



Original Article

Safety and efficacy of tocilizumab in COVID-19: A systematic evaluation of adverse effects and therapeutic outcomes



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ABSTRACT

Background: While COVID-19 has transitioned from a pandemic to an endemic state, the management of its persistent complications continues to present substantial clinical challenges. Tocilizumab, an interleukin-6 receptor antagonist endorsed by the World Health Organization (WHO) for severe COVID-19 management, remains a critical therapeutic intervention. This systematic evaluation provides a comprehensive assessment of tocilizumab's safety and efficacy profile to inform clinical decision-making.

Methods: The study involved exhaustive search across multiple databases (PubMed, SCOPUS, WoS, BIOSIS) utilizing MeSH terms and Boolean operators to identify relevant studies. Methodological worthiness was rigorously evaluated utilizing the Risk of Bias 2 (RoB 2) tool. The statistical analysis of the findings incorporated one-way ANOVA, Mann-Whitney U tests, and Pearson's correlation coefficient (r) with 95% confidence intervals to quantify adverse effects and therapeutic outcomes.

Results: The analysis of nine studies encompassing diverse demographic populations (ages ≥ 2 years, both sexes) established a clear safety profile for tocilizumab. The treatment demonstrated a statistically important association ($P < 0.05$) with mild adverse effects (nausea, diarrhea, headache, fatigue; $r = 0.62$, 95% CI = 0.59–0.71) and moderate adverse effects (tremors, urinary difficulties, mood changes; $r = 0.54$, 95% CI = 0.47–0.60). More concerning were the severe adverse effects, including hepatobiliary dysfunction and hypersensitivity reactions ($r = 0.36$, 95% CI = 0.32–0.41), with rare but critical instances of acute liver failure ($r = 0.18$, 95% CI = 0.15–0.22). Notably, despite this safety profile, tocilizumab exhibited significant therapeutic efficacy ($P < 0.01$) in ameliorating COVID-19 symptoms, particularly in cases complicated by cytokine storm syndrome.

Conclusion: This study confirms tocilizumab's position as a valuable therapeutic agent for COVID-19 complications while highlighting the necessity for judicious patient selection and vigilant monitoring due to its potential for significant adverse effects. The findings underscore the importance of pre-treatment screening, adherence to contraindications, and ongoing pharmacovigilance to optimize risk-benefit ratios.

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Abbreviations: COVID-19, Coronavirus disease 2019; RoB, Risk of bias; CI, Confidence interval; ANOVA, Analysis of variance; Mabs, Monoclonal antibodies; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; FDA, Food and Drug Administration; MeSH, Medical subject headings; IBM, International Business Machine Corporation

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Introduction

Monoclonal antibodies (MAbs), due to their high specificity, have attained an important role in the medical field. In biomedical research, MAbs are used not only for identification but also for treating and preventing diseases. In the living system, B-cells produce MAbs in reaction to infectivity [1]. With advancements in technology, several methods such as hybridoma, phage display, and transgenic mice have been developed, leading to the production of large quantities of MAbs [2]. Currently, > 600 MAbs have been permitted for various clinical conditions, including the treatment of cancer, immune disorders, and infectious diseases [3].

MAbs are known for their high precision of action and lengthier half-life. New molecular techniques have advanced their specificity, minimized immunogenic reactions, and enhanced the risk/benefit ratio [4]. These advantages have contributed to a higher endorsement rate ($\approx 20\%$) for MAbs in comparison to other therapeutic agents [5].

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is accountable for coronavirus disease 2019 (COVID-19). Many regions of the world continue to suffer from COVID-19 as the disease spreads and infects the population [6]. While many individuals experience mild symptoms, in some cases, it can result into fatalities. COVID-19 has produced the loss of many precious lives across almost all countries and contributed to a severe economic slowdown. Nearly every region of the world has witnessed outbreaks, and new cases continue to be reported [7]. Although several restrictions that were imposed during the peak of COVID-19 have been relaxed, people still avoid large gatherings and show apprehensions at the incidences of any outbreak of viral infections, including the seasonal flu [7,8].

Numerous therapeutic interventions have been tested to control the spread of the infection. However, to date, no specific agent has been found that guarantees safe and effective control of COVID-19 [9]. MAbs, due to their specificity, have been tested against COVID-19. MAbs such as casirivimab, imdevimab, bamlanivimab, etesevimab, sotrovimab, and tocilizumab have got emergency use authorization for COVID-19 infected patients. These MAbs target the proteins of SARS-CoV-2 that help the virus bind to human cells [10]. Additionally, some of them also reduce the action of cytokines, thereby minimizing the inflammatory reactions considered to be responsible for COVID-19 complications [11]. Among these, the U.S. Food and Drug Administration (FDA) has approved tocilizumab on 24th June 2021 for treating patients diagnosed with COVID-19 [12].

Tocilizumab has received FDA emergency use authorization for the treatment of hospitalized adult and paediatric (above 2 years) COVID-19 patients [13]. The mechanism of action of tocilizumab involves binding to interleukin-6 receptors, inhibiting pro-inflammatory responses in a variety of cells, including lymphocytes, monocytes, fibroblasts, and B-cells [14]. However, the administration of the drug has been associated with several adverse effects, such as headaches, diarrhea, insomnia, elevated alanine transaminase levels, and hypersensitivities [15]. Like other MAbs, tocilizumab is contraindicated in pregnancy, in infants, and in severely ill or comorbid patients [16].

As COVID-19 has been found to produce complications in particular groups of patients, such as those with comorbidities, there are concerns about the use of MAbs, including tocilizumab [17]. In the dearth of a safe and efficient therapy, coupled with the ongoing spread of COVID-19, fear among the public about how to manage the disease has increased [18]. Conducting comprehensive research on the safety and efficacy of approved medications such as tocilizumab could provide valuable data that addresses these concerns among both the public and healthcare providers [19]. Some previous studies have provided an overview of the adverse reactions commonly observed in clinical settings [14,15]. However, a comprehensive

analysis of each adverse effect, scientifically categorized as mild, moderate, severe, or lethal, has not been thoroughly explored in the literature. Furthermore, the precise efficacy of tocilizumab at different time intervals when administered to COVID-19 patients remains inadequately documented. Therefore, the present study focuses on categorizing the incidences of common adverse effects and analysing the role of tocilizumab in terms of safety and efficacy in the management of COVID-19. The study analysed scientific reports and articles on tocilizumab published in the literature between 2021 and 2024.

Methodology

According to the updated list of drugs approved by the FDA, tocilizumab has been authorized on 24th June 2021, for managing complications in clinical conditions diagnosed with COVID-19. The recommended dose is 12 mg/kg for humans weighing less than 30 kg, and 8 mg/kg for patients above 30 kg [20]. The safety analysis of the medicine was conducted following procedures described in the literature [20–23].

The workflow and brief summary of the study are represented in Fig. 1. The analysis of the data might aid in identifying the common incidences of adverse effects of a monoclonal antibody, besides establishing its efficacy in COVID-19.

Literature search strategy

The exploration strategy combined Medical Subject Headings (MeSH) and free-text terms, using Boolean operators to optimize both the sensitivity and specificity of the search. The Boolean operator "AND" was used to link key concepts, ensuring that the studies retrieved contained relevant information. Electronic scientific literature searches of PubMed, SCOPUS, Web of Science, and BIOSIS were conducted from January 2021 to August 2024, utilizing keywords such as "COVID-19 drugs OR Coronavirus monoclonal antibodies OR Tocilizumab AND Safety OR Side effects AND Efficacy AND Clinical Tests OR Human Trials AND Approved."

Eligibility criteria

Studies that met the below-mentioned criteria were incorporated in this review:

- Articles published in English containing comprehensive information about COVID-19 drugs and the number of volunteers with their permission.
- Studies such as cross-sectional, cohort, and case-control available between 2021 and 2024.
- Studies that used human volunteers for COVID-19 monoclonal antibody evaluation.
- Studies determining the safety of COVID-19 monoclonal antibodies, including dosage, interval, adverse reactions, and an understandable procedure for recording unexpected events.
- Peer-reviewed and indexed journals with good impact factors were accessed, providing clear statistical information along with their significance.

Researches that did not meet these criteria were barred. Furthermore, research with overlapping datasets, replicated reports, or records that could not be retrieved were also omitted [23].

Study selection

The authors autonomously searched the literature for tocilizumab. The eligibility selection was conducted in two steps: the 1st step involved screening titles and abstracts of the extracted data,

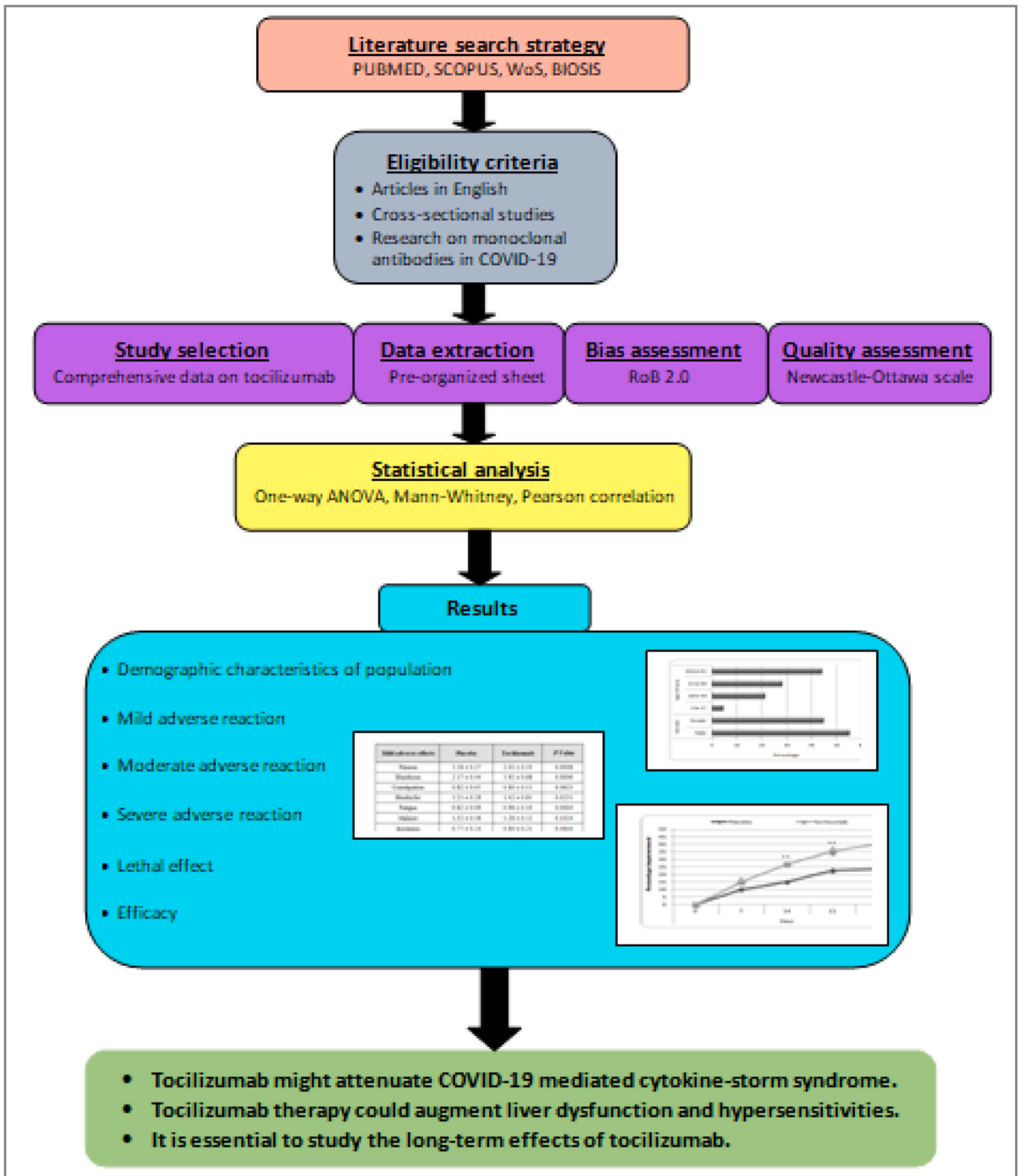


Fig. 1. A schematic representation of the workflow, including the analysis and key highlights of the study.

while the 2nd step involved screening the full-text research articles of the abstracts retrieved in the 1st step. Any discrepancies in the findings were resolved through discussions with the supervisor and/or subject experts.

Data extraction protocol

The authors used a customized data retrieval format to separately collect information. The collected information contained key

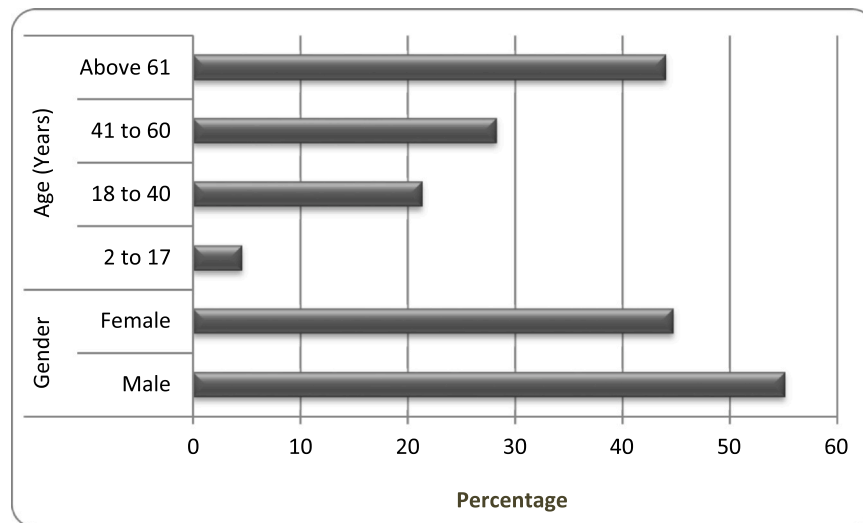


Fig. 2. Demographic characteristics of the participants in the systematic analysis to assess the safety and efficacy of tocilizumab.

features of the study plan, a description of the study population, and study findings. Key information considered essential for evaluating the content included the English language, study place, number of participants, study intent, study procedure, dosage, treatment interval, route of treatment, ethical endorsement, statistical tests, and biochemical measurements [21]. The most observed adverse effects of tocilizumab were categorized as mild, moderate, severe, and lethal. The efficacy of tocilizumab was evaluated based on the improvement of COVID-19 symptoms over various time durations.

Bias assessment

Bias in this systematic study was assessed using the Revised Cochrane Risk-of-Bias tool for randomized trials (RoB 2.0) [24]. This tool provides a structured evaluation of bias across multiple domains, ensuring a thorough analysis of the hazard of bias in the included literature.

Quality assessment

The Newcastle-Ottawa Scale tool was used to assess the risk of bias in cross-sectional settings [25]. The tool includes several domains, with important ones being the sampling plan, description of statistical methods, and findings. The authors blindly analyzed the eminence of the included literature, and any discrepancies were resolved through dialogue with the administrator/subject specialist.

Ethical considerations

This work aimed to systematically represent data from several online resources in a methodical mode for community benefit and to encourage more investigation in the rising area of microbe-mediated illness. The data collection process adhered to established policies and trials described in the literature [26]. Data from non-private domains, including certified websites and available scientific literature, were cautiously retrieved. Efforts were made to ensure the privacy of persons, groups, and institutions. The study extracted publicly available information that is not private, reusable, or re-allocated, with no limitations on its use. No restricted, private, or secluded data was utilized. Additionally, details that were contentious, partial, lacked ethical authorization, or employed improper statistical methodologies were barred. All information used in data extraction was appropriately quoted in the manuscript. Measures were taken to reduce bias and faults, including blinding the findings,

etiquette, and employing the Newcastle-Ottawa tool. Established statistical tests frequently employed in the studies were applied to additionally reduce the likelihood of errors in data interpretation.

Statistics

An Excel spreadsheet was used to record data from the retrieved articles. Incidents of different adverse effects were represented as mean \pm standard deviation. Statistical analysis was conducted using IBM SPSS 21.0 software. The findings were analyzed, and the statistical implication of the results among groups was assessed using One-way ANOVA, followed by a non-parametric post-hoc test [22,23]. The non-parametric methods utilized in the work were the Mann-Whitney *U* test for variables and Pearson's correlation coefficient for the study population after tocilizumab treatments. A preset confidence interval (95%) was applied when assessing the data. The findings were considered significant if the *P* value was < 0.05 .

Results

The literature search in this study identified over 800 articles, but only 9 articles were included for the current study based on the pre-determined inclusion characteristics. These articles scored more than 3 on the Newcastle-Ottawa Scale.

The demographic distinctiveness of the participants are shown in Fig. 2. The study comprised 55.2% male and 44.8% female subjects. In terms of age distribution, the largest group of participants was aged above 61 years (44.1%), followed by those aged 41–60 years (28.3%), 18–40 years (21.4%), and 2–17 years (4.6%).

The analysis of the incidences of mild adverse effects showed that after the administration of tocilizumab, a marked raise was found in nausea ($P < 0.001$), diarrhea ($P < 0.001$), headache ($P < 0.05$), and fatigue ($P < 0.001$) in comparison to the placebo. The proportion increase in these effects was found to be 70.3% for nausea, 66.8% for diarrhea, 17.3% for headache, and 17.1% for fatigue (Table 1).

Table 2 shows the incidences of moderate adverse effects observed after the administration of tocilizumab. The analysis of the data indicated that tocilizumab significantly ($P < 0.05$) increased tremors, difficulty in urination, mood changes, and rashes compared to the placebo. Tocilizumab was found to enhance these effects by 5.9% for tremors, 5% for difficulty in urination, 10.9% for mood changes, and 10.2% for rashes compared to the placebo.

Table 1

Incidences of mild adverse effects observed in systemic analysis following tocilizumab administration.

Mild adverse effects	Placebo	Tocilizumab	P-Value
Nausea	1.18 ± 0.27	2.01 ± 0.33	0.0008
Diarrhea	2.17 ± 0.44	3.92 ± 0.68	0.0006
Constipation	0.82 ± 0.05	0.80 ± 0.11	0.0623
Headache	1.21 ± 0.28	1.42 ± 0.81	0.0231
Fatigue	0.82 ± 0.09	0.96 ± 0.10	0.0004
Malaise	1.32 ± 0.38	1.28 ± 0.52	0.1024
Insomnia	0.77 ± 0.24	0.80 ± 0.21	0.0844

Values are represented as mean ± SD. **Statistics:** One-way ANOVA followed by Mann-Whitney *U* test. **P* < 0.05 compared with placebo. Total number of COVID-19 patients = 24,388 [Placebo = 11,870 and Tocilizumab = 12,518].

Table 2

Incidences of moderate adverse effects observed in systemic analysis following tocilizumab administration.

Moderate adverse effects	Placebo	Tocilizumab	P-Value
Tremors	0.51 ± 0.06	0.54 ± 0.08	0.0082
Visual disturbances	0.40 ± 0.02	0.39 ± 0.09	0.0552
Difficulty in urination	0.38 ± 0.05	0.42 ± 0.07	0.0349
Mood changes	0.55 ± 0.08	0.61 ± 0.04	0.0295
Change in blood pressure	0.34 ± 0.04	0.35 ± 0.06	0.0848
Change in blood glucose	0.68 ± 0.08	0.70 ± 0.09	0.0741
Rashes	0.82 ± 0.14	0.91 ± 0.27	0.0410

Values are indicated as mean ± SD. **Statistics:** One-way ANOVA followed by Mann-Whitney *U* test. **P* < 0.05 when compared with placebo. Total number of COVID-19 patients = 24,388 [Placebo = 11,870 and Tocilizumab = 12,518].

The occurrences of severe adverse effects after tocilizumab administration are summarized in Table 3. The values indicated that tocilizumab marked (*P* < 0.05) enhanced liver dysfunction and severe allergic reactions, with percentage increases of 22.1% and 8.2%, respectively. However, the treatment did not significantly alter heart rhythm, birth defects, acute kidney injury, seizures, or blood dyscrasias compared to the placebo.

The analysis of the incidences of important lethal adverse effects indicated that the administration of tocilizumab significantly (*P* < 0.05) increased liver dysfunction (7.7%) in comparison to the placebo. However, the administration did not significantly affect other lethal effects. Furthermore, the data showed that tocilizumab significantly (*P* < 0.05) diminished the death rate in clinical conditions compared to the placebo. The percentage reduction in the mortality rate was found to be 7.5% (Table 4).

The Pearson correlation analysis for the incidences of adverse effects is shown in Table 5. The highest correlation coefficient for the placebo was found for severe adverse effects (*r* = 0.19, 95% CI = 0.16 / 0.23), while the lowest was observed for moderate adverse effects (*r* = 0.09, 95% CI = 0.08 / 0.11). In contrast, the highest correlation coefficient for tocilizumab was recorded for mild adverse effects (*r* = 0.62, 95% CI = 0.59 / 0.71), and the lowest was observed for lethal effects (*r* = 0.18, 95% CI = 0.15 / 0.22).

Table 3

Incidences of severe adverse effects observed in systemic analysis following tocilizumab administration.

Severe adverse effects	Placebo	Tocilizumab	P-Value
Liver dysfunction	0.90 ± 0.25	1.10 ± 0.36	0.0024
Abnormal heart rhythm	0.51 ± 0.08	0.52 ± 0.04	0.0653
Severe allergic reactions	0.73 ± 0.05	0.79 ± 0.09	0.0265
Birth defects	0.08 ± 0.01	0.08 ± 0.03	0.0646
Acute kidney injury	0.29 ± 0.03	0.30 ± 0.05	0.1364
Seizures	0.11 ± 0.04	0.12 ± 0.08	0.0714
Blood dyscrasias	0.30 ± 0.09	0.35 ± 0.04	0.0582

Values are indicated as mean ± SD. **Statistics:** One-way ANOVA followed by Mann-Whitney *U* test. **P* < 0.05 when compared with placebo. Total number of COVID-19 patients = 24,388 [Placebo = 11,870 and Tocilizumab = 12,518].

Table 4

Incidences of lethal adverse effects observed in systemic analysis following tocilizumab administration.

Lethal adverse effects	Placebo	Tocilizumab	P-Value
Liver failure	0.26 ± 0.03	0.28 ± 0.09	0.0178
Haemorrhage	0.19 ± 0.02	0.18 ± 0.06	0.0826
Renal failure	0.10 ± 0.04	0.09 ± 0.05	0.0907
Cardiovascular collapse	0.15 ± 0.01	0.14 ± 0.08	0.0681
Brain damage	0.08 ± 0.01	0.08 ± 0.02	0.0731
Respiratory failure	0.12 ± 0.04	0.13 ± 0.07	0.1128
Mortality	0.43 ± 0.09	0.40 ± 0.06	0.0394

Values are represented as mean ± SD. **Statistics:** One-way ANOVA followed by Mann-Whitney *U* test. **P* < 0.05 compared with placebo. Total number of COVID-19 patients = 24,388 [Placebo = 11,870 and Tocilizumab = 12,518].

The proportion improvement (efficacy) in the symptoms of COVID-19 after the administration of tocilizumab is shown in Fig. 3. Efficacy was evaluated at different time intervals following tocilizumab treatment. Result analysis showed that tocilizumab treatment marked (*P* < 0.001) reduced symptoms at the 7, 14, 21, and 28-day intervals.

Discussion

The current study systematically determined the safety and efficacy of tocilizumab, a monoclonal antibody approved for managing COVID-19 complications. As the global healthcare community grapples with the long-term after-effects of the widespread epidemic, understanding the therapeutic potential and limitations of treatments like tocilizumab is critical.

Safety profile of tocilizumab

Mild adverse effects

The analysis revealed that tocilizumab is associated with a range of adverse effects, beginning with mild symptoms such as nausea, diarrhea, headache, and fatigue. These effects were significantly (*P* < 0.001) more frequent in the tocilizumab group compared to placebo. While these conditions are usually transient and self-limiting, they can impact a patient's worthiness of life and adherence to medications. The occurrence of these mild adverse effects is consistent with the known side effect profile of monoclonal antibodies and other immunomodulatory therapies [16,27]. For instance, nausea and fatigue are commonly reported in patients receiving biologic therapies, likely due to the systemic effects of immune modulation [27].

The transient nature of these symptoms suggests that they may not require additional medical intervention in most cases. However, patient education and supportive care are essential to manage these effects effectively. For example, antiemetics can be prescribed for nausea, while adequate hydration and rest can alleviate fatigue. These values are supported by prior studies that emphasize the importance of symptom management in improving patient outcomes during monoclonal antibody therapy [16].

Moderate adverse effects

Moderate adverse effects, including tremors, mood changes, difficulty in urination, and rashes, were also significantly (*P* < 0.05) higher in the tocilizumab group. Tremors, which may result from the drug's interference with neuromuscular activity, are a known side effect of monoclonal antibodies that target inflammatory pathways [28]. Difficulty in urination, on the other hand, could stem from reduced renal blood flow or neurogenic defects in the urinary system, both of which have been linked to systemic inflammation and immune modulation [28].

Mood changes, such as anxiety or depression, are likely linked to disturbances in biogenic amines in the brain, particularly serotonin

Table 5
Pearson correlation analysis between incidences of adverse effects and treatment protocols.

Adverse effects	Placebo		Tocilizumab		P-Value
	Correlation coefficient (r)	95 % CI (Lower and upper)	Correlation coefficient (r)	95 % CI (Lower and upper)	
Mild	0.12	0.09–0.15	0.62	0.59–0.71	0.0003
Moderate	0.09	0.08–0.11	0.54	0.47–0.60	0.0009
Severe	0.19	0.16–0.23	0.36	0.32–0.41	0.0004
Lethal	0.16	0.12–0.19	0.18	0.15–0.22	0.0215

Statistics: One-way ANOVA and Pearson correlation analysis. P-values compared with placebo.

and dopamine, which can be influenced by systemic inflammation and cytokine modulation [29]. Rashes, often indicative of hypersensitivity reactions, are a common immunological response to protein-based therapies like monoclonal antibodies [30]. These moderate adverse effects may necessitate adjustments in therapy, such as dose reduction or discontinuation, as well as specific treatments like antihistamines for rashes or antidepressants for mood changes. In some cases, short-term hospitalization may be required to manage severe symptoms [31].

The occurrence of these effects underscores the importance of close monitoring and patient stratification. For instance, patients with a history of neurological or psychiatric disorders may require additional precautions when prescribed tocilizumab. Similarly, those with pre-existing renal or urinary conditions should be closely monitored for signs of urinary dysfunction. These findings align with previous reports that highlight the need for personalized treatment plans when using monoclonal antibodies [31].

Severe adverse effects

Severe adverse effects, such as liver dysfunction and severe allergic reactions, were significantly ($P < 0.05$) more frequent with tocilizumab. Elevated alanine transaminase (ALT) levels, indicative of liver damage, have been previously reported with tocilizumab use and are a known risk of monoclonal antibody therapies [32]. The mechanism underlying this hepatotoxicity is not fully understood but may involve immune-mediated liver injury or direct toxicity from drug metabolites [32].

Hypersensitivity reactions, though rare, are a significant concern with monoclonal antibodies due to their protein-based nature, which can trigger immune responses in susceptible individuals [33].

These reactions can range from mild rashes to life-threatening anaphylaxis, necessitating immediate medical intervention. The occurrence of severe adverse effects highlights the importance of pre-treatment screening, including liver function tests and hypersensitivity assessments, as recommended in clinical guidelines [15,30].

Furthermore, tocilizumab is contraindicated in patients with a history of liver disease or severe allergic reactions, emphasizing the need for careful patient selection [35]. In cases where tocilizumab is deemed necessary, regular monitoring of hepatic function and prompt management of hypersensitivity reactions are essential to minimize risks. These findings are consistent with previous studies that advocate for a cautious approach when using monoclonal antibodies in high-risk populations [34].

Lethal adverse effects

Lethal adverse effects, particularly liver failure, were significantly ($P < 0.05$) associated with tocilizumab. Hepatotoxicity is a well-documented complication of monoclonal antibody therapies, often exacerbated in seriously ill or comorbid clinical conditions, as seen in severe COVID-19 cases [36]. The risk of liver failure underscores the importance of regular monitoring of hepatic function and the need for alternative therapies in patients with pre-existing liver conditions [15,32].

Despite these risks, tocilizumab significantly ($P < 0.05$) reduced mortality rates compared to placebo, likely due to its ability to attenuate cytokine storms and associated complications [37]. This dual nature of tocilizumab—offering significant therapeutic benefits while posing serious risks—highlights the need for a balanced approach to its use. Clinicians must evaluate the potential advantages against the unwanted hazards, specifically in high-risk populations,

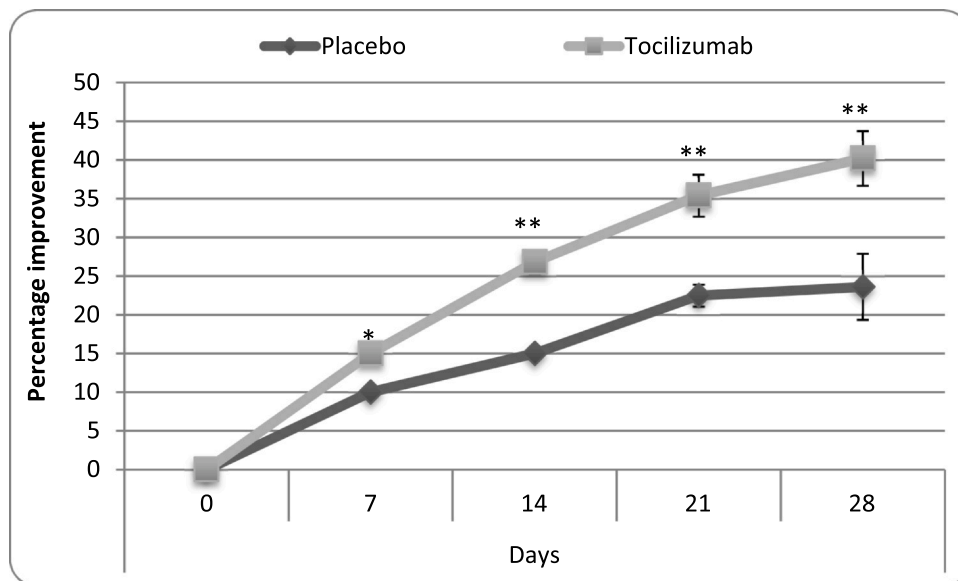


Fig. 3. Systemic analysis of the percentage improvement (efficacy) in COVID-19 symptoms following treatment with tocilizumab. Values are indicated as mean \pm SD. **Statistics:** One way ANOVA followed by Mann-Whitney U test. * $P < 0.05$, ** $P < 0.001$ in comparison with placebo. Total number of COVID-19 patients = 24,388 [Placebo = 11,870 and Tocilizumab = 12,518].

and ensure that patients are closely monitored throughout the treatment course.

Efficacy of tocilizumab

The efficacy analysis demonstrated that tocilizumab significantly ($P < 0.01$) improved COVID-19 symptoms over a 28-day treatment period. Symptom improvement began as early as day 7, with a 40% reduction in severity by day 28. This aligns with the drug's mechanism of action, which involves inhibiting interleukin-6 (IL-6) receptors, thereby reducing the cytokine-mediated inflammatory cascade that drives severe COVID-19 complications [37].

Clinical Relevance: The ability of tocilizumab to mitigate cytokine storms is particularly significant in real-world practice, as these hyperinflammatory responses are a chief contributor to morbidity and mortality in severe COVID-19. By modulating the immune response, tocilizumab not only accelerates symptom relief but also reduces the risk of critical complications such as acute respiratory distress syndrome (ARDS) and multi-organ failure [37]. These findings underscore its role as a *time-sensitive intervention* for moderate to severe COVID-19, especially in high-risk patients with elevated inflammatory markers (e.g., elevated CRP or IL-6 levels) or early signs of clinical deterioration.

Therapeutic Implications: While the drug's efficacy is clear in this cohort, clinicians should consider individual patient factors, such as disease stage, comorbidities, and vaccination status, when initiating therapy. Further research is needed to refine protocols for specific subpopulations (e.g., immunocompromised patients) and emerging variants.

Correlation between tocilizumab and adverse effects

Correlation analysis revealed a moderate association between tocilizumab therapy and mild ($r = 0.62$, 95% CI = 0.59–0.71) and moderate ($r = 0.54$, 95% CI = 0.47–0.60) adverse effects. Severe adverse effects suggested a mild association ($r = 0.36$, 95% CI = 0.32–0.41), while lethal effects had a weak correlation ($r = 0.18$, 95% CI = 0.15–0.22) [38]. These findings highlight the need for vigilant monitoring, particularly in patients with predisposing factors for severe adverse effects.

The correlation between tocilizumab and adverse effects underscores the importance of patient stratification and personalized treatment plans. For instance, subjects with pre-existing liver disease or a history of hypersensitivity reactions should be carefully evaluated before initiating tocilizumab therapy. Similarly, those with neurological or psychiatric conditions may require additional precautions to manage mood changes or tremors. These findings align with previous studies that emphasize the need for a tailored approach to monoclonal antibody therapy [31].

Future implications and limitations

While our findings support tocilizumab as a therapeutic option for moderate to severe COVID-19, this study has limitations that warrant acknowledgment. First, the analysis grouped all COVID-19 patients without stratification by disease stage, severity, or organ systems involved—factors that may influence treatment response and adverse effects. Future studies should prioritize subgroup analyses to refine patient selection and optimize outcomes. Second, our cohort lacked representation from specific high-risk populations, such as pregnant individuals, lactating women, infants, and patients with multiple comorbidities, limiting generalizability to these groups. Third, the long-term safety profile of tocilizumab—including risks of chronic adverse effects or interactions in vaccinated individuals—remains underexplored and merits longitudinal investigation. Additionally, the evolving landscape of SARS-CoV-2 variants poses a dynamic challenge; the drug's efficacy may vary with emerging subtypes, necessitating ongoing pharmacovigilance

and adaptive clinical trials. Addressing these gaps will be critical to guiding evidence-based use of tocilizumab in a rapidly changing pandemic context.

Conclusion

In conclusion, tocilizumab represents a valuable therapeutic option for managing COVID-19 complications, particularly in patients at risk of cytokine storm syndrome. However, its association with mild to severe adverse effects, including liver dysfunction and hypersensitivity reactions, necessitates careful patient selection and monitoring. Pre-treatment screening, adherence to contraindications, and regular updates on its safety and efficacy are essential to optimize its use. Future research should focus on evaluating tocilizumab in underrepresented populations and exploring its long-term effects to establish a comprehensive safety and efficacy profile.

Ethical Approval

The study obtained ethical approval from AlMaarefa University's Institutional Review Board (Riyadh, Saudi Arabia) for conducting scientific analysis on data sourced from electronic resources.

CRediT authorship contribution statement

Conceptualization, O.A, A.H.A and S.I.R; Data curation, S.M.B.A and R.G; Methodology, A.K, M.I and T.D; Project administration, S.I.R and S.M.B.A; Supervision, S.I. R; Writing – original draft, O.A, A.H.A, R.G, A.K., M.I, T.D; Writing –review & editing, S.I.R, S.M.B.A; Funding support, M.I, T.D, O.A. All authors have read and agreed to the published version of the manuscript.

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Declaration of Competing Interest

None declared.

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