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META-ANALYSIS

Adverse events associated with monoclonal antibodies used for treatment of COVID-19: A systematic review and meta-analysis

Htet Htet | Han You Kyung | Ismail Abdul Sattar Burud | Heethal Jaiprakash | Thiruselvi Subramaniam | Igor Iezhitsa | Renu Agarwal

School of Medicine, IMU University, Kuala Lumpur, Malaysia

Correspondence
Htet Htet, School of Medicine, IMU University, Malaysia.
Email: hhnoel@gmail.com

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Aims: This review aimed to synthesise the evidence related to the incidence of serious and non-serious adverse events with the use of monoclonal antibodies (mAbs) among COVID-19 patients.

Methods: Databases were searched from January 2020 to September 2023 for randomized clinical trials (RCTs) that used mAbs for the treatment of COVID-19 regardless of disease severity. Study screening, data extraction and data analysis were performed independently by two reviewers. The Cochrane risk of bias 1.0 tool was used for methodological quality assessment.

Results: Sixteen studies were identified for analysis with 9682 participants in the intervention arm and 10 115 participants in the control arm. Seven trials reported hepatoxicity and there was a statistically significant increase in the chance of hepatoxicity among patients treated with mAbs compared to those given standard of care (SoC) or placebo with risk ratio (RR) = 1.70, 95% confidence interval (CI) 1.29–2.24. Five trials reported for neutropenia and there was a statistically significant association of neutropenia with the use of mAbs compared to SoC or placebo with RR = 4.03, 95% CI 1.74–9.34. Ten trials reported any disease-related serious adverse events related to the disease and there was a reduction of risk compared to SoC/placebo, although this reduction was not statistically significant (RR = 0.88, 95% CI 0.70–1.11).

Conclusions: The use of mAbs was found to be associated with an increased risk of hepatoxicity and neutropenia compared to SoC/placebo among COVID-19 patients with moderate certainty of evidence. Long-term observational studies are recommended to observe post-COVID adverse events related to the use of mAbs.

KEYWORDS
adverse events, COVID-19, hepatoxicity, meta-analysis, monoclonal antibodies, neutropenia, tocilizumab

1 | INTRODUCTION

The emergence of SARS-CoV-2 in December 2019 marked the beginning of a global health crisis, with the first fatal case reported on 11 January 2020.[1] By 25 February 2024, this unprecedented worldwide spread of COVID-19 had resulted in more than 774 million cases and 7.03 million fatalities.[2] The World Health Organization (WHO) provides up-to-date clinical practice recommendations for COVID-19 treatment, continually assessing new evidence from the international community and first responders.[3,4]

COVID-19 treatment guidelines include antiviral agents, mAbs, **Janus Kinase (JAK)** inhibitors and **corticosteroids**, and the treatment regimens differ depending on the severity. Convalescent plasma and **hydroxychloroquine** were no longer recommended for the treatment of COVID-19 based on the evidence observed. Adjoining efforts to repurpose existing medications, significant attention has been directed towards developing innovative therapeutic strategies. Among these, mAbs emerged as a particularly promising avenue for the treatment of COVID-19. Recommended mAbs included **casirivimab/imdevimab**, **sotrovimab**, **tocilizumab** (TCZ), **bamlanivimab** and **sarilumab**. Casirivimab/imdevimab act on the two distinct receptor binding sites of **SARS-CoV-2 spike glycoprotein**, and subsequently prevent the virus from infecting host cells.[5] These drugs received first approval in Japan in July 2021 for the treatment of COVID-19 infection.[5] The most reported adverse drug event of sotrovimab was immediate injection-site reactions after subcutaneous injection, while other adverse drug events included nausea, rash, dizziness and chills.[5]

The early clinical course of COVID-19 was mainly due to viral replication and later phases were mainly due to dysregulated immune system and its inflammatory responses. Hence, the treatment of early COVID-19 was focused mainly on inhibition of viral replication and the later phases usually employed immunosuppressive, anti-inflammatory and anti-thrombotic drugs. According to the latest guidelines, there is no role for monoclonal antibodies in non-hospitalized adults with mild to moderate COVID-19 infection who do not require oxygen therapy.[6] However, hospitalized patients who require oxygen therapy, who are receiving **dexamethasone** therapy, who are experiencing rapidly increasing oxygen requirements, who have signs and symptoms of systematic inflammation, who require heated humidified high-flow therapy (HFNC) oxygen therapy, non-invasive ventilation (NIV), mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO) are recommended to use intravenous TCZ or per-oral (PO) **baricitinib**. If baricitinib or TCZ is not available or feasible to use, PO **tofacitinib** can be used instead of PO baricitinib, and intravenous (IV) sarilumab can be used instead of IV TCZ.[6]

Sotrovimab is a recombinant human mAb which is designed to target SARS-CoV-2 in the early stages of COVID-19 progression.[7,8] Initially approved for emergency use in the United States in May 2021, sotrovimab has since been authorized in several other countries. The commonly reported adverse reactions include hypersensitivity, infusion-related reactions and diarrhoea. [8] TCZ and sarilumab are both **interleukin-6 (IL-6) receptor** blockers with immunomodulatory effects that may be particularly significant in patients with COVID-19 who have inflammatory and dysregulated immune systems.[7] The United States Food and Drug Administration (FDA) granted approval for IL-6 blockers in June 2021 for the treatment of COVID-19 infection.[9] The typical adverse drug reactions (ADRs) on long-term usage were increased liver enzymes, neutropenia, injection-site reaction and upper respiratory tract infections.[10]

The adverse drug reactions of a medication which occurred during, before and after treatment should be considered when prescribing a medication.[10,11] A key factor in treatment success is understanding the adverse effects and drug–drug interactions of the medications prescribed. Several studies have reviewed the side effects of COVID-19 treatments, including vitamin D, **zinc**, **remdesivir**, hydroxychloroquine and **chloroquine**, **azithromycin**, **amantadine**, **aspirin**, and many others. Some of these treatments, however, were outdated and were no longer recommended.[11,12] A narrative study published by Chiu et al. summarized the safety profile of drugs used for the treatment of COVID-19 based on 30 case reports, three case series and ten randomized trials.[13] The mechanisms of action varied among the different mAbs : some target the COVID-19 spike protein (e.g., casirivimab and imdevimab combination, **regdanvimab**, sotrovimab, **tixagevimab** and **cilgavimab**), and some drugs act by modulating the immune system as recombinant humanized anti-**IL-6** receptor monoclonal antibodies.[6] The majority of these drugs obtained approval as Emergency Use Authorization (EUA) and their adverse effects have not been investigated at the time these agents obtained approval. Additionally, some mAbs have had their EUA approval revoked, and their long-term adverse effects have never been looked into.

Since the use of mAbs in severely ill COVID-19 patients has always been a part of the clinical practice guidelines in different regions, it is important to analyse the relevant findings in the current literature to understand the possible adverse drug events associated with their use. However, the reporting of the serious and non-serious adverse events of the WHO-recommended treatment regimens for COVID-19 infections on a long-term basis remains lacking in the literature, except for meta-analyses largely focusing on individual treatment regimens. Several systematic reviews and meta-analyses have been done to evaluate the use of TCZ in COVID-19 patients.[14–17] However, a systematic review has not been performed on the safety profile exclusively of monoclonal antibodies. Hence, the current systematic review and meta-analysis aimed to synthesise the evidence related to the incidence of serious and non-serious adverse events with the use of mAbs among COVID-19 patients.

2 | METHODS

This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist 2020 (Supplementary Table S6).[18] The protocol for this study has been registered with Prospero under the registration number CRD42023447055 and with INPLASY under the registration number INPLASY202380026.[19,20]

2.1 | Search strategy

Four databases – PubMed, OVID Medline, the Cochrane Library (CENTRAL), WHO Global literature on Coronavirus Disease – along with the clinical trial registries were searched from January 2020 to September 2023 to identify studies meeting the inclusion criteria. Search strings were constructed using the appropriate Boolean operators (AND, OR) and Medical Subject Headings (MeSH). The title/abstract field function was also used for search terms. Additionally, the reference lists of included studies were also searched for relevant or missing studies. The full search strategy for the Cochrane CENTRAL library is provided in Supplementary Table S7. Study selection and data extraction were carried out independently by two authors using the COVIDENCE web-based software.[21] All details are available upon request.

2.2 | Inclusion criteria

Randomized controlled trials (RCTs), which measured and reported the adverse effects or adverse events related to the use of mAbs among COVID-19 patients, were included. The PICOs criteria for inclusion were as follows:

- Participants (P): Patients with polymerase chain reaction (PCR)-approved COVID-19 infection, regardless of any age, gender and disease severity.
- Intervention (I): Any intervention that included mAbs (TCZ, sarilumab, imdevimab, casirivimab, sotrovimab and bamlanivimab) regardless of the dosage regimen.
- Control/comparator (C): Alternative WHO-approved treatment regimens or standard of care (SoC), usual care (UC) or placebo.
- Outcomes (O): The proportion of people with one or more serious adverse events and the proportion of people with one or more non-serious adverse events including organ-specific adverse events (hepatoxicity, renal toxicity), haematological reactions (neutropenia), treatment-related reactions (infusion reactions).
- Study (S): RCTs.

2.3 | Exclusion criteria

We excluded observational studies, case reports, non-randomized controlled trials, trials including patients who were not confirmed as COVID-19 positive, those that did not use mAbs as interventions, studies that did not report the adverse outcomes, ongoing studies and studies not published in English.

2.4 | Study selection

Two investigators (H.K., H.H.) independently screened the titles and abstracts of items discovered from the database search and retrieved the full text of all potentially relevant articles. If studies had duplicated publications, the maximum amount of data was extracted from the available publications. Furthermore, we conducted a manual search through the reference list of included studies and the reviews. Subsequently, the same two investigators independently assessed the full-text articles for eligibility based on the inclusion criteria. Any discrepancy was resolved with the third investigator (I.B.).

2.5 | Definition of serious and non-serious adverse events

The proportion of individuals experiencing serious adverse events was determined based on the International Conference on Harmonization (ICH) guidelines for serious adverse events. According to the ICH guidelines, serious adverse events include any event leading to death; is life-threatening; requires hospitalization or prolongation of existing hospitalization; results in persistent or significant disability; congenital birth or anomaly; and any important medical event which may have jeopardized the patient or requires intervention to prevent it. All other adverse events were categorized as non-serious.[22]

2.6 | Data extraction

Data extraction was performed using the COVIDENCE systematic review web-based software. Two investigators extracted information including the authors' names, publication year, study country, study design, population characteristics, name of the interventions, dosage regimen, any reported adverse effects, gender, age and funding sources. Data was extracted independently by H.K. and H.J. and any discrepancies were reviewed by the third investigator (R.A.). Quality of life was not reported in all RCTs, probably due to the nature of the COVID-19 pandemic and disease severity.

2.7 | Methodological quality assessment

The Cochrane Risk of Bias 1.0 tool was used to critically assess all eligible studies, with H.K. and T.S. conducting the assessment independently. Four primary criteria were assessed: randomization, allocation concealment, blinding of participants and personnel and blinding of outcome assessors. The third reviewer (I.I.) resolved any discrepancies among the two assessors.

2.8 | Data analysis

Studies were grouped based on their reported outcomes as follows: (i) incidence of hepatoxicity; (ii) incidence of renal toxicity; (iii) incidence of neutropenia; (iv) incidence of infusion reactions; and (v) incidence of any serious adverse events. Adverse events were categorized based on the severity (serious or non-serious), based on the

organ system (e.g., hepatoxicity or renal toxicity), or grading (grade 1 – mild, asymptomatic) or grade 5 (death related to AE). Data extraction was performed independently by two investigators (H.K. and H.H.) using COVIDENCE and Microsoft Excel. Any discrepancies were resolved by the third investigator (R.A.). For dichotomous outcomes, risk ratio with 95% confidence interval (CI) was used as an effect measure for data analysis. Data preparation for synthesis was done using Microsoft Excel after extracting data in COVIDENCE. Some data related to hepatoxicity were reported as hepatoxicity in some studies and increased liver enzymes in a few studies. Those data were combined for data analysis after discussion and agreement within the study team. Subgroup analysis was carried out based on the different mAbs reported. Random effect models were used for pooled effect estimates in instances of high heterogeneity, while fixed-effect models were employed for pooled effect estimates when low heterogeneity was observed. I^2 values greater than 50% were taken as high heterogeneity. The Mantel–Haenszel approach was used, and funnel plot asymmetry was assessed using Egger's test. Data analysis was done using the Review Manager web version.[23] A significance level of $P < 0.05$ was considered statistically significant. Certainty of evidence was analysed using GRADEpro GDT (Guideline Development Tool) web-based application.[24]

2.9 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/2024.[25–28]

3 | RESULTS

3.1 | Study selection

Database search yielded 5377 articles, of which 516 were selected for full-text review. The study search result was illustrated using the PRISMA flow chart (Figure 1). An additional 25 studies were identified from hand searching. The final number of studies that met the inclusion criteria and that were eligible for inclusion was 16, all of which were selected for data extraction.[29–44]

3.2 | Characteristics of included studies

Overall, this analysis included 16 studies with a total of 19 797 participants with 9682 in the treatment arm and 10 115 participants in the control arm. The mAbs administered to the treatment arm subjects included tocilizumab (eleven studies),[29–31,33–39,44] imdevimab and casirivimab (two studies),[40,43] sarilumab (one study)[32] sotrovimab (one study)[42] and bamlanivimab (one study).[41] TCZ was the most frequently used mAb among the included studies. Standard of care (SoC) or usual care (UC) were allowed in the majority of the studies in both arms (Supplementary Table S8). Four studies were conducted as multi-country clinical trials,[32,34,42,43] one was conducted in Italy,[36] three in the USA,[29,35,41] three in the UK,[31,33,40] and one study each was conducted in Brazil,[38] China,[39] France,[30] Greece[44] and India.[37] The majority of the included studies were open labelled ($n = 10$)[30,31,33,36–41,44] and the remainder were double-blind studies ($n = 6$).[29,32,34,35,42,43] Most participants were severe pneumonia, serious and critical, and moderate to severe pneumonia patients. The characteristics of these studies are summarized in Table 1 and Supplement Table S8.

3.3 | Methodological quality assessment

Overall, majority of the included studies demonstrated a low risk of bias in terms of randomization. However, due to the unique nature of the pandemic, severity of the disease, and route of administration of mAbs, allocation concealment, blinding of participants and personnel and blinding of outcome assessors were often classified as unknown or at high risk of bias in most studies (Figure 2 and Supplementary Figure S1).

3.4 | Reported adverse effects related to mAbs

3.4.1 | Incidence of hepatoxicity (increased liver transaminases)

Among the included studies, seven RCTs with a total of 1715 participants reported the incidence of hepatoxic events, characterized by an increase in liver transaminases (up to three times of normal value).[29,32,34,36,38,39,44] The analysis of pooled data indicated that there was a statistically significant increase in the incidence of hepatoxicity in the treatment arm compared to the control arm (RR = 1.70, 95% CI 1.29–2.24) (Figure 3). A fixed-effect model was used due to low heterogeneity ($I^2 = 0\%$, $P = 0.85$). However, the asymmetrical funnel plot suggested a high chance of publication bias (Supplementary Figure S2).

3.4.2 | Incidence of renal toxicity

Among the included studies, two RCTs with a total 381 participants reported the incidence of renal toxicity events.[30,44] The analysis of pooled data showed that there was no statistically significant increase in incidence of renal toxicity due to administration of mAbs among COVID-19 patients (RR = 1.03, 95% CI 0.2–5.18) (Figure 4). A fixed-effect model was applied due to low heterogeneity ($I^2 = 0\%$, $P = 0.44$). One study compared TCZ *vs.* SoC, and the other study compared TCZ *vs.* baricitinib, a JAK inhibitor.[30,44] Hence, a significant difference among the two subgroups was observed. Publication bias was not assessed due to the low number of included studies.

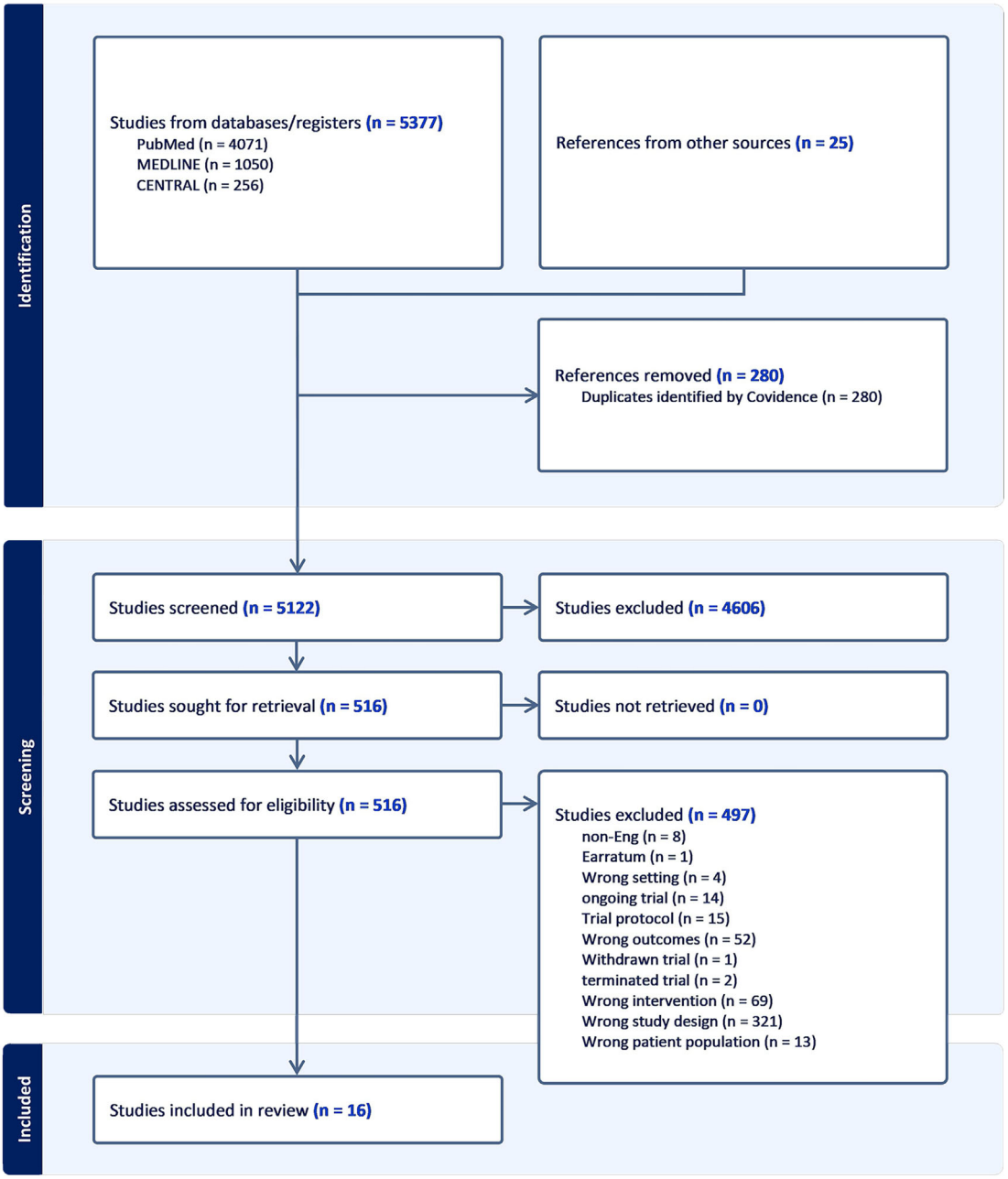

FIGURE 1 Study selection process.

3.4.3 | Incidence of neutropenia

There was a total of five RCTs with 1357 participants that reported the incidence of neutropenia.[29,32,34,36,38] The analysis of pooled data showed that there was a statistically significant increase in the incidence of neutropenia among the COVID-19 patients treated with mAbs compared to those that received SoC/placebo (RR = 4.03, 95% CI 1.74–9.34). A fixed-effect model was used due to low heterogeneity ($I^2 = 0\%$, $P = 0.49$). Subgroup analysis indicated that tocilizumab increases the risk of neutropenia significantly (RR = 5.99, 95% CI 2.06–17.43) compared to SoC/placebo, while sarilumab showed no significant risk of neutropenia compared to SoC/placebo (RR = 1.15, 95% CI 0.25–5.26) (Figure 5). The asymmetrical funnel plot suggested a higher likelihood of publication bias (Supplementary Figure S3).

3.4.4 | Incidence of infusion reactions

Four RCTs with a total of 3024 participants reported infusion reactions.[29,41–43] The analysis of pooled data showed that there was an increased chance of infusion reaction due to administration of mAbs

TABLE 1 Characteristics of included studies.

No	Study name	Study country	Study duration	Ethnic	Blinding (DB/SB/OL)	Patient population and disease severity *n* (%)	Total patients (*n*)	Patients in groups (intervention/control)	Age years ± SD/range	Male *n* (%)	Follow up period (day)	Funding
1	Stone 2020[29]	Boston, US	April 20, 2020–June 15, 2020	American Indian or Alaska Native/ Asian/Black/ Native Hawaiian or Pacific Islander/ White/ Other/ unknown	DB	Hyperinflammatory states	242	161 81	61.6 (46.4–69.7) 56.5 (44.7–67.8)	96 (60) 45 (55)	Time-to-event analyses	Genentech
2	Hermine 2021[30]	France	March 31, 2020–April 18, 2020	Not stated	OL	Moderate, severe, or critical pneumonia	131	63 67	64 (57.1–74.3) 63.3 (57.1–72.3)	44/63 (70) 44/67 (66)	28 days	Ministry of Health,
3	Gordon 2021[31]	UK	March 9, 2020–November 19, 2020	White/ Asian/Black/ Mixed and Other	OL	Critically ill COVID-19 patients (severe category)	895	353 48 402 (3 arms)	61.4 ± 12.7	629 (73)	21 days	Multiple international funders (including Roche and Sanofi)
4	Lescure 2021[32]	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain	March 28, 2020–July 3, 2020	Asian/Black/ White/ Other/ Hispanic or Latino	DB	Severe or critical	416	159 173 84	58.0 (51.0–67.0) 58.0 (48.0–67.0) 60.0 (53.0–69.5)	108 (68) 99 (57) 54 (64)	60 days	Sanofi and Regeneron Pharmaceuticals
5	RECOVERY 2021[33]	UK	April 23, 2020–January 24, 2021	White, Black, Asian, or minority ethnic and unknown	OL	Severe COVID-19 characterized by hypoxia and substantial inflammation	4116	2022 2094	63.3 (13.7) 63.9 (13.6)	1337 (66) 1437 (69)	28 days	UK Research and Innovation

(Continues)

TABLE 1 (Continued)

No	Study name	Study country	Study duration	Ethnic	Blinding (DB/SB/OL)	Patient population and disease severity *n* (%)	Total patients (*n*)	Patients in groups (intervention/control)	Age years ± SD/range	Male *n* (%)	Follow up period (day)	Funding
6	Rosas 2021[34]	Nine countries in Europe and North America	April 3, 2020–May 28, 2020	American Indian or Alaska Native/ Asian/Black/ Native Hawaiian or Pacific Islander/ White/ Multiple/ unknown	DB	Severe Covid-19 pneumonia	438	294 144	60.9 ± 14.6 60.6 ± 13.7	205 (69.7) 101 (70.1)	28 days	F. Hoffmann–La Roche and the Department of Health and Human Services; COVACTA
7	Salama 2021[35]	USA	March 28, 2020–October 4, 2020	Hispanic or Latino, American Indian or Alaska Native, Black	DB	Non-ICU	389	249 168	56.0 ± 14.3 55.6 ± 14.9	150 (60.2)	60	Genentech; EMPACTA
8	Salvarani 2021[36]	Italy	March 31, 2020–June 11, 2020	Not stated	OL	Mild acute respiratory distress syndrome (PaO2/ FIO2 ratio between 200- and 300-mmHg)	123	60 63	61.5 (51.5–73.5) 60.0 (54.0–69.0)	40 (66.7) 37 (56.1)	14 days	Partly funded by the Italian Ministry of Health
9	Soin 2021[37]	India	May 30, 2020, and August 31, 2020	Not stated	OL	Moderate to severe	179	91 88	56 (47–63) 54 (43–63)	76 (84) 76 (86)	28 days	Medanta Institute of Education and Research, Roche India, Cipla India, and Action COVID-19 India
10	Veiga 2021[38]	Brazil	May 8, 2020–July 17, 2020	Not stated	OL	Severe or critical	129	65 64	57.4 (15.7) 57.5 (13.5)	44 (68) 44 (69)	15 days	Coalition covid-19 Brazil.
11	Zhao 2021[39]	China	February 2, 2020–March 15, 2020	Not stated	OL	Common/Severe/ Critical	26	14 7 5	75 (34–81) 70 (45–89) 71 (48–77)	6 (42.9) 5 (71.4) 3 (60)	14 days	Chinese COVID-19 scientific research emergency project,

TABLE 1 (Continued)

No	Study name	Study country	Study duration	Ethnic	Blinding (DB/SB/OL)	Patient population and disease severity *n* (%)	Total patients (*n*)	Patients in groups (intervention/control)	Age years ± SD/range	Male *n* (%)	Follow up period (day)	Funding
12	RECOVERY 2022[40]	UK	September 18, 2020–May 22, 2021	White, Black, Asian, or minority ethnic and unknown	OL	Not stated	9785	4839 4946	61.9 (14.6) 61.9 (14.4)	3033 (63) 3095 (63)	28 days	UK Research and Innovation
13	Farcy 2022[41]	Florida, USA	December 17, 2020–January 17, 2021	Not stated	OL	Have had one or more mild to moderate symptoms; presented to our hospital within 10 days of symptom onset	327	201 120	64.2 ± 12 66.3 ± 13.2	118 (58.8) 75 (62.5)	30 days	Not stated
14	Gupta 2022[42]	Brazil, Canada, Peru, Spain, and the US	August 27, 2020, through March 11, 2021	Latinx/Not Latinx	DB	High risk for COVID-19	1057	528 529	53 (41.5–62) 53 (43–63)	229 (43) 256 (48)	29 days	Vir Biotechnology Inc and GlaxoSmithKline
15	Somersan-Karakaya 2022[43]	United States, Brazil, Chile, Mexico, Moldova, and Romania	10 June 2020–9 April 2021	Hispanic or Latino/Not Hispanic or Latino/Not reported	DB	COVID-19 patients on low-flow/no oxygen	1197	457 455 452	62.0 (20–100)	647 (54.1)	28 days	Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response, and Biomedical Advanced Research and Development Authority
16	Karampitsakos 2023[44]	Greece	October 20, 2021–May 7, 2022	Not stated	OL	PaO2/FiO2 ratio of <200	251	126125	72.0 (62.0–83.0) 73.0 (61.0–83.0)	74 (58.7) 74 (59.2)	28 days	Not stated

Abbreviations: DB, double blind; SB, single blind; OL, open label; SO2, oxygen saturation; PaO2, partial pressure of oxygen in the alveoli; FiO2, fraction of inspired oxygen; PaO2/FiO2 ratio (P/F ratio), ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen.

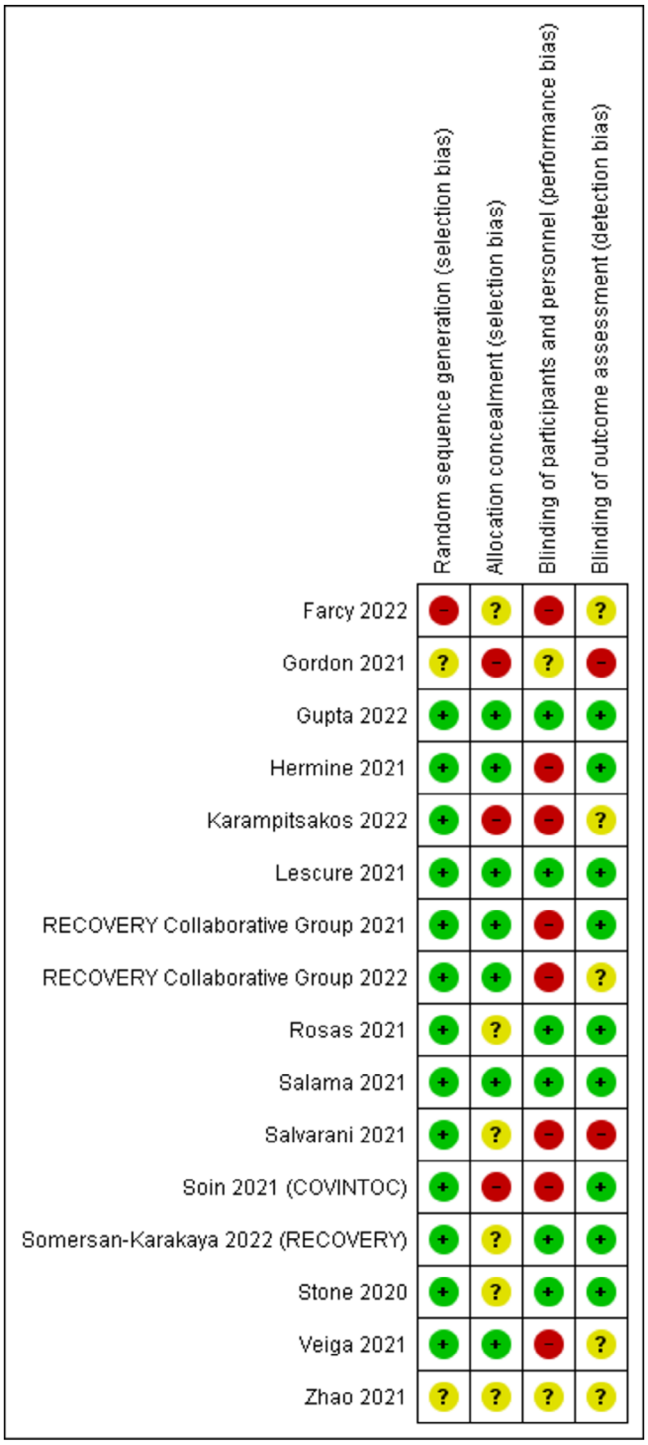

FIGURE 2 Methodological quality assessment of included studies.

among COVID-19 patients (RR = 1.21, 95% CI 0.63–2.34) but the difference was not statistically significant. There was low heterogeneity ($I^2 = 0\%$, $P = 0.63$) and a fixed-effect model was employed. Subgroup analysis showed no statistically significant difference between the intervention and comparison groups (Figure 6). The asymmetrical funnel plot suggested a higher likelihood of publication bias (Supplementary Figure S4).

3.4.5 | Incidence of any disease-related serious adverse events (SAEs)

Among all, there were a total of ten RCTs with 11 149 participants that reported the incidence of other SAEs among the studies included.[30–35,37,38,40,42] Analysis of pooled data showed that the incidence of disease-related SAEs (e.g., septic shock, viral sepsis, bacterial sepsis, acute respiratory distress syndrome, etc.) was reduced in the mAbs treatment arm (RR = 0.88, 95% CI 0.70–1.11) but not statistically significantly (Figure 7). Upon sub-group analysis, the TCZ group showed a statistically significant reduction in the incidence of disease-related SAEs compared to the comparators (RR = 0.80, 95% CI 0.70–0.91). The asymmetrical funnel plot suggested a higher likelihood of publication bias (Supplementary Figure S5). In our findings, two studies included participants with a history of cancer,[29,30] one study included participants with a history of renal replacement therapy, or systematic corticosteroid therapy before dosing,[32] two studies included participants with a history of human immunodeficiency virus (HIV) infection,[33,40] one study included participants who were taking antiretroviral therapy,[36] one study included participants who had a history of haematological malignancies,[38] one study included participants who were taking immunosuppressant treatment,[41] two studies included participants who were immunocompromised[43,44] and six studies did not report specific information in the demographics of the included participants.[31,34,35,37,39,42] However, the studies that included immunocompromised participants did not report their adverse effects specifically (Supplementary Table S11).

3.4.6 | Certainty of evidence

GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) analysis was conducted for all outcomes. The evidence suggested that there were higher chances of hepatoxicity, neutropenia and infusion reactions upon usage of mAbs with moderate certainty of evidence. The incidence of renal toxicity with the use of mAbs was found to have low certainty of evidence. The mAbs could reduce the incidence of any disease related to SAE with very low certainty of evidence (Supplementary Table S9).

4 | DISCUSSION

This systematic review and meta-analysis was carried out to determine the incidence of various adverse events in relation to the use of mAbs among patients with COVID-19. The screening of search items for inclusion/exclusion criteria yielded 16 RCTs that reported adverse events in the safety profile of mAbs used in COVID-19. Collectively, these 16 RCTs included 9682 participants in the intervention arm and 10 115 in the control arm. The mAbs used in the selected RCTs included TCZ,[29–31,33–39,44] sarilumab,[32] imdevimab/casirivimab,[40,43] sotrovimab[42] and bamlanivimab.[41] The most frequently used mAb was TCZ.

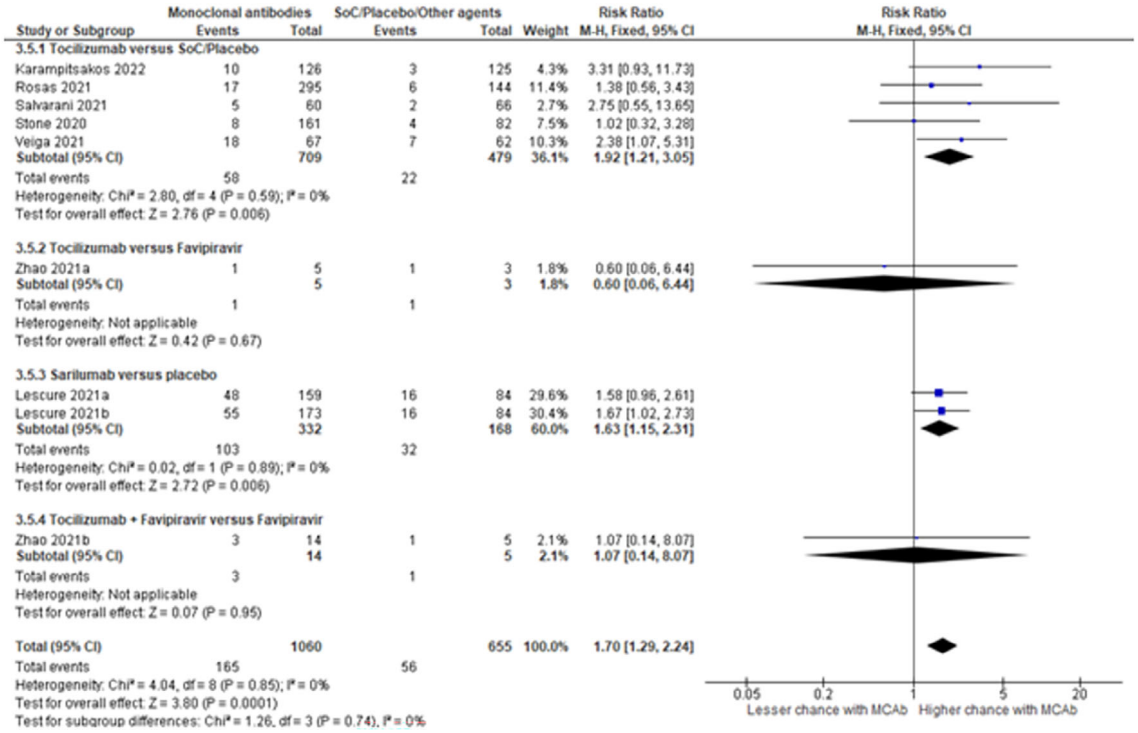

FIGURE 3 Incidence of hepatotoxicity across different mAbs used in COVID-19 treatment.

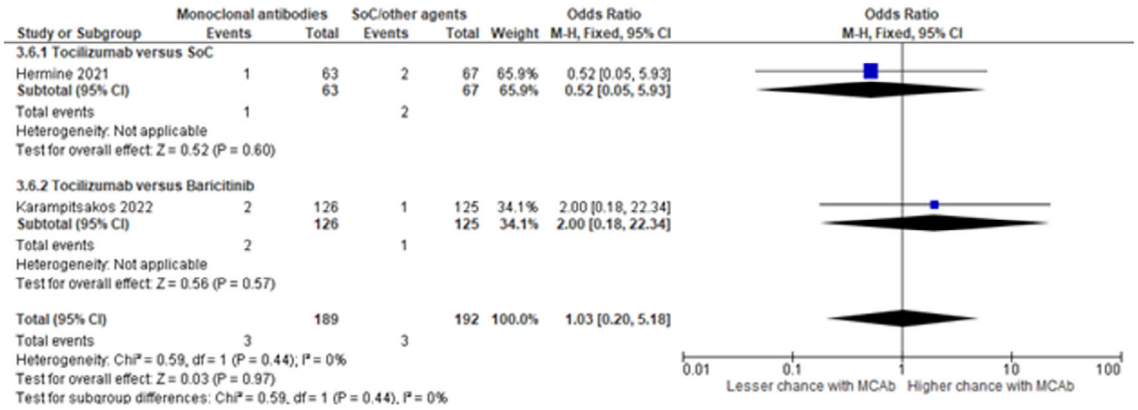

FIGURE 4 Incidence of renal toxicity across different mAbs used in COVID-19 treatment.

The most commonly used mAbs for COVID-19 treatment or pre-exposure prophylaxis were casirivimab and imdevimab (REGEN-COV), sotrovimab, bamlanivimab, bamlanivimab and **etesevimab**, **bebtelovimab**, tixagevimab and cilgavimab (Evusheld), TCZ, **regdanvimab**, **sarilumab** and **vilobelimab**. Among these, TCZ and sarilumab were repurposed medicines and the rest were manufactured during the pandemic with EUA for the treatment of COVID-19. Pemivibart was a new product, and its purpose is for pre-exposure prophylaxis of COVID-19, and its EUA is still ongoing. The tixagevimab and cilgavimab (Evusheld) combination was also approved for pre-exposure prophylaxis. Sarilumab was only approved as an alternative if none of the recommended immunomodulatory therapies for the management of COVID-19 were available or feasible to use. Apart from TCZ, sarilumab and regdanvimab, the remaining mAbs had been revoked due to lack of effectiveness in new variants of COVID-19 (Supplementary Table S10). As of August 2024, emergency use authorization of tocilizumab and sarilumab was still ongoing. The detailed mechanism of action and current status of different mAbs are explained in Supplementary Table S10.[6]

The mAbs have emerged as powerful therapeutic options for the treatment of serious illnesses involving immune-mediated responses as significant pathogenetic mechanisms. Hence, it was not surprising that the use of mAbs emerged as one of the therapeutic options in the treatment of severe COVID-19 infection which involved immune-mediated surge in the production of several cytokines resulting in severe and sometimes fatal inflammatory reactions manifesting as

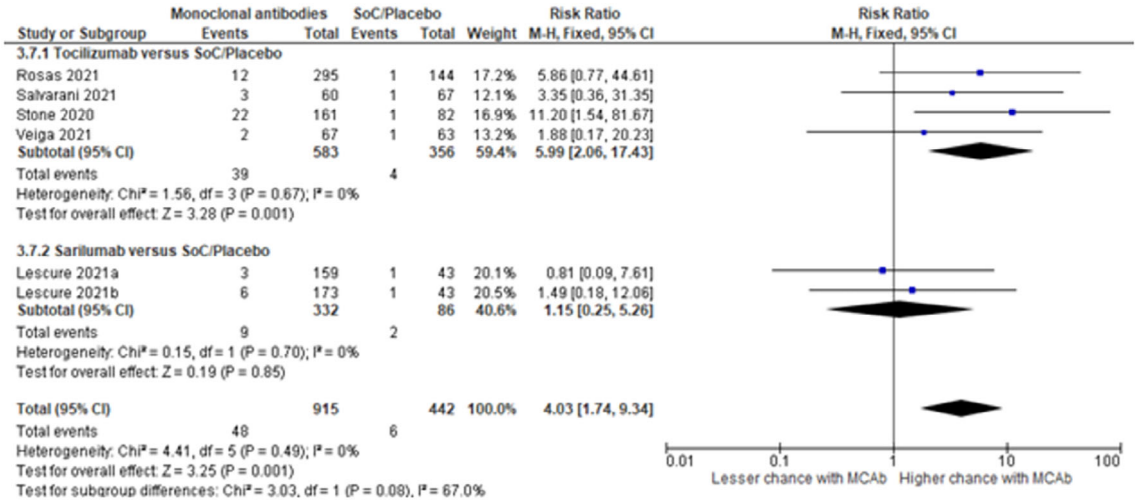

FIGURE 5 Incidence of neutropenia across different mAbs used in COVID-19 treatment.

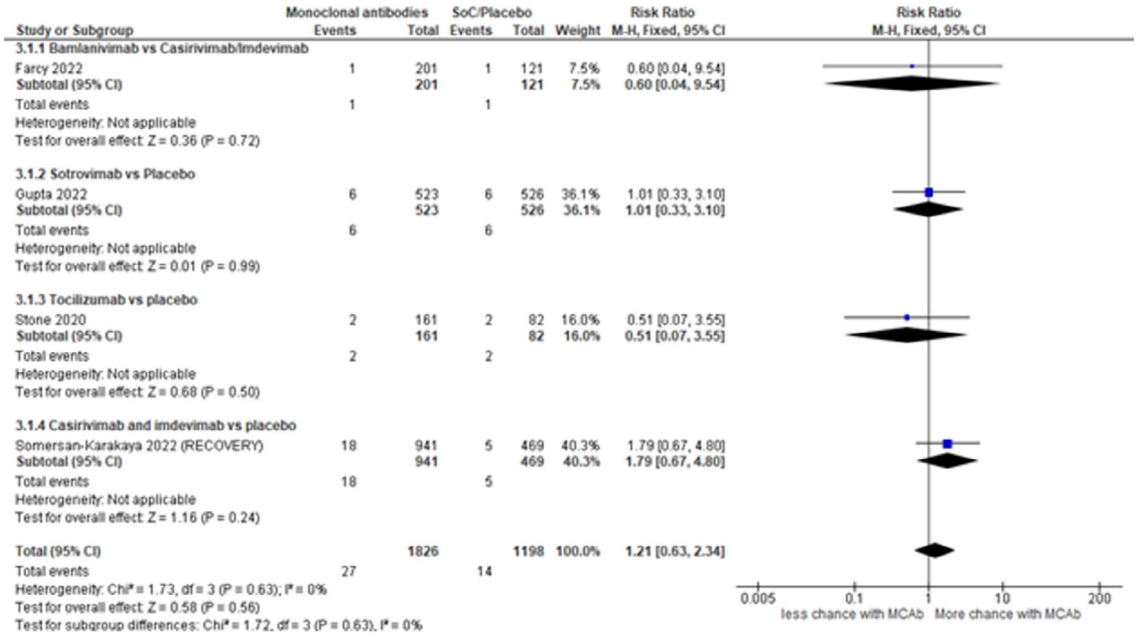

FIGURE 6 Incidence of infusion reactions across different mAbs used in COVID-19 treatment.

respiratory and non-respiratory consequences. Due to the neutralizing properties, the use of mAbs in COVID-19 aimed to suppress the immune-mediated inflammatory reaction either by targeting the virus or the inflammatory cytokines. While the benefits of the use of several mAbs had been widely described, their adverse effects had also been recognized.[45–48] Since the majority of mAbs were investigational agents and had obtained approval with EUA during the pandemic, in this study, we investigated the reported adverse effects of different mAbs from a clinical point of view regardless of the mechanisms of actions of the individual drug. To the best of our knowledge, not all ADRs may be directly explainable by the known mechanisms of actions of medications.

Among the 16 included studies, an estimated 60% of the studies provided data on causation between the adverse effects and the interventional drugs or control arms (Supplementary Table S11). However, this percentage did not include all adverse events reported in individual studies. For instance, most study investigators reported the causation for SAEs, including fatal outcomes,[29,32,33,35,36,40,42] hypersensitivity to infusion,[29,34,41,42] the most adverse effects or as a general statement,[37] no specific statement,[38,44] and increased transaminase.[39] A study by Somersan-Karakaya et al. reported treatment-emergent adverse events resulting in death in the placebo group *vs.* the treatment intervention group. However, these adverse events were considered to be associated with COVID-19 and its complications by the sponsor.[43]

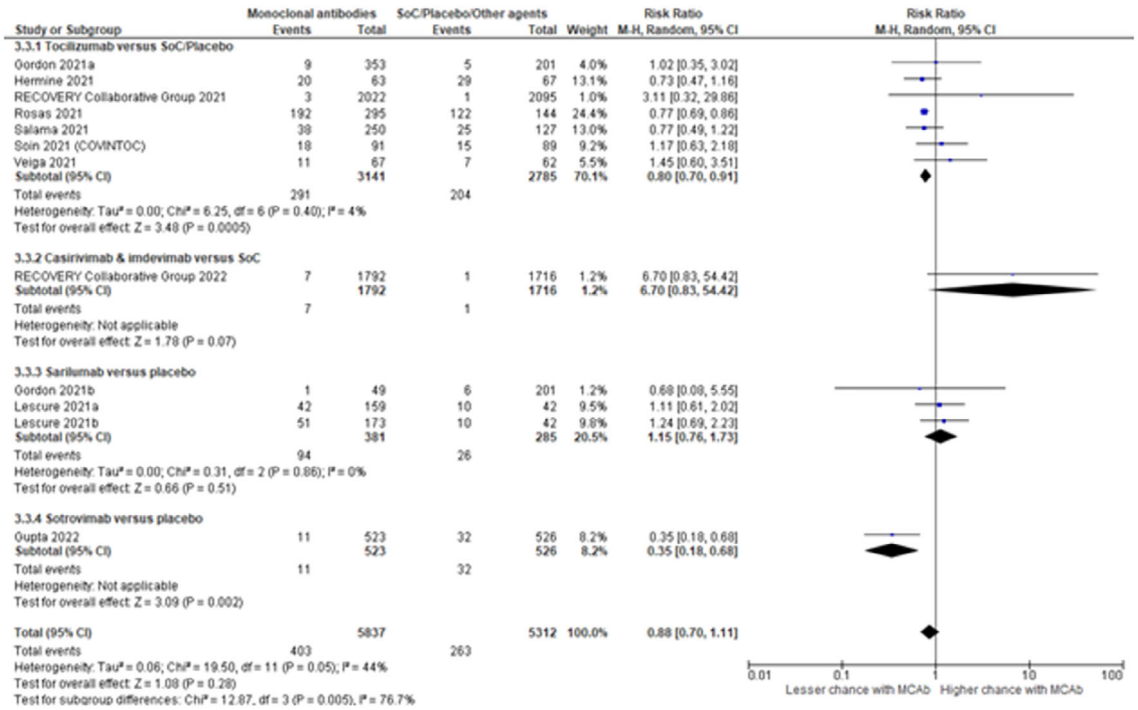

FIGURE 7 Incidence of any disease-related SAEs across different mAbs used in COVID-19 treatment.

Since the use of mAbs in severely ill COVID-19 patients was a part of practice guidelines, it is important to analyse the relevant findings in the current literature to understand the possible adverse drug events associated with their use. Several systematic reviews and meta-analyses have been done to evaluate the use of tocilizumab in COVID-19 patients.[14–17,49] However, there is still a need for a systematic review of their safety profile. The meta-analysis in the current study revealed that the use of mAbs was likely to be associated with an increased chance of hepatoxicity and neutropenia compared to the patients treated with SoC/placebo as indicated by a statistically significant risk ratio and 95% CI. The GRADE approach (Grading of Recommendations, Assessment, Development and Evaluation) analysis in our study suggested that mAbs may increase hepatoxicity and neutropenia with moderate certainty of evidence.

In accordance with the findings of the current study, several cases of tocilizumab-induced liver injury have been reported previously.[50–52] The TCZ had minimal hepatic metabolism, and the mechanism of liver injury had many postulated theories. Some studies reported that hepatic injury by TCZ could be due to its effect on the immune system as an immunosuppressant as well as due to its inhibition of IL-6 which was important in liver regeneration.[53] The IL-6-TCZ-**STAT3** pathway was crucial for liver regeneration and the binding of IL-6 to its receptor can activate the JAK-STAT3 pathway. Since TCZ inhibits IL-6, it will block the JAK/STAT3 pathway which could lead to hepatic injury to drug-induced liver injury (DILI) by enhancing hepatic apoptosis and inhibiting liver regeneration.[9] A study by Kim et al. in 2023 on TCZ-related neutropenia in patients with rheumatoid arthritis (RA) reported that baseline neutrophil count was a risk factor for TCZ-related neutropenia.[54] The TCZ was found to reduce the number of circulating neutrophils by affecting migration and/or bone marrow trafficking. However, the function of the neutrophils was not affected.[55] It was also postulated that SARS-CoV-2 might bind to **angiotensin-converting enzyme 2** (ACE2) on cholangiocytes which could lead to cholangiocytes dysfunction, inflammatory response and liver injury.[56] Moreover, liver injury in COVID-19 patients could also be related to disease severity, and studies have proposed that the incidence of liver injury in individuals with severe COVID-19 is notably higher compared to mild cases. Other reports suggested that hepatic, pancreatic and pulmonary reactions may occur after a median of 15 days after tocilizumab administration.[57] It had been observed that tocilizumab-related hepatotoxicity was more likely when it was combined with other hepatotoxic drugs.[58] Careful monitoring of hepatic function has therefore been recommended.[59]

Neutropenia may be a direct effect of mAbs, or it could result from immune-mediated responses. In addition, patient-related factors such as comorbid conditions, concurrent medications and genetics may also be contributory factors.[60] In accordance with our findings, a higher risk of neutropenia with the use of tocilizumab has been reported earlier.[61] TCZ was reported to cause transient neutropenia in a dose-dependent manner among patients with RA.[62] In fact, a study in Japan reported Common Terminology Criteria for Adverse Events (CTCAE) grade 2 and 3 neutropenia in 15% and 6% of the RA patients who were receiving TCZ.[63] Moreover, a case of severe prolonged neutropenia following the administration of tocilizumab was reported in a COVID-19 patient in 2020.[64] Other studies also reported neutropenia as the most common adverse event of TCZ. Moreover, there were incidences requiring discontinuation of treatment due to TCZ-related

severe neutropenia.[62,65,66] A higher risk of infection could be another presentation of neutropenia.[67] It has therefore been recommended that the occurrence of neutropenia be monitored by the absolute neutrophil count.[62]

Additionally, we observed that the use of mAbs was associated with a higher chance of infusion reactions with moderate certainty of evidence; the effect measure, however, was not statistically significant. Several studies had reported the occurrence of hypersensitivity reactions and anaphylactic shock with intravenous infusion of mAbs.[68–72] While it is highly probable that the infusion reactions to mAbs result from IgE-mediated reactions, the cause of hepatic injury and neutropenia related to mAbs remains rather uncertain. Nevertheless, care should be taken to avoid the consequences of severe hypersensitivity reactions during the use of mAbs.

In a multicentre study by Mori et al. in 2015 among patients with RA and renal insufficiency, TCZ showed good efficacy and safety as well as tolerability profile, despite concomitant use of methotrexate.[73] Two case reports from Japan observed that TCZ preserved renal function in RA with AA amyloidosis and end-stage kidney disease patients.[74] Another case report from Croatia showed that an RA patient who was on haemodialysis due to end stage renal disease (ESRD), benefited from the introduction of TCZ and the patient was able to achieve sustained clinical remission for 4 years with no reported adverse effect.[75] In accordance with these reports, our study did not find an increased risk of renal toxicity due to mAbs use among COVID-19 patients. However, in a cohort study, an increased risk of acute kidney injury and renal impairment were reported after the use of tocilizumab in critically ill COVID-19 patients, although the overall survival was improved.[76] These findings indicated the need for long-term observational studies.

For RA, the usual dose of TCZ is an 8 mg/kg intravenous infusion every 4 weeks or 162 mg/kg weekly subcutaneous injection. For COVID-19 treatment, TCZ is usually prescribed as an 8 mg/kg intravenous infusion, followed by three additional doses if there is no improvement after the first dose. If related to cumulative dose, the risk of TCZ-mediated hepatoxicity in RA and giant cell arthritis could be greater than the risk for COVID-19 treatment.[76] A study by McCreary et al. in 2022 reportedthe efficacy and safety of mAbs for treatment of SARS-CoV2 infection during pregnancy. There was no difference in obstetric-associated safety outcomes between mAbs and comparison arms. The mAbs included in the study were bamlanivimab and etesevimab, casirivimab and imdevimab, or sotrovimab.[53,77]

Although some studies had reported adverse events in relation to the use of TCZ, there remained a gap in the details.[77,78] One of the studies reported no significant decrease in the risk of serious adverse events among the TCZ-treated arm compared to the control arm. A systematic review and meta-analysis by Peng et al. in 2022 reported no significant decrease in the risk of serious adverse events among the TCZ arm compared to the control arm.[79] In contrast, the analysis of our study showed that the use of mAbs was associated with a lesser chance of any serious adverse events or any adverse events graded ≥3 compared to the use of SoCs/placebo/other agents. The serious adverse events reported in the included studies were deaths, acute coronary syndrome, seizures, pulmonary embolism, colonic ulcer bleeding, pulmonary fibrosis, etc.[37] However, ADRs reported in the included studies could be due to the complications of the disease as well. A lesser chance of any disease-related serious adverse events in the mAbs arms could also be considered an indicator of its efficacy since it may indicate a delayed progression of the disease or an increased risk of disease-related adverse events in the comparator arm. Nevertheless, this interpretation may not be conclusive since not all trials reported treatment-related or non-treatment-related serious adverse events consistently.

4.1 | Strengths and limitations

While the findings of this study were of considerable significance, there were some limitations of this study including variations in the regimens (dosing, timing and routes of administration), comorbidities of the patients, other physiological factors such as body mass index (BMI) and severity of the COVID-19 infection across the included studies. The follow-up duration was different across the studies. Quality of life was not reported in the included studies which might be due to the nature of the disease, and the pandemic situation. We reported the adverse effects by organ systems regardless of the mechanism of action of the different mAbs. Nevertheless, the study highlighted the possibility of some adverse events with the use of mAbs among COVID-19 patients and prompted for possible measures to mitigate the risk.

A potential limitation was the omission of some reported adverse effects. For adverse effects such as "infections", individual study reports did not determine whether these were "treatment-related". For instance, adverse events such as "adult respiratory distress syndrome (ARDS)" were most likely to be a "disease-related complication" rather than a "treatment-related adverse effect", yet in our opinion, it was reported under adverse events in general. Hence, we omitted some outcomes with the possibility of controversial interpretation in our report (Supplementary Table S11). Additionally, COVID-19 infection was not self-limited in the immunocompromised population. For instance, the Omicron variant may cause a less severe disease course in the general population, but it was not the same for the immunocompromised population.[80] Most COVID-19 guidelines were structured for disease severity such as mild, moderate, or severe but did not focus much on host factors such as immunity. This had led to the lack of evidence-based clinical practice guidelines for immunocompromised patients with COVID-19 infection (Supplementary Table S12).

Exclusion of mAbs which are used in post-exposure prophylaxis of COVID-19 represented an additional limitation. The mAbs used for post-exposure prophylaxis such as AZD7442 (tixagevimab/cilgavimab) were not included in this study because of the difference in nature of the dosage regimen of prophylaxis and treatment, and consequent clinical outcomes.

4.2 | Implications

The findings of this study indicated the potential risk of specific adverse events which prompted measures to mitigate the risk. The possibility of enhanced adverse events due to comorbidities and the drug–drug interactions should also be considered while prescribing multi-drug regimens in COVID-19 patients or similar illnesses. Further analysis of relevant studies may confirm if the results of this study could be applied in other patient populations.

5 | CONCLUSION

In conclusion, the use of mAbs was found to be associated with an increased chance of hepatoxicity and neutropenia compared to SoC/placebo among COVID-19 patients with low certainty of evidence. The analysis also indicated an increased chance of infusion reactions with the use of mAbs among this patient population. The disease-related serious adverse events were likely to reduce with the use of mAbs as compared to SoC/placebo, suggesting a possible reduction in disease progression by mAbs. Long-term observational studies are recommended to observe for post-COVID adverse effects related to mAbs.

AUTHOR CONTRIBUTIONS

H.H. initiated the concept, design, extraction, analysis and interpretation of results and the preparation of the manuscript. H.K. was involved in extraction and analysis. R.A. and I.I. were involved in study screening, study selection and data extraction. I.B., T.S. and H.J. were involved in study screening, selection, data extraction and quality appraisal of studies. All authors made suggestions, provided contributions and agreed for the approval of the final manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no competing interests to declare.

DATA AVAILABILITY STATEMENT

Detailed data are reported in supplementary tables and figures. More detailed data extraction and analysis is available upon request.

ORCID

Htet Htet https://orcid.org/0000-0003-2143-8629
Han You Kyung https://orcid.org/0009-0005-8428-6177
Ismail Abdul Sattar Burud https://orcid.org/0000-0003-0326-424X
Heethal Jaiprakash https://orcid.org/0000-0001-9948-4428
Thiruselvi Subramaniam https://orcid.org/0000-0001-7073-8092
Igor Iezhitsa https://orcid.org/0000-0002-2852-8486
Renu Agarwal https://orcid.org/0000-0002-3050-7449

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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