichia coli (76), Burkholderia cepacia, Stenotrophomonas maltophilia (77), Acinetobacter baumannii, Klebsiella pneumonia, Aspergillus flavus, Candida glabrata, and Candida albicans (78)).

In light of the higher risk of secondary infection incidents among the patients admitted to ICU, or in critically ill patients, it is necessary to evaluate the rate of superimposed infections following TCZ administration in these subgroups. To establish TCZ safety, the meta-analysis conducted by Belletti et al. provides evidence indicating that the risk of secondary infections and other adverse events did not increase in the TCZ arm when compared with patients who received SOC only (67). Similarly, a living systematic review and meta-analysis showed a lower risk of secondary infections and no higher risk of serious adverse events (49).

In the meta-analysis published in the JAMA, 28-day secondary infection was defined as the most important safety outcome, which was approximately similar between the two arms of the study. The authors also considered 90-day superimposed infection as an additional secondary outcome, but due to the data limitation, it could not be estimated (79). Using the random-effects model, Rubio-Rivas et al. also reported that the pooled risk of secondary infections in patients who received TCZ was low (80), which is in line with Rezaei et al., findings with low pooled RR: 1.24 (95% CI: 0.98 to 1.56; p = 0.07; I^2 = 66.5%) (45). However, some publications documented the rising risk of superimposed infection and candidemia subsequent to TCZ use, which is most likely due to the suppression of the immune system (81), particularly in patients with predisposing conditions and co-morbidities (82, 83). In this line, a meta-analysis conducted by Peng et al. also highlighted the higher risk of fungal co-infection after the TCZ administration (2.75%, p = 0.036), particularly in Caucasian subgroups and patients received 400 mg TCZ in comparison with other anti-inflammatory treatments such as sarilumab and anakinra (84).

Besides, Hariyanto et al. performed a meta-analysis to assess the risk of thromboembolism incidents beyond the sec-

ondary infection.

Intriguingly, the results of the sub-group analysis showed that treatment by TCZ has high safety, which was not associated with either incidence of thromboembolism incident, or secondary infection (85). However, they concluded that TCZ did not exert therapeutic efficacy at least in part in the setting of CRS-independent COVID-19 (85).

It can be concluded that TCZ is categorized as a safe biological agent with a low risk of bacterial/fungal co-infections. However, the rare reports of secondary infection incidents following TCZ administration can be observed in Caucasian patients, in those with immunodeficiency, and immunosuppressed recipients.

4. Combination therapy

Calling attention, the TCZ adjuvant therapy has been deemed to exert significant clinical benefits compared with the monotherapy strategy. In this regard, the function of CYP450 enzymes in drug metabolism also plays a crucial role. Noteworthy, the higher serum levels of IL-6 can suppress the function of pivotal CYP enzymes, comprising 3A4, 2C19, 2C9, and CYP1A2. Therefore, it can be inferred that inhibition of IL-6 receptors mediated by TCZ can indirectly affect the expression of CYP 450 enzymes. According to this scenario, the use of TCZ appears pharmacologically favorable due to a lower rate of drug-drug interactions without needing dose adjustment, when co-administered with other non-COVID-19 medications (86).

4.1. Co-treatment of TCZ with steroid anti-inflammatory drugs (Corticosteroids)

Corticosteroids (e.g., dexamethasone or methylprednisolone) have become the SOC, while TCZ is merely recommended for use in addition to corticosteroids in hospitalized patients under certain conditions, such as rapid respiratory decompensation, and systemic hyperinflammation induced by COVID-19 (62), because of supplementary benefits in critically ill COVID-19 patients. A meta-analysis of available RCTs suggested a higher efficacy of the TCZ-corticosteroids therapy in favor of a higher survival rate (87), and reduced risk of invasive MV in those with evidence of systemic inflammation, needing oxygen, or receiving ventilation within 24 h. Hence, large-scale RCTs are lacking to better understand the safety and effectiveness of TCZ-corticosteroid combination therapy.

To investigate the survival benefits in case of moderate-to-severe COVID-19 in a non-ICU setting, the results of a network meta-analysis revealed that a high-dose corticosteroid plus TCZ was associated with a low mortality rate (OR: 0.04, 95% CI: 0.01–0.17, $p < 0.001$) (88).

Intriguingly, the results of another meta-analysis yielded favorable outcomes for TCZ and showed that TCZ was superior to corticosteroids in reducing mortality rate, particularly in patients with severe COVID-19. However, evidence for a beneficial effect in the reduction of invasive MV was lacking (89). In the network meta-analysis, TCZ + corticosteroid therapy indicates a reduction of mortality risk, with thirty-five fewer deaths per 1000 severe or critical patients (90).

Based on the 2021 update of the European Alliance of Associations for Rheumatology (EULAR) points to consider (PtCs), it has been well-established that TCZ in combination with glucocorticoids (mainly Dexamethasone) is associated with clinical improvement in COVID-19 patients requiring supplemental oxygen therapy and declines the disease progression (91). Notably, a meta-analysis showed that in TCZ + systemic corticosteroid therapy, both pooled crude (unadjusted) and adjusted analysis, estimated that mortality rates were lower than the SOC arm (RR=0.62, 95% CI: 0.42–0.91; I^2 = 60%, and RR = 0.58, 95% CI: 0.42– .81; I^2 = 71%, respectively). Nonetheless, no significant difference was found in superimposed infections (92).

4.2. Co-treatment of TCZ with antiviral medications

According to the results reported by a recent network meta-analysis, in comparison with SOC and other interventions (dexamethasone, Hydroxychloroquine, ritonavir/lopinavir), remdesivir administration (100/200 mg, 10 days) was associated with a lower occurrence of severe adverse events analyzed by the fixed-effect model, which was followed by TCZ (90). In addition, it has been also revealed that remdesivir is superior to TCZ in terms of lower mortality risk, time of clinical improvement, and clinical recovery (41). There is also limited data supporting TCZ + remdesivir synergistic potential or even any contraindication in ill patients with COVID-19.

4.3. Co-treatment of TCZ with IVIG/ Convalescent plasma/ Vasopressors/ Hemoperfusion

Beyond the TCZ benefits regarding the time required for clinical recovery, the improvement of oxygenation, and subsequent reduction of the MV necessity, TCZ led to a shortened duration of vasopressor support, as well (93). Although there is limited data about the possible benefit of TCZ+IVIG administration in eligible patients, a systematic review assessed the COVID-19-associated multisystem inflammatory syndrome in children (MIS-C), the co-treatment of TCZ + immunoglobulins (IVIG/ convalescence plasma, as an enriched source of neutralizing Abs) remarkably diminished the mean LOS, increased the discharge rate (95.5%), and a significant improvement of discharge/deceased ratio, with a low rate of complications (i.e., multi-organ failure and respiratory failure) was observed when compared with the groups who did not receive a combination therapy (94). However, TCZ combination and convalescent plasma could not be regarded as a therapeutic choice for COVID-19 patients living in low- and middle-income countries (95). Overall, the reduction of mortality rate is considered the main outcome of combination pharmacotherapy, which is yielded by a high dose of corticosteroids (especially dexamethasone)

and TCZ in ill patients. However, the clinical importance of the TCZ add-on to corticosteroid therapy in terms of time-to-progression/recovery is unclear, yet.

5. TCZ administration in vaccinated patients with recurrent infection with SARS-CoV-2

In the next step, we intended to explore the efficacy of TCZ in high-risk patients who received the vaccine but were hospitalized due to COVID-19 reinfection caused by evolved variants. However, the data was too limited in this area to be discussed in detail.

6. TCZ efficacy in pregnant women with COVID-19

Given that pregnant women are commonly excluded from the clinical studies designed for COVID-19, data is restricted. Pregnant women are categorized as a high-risk population in terms of the development of severe COVID-19-related complications, underscoring the importance of receiving safe and effective therapies (96). Clinical data on TCZ treatment in the pregnant subgroup is mainly available from the Roche Global Safety Database and the European League Against Rheumatism (EULAR) task force (97, 98). Besides, the rate of placental and breastmilk transport of maternal IgG1 (99) and fetal exposure of TCZ is very low (due to the drug's large size and hydrophilicity), therefore, the first trimester could not be considered a concerning teratogenicity risk against organogenesis in the primate model (100). Due to pharmacokinetic reasons and increased blood volume during pregnancy, the drug concentrations should be adjusted.

In comparison to the baseline rates in non-pregnant patients, there was no increased risk of congenital malformation incidence following TCZ treatment (pregnant group 4.5%; non-pregnant group 3.0–4.0%) (97). Whereas, spontaneous abortion (15–20%) and the rate of preterm delivery (31.1%), respectively, were higher in pregnant patients who received TCZ (97). In the setting of COVID-19, although there is limited data on drug safety in the second and third trimesters, the TCZ administration was considered a therapeutic option, particularly in either non-critically ill pregnant patients with respiratory failure who received corticosteroids + remdesivir, or in the critical ill subjects who received corticosteroid (96, 101).

According to Naranjo's causality algorithm, some rare complications such as hepatotoxicity and viral reactivation were reported upon the TCZ treatment (102). Despite limited evidence, the majority of data indicated that the TCZ utilized in pregnant patients did not appear to have unfavorable effects on both mothers and newborns. However, close monitoring for preventing superimposed infections has been strongly recommended (103). Taken together, it can be inferred that TCZ has the potential to be categorized as a recommended medication for pregnant patients with severe COVID-19. Although preterm deliveries and abortions have been occasionally observed among pregnant patients who received TCZ, it could be attributed to other confounding factors.

In Table 1 and Table 2, we intended to extract the data achieved by different types of reviews with/without meta-analysis along with an umbrella review.

Figure 4 illustrates the algorithm of TCZ administration, designed for optimum management and clinical improvement of hospitalized COVID-19 patients, following the pooled estimations and available guidelines.

Irrespective of the heterogeneity of the available meta-analyses, overwhelming evidence reported the beneficial effects of TCZ rather than the inefficacy or worsening of the conditions caused by the drug. Also, numerous meta-analyses with predefined primary and secondary endpoints declared that TCZ represents a good safety profile, as well as the desirable therapeutic efficacy, most likely in patients with respiratory failure, severe, and/or critical COVID-19, but not in non-severe cases. Hence, considering disease severity and stage of the disease, TCZ therapy in hospitalized COVID-19 patients is currently being rather recommended in those with worsening respiratory function, respiratory failure, hypoxia, and high CRS levels according to laboratory assessment.

7. Limitations of studies

1) The eligibility criteria and primary/secondary outcomes should be precisely selected based on the infectious disease's underlying pathophysiology and the exact pharmacology of the potential therapeutic agents to best assess clinical efficacy. 2) Regarding severe adverse events, some articles did not indicate which events have been defined as adverse events. 3) The time course of drug administration, received dose (s), and dosage schedule were not mentioned, in detail. 4) Most of the studies evaluated the TCZ potential in the development of secondary infection, and did not indicate the kind of infections (bacterial or fungal, etc…) and/or other adverse reactions. 5) A large body of recent RCTs have mainly focused on TCZ benefits, while data on other IL-6 receptor antagonists such as sarilumab are limited and not supportive to further compare similar medications, 6) There are some variations in the definition of the SOC; in some studies, it has not been determined which drugs were considered the SOC. For example, some studies defined SOC as a control group composite of Hydroxychloroquine + lopinavir/ritonavir (with/without azithromycin), while in other studies patients treated with dexamethasone alone or in combination with some anti-viral agents (such as remdesivir) were defined as SOC. 7) Due to the excessive overlapping of clinical studies included in various meta-analyses, it is challenging to estimate the exact number of affected patients and the validity of concluded results.

In the case of the recent Umbrella review, some limitations were also specifically found as follows:

The type of mortality has not been defined and the authors

merely indicated the alternation of mortality rate following TCZ treatment. Moreover, the criteria for disease severity and TCZ route of administration were not clear. The authors also did not mention the kind of MV assessed (invasive/non-invasive).

8. Conclusion

Based on the findings of the study: 1) the TCZ potentially reduced the mortality rate (both short-term and all-cause 28-30-day mortalities) and MV requirement with minimized adverse events derived by SARS-CoV-2 infection, if administered in the right time course in severe COVID-19 with critical pulmonary symptoms. 2) Considering the safety of TCZ in ICU patients, there is limited data regarding TCZ's impact on the length of ICU admission. However, according to the adjusted estimations, the efficacy of TCZ, in reducing ICU admission and ICU mortality rate, has been reported, particularly during the planned combination therapy with either SOC or simple O2 therapy, 3) Regarding the TCZ effect in patients who received vasopressor support, it, at least in part, led to a shortened duration of treatment.
4 & 5) Combination therapy with corticosteroids, IVIG, and some non-pharmacological interventions (e.g., O2 therapy) augmented the recovery time, particularly in favor of the survival rate of ill patients, and 6) Data is lacking to prove the effectiveness of TCZ in patients with recurrent SARS-CoV-2 infection upon receiving the COVID-19 vaccine, which is recommended to be addressed in future research. Overall, it is greatly recommended to consider some co-founding factors, including race, ethnic differences, etc., for study design in possible epidemic/pandemic conditions in the future. Also, it is worth noting that personalized medicine based on the treatment algorithm provided in Figure 4 could be considered in the clinician's decision-making policy.

9. Declarations

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9.2. Conflict of interest

The authors of this manuscript declared that they have no conflict of interest.

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This manuscript did not receive any grant for this study.

9.4. Authors' contribution

The authors confirm their contribution to the paper as follows: AR, contributed to writing the first draft and depicted the figures; FM, performed the Search Strategy; AM, Revised the manuscript; STT, performed the Search Strategy, AA, contributed to writing the first draft and advising; HS, Supervised and contributed to the study conception and design. All authors read and approved the final version of the manuscript.

9.5. Data availability

All Authors declared that data from the study are available and will be provided if anyone needs them.

9.6. Using artificial intelligence chatbots

For preparing this manuscript artificial intelligence (AI) has not been applied either in the search process or drafting.

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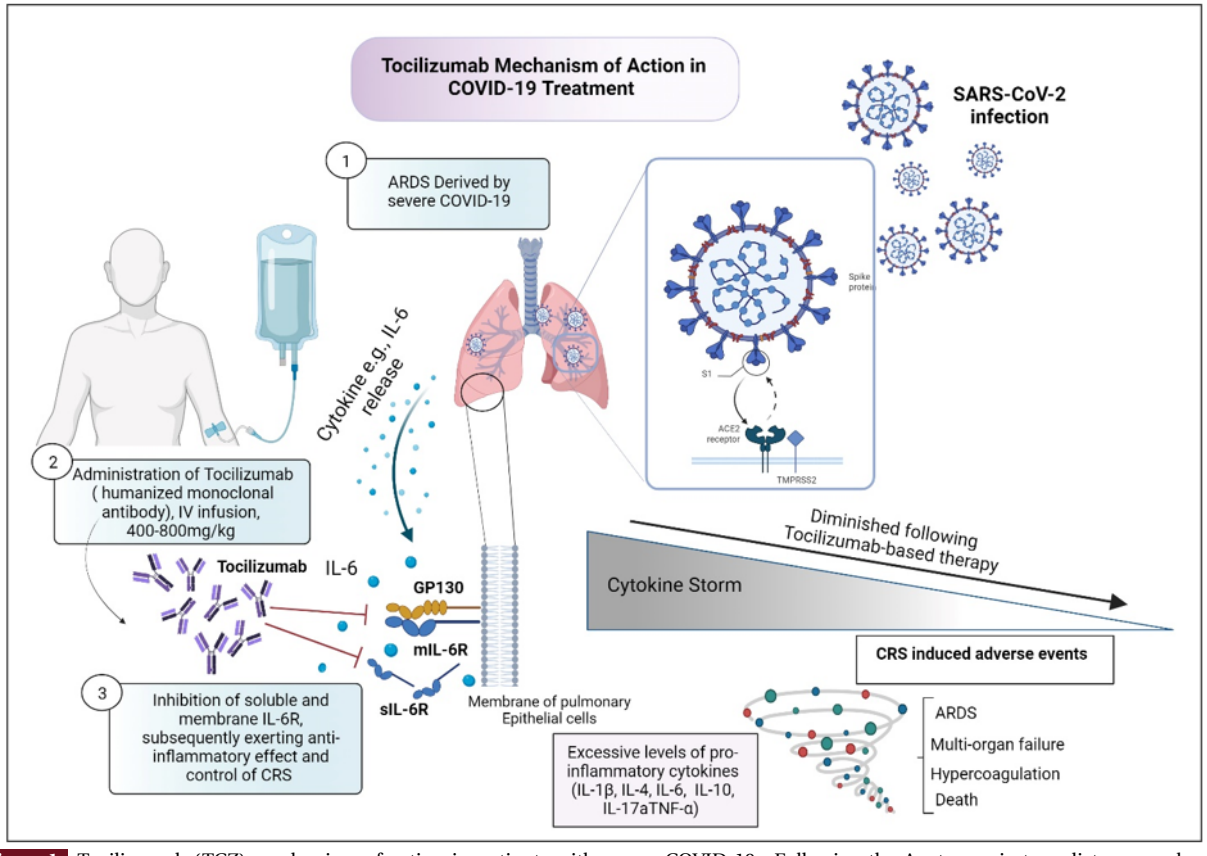

Figure 1: Tocilizumab (TCZ) mechanism of action in patients with severe COVID-19. Following the Acute respiratory distress syndrome (ARDS) induced by SARS-CoV-2, the robust release of pro-inflammatory cytokines, named cytokine storm, can occur, which subsequently worsens the patients' clinical symptoms. During the inflammatory phase, IV infusion of the anti-IL6 agent, TCZ, by blocking IL-6 both soluble (sIL-6) and membrane (mIL-6) receptors, can remarkably alleviate cytokine release syndrome (CRS)-related adverse events. The figure was created with BioRender.com.

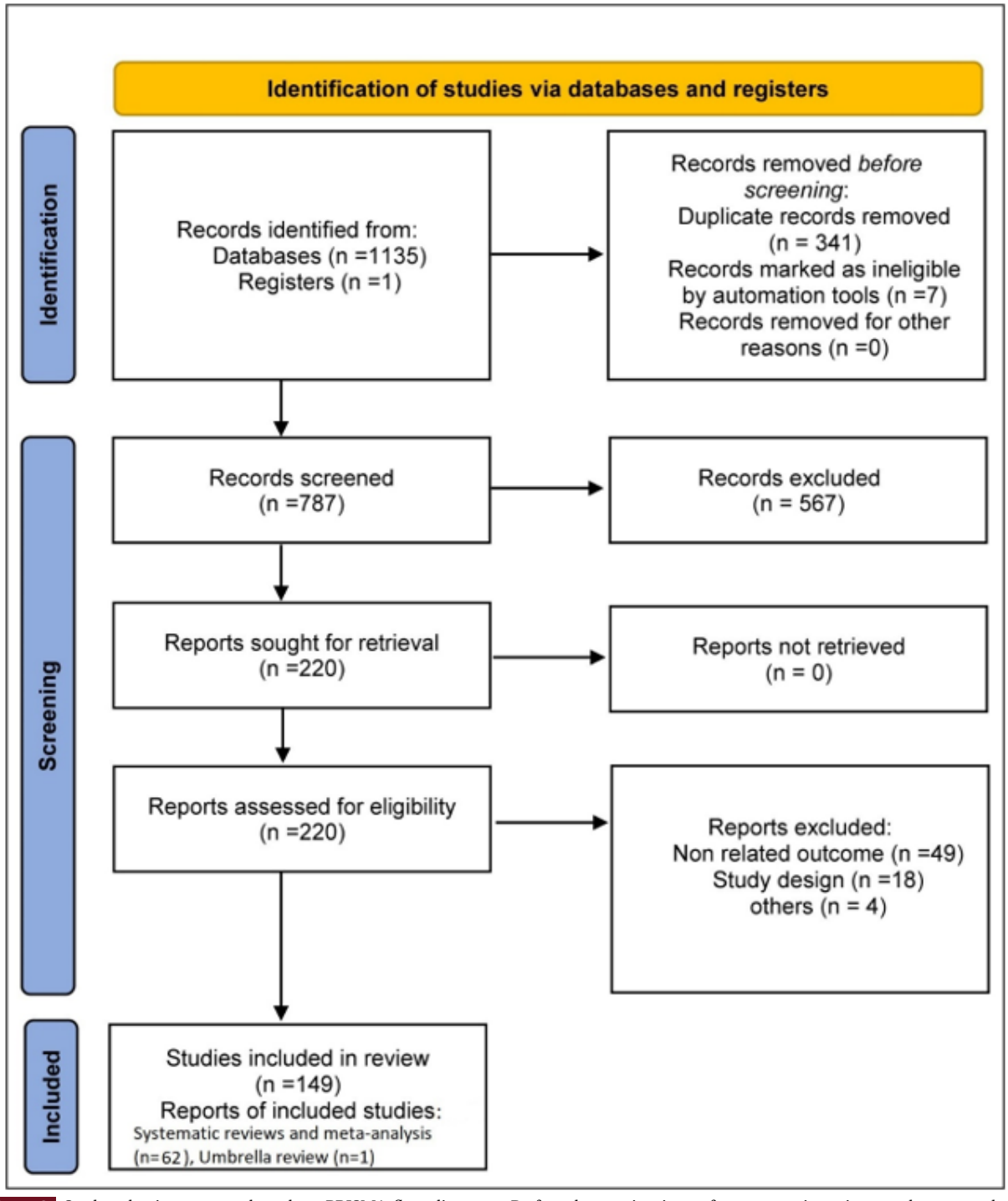

Figure 2: Study selection process based on PRISMA flow diagram. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) and the review criteria details are described in the Methods section.

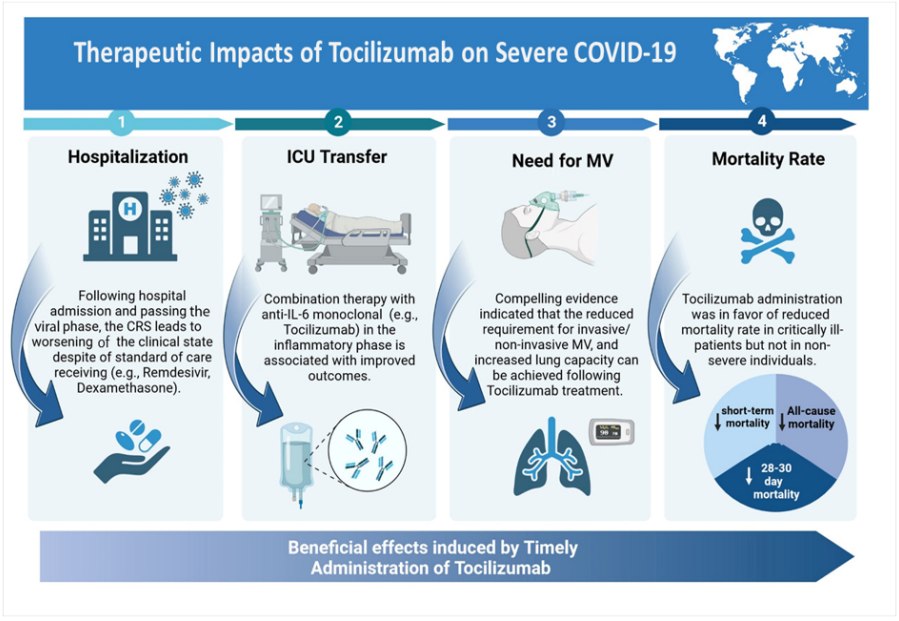

Figure 3: The Clinical improvement following Tocilizumab (TCZ) therapy in patients with severe COVID-19. The figure was created with BioRender.com. CRS: cytokine release syndrome; ICU: intensive care unit; MV: mechanical ventilation.

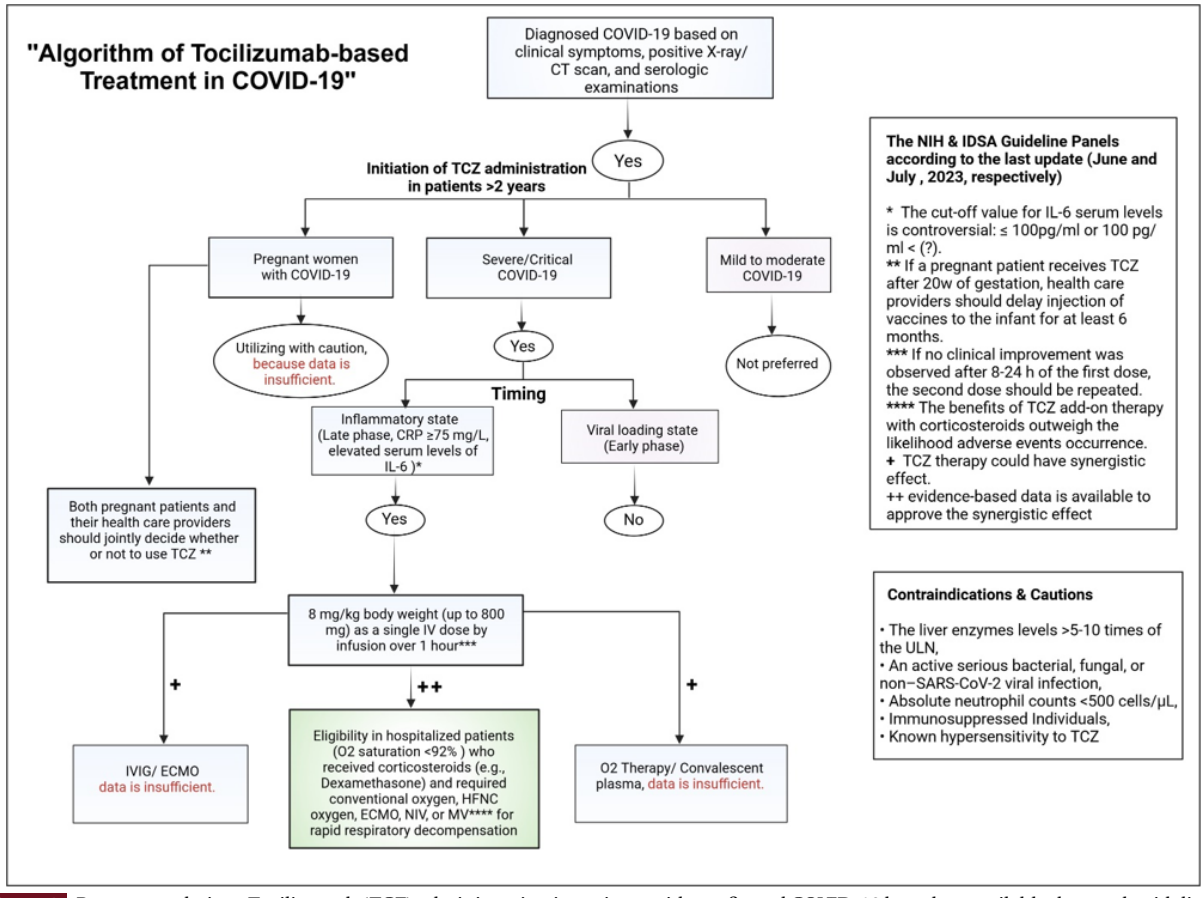

Figure 4: Recommendations Tocilizumab (TCZ) administration in patients with confirmed COVID-19 based on available data and guidelines. Created with BioRender.com. Abbreviations: CT: computed tomography; CRP: C-reactive Protein; ECMO: Extracorporeal Membrane Oxygenation; IVIG: Intravenous immunoglobulin; HFNC oxygen: high-flow nasal cannula oxygen; IDSA: The Infectious Diseases Society of America; IV: Intravenous; MV: Mechanical Ventilation; NIH: National Institutes of Health; NIV: Non-Invasive Ventilation; TCZ: Tocilizumab; ULN: upper limit normal. The figure was created with BioRender.com.

Table 1: Extracted Data from the included studies

Study	Type of review	Study size	Risk of bias Assessment tool	Models of meta-analysis	COVID-19 Severity Scale	TCZ dose/ Route of administration/ treatment in early or late phase
Rezaei Tolzali et al., 2022 (51)	Umbrella	Unable to report	A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist	Dersimonian and Laird random-effects method, binary outcomes = RRs and aHRs, continuous outcomes= WMDs	Not mentioned.	Not mentioned.
Jiang et al ., 2021 (50)	Meta-analysis	Case: 6568 Control: 11,660	Not assessed	Dersimonian and Laird method data in the random-effects model and used the Mantel-Haenszel method in the fixed-effects model	Severe-Critical	IV, TCZ, at a dose of 8 mg/kg body weight (up to 800 mg), up to twice, 12 h apart, 400mg, 400-800 mg
Belletti et al., 2021 (67)	Meta-analysis	15 multi-center RCTs were included (9,320 patients)	Cochrane risk-of-bias tool	Fixed-effects TSA	Moderate to Severe	IV, TCZ, at a dose of 8 mg/kg body weight (up to 800 mg), up to twice, 12 h apart,200mg, 400-800 mg, 6 mg/kg
Domingo et al., 2021 (79)	Meta-analysis	Total 27 trials = 10 930 patients for three IL6 antagonists, 19 trials for TCZ:	Rob 2	Fixed-effects meta-analysis	Not mentioned.	Low: 4 mg/kg or high: >4 mg/kg
Avni et al., 2021 (31)	Living SR and meta-analysis	Eight RCTs = 6481 patients	Cochrane risk-of-bias tool	Fixed-effect model (Mantel–Haenszel method)	Severe non-critical (moderate to severe)	IV, 8mg/kg within 24h of organ support, the second dose allowed after 12-24h
Alkofide et al., 2021 (92)	Meta-analysis	Seventeen studies	Rob 2	Dersimonian and Laird random-effects models	Severe form	Methylprednisolone: 250 mg IV pulse or 0.5-1 mg/Kg daily for five days. TCZ: IV 8 mg/kg as the dose, SC in one study
Yousef et al., 2020 (94)	SR	56 publications (n = 646 patients)	Not applicable	Not assessed.	Severe	Not mentioned.
Grygiel-Górniak et al., 2021 (93)	Review	Not assessed	Not applicable	Not applicable	Severe patients	8 mg/kg up to 400 mg 28 60-minute single I.V. infusion
Zhang et al., 2021 (104)	Meta-analysis	Eleven studies with 6579 patients were included in our meta-analysis, of which 3406 and 3173 were assigned to TCZ and control groups.	Cochrane risk-of-bias tool	Random-effects model	Not mentioned	The doses varied from 400 mg- 800 mg and were administered I.V. for more than 1 hour. The maximum dose was 800mg/d
Moosazadeh et al., 2021 (87)	Meta-analysis	Five studies (n= 460 patients)	Not assessed	Random-effect model	Not mentioned	Not mentioned

Table 1: Extracted Data from the included studies (continue)

Study	Type of review	Study size	Risk of bias Assessment tool	Models of meta-analysis	COVID-19 Severity Scale	TCZ dose/ Route of administration/ treatment in early or late phase
Mutua et al., 2022 (105)	Meta-analysis	RCTs= 3,358 participants	Cochrane risk-of-bias tool	Random-effects model using the Dersimonian and Laird method	Progression to severe disease (evaluated in non-severe and severe)	One RCT: single dose; 8 RCTs allowed a second dose if needed
Selvarajan et al., 2021 (41)	Network meta-analysis	11 RCTs were multicenter studies: 6579 patients	Revised Cochrane Risk of Bias tool for randomized trials (Rob)	Random-effects model	Not mentioned	400 to 800 mg/d in the included studies and the optimal effective dose of TCZ remains uncertain.
Piscoya et al., 2022 (32)	Meta-analysis	Nine Randomized controlled trials (RCTs, n=7,021) and nine IPTW cohorts (n=7796)	Rob 2 and ROBINS-I	Inverse variance random-effects meta-analyses using GRADE methodology	Moderate to severe	Nine RCTs used TCZ doses: of 8 mg/kg and five of them used a second dose; follow-up times ranged between 14 and 28 days. The IPTW cohort studies had reported a wider variety of dosing ranging from 4–8 mg/kg or some using a total daily dose of 400-800 mg.

aHRs: adjusted Hazard Ratios; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation; ICU: Intensive Care Unit; IPTW: Inverse Probability Treatment Weighting; IV: Intravenous; RCT: Randomized Clinical Trials; RRs: Risk Ratios; Rob 2: Risk of Bias tool–version 2; SC: Subcutaneous; TCZ: Tocilizumab; TSA: Trial Sequential Analysis; WMDs: Weighted Mean Differences; SR: systematic review; ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions.

Supplementary table 1: The methodological quality of included studies using JBI appraisal tools (https://jbi.global/critical-appraisal-tools)

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Quality*
Alkofide, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Yes	Good
Avni, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Unclear	Yes	Good
Belletti, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Domingo, 2021	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Grygiel-Górniak, 2021	A narrative review											
Jiang, 2021	Yes	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Medium
Moosazadeh, 2021	Yes	Yes	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Medium
Mutua, 2022	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Piscoya, 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Selvarajan, 2021	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Shaikh Yousef, 2021	Yes	Yes	Unclear	Yes	No	No	Yes	N/A	N/A	Yes	Yes	Low
Zhang, 2022	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

*Overall quality: > 80% = good; 60 – 80% = medium; 50 – 60% = low.
Q1. Is the review question clearly and explicitly stated?
Q2. Were the inclusion criteria appropriate for the review question?
Q3. Was the search strategy appropriate?
Q4. Were the sources and resources used to search for studies adequate?
Q5. Were the criteria for appraising studies appropriate?
Q6. Was critical appraisal conducted by two or more reviewers independently?
Q7. Were there methods to minimize errors in data extraction?
Q8. Were the methods used to combine studies appropriate?
Q9. Was the likelihood of publication bias assessed?
Q10. Were recommendations for policy and/or practice supported by the reported data?
Q11. Were the specific directives for new research appropriate?
N/A: not applicable.

Table 2: The Clinical outcomes of various systematic reviews regarding the TCZ treatment in COVID-19

Author	All-cause mortality in-hospital mortality (short-term, 14-day, 28-day mortality	MV (Invasive, non-invasive, free-days)	Hospital discharge	ICU transfer	Secondary infection/ Neutropenia	Combination Therapy with TCZ	Outcomes
Rezaei Tolzali et al., 2022 (51)	TCZ administration resulted in substantially lower odds of death when compared to the control group (RR= 0.78; 95%CI: 0.71–0.85, I^2 = 40.8%). TCZ treatment significantly decreased the risk of mortality by 48%	Eight retrospective studies and seven RCTs (n=5792 patients) had a significantly lower risk of requiring MV (RR= 0.77; 95%CI: 0.64–0.92, I^2 = 44.9%), increased the number of ventilator-free days, (WMD: 3.38; 95%, CI: 0.51–6.25, I^2 = 75.8%). In subgroup analysis: RCTs, but not retrospective studies	In eleven retrospective cohorts and four RCTs (n=7159), a significantly higher rate of hospital discharge was observed (RR= 1.12; 95%CI:1.03–1.22, I^2 = 64.1%, Subgroup analysis: in retrospective cohort studies showed improved hospital discharge.	Three retrospective studies, one prospective cohort, and four RCTs (n= 1052 patients) revealed that TCZ has no potential to reduce the overall risk of ICU admission (RR= 0.85; 95%CI: 0.65–1.11, I^2 = 57.7%).	No elevated risk of secondary infection (RR= 1.00; 95%CI: 0.80 –1.26, I^2 = 77.1%)	Not assessed	TCZ reduced the risk of intubation, mortality, and the length of hospital stay, without increasing the risk of superimposed infections. Therefore, TCZ can be considered an effective therapeutic agent for treating patients with COVID-19.
Jiang et al., 2021 (50)	TCZ significantly decreased mortality (OR= 0.81, 95% CI: 0.69–0.95, P = 0.008).	No significant associations were observed between TCZ and mechanical ventilation.	No significant associations were observed between TCZ and hospital discharge.	Not assessed	No significant associations were observed between TCZ and elevated secondary infection risk.	Not assessed	TCZ significantly decreased mortality with no increased discharge, secondary infection risk, adverse events, and mechanical ventilation in a meta-analysis.
Belletti et al., 2021 (67)	TCZ reduced all-cause mortality at the longest follow-up (1315/5,380 [24.4%] in the IL-6 inhibitors group, RR=0.90; 95% CI: 0.84 to 0.96; p for effect=0.003, I^2=0%, TCZ and Sarilumb 28/30-day mortality with a significant improvement (1193/4,967 [24%] [RR=0.92; 95% CI: 0.85 to 0.99; p=0.03, I^2=0%)]	A significant reduction in the need for intubation (171/1933 [8.8%] versus 180/1649 [10.9%]; RR=0.73; 95% CI: 0.60 to 0.88; p=0.001; I^2=0%	Not assessed	Not assessed	Not assessed	Not assessed	TCZ administration may be beneficial in COVID-19 pneumonia, by reducing the risk of death and the risk of intubation without increasing the risk of secondary infections and adverse events.
Domingo et al., 2021 (79)	The summary OR TCZ/ Sarilumab+ Corticosteroid treatment= 0.78, TCZ/Sarilumab alone= 1.09	0.77 (95% CI: 0.70- 0.85; P < .001) for all IL-6 antagonists, 0.74 (95% CI: 0.66-0.82) for TCZ, and 1.00(95% CI: 0.74-1.35) for sarilumab	Not assessed	Not assessed	The ORs were 0.95 (95% CI: 0.77-1.16) for TCZ and 1.03 (95% CI: 0.80-1.32) for sarilumab	Corticosteroids	The 28-day all-cause mortality was lower among patients who received IL-6 antagonists.

Table 2: The Clinical outcomes of various systematic reviews regarding the TCZ treatment in COVID-19 (continue)

Author	All-cause mortality in-hospital mortality (short-term, 14-day, 28-day mortality	MV (Invasive, non-invasive, free-days)	Hospital discharge	ICU transfer	Secondary infection/ Neutropenia	Combination Therapy with TCZ	Outcomes
Avni et al., 2021 (31)	Reduction of 28–30-day all-cause mortality (RR = 0.89, 95% CI: 0.82–0.96), but not in subgroup analysis of critically ill patients (RR = 0.94, 95% CI: 0.74–1.19) Death or MV at 14/28 days reduction with TCZ, RR= 0.83, 95% CI: 0.74–0.90, I^2=0%.	TCZ significantly reduced risk for MV (RR= 0.79, 95% CI: 0.68–0.91, I^2= 0%)	Not assessed	TCZ Significantly reduced risk for ICU admission (RR= 0.68, 95% CI: 0.50–0.92, I^2=6%)	TCZ significantly reduced the risk of superinfections (RR= 8.70, 95% CI: 2.34–32.39).	No mortality benefit with TCZ was demonstrated in studies that used steroids for >80% of patients.	TCZ reduces 28-30-day all-cause mortality, ICU admission, superinfections, and MV, as well as the combined endpoint of death or MV. Among critically ill patients, and when steroids were used for most patients, no mortality benefit was demonstrated.
Alkofide et al., 2021 (92)	The adjusted Mortality rates were also lower in the combination arm (RR= 0.58, 95% CI: 0.42 – 0.81; I^2=71%).	Not assessed	Not assessed	Not assessed	No change in risk of superinfection RR was 1.11, 95% CI (0.81 – 1.53), I^2 was 0%, (p = 0.84)	Adjusted mortality rates were lower in combination with corticosteroids (RR=0.58, 95% CI: 0.42 – 0.81; I^2=71%).	TCZ and SCT compared to SOC had lower mortality rates.
Yousef et al., 2020 (94)	Not assessed	Not assessed	A combination treatment of TCZ +IVIG had a mean length of stay in hospital of 7 ± 3 days and 95.5% (n =21/22)	Not assessed	Not assessed	IVIG	A combination treatment of TCZ and IVIG improved the outcome in COVID-19 patients with pediatric inflammatory multisystem syndrome
Grygiel-Górniak et al., 2021 (93)	Mortality rate reduced.	TCZ decreased the likelihood of invasive mechanical ventilation.	Not assessed	Not assessed	Not assessed	Not assessed	TCZ minimizes the duration of vasopressor support
Zhang et al., 2022 (104)	Tocilizumab significantly reduced the 28 to 30-day mortality (relative risk [RR]= 0.89,95% CI 0.80-0.99, P=.04).	Incidence of MV was significantly reduced (RR = 0.79, 95% CI 0.71-0.89, P<001).	TCZ significantly reduced time-to-hospital discharge (hazard ratio=1.30, 95%CI: 1.16-1.45, P<.001).	TCZ significantly reduced ICU admission (RR=0.64, 95% CI 0.47-0.88, P=.006).	TCZ significantly reduced serious infection (RR=0.61, 95% CI: 0.40-0.94, P=.02).	Not assessed	Pregnant patients with COVID-19 who received TCZ were often critically ill and corticosteroid use was uncommon. There is little data on TCZ exposure in the second and third trimesters when transplacental transport is the highest.

Table 2: The Clinical outcomes of various systematic reviews regarding the TCZ treatment in COVID-19 (continue)

Author	All-cause mortality in-hospital mortality (short-term, 14-day, 28-day mortality	MV (Invasive, non-invasive, free-days)	Hospital discharge	ICU transfer	Secondary infection/ Neutropenia	Combination Therapy with TCZ	Outcomes
Moosazadeh et al., 2021 (87)	The risk of death for COVID-19 patients treated with the combination of corticosteroids and TCZ was 0.74 (95% CI: 0.36–1.50).	Not assessed	Not assessed	Not assessed	Not assessed	Corticosteroids	The risk of death in COVID-19 patients who were treated with corticosteroids and TCZ was lower than in the TCZ alone (26%) and control groups (52%).
Mutua et al., 2022 (105)	The overall mortality rate was lower in the TCZ group, but the difference was not statistically significant ([OR], 0.87; 95% CI: 0.73-1.04; I^2, 15%).	In the treatment group with TCZ, patients were 26% less likely to progress to MV (OR, 0.74; 95% CI 0.64-0.86; I^2, 0%).	Not assessed	The TCZ group had a 34 % lower rate of ICU admission (OR= 0.66; 95% CI: 0.40-2.14; I^2, 29%)	Over 43% lower risk of severe infection (OR, 0.57; 95% CI: 0.36-0.89; I^2, 21%)	Not assessed	TCZ is well tolerated. This drug does not exhibit significant benefits on survival but may have a role in preventing progression to ICU admission and MV.
Selvarajan et al., 2021 (41)	TCZ significantly reduced the 28 to 30-day mortality (relative risk [RR]=0.89, 95% CI: 0.80-0.99, P=.04).	TCZ significantly decreased the incidence of MV (RR = 0.79, 95% CI: 0.71-0.89, P<.001)	TCZ significantly reduced time-to-hospital discharge (HR=1.30, 95% CI 1.16-1.45, P<.001)	TCZ significantly reduced ICU admission (RR=0.64, 95% CI: 0.47-0.88, P=.006).	TCZ significantly reduced secondary infection (RR=0.61, 95% CI: 0.40-0.94, P=.02).	Not assessed	TCZ reduced short-term mortality, incidence of MV, composite outcome of death or MV, intensive care unit admission, serious infection, serious adverse events, and time-to-hospital discharge in hospitalized COVID-19 patients.
Piscoya et al., 2022 (32)	TCZ reduced all-cause mortality in RCTs (RR= 0.89, 95%CI: 0.81–0.98, p = 0.03) but not cohorts.	TCZ significantly reduced the need for MV (RR= 0.80, 95% CI: 0.71–0.90, p =0.001).	TCZ significantly decreased the length of stay in the hospital (MD:1.92 days, 95%CI: 3.46 to -0.38, p =0.01).	Not assessed	A higher risk of neutropenia and abnormal liver function with TCZ was reported.	Not assessed	TCZ has a potential therapeutic role in hospitalized COVID-19 patients and non-significantly increased clinical improvement. No differences in the risk of adverse events such as bacteremia or infection were observed.

CI: Confidence Interval; ICU: Intensive Care Unit; IVIG: Intravenous immunoglobulin; MV: Mechanical Ventilation, RCT: Randomized Clinical Trial; RR: Risk Ratio; SCT: Systemic Corticosteroid Therapy; SOC: Standard of care; TCZ: Tocilizumab; OR: odds ratio; WMD: weighted mean difference; MD: mean difference.