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Investigating the impact of Tocilizumab, Sarilumab, and Anakinra on clinical outcomes in COVID-19: A systematic review and *meta*-analysis

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ABSTRACT

Background: Monoclonal antibodies (mAbs) are currently under investigation as a potential therapeutic option for COVID-19. Clinical trials are examining their efficacy in lowering mortality rates and the requirement for mechanical ventilation (MV). It is necessary to conduct a thorough examination of current randomized controlled trials (RCTs) in order to provide more definitive evidence on their effectiveness for COVID-19 patients. This *meta*-analysis aims to analyze RCT results on the impact of three mAbs (Anakinra, Sarilumab, Tocilizumab) on COVID-19 patient outcomes.

Method: The *meta*-analysis was conducted in accordance with the PRISMA guidelines. Eligible RCTs were conducted to evaluate the effectiveness of three mAbs in treating patients with COVID-19. These trials were identified by searching various databases up to April 1, 2024. In total, this *meta*-analysis incorporated 19 trials with a total of 8097 patients. Pooled relative risk and studies' heterogeneity were assessed by statistical analysis, which involved the use of fixed effects models and subgroup analysis.

Result: The administration of mAbs (Tocilizumab, Sarilumab, and Anakinra) showed various results in the management of COVID-19 patients. While the overall pooled data did not reveal a significant reduction in the need for MV, the study found that the use of mAbs was associated with a decreased risk of clinical worsening (pooled relative risk: 0.75, 95 % CI [0.59, 0.94], $p = 0.01$) and an increased probability of discharging COVID-19 patients by day 28 or 29 (pooled relative risk: 1.17, 95 % CI [1.10, 1.26]). Notably, the subgroup analysis revealed that Tocilizumab had a significant effect in reducing the risk of clinical worsening compared to Sarilumab. Additionally, the analysis of mortality outcomes indicated that the administration of mAbs had the potential to decrease the overall risk of mortality over time (pooled RR: 0.90, 95 % CI [0.83, 0.97], $p = 0.01$).

Conclusion: In summary, our *meta*-analysis suggests that mAbs, particularly Tocilizumab, may play a valuable role in managing COVID-19 by reducing the risk of clinical worsening, improving hospital discharge rates, and decreasing mortality.

1. Introduction

Late in 2019, the first case of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported. Coronavirus disease 2019 (COVID-19) was identified as a significant global health risk [1]. The World Health Organization (WHO) has estimated that the total cumulative reported COVID-19 cases worldwide up to February 11th, 2024 amount to a staggering 774,631,444 [2]. Rapid progression of COVID-19 to acute respiratory distress syndrome is estimated to occur in up to 41 % of severe COVID-19 patients [3]. The range of symptoms associated with COVID-19 can vary from asymptomatic to experiencing minor respiratory disorders, severe pneumonia, and even acute

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Table 1
Information on included articles in the *meta*-analysis.

ID	First Author (Reference)	Published Year	Country[a]	Monoclonal Ab[b]	Dose	N. dose	Reported Day	Comparator arm[c]	Sample size (IG)	Mechanical ventilation (IG)	Death (IG)	Sample size (CG)	Mechanical ventilation (CG)	Death (CG)	Clinical Worsening (Effect Size)	Effect size value	LCI	UCI	Discharged at day 28 (Effect size)	Effect size value	LCI	UCI	References
1	Stone et al.	2020	US	T	8 mg/kg	1	28	P	161	11	9	82	8	3	HR	1.11	0.59	2.1	HR	1.08	0.81	1.43	[20]
2	Hermine et al.	2020	France	T	8 mg/kg	1	14	UC	63	5	7	67	14	6	–	–	–	–	–	–	–	–	[21]
3	Hermine et al.	2020	France	T	8 mg/kg	1	28	UC	63	–	7	67	–	8	–	–	–	–	–	–	–	–	[21]
4	Salama et al.	2020	MC	T	8 mg/kg	1/2	28	P	249	–	26	128	–	11	HR	0.55	0.33	0.93	HR	1.16	0.91	1.48	[22]
5	Salvarani et al.	2021	Italy	T	8 mg/kg	2	14	UC	60	5	1	63	2	1	Rate Ratio	1.05	0.59	1.86	–	–	–	–	[23]
6	Sancho-López et al.	2021	Spain	S	200 mg	1	28	UC	28	–	–	102	–	–	Relative Risk	0.2	0.03	1.57	–	–	–	–	[24]
7	Sancho-López et al.	2021	Spain	S	400 mg	1	28	UC	70	–	–	102	–	–	Relative Risk	1.34	0.61	2.97	–	–	–	–	[24]
8	Sancho-López et al. [overall]	2021	Spain	S	200/400 mg	1	28	UC	99	–	2	102	–	2	Relative Risk	1.03	0.48	2.2	–	–	–	–	[24]
9	Veiga et al.	2021	Brazil	T	8 mg/kg	1	15	UC	65	7	11	64	11	2	–	–	–	–	–	–	–	–	[25]
10	Veiga et al.	2021	Brazil	T	8 mg/kg	1	29	UC	65	4	14	64	4	6	–	–	–	–	–	–	–	–	[25]
11	Kharazmi et al.	2021	Iran	A	100 mg	14	14	UC	15	0	5	15	2	7	–	–	–	–	–	–	–	–	[26]
12	Mariette et al.	2022	France	S	400 mg	1/2*	14	UC	68	15	6	76	9	8	–	–	–	–	–	–	–	–	[33]
13	Mariette et al.	2022	France	S	400 mg	1/2	28	UC	68	–	8	76	–	14	–	–	–	–	HR	1.19	0.81	1.75	[33]
14	Soin et al.	2021	India	T	6 mg/kg	1/2	28	UC	91	14	11	88	13	15	–	–	–	–	–	–	–	–	[27]
15	Soin et al.	2021	India	T	6 mg/kg	1/2	14	UC	91	–	8	88	–	9	Risk Diff	−3.7	−18.2	11.2	–	–	–	–	[27]
16	Abani et al.	2021	UK	T	400–800 mg	1/2	28	UC	2022	265	621	2094	343	729	–	–	–	–	Rate Ratio	1.22	1.12	1.33	[28]
17	Tharaux et al.	2021	France	A	100&200 mg	3&6‡	14	UC	59	–	9	55	–	13	–	–	–	–	–	–	–	–	[29]
18	Tharaux et al.	2021	France	A	100&200 mg	3&6‡	28	UC	59	–	13	55	–	13	–	–	–	–	HR	0.91	0.56	1.48	[29]
19	Lescure et al.	2021	MC	S	200 mg	1	29	P	159	–	16	84	–	7	–	–	–	–	–	–	–	–	[30]
20	Lescure et al.	2021	MC	S	400 mg	1	29	p	173	–	14	84	–	7	–	–	–	–	–	–	–	–	[30]
21	Rosas et al.	2021	MC	T	8 mg/kg	1	28	p	430	45	78	210	20	41	–	–	–	–	HR	0.97	0.78	1.19	[32]
22	Bräu et al.	2021	MC	T	8 mg/kg	1/2	28	p	294	51	58	144	33	28	HR	0.61	0.4	0.94	HR	1.35	1.02	1.79	[31]
23	Audemard-Verger et al.	2022	France	A	200&400 mg	7&3†	14	UC	35	4	6	32	3	0	–	–	–	–	–	–	–	–	[34]
24	Audemard-Verger et al.	2022	France	A	200&400 mg	7&3†	28	UC	35	0	9	32	1	3	–	–	–	–	–	–	–	–	[34]
25	Merchante et al.	2022	Spain	S	200 mg	1	28	UC	37	6	4	39	4	3	HR	0.87	0.37	2.06	HR	0.98	0.6	1.6	[35]
26	Merchante et al.	2022	Spain	S	400 mg	1	28	UC	39	3	0	39	4	3	HR	0.41	0.14	1.18	HR	1.23	0.76	1.96	[35]
27	Jonas et al.	2023	Sweden	A	100 mg	28	28	UC	28	3	2	27	6	2	–	–	–	–	–	–	–	–	[37]
28	Jonas et al.	2023	Sweden	T	8 mg/kg	1	28	UC	22	3	2	27	6	2	–	–	–	–	–	–	–	–	[37]
29	Patricia et al.	2023	Spain	A	100 mg	60	28	UC	84	–	4	81	–	5	–	–	–	–	–	–	–	–	[36]
30	Kyriazopoulou et al.	2024	Rome	A	100 mg	10	28	P	263	–	10	130	–	12	–	–	–	–	–	–	–	–	[38]

[a] : MC(Multiple-Country).
[b] : T(Tocilizumab), A(Anakinra), S(Sarilumab).
[c] : UC (Usual care), P(Placebo).
* Additional dose was considered based on the patient's condition by the physician.
† The patients were administered an IV injection of anakinra at a dose of 400 mg/day (100 mg every 6 h) for 3 days, followed by an IV injection of anakinra at a dose of 200 mg/day (100 mg every 12 h) for 7 days.
‡ Anakinra was given intravenously at a dose of 200 mg twice daily for a total of 400 mg on days 1–3, followed by 100 mg twice daily for a total of 200 mg on day 4, and 100 mg once on day 5.

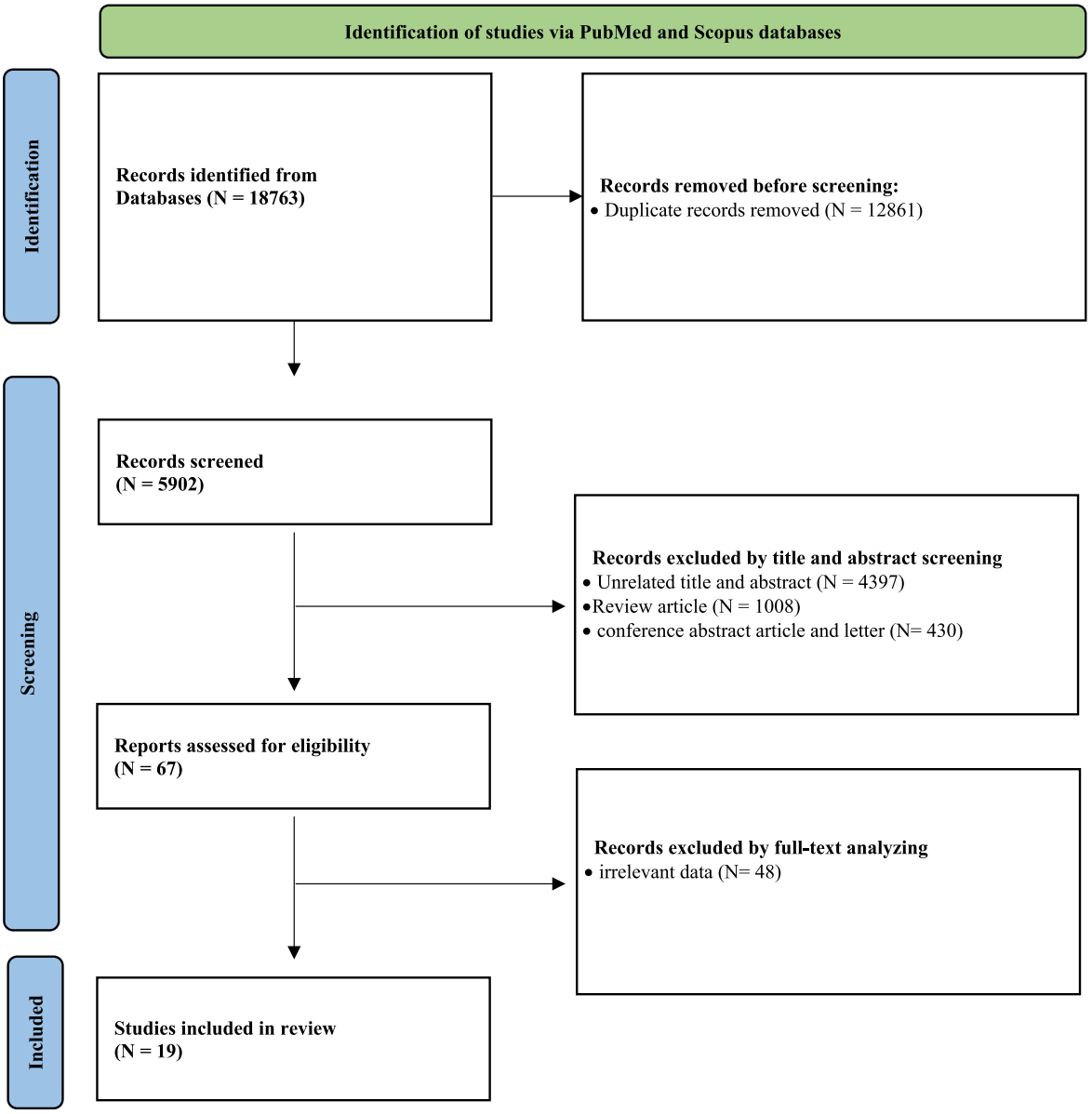

Fig. 1. The PRISMA flow diagram for screening process of the recovered records.

Table 2
JBI Critical Appraisal Checklist for Randomized Controlled Trials; Y: Yes, N: NO, U: Unclear, NA: Not available, I: Included.

Questions	Salvarani et al.	López et al.	Veiga et al.	Kharazmi et al.	Mariette et al.	Soin et al.	Salama et al.	Verger et al.	Merchante et al.	Hermine et al.	Abani et al.	Stone et al.	Tharaux et al.	Lescure et al.	Rosas et al.	Bräu et al.	Patricia et al.	Kyriazopoulou et al.	Jonas et al.
1. Was true randomization used for assignment of participants to treatment groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2. Was allocation to treatment groups concealed?	Y	Y	Y	U	Y	Y	Y	N	Y	Y	Y	U	Y	Y	Y	Y	Y	U	Y
3. Were treatment groups similar at the baseline?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
4. Were participants blind to treatment assignment?	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	Y	Y	N	Y	N
5. Were those delivering treatment blind to treatment assignment?	N	N	N	N	N	N	Y	N	N	N	N	Y	N	Y	Y	Y	N	Y	N
6. Were outcomes assessors blind to treatment assignment?	N	N	N	N	Y	N	Y	N	N	U	Y	Y	N	Y	Y	U	N	U	U
7. Were treatment groups treated identically other than the intervention of interest?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Y	Y	U	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	N
9. Were participants analyzed in the groups to which they were randomized?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
10. Were outcomes measured in the same way for treatment groups?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
11. Were outcomes measured in a reliable way?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	U
12. Was appropriate statistical analysis used?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Was the trial design appropriate for the topic, and any deviations from the standard RCT design accounted for in the conduct and analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Overall appraisal:	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I	I

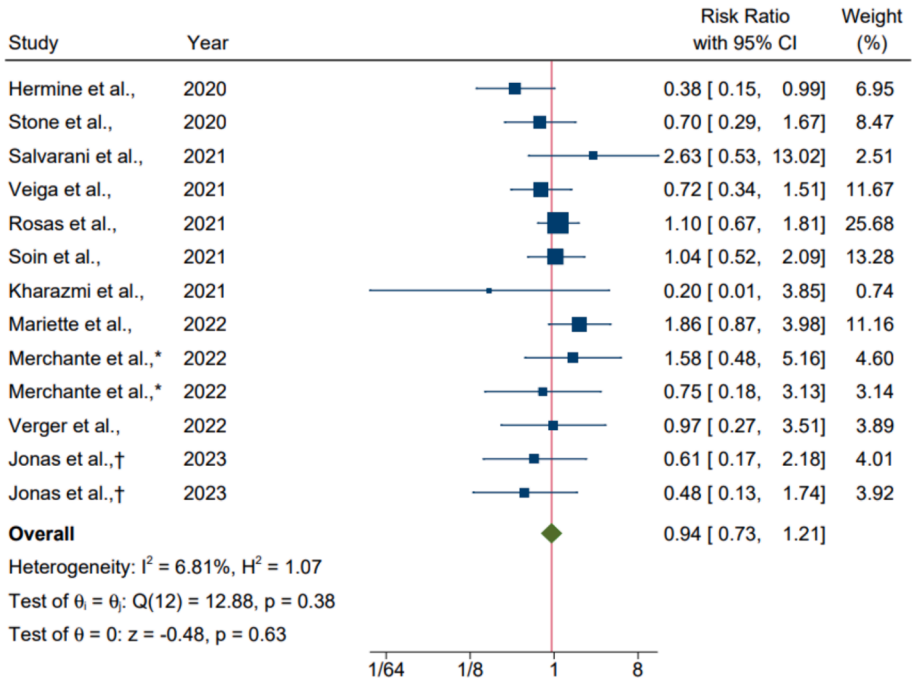

Fig. 2. A fixed effects model was used to calculate the pooled risk ratio (RR). Overall, monoclonal antibodies (mAbs) did not significantly reduce the risk of requiring mechanical ventilation (MV), with a pooled RR of 0.94, 95 % CI [0.73, 1.21], p = 0.63. * Merchante et al., administered two different doses of Sarilumab (200 mg and 400 mg) with varying sample sizes for each dose. † Jonas et al., examined two types of mAbs (Tocilizumab and Anakinra) with different sample sizes for each.

respiratory distress syndrome (ARDS) [4]. Despite an overall mortality rate of 6.36 %, it is noteworthy that the predominant cause of mortality was severe COVID-19 infections [5]. Creating the best and most efficient treatments for COVID-19 is crucial for reducing the severity and death rate of the disease. Potential targets for the management of COVID-19 include components of the virus and the host immune system. SARS-CoV-2 infection may cause an exaggerated immune response, resulting in cytokine storms and leading to severe respiratory distress and organ failure [6]. Monoclonal antibodies (mAbs) are suggested as a potential treatment for COVID-19. Recently, mAbs targeting inflammatory cytokines have received emergency use permission (EUA) from the FDA as investigational therapy for COVID-19 [7]. Monoclonal antibodies identify a single epitope of an antigen, whereas polyclonal antibodies identify several epitopes. The different regions can be used to target specific molecules such as the S2-protein, cytokines, and cytokine receptors [8].

Tocilizumab and Sarilumab are monoclonal antibodies designed to selectively bind to the interleukin-6 receptor (IL-6R), a crucial component in the inflammatory response linked to severe cases of COVID-19 [9,10]. Further, Anakinra is a recombinant human interleukin-1 receptor antagonist that inhibits the action of interleukin-1, a cytokine that plays a role in the inflammatory response [11]. mAbs have the potential to reduce inflammation and enhance outcomes in patients at risk of developing respiratory failure [12]. The previous *meta*-analysis (up to February 30th, 2022) included different study settings (prospective and retrospective studies) [13]. However, our *meta*-analysis assessed the efficacy of administering Tocilizumab, Sarilumab, and Anakinra in reducing the need for mechanical ventilation (MV), mortality rates, progression to clinical worsening, and discharging COVID-19 hospitalized patients in RCTs.

2. Method

2.1. Eligibility criteria

Only RCTs assessing the clinical effectiveness of tocilizumab, sarilumab, or anakinra and their comparators in treating COVID-19. All RCT records which had examined the effect of considered mAbs, with at least one outcome, such as mortality or the need for MV were included in our study.

Filtered criteria included: (i) case reports, (ii) single-arm studies, (iii) cohort studies, (iv) pharmacokinetic studies, and (v) *in vitro* studies.

2.2. Search strategy

All included studies were initially identified by conducting a systematic search on Scopus, PubMed, Web of Science up to April 1, 2024, using the following keywords: “SARS”, “Corona”, “Coronaviruses”, “SARS-CoV-2”, “SARS-CoV”, “COVID 19”, “COVID-19”, “monoclonal antibody”, “antibodies”, “monoclonal”, ”Sarilumab”, “Anakinra”, “Tocilizumab”, “TCZ”. In order to ensure meticulousness, a manual search was conducted using reference lists of previous studies.

2.3. Selection process

Tow authors (M.A and A.T) separately conducted the search process and investigated the identified papers to reduce possible biases. The differences were resolved by the third author (M.H.P). The systematic search of online databases was performed using the databases’ fit syntax andEndNote (version 20) was recruited to manage the recovered records. After removing duplicate entries, the screening flow was proceeded via scrutiny of title, abstract anf full text. To reach the precise data the Rayyan online screening tool was also used [14].

2.4. Data items

The extracted data from each record includes the first author, publication year, country, doses of mAbs, name of mAb, sample size for the control group and intervention group, number of deaths related to COVID-19, number of patients requiring MV, number of patients progressing to clinical worsening, and number of patients discharged at day 28 in each group.

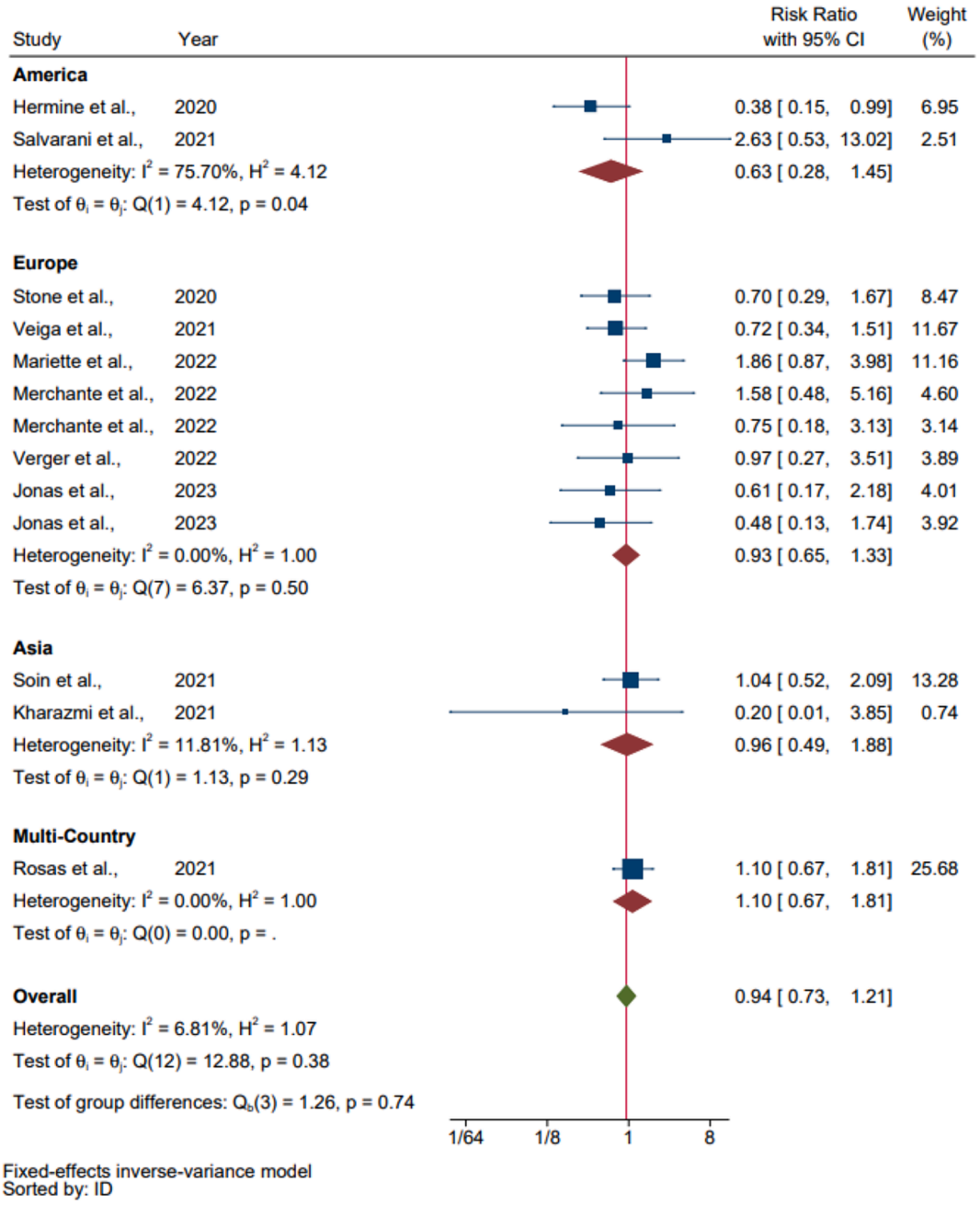

Fig. 3. Subgroup analysis of monoclonal antibody efficacy in reducing the risk of MV in different regions. No significant difference was found in the region subgroup analysis (p = 0.74).

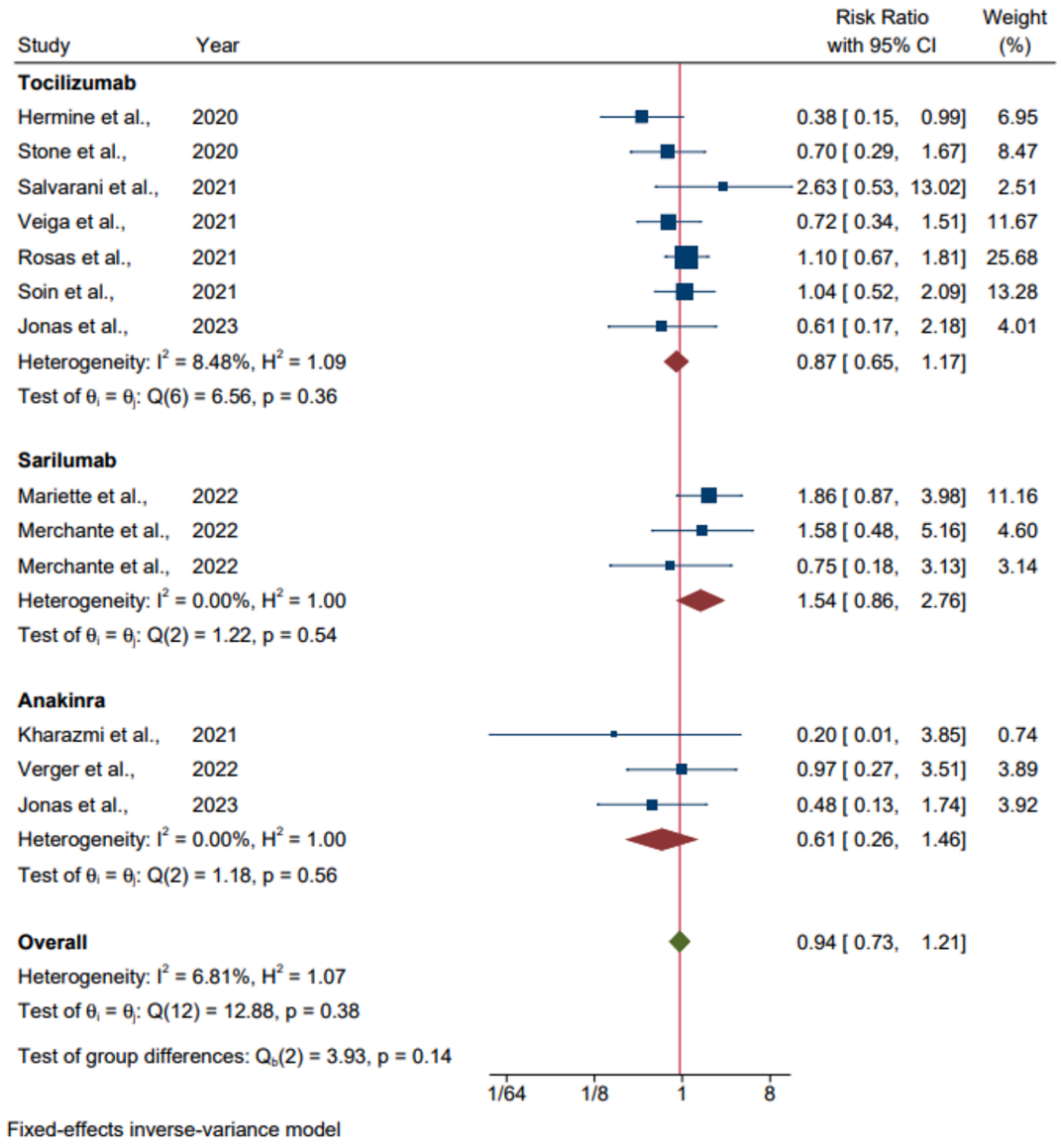

Fig. 4. Comparative efficacy of different monoclonal antibody types in reducing MV risk. None of the mAbs demonstrated significant effect against the requirement for mechanical ventilation.

2.5. Quality assessment of included articles

Critical appraisal checklist JBI (JBI RCTs Appraisal tool 2017) was utilized to assess the risk of bias of included RCTs [15].

2.6. Statistical analysis

Statistical analysis was conducted using STATA 17.0 (STATA Corp., LLC, Revision, June 14, 2021). Heterogeneity was assessed using the Cochran's Q test and Higgins I^2 index, with significance defined as $P \leq 0.1$ [16,17]. The fixed effects model (Invers-variance method) was utilized to pool the relative risks of studies. Statistically significant outcomes were determined by 95 % CIs for the pooled relative risk not covering 1 in the forest plot.

Sensitivity analyses using the leave-one-out approach were conducted with the metaninf command. Publication bias was evaluated by employing Egger's linear regression test and Begg's methods, considering statistical significance as a two-sided P-value $P \leq 0.05$ [18,19].

3. Result

3.1. Descriptive statistics

After removing duplicates, 5902 records were identified as a result of a systematic search of databases. Of these, 5835 studies were excluded based on title and abstract screening for the following reasons: *meta*-analysis, review, conference abstract article without full text, irrelevant data, and non-RCT article.

In the full-text review, 48 articles were excluded due to irrelevant data. Ultimately, 19 papers were included in the *meta*-analysis Table 1. The selection procedure summary was depicted in the Prisma flowchart (Fig. 1). Three articles were published in 2020 [20–22], followed by ten in 2021 [23–32], three in 2022 [33–35], and two in 2023 [36,37]. Additionally, one paper was published in 2024 [38]. France has conducted the most research among the countries. Ten articles investigated Tocilizumab, four specifically targeted Sarilumab, and six trials evaluated the efficacy of Anakinra. Table 2 displays the results of the quality assessment.

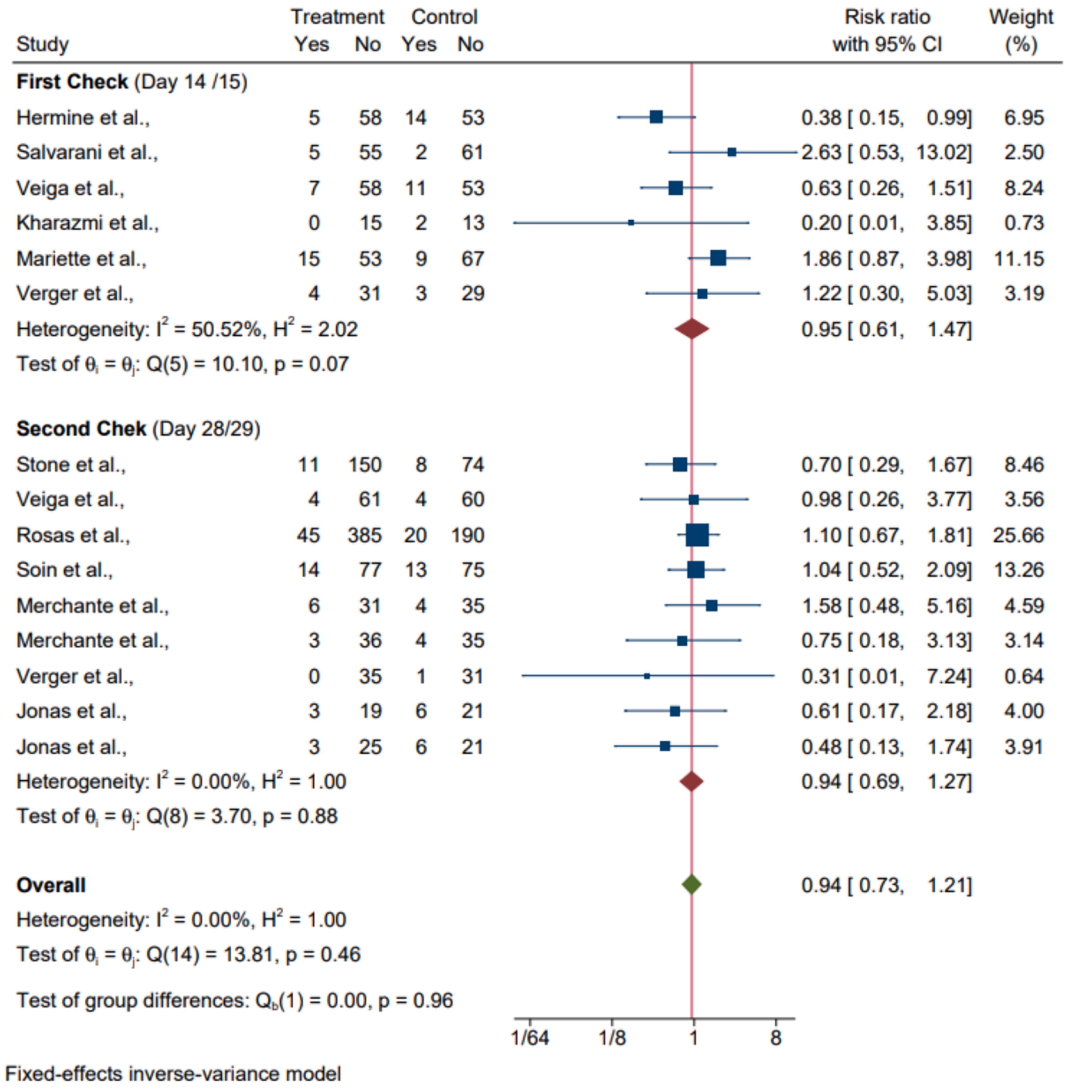

Fig. 5. Efficacy of monoclonal antibodies in reducing MV risk over time (first and second checkpoint). Non-significant outcome was observed in terms of the efficacy of mAbs to reduce the risk of needing MV over time.

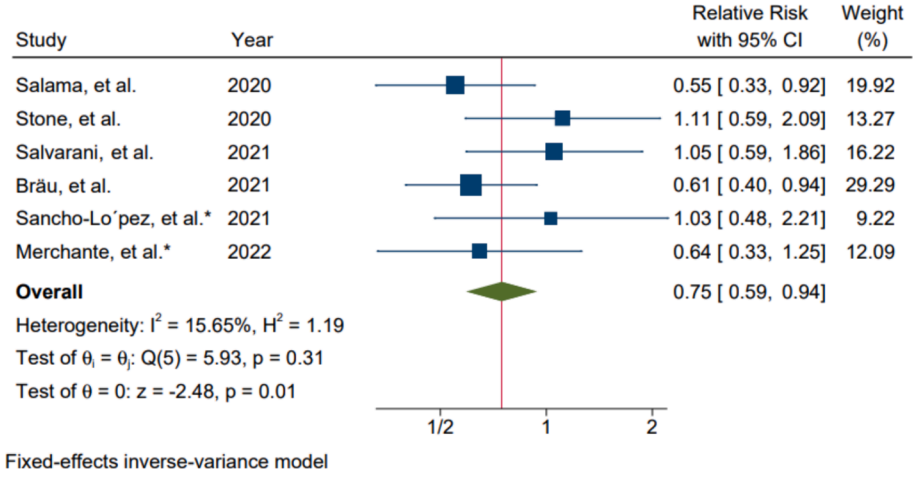

Fig. 6. Efficacy of monoclonal antibodies in reducing the risk of clinical worsening. the pooled data demonstrated that the use of mAbs significantly reduced the risk of clinical worsening (p = 0.01). *The extracted relative risks from each study that examined different doses of a specific mAb were pooled together, without consideration of time or dose.

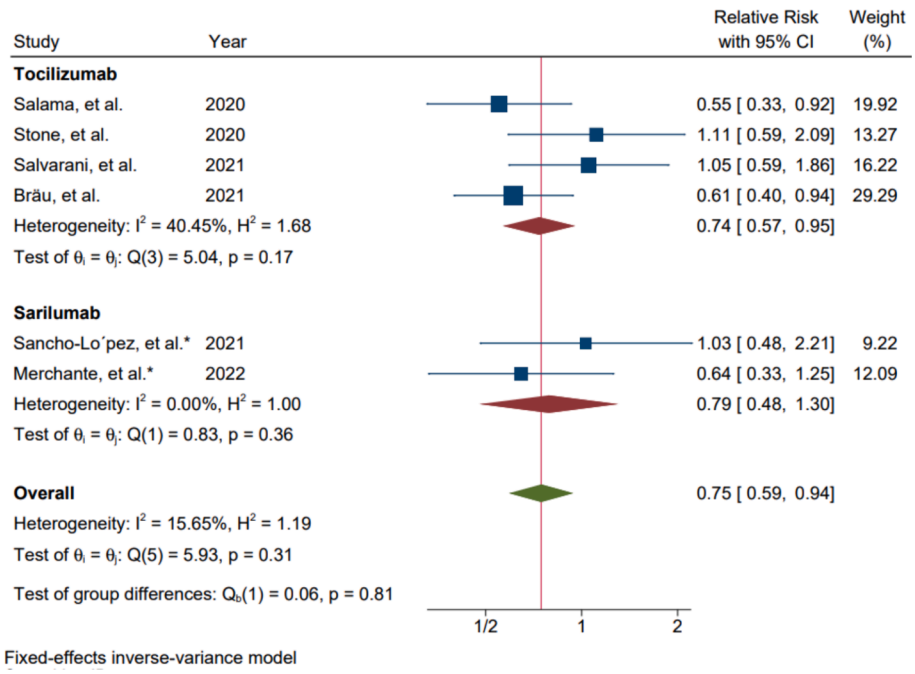

Fig. 7. Comparative efficacy of Tocilizumab and Sarilumab in reducing the risk of clinical worsening in COVID-19 Patients. Results revealed that Tocilizumab had a significant effect against the clinical worsening (pooled relative risk of 0.74, 95 % CI [0.57, 0.95]). *The extracted relative risks from each study that examined different doses of a specific mAb were pooled together, without consideration of time or dose.

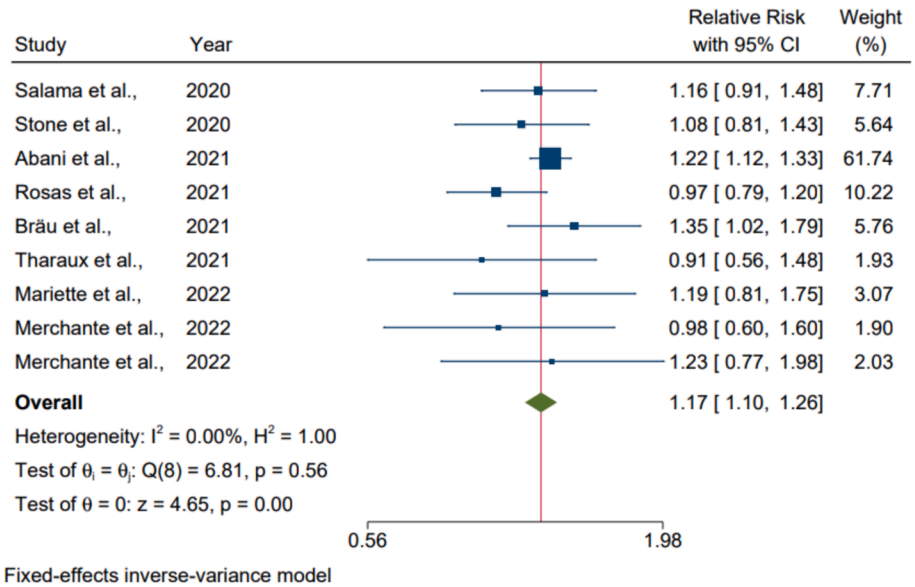

Fig. 8. Effect of mAbs on time to hospital discharge in COVID-19 patients. The analysis demonstrates that the probability of discharging by day 28 or 29 is significantly higher in the treatment group compared to the control (p = 0.00).

3.2. *Required for mechanical ventilation*

The need for MV in COVID-19 patients who received mAbs was compared to control groups (Fig. 2). The Risk Ratio (RR) for MV, without considering the specific types of mAbs, was not significant (pooled RR: 0.94, 95 % CI [0.73, 1.21], p = 0.63, I^2 = 6.81 %).

3.2.1. *Subgroup analysis for MV*

In addition to the overall RR, the risk of MV was analyzed in three subgroups based on mAb type, region, and checkpoint. Fig. 3 shows that there is a high heterogeneity in studies conducted in the American continent (I^2 = 75.70 %, p = 0.04). Furthermore, there was no significant difference in the region subgroup analysis, p = 0.74.

Fig. 4 shows that, while insignificant, Anakinra yielded a more favorable outcome in reducing the need for MV (RR: 0.61, 95 % CI [0.26, 1.46]) compared to the other groups. Conversely, Sarilumab was associated with the worst outcome (RR: 1.54, 95 % CI [0.86, 2.76]). However, none of the groups (Tocilizumab, Sarilumab, Anakinra) demonstrated significant pooled data against the requirement for MV (p = 0.36, p = 0.54, p = 0.56 respectively). Based on the time duration, Fig. 5 depicts that the first (day 14 or 15) and the second (day 28 or 29) checkpoints yield similar outcomes (non-significant) in terms of the efficacy of mAbs to reduce the risk of needing MV. This efficacy has remained relatively stable over time, with an RR of 0.95, 95 % CI [0.61,

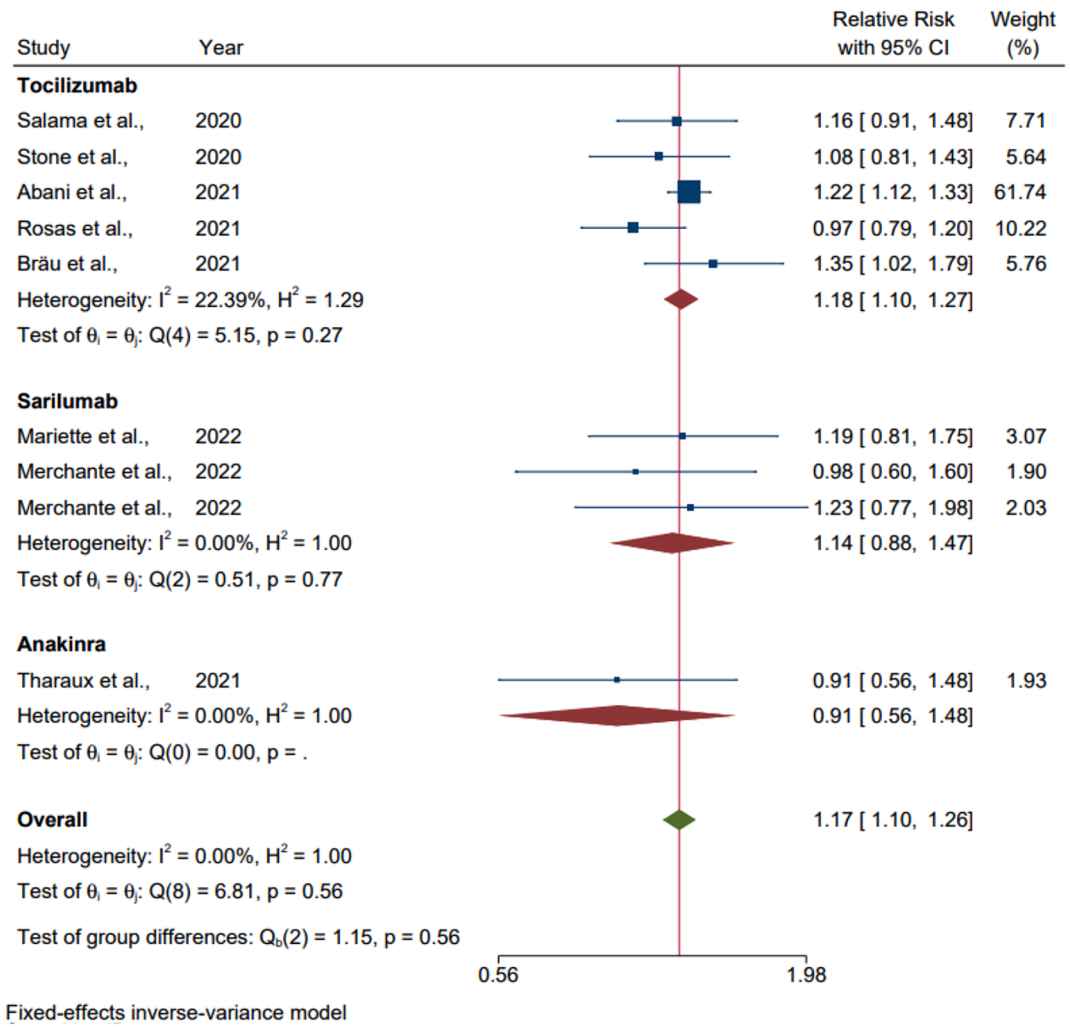

Fig. 9. Subgroup analysis based on mabs in reducing hospital stay duration. Among the studied antibodies, only Tocilizumab showed a significant relative risk (1.18, 95 % CI [1.10, 1.27])

1.47] for the first checkpoint and 0.94, 95 % CI [0.69, 1.27] for the second checkpoint.

3.3. Clinical worsening risk

All studies evaluating the risk of clinical worsening were included (each used their own set of criteria to define clinical worsening). Generally, clinical worsening can be defined as a clinical event that leads to treatment failure. According to the studies provided, clinical worsening can encompass several occurrences, including death, withdrawal from the study while hospitalized, transfer to the intensive care unit (ICU), initiation of invasive MV, utilization of high-flow nasal oxygen, CPAP, and non-mechanical ventilation.

Intriguingly, Among the studies reporting the risk of clinical worsening (Fig. 6), the pooled data indicated that the use of mAbs in the treatment group significantly reduced the overall risk of progression to clinical worsening (overall pooled relative risk: 0.75, 95 % CI [0.59, 0.94], p = 0.01).

3.3.1. Subgroup analysis for clinical worsening

Subgrouping the data based on mAbs revealed that Tocilizumab had a significant effect against the progression to clinical worsening (pooled relative risk of 0.74, 95 % CI [0.57, 0.95]) but not Sarilumab (pooled relative risk 0.79, 95 % CI [0.48, 1.30])(Fig. 7).

3.4. Discharging by day 28 or day 29

Upon analyzing the pooled data from studies, it was found that the probability of discharging by day 28 or 29 was higher in the treatment group compared to the control group (Fig. 8), with a pooled relative risk of 1.17, 95 % CI [1.10, 1.26]. Subgroup analysis revealed that both Tocilizumab and Sarilumab were associated with positive effects in reducing the time of hospital discharge, but only Tocilizumab showed a significant effect size (Fig. 9).

3.5. Mortality

The pooled effect size indicates that in total (Fig. 10), the administration of mAbs (Tocilizumab, Sarilumab, Anakinra) has the potential to reduce the risk of mortality over time when compared to control groups, with a pooled RR of 0.90, 95 % CI [0.83, 0.97], (p = 0.01).

3.5.1. Mortality subgroup analysis

Based on data from European patients, the use of mAbs showed a significant therapeutic response, with a decrease in mortality rate (pooled RR: 0.88, 95 % CI [0.81, 0.96]) (Fig. 11). Notably, Tocilizumab has demonstrated a particularly positive outcome compared to other treatments in reducing mortality rates (pooled RR: 0.91, 95 % CI [0.84, 0.98]) (Fig. 12). Furthermore, there is potential benefit in administering a higher dose of sarilumab (400 mg) rather than a lower dose (200 mg),

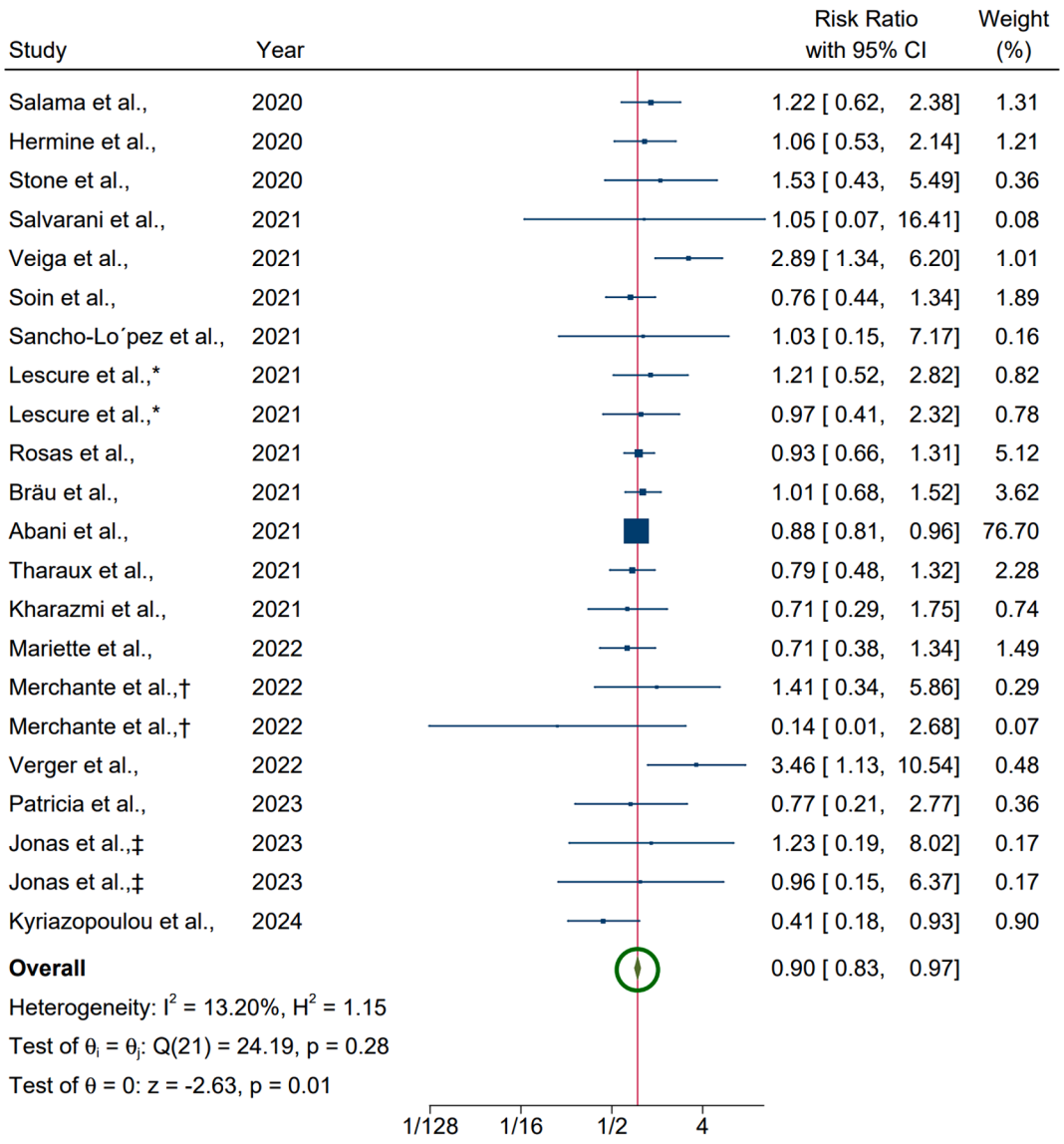

Fig. 10. Overall risk of mortality with mAbs treatment. *†Merchante et al., and Lescure et al., administered two different doses of Sarilumab (200 mg and 400 mg) with varying sample sizes for each dose. ‡ Jonas et al., examined two types of mAbs (Tocilizumab and Anakinra) with varying sample sizes for each.

as it may further decrease the risk of mortality, although this effect was not statistically significant (pooled RR: 0.83, 95 % CI [0.36–1.91] vs 1.26, 95 % CI [0.61–2.60]) (Fig. 13). Additionally, studies evaluating the risk of mortality at a longer time point (second checkpoint) have shown significant results in reducing mortality. however, such an outcome was not observed for the first checkpoint (Fig. 14), suggesting that the effectiveness of mAbs in reducing mortality may fulfill over time (pooled RR: 0.90, 95 % CI [0.83, 0.97]).

3.6. Publication bias

The Egger's test, Begg's test (Table 3), and visual inspection of funnel plots (Fig. 15) were utilized to assess the bias of publications for each outcome. The analytical outcomes revealed that there is no potential publication bias and methodological uniformity across included publications.

3.7. Sensitivity analysis

Sensitivity analysis was conducted to evaluate the influence of each publication on the overall effect size (ES). The systematic elimination of studies, one by one, from each group is presented in Fig. 16.

4. Discussion

Our *meta*-analysis examined the impact of three monoclonal antibodies (Tocilizumab, Sarilumab, and Anakinra) on the treatment of COVID-19 patients in comparison with control group. The findings suggest that mAbs, particularly Tocilizumab, could potentially reduce the severity of COVID-19 and improve clinical outcomes, such as reducing the risk of clinical worsening, improving hospital discharge rates, and decreasing mortality. The lack of significant effect on the need for MV across the different mAbs is an interesting observation that warrants further investigation.

Furthermore, it is important to investigate the optimal dosing and timing strategies for mAbs administration, as the *meta*-analysis findings suggest different effect sizes for each dose, of Sarilumab. The decrease in risk of mortality may be more pronounced at longer time period. Understanding the temporal dynamics of the immune response and the evolution of the disease could guide the most effective treatment protocols.

In a subgroup analysis, the results suggest that mortality reduction

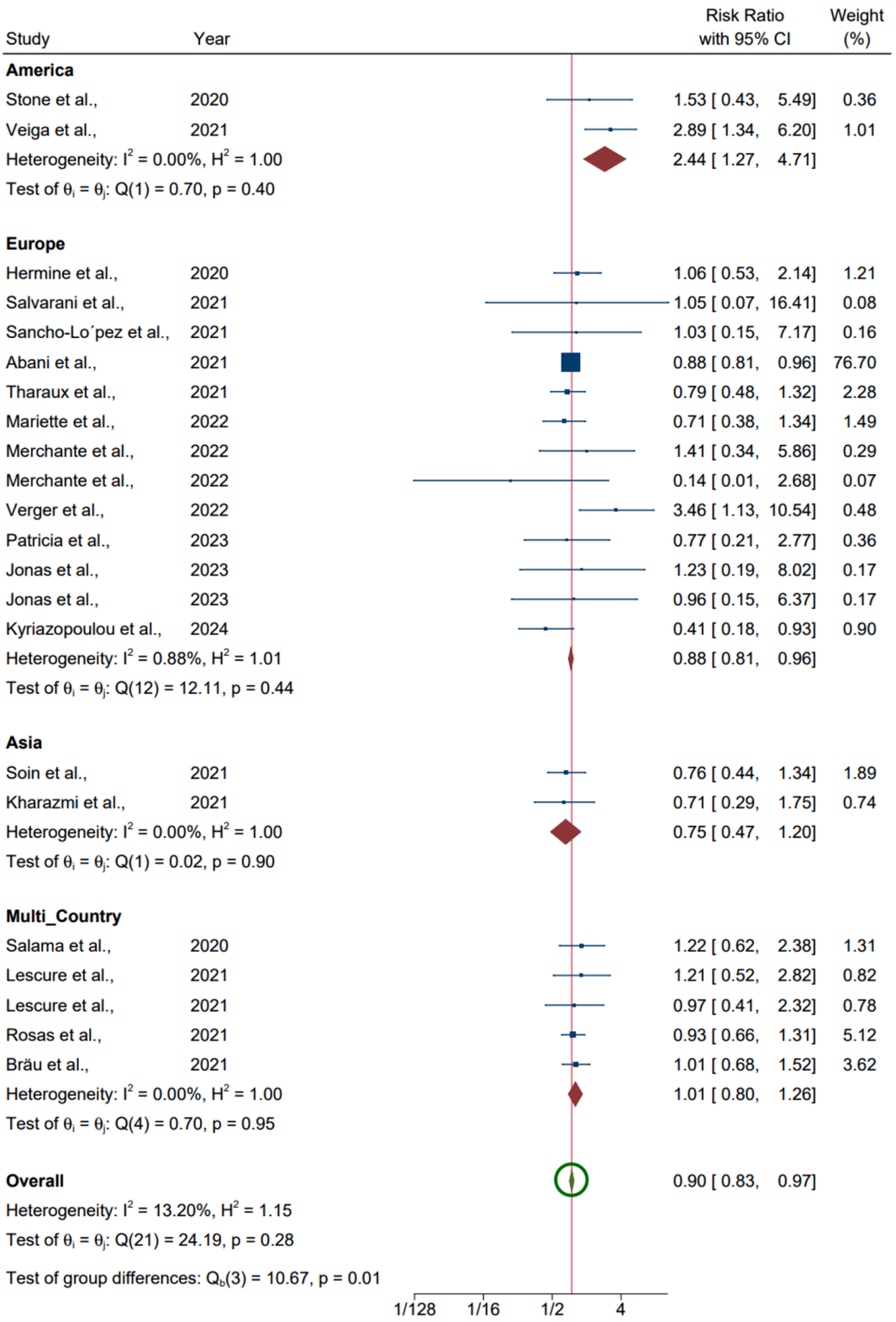

Fig. 11. Therapeutic efficacy of mAbs in mortality rate accordance with regional subgroup analysis. Studies on European patients, showed a significant decrease in mortality rate in mAbs treating group in comparison with control group (pooled RR: 0.88, 95 % CI [0.81, 0.96]).

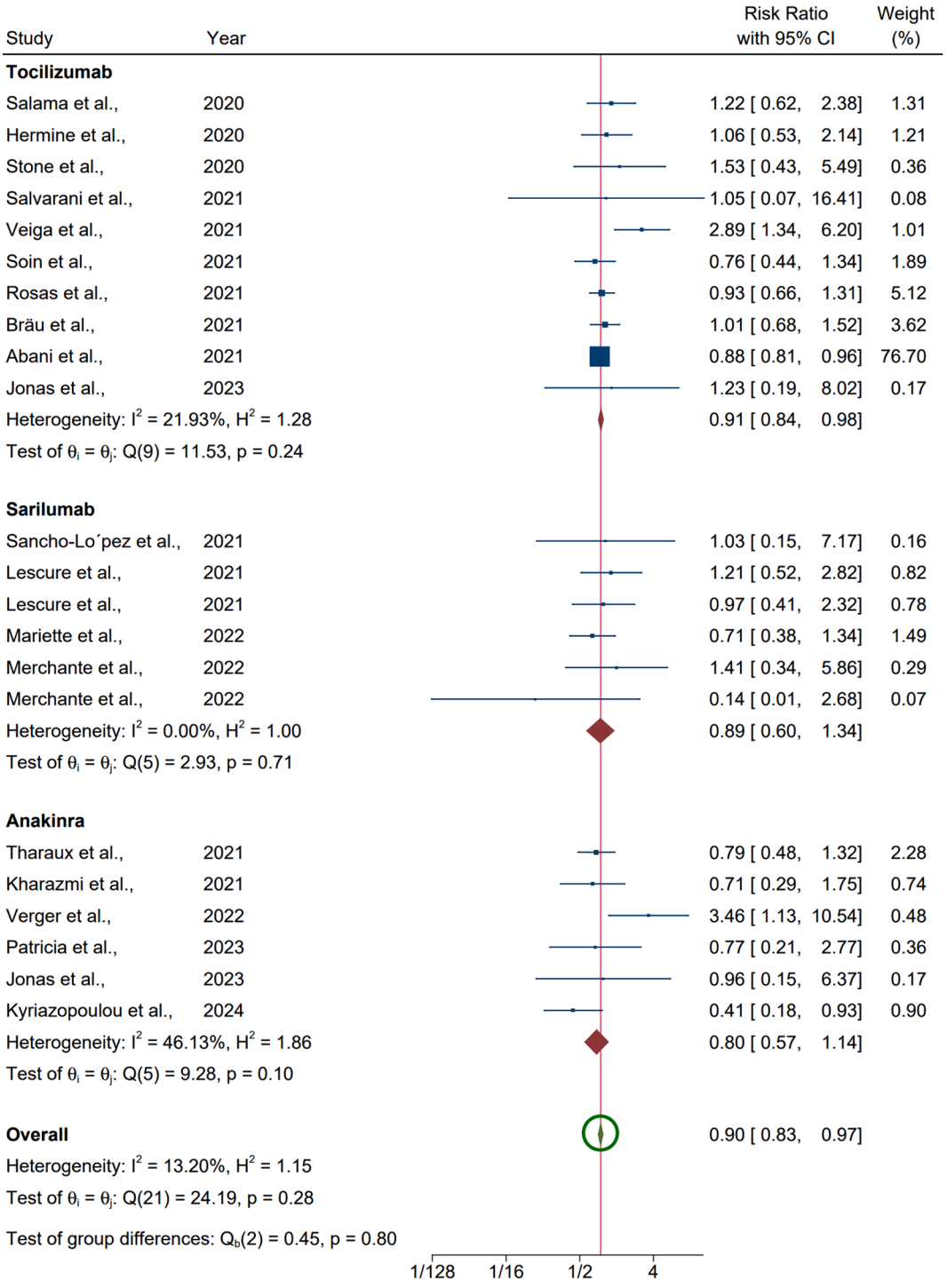

Fig. 12. Evaluating the risk of mortality in different mAbs groups. Tocilizumab showed a significant positive outcome compared to other mAbs in reducing mortality rates (pooled RR: 0.91, 95 % CI [0.84, 0.98]).

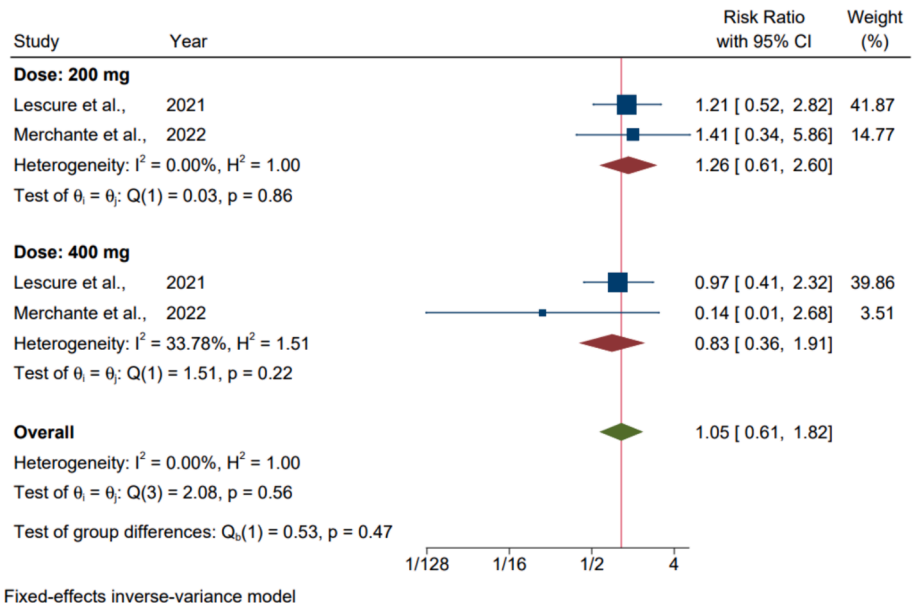

Fig. 13. Forest plot comparing the mortality risk in subgroups for two different doses of Sarilumab. No statistically significant difference was observed between mAbs ($p = 0.47$).

was particularly pronounced in European patients, highlighting a potential regional variation in response. The *meta*-analysis identified significant heterogeneity across studies' region, concerning MV outcomes, emphasizing the need for further research to understand the factors contributing to this variability.

While the subgroup analyses provide valuable insights, they are limited by the number of studies within each subgroup, especially in the region subgroup for MV and optimized dose for Sarilumab. Larger, well-designed studies are needed to confirm the observed trends.

Tocilizumab, Sarilumab, and Anakinra are kinds of mAbs that target different pathways and can efficiently decrease multisystem inflammation. Tocilizumab and Sarilumab block the interleukin-6 (IL-6) receptor, which inhibits IL-6 signaling and reduces inflammation. Tocilizumab binds both soluble and membrane-bound IL-6 receptors, while Sarilumab only binds to the membrane-bound receptor [9]. By blocking IL-6 signaling, these agents can efficiently control conditions resulting from high IL-6 levels, such as acute respiratory distress syndrome and systemic juvenile idiopathic arthritis [39,40].

Anakinra is a recombinant protein that selectively targets interleukin-1 (IL-1), a significant pro-inflammatory cytokine. Anakinra functions by competitively blocking IL-1 receptors, therefore inhibiting the effects of IL-1 [11]. Anakinra may be superior to IL-6 inhibitors for conditions in which IL-1 is the primary driver of the disease. Each of the three biomolecular agents has the potential to reduce inflammation by targeting IL-6 or IL-1, allowing for personalized therapy strategies based on the causes of multisystem inflammation in patients.

According to the results, categorizing patients based on their cytokine levels could improve the treatment success rate. In addition, the timing of the intervention is essential.

A systematic review and *meta*-analysis was conducted by Piscoya et al., to assess the efficacy and safety of Tocilizumab in hospitalized COVID-19 patients [41].

They considered major databases including PubMed, EMBASE, Scopus, Web of Science, Cochrane Library, medRxiv, and Preprints to be searched from inception to March 4, 2021. RCTs and higher quality inverse probability of treatment weighting (IPTW) cohort studies comparing Tocilizumab with standard care in hospitalized adult COVID-19 patients were included. A total of nine RCTs involving 7021 patients and nine IPTW cohorts involving 7796 patients met the inclusion criteria. In compliance with our study, their *meta*-analysis showed that Tocilizumab significantly reduced all-cause mortality compared to standard care in RCTs (RR: 0.89, 95 % CI 0.81–0.98, moderate quality of evidence) but the reduction was not significant in cohorts (RR: 0.67, 95 % CI 0.44–1.02, very low quality of evidence). Contrary to our study, they concluded that Tocilizumab significantly decreased the need for MV in RCTs (RR: 0.80, 95 % CI 0.71–0.90, moderate quality of evidence). They found that there were no significant differences in clinical worsening between the two groups. While a significant protective effect was discovered for Tocilizumab in our study. The moderate quality of evidence indicates more research is still needed.

Furthermore, Gupta et al. provided a systematic review and *meta*-analysis to examine the effects of Tocilizumab in hospitalized patients with COVID-19 who did not require MV [42]. They performed an online database search on PubMed, Embase, Google Scholar, and the Cochrane Library from inception until April 19, 2021. The inclusion criteria consisted of RCTs that compared the efficacy of Tocilizumab with standard care treatment (steroids, antibiotics, antivirals) in adult patients who were hospitalized with COVID-19 and were not on MV at the time of receiving Tocilizumab. The main result was a composit of either needing MV or mortality within 28 days. The secondary outcomes were the mortality rate within 28 days and the incidence of serious adverse events. A total of 6 RCTs involving 3013 patients (1651 in the Tocilizumab group and 1362 in the control group) were included. This systematic review and *meta*-analysis showed that Tocilizumab significantly reduced the primary composite outcome of MV or 28-day mortality in hospitalized COVID-19 patients.. While 28-day mortality was not significantly reduced, this may be a limitation of using short-term mortality as an outcome in critical trials. Some limitations included variability in outcomes reported across studies and limited data on long-term outcomes and adverse events.

On the other hand, a systematic search of major databases including PubMed, Cochrane Library, Embase, medRxiv and bioRxiv was conducted to identify studies comparing the efficacy of Tocilizumab to other treatments for COVID-19. Only retrospective observational studies published until May 24, 2020 reporting outcomes such as mortality, ICU admission, and need for MV were included [43]. After screening, seven retrospective studies with a total of 592 patients were included in the *meta*-analysis. The Tocilizumab group had 240 patients while the control group consisted of 352 patients. Mortality in the Tocilizumab group was 16.3 % compared to 24.1 % in the control group, though the difference

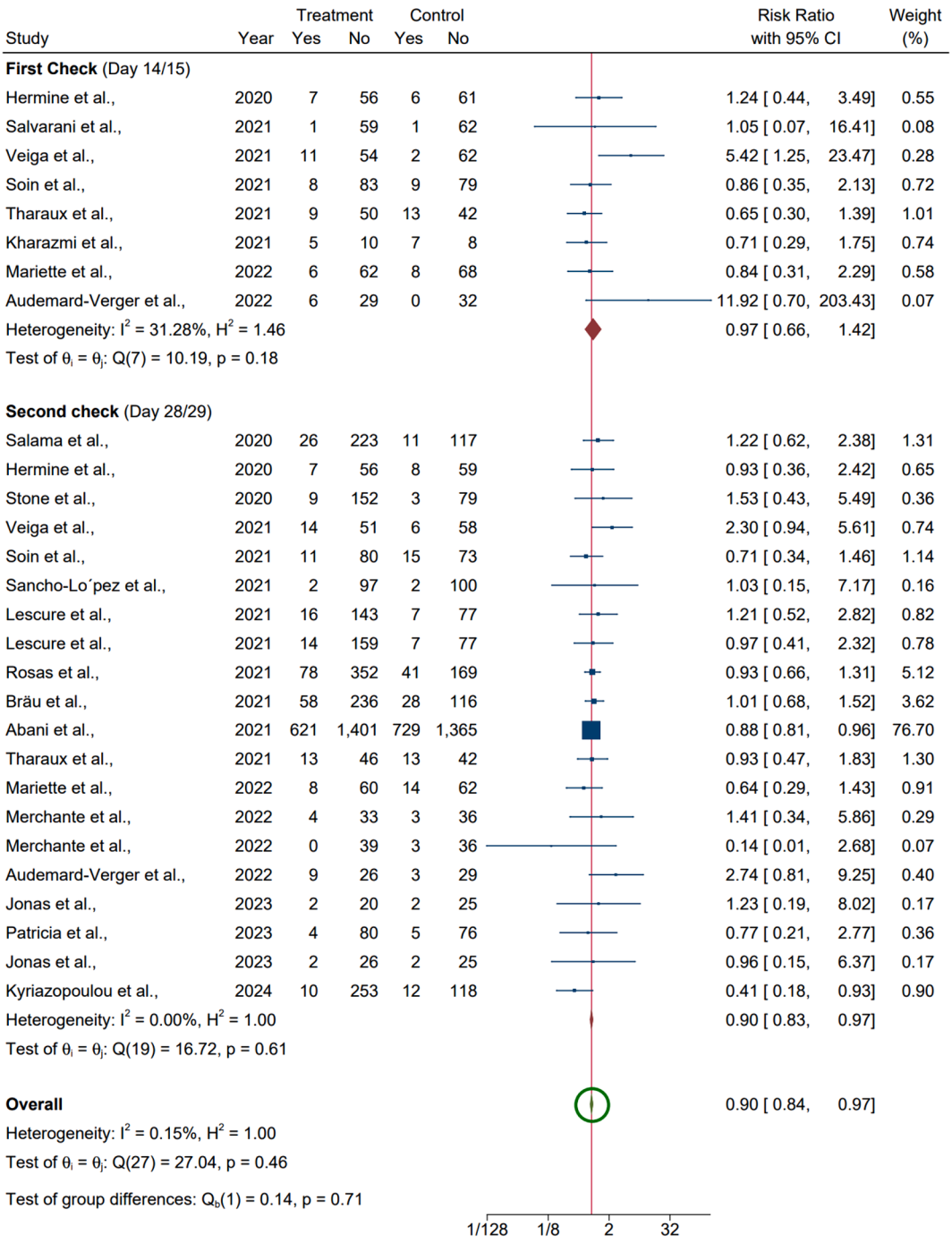

Fig. 14. Comparison of the impact of mAbs at different time points (first and second checkpoint) on the risk of mortality. Second checkpoint showed significant results compared to the first checkpoint.

Table 3
The results of publication bias in each outcome.

Outcome	Egger's P value	Begg's P value
Mechanical ventilation (MV)	0.348	0.669
Clinical worsening risk	0.181	0.452
Discharging by day 28 or day 29	0.216	0.466
Mortality	0.317	1.00

was not statistically significant (RR: 0.62, 95 % CI 0.31–1.22, $I^2 = 68$ %). Risk of ICU admission and MV requirements were also similar between the two groups.

However, some limitations were notified for this publication including lack of randomized studies, small sample sizes, heterogeneous populations and treatments. Finally, they stated that the earlier administration of Tocilizumab may potentially show better results but timing effects remain unclear. Adverse events associated with Tocilizumab like secondary infections also require further investigation.

Our *meta*-analysis provided valuable data for decision-making in clinicacl guidline., informing public health policies, and preparing for future pandemics, considering the economic burden and potential risks

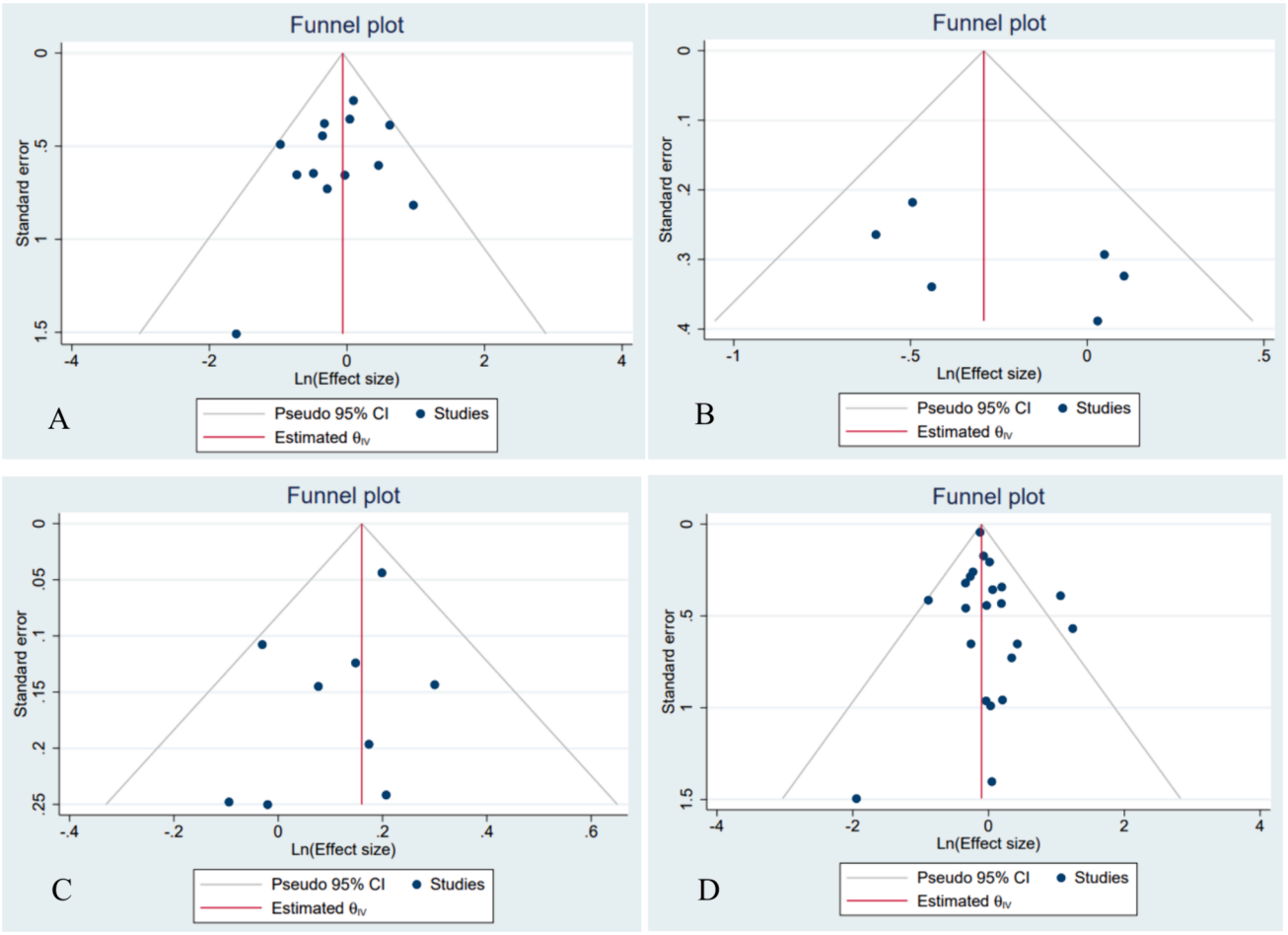

Fig. 15. Funnel plots of studies, **A**. Mechanical ventilation (MV), **B**. Clinical worsening risk, **C**. Discharging by day 28 or day 29, **D**. Mortality. The funnel plots depicted a relative symmetry in the included studies. This suggests the absence of potential publication bias and reveals methodological uniformity across all publications.

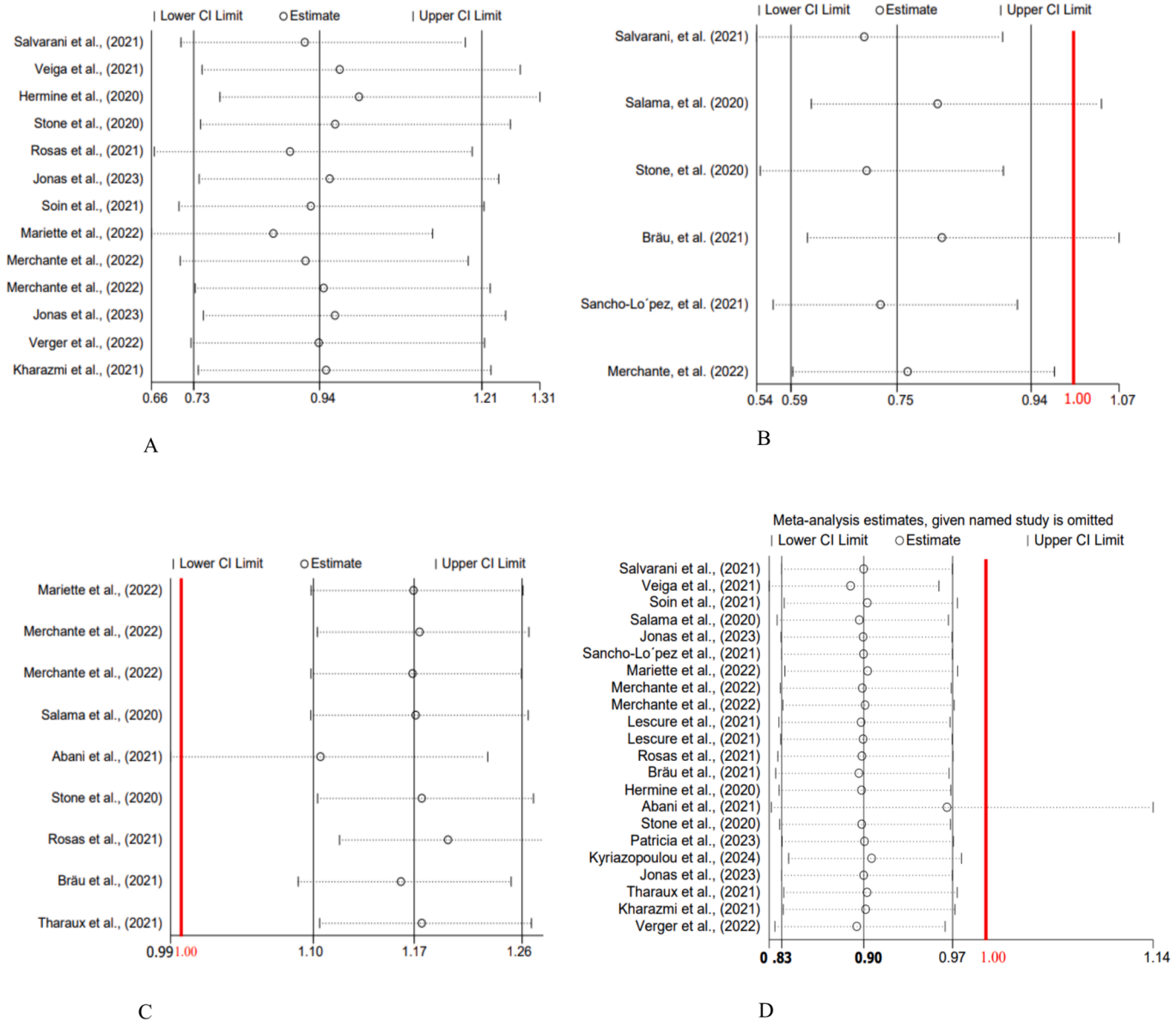

Fig. 16. The Metaninf function was utilized to perform a sensitivity analysis, assessing the impact of each included study on the overall effect size (ES). **A.** Mechanical ventilation; The sensitivity analysis indicates that the pooled effect size was not influenced by any of the studies. **B.** Clinical worsening risk; The sensitivity analysis indicates that the pooled effect size was significantly sensitive to Salama et al., (2020) and Bräu et al., (2021) studies. If these studies are excluded, the pooled effect size is not significant., **C.** Discharging by day 28 or day 29; The sensitivity analysis reveals that the pooled effect size is significantly influenced by the study conducted by Abani et al., (2021). Excluding the study results in a non-significant pooled effect size., **D.** Mortality; The pooled effect size is significantly sensitive to the study of Abani et al., (2021). Excluding the study leads to a non-significant pooled effect size.

associated with mAbs use during the COVID-19 pandemic.

5. Conclusion

To sum up, our *meta*-analysis provides valuable insights into the potential role of mAbs, especially Tocilizumab, in the management of COVID-19. The findings suggest a beneficial effect on reducing the risk of clinical worsening, improving hospital discharge rates, and decreasing mortality.

CRediT authorship contribution statement

Yousef Jafari Abarghan: Writing – original draft. **Mohammad Heiat:** Writing – review & editing. **Abolfazl Jahangiri:** Investigation, Formal analysis. **Mohammad Hossein Peypar:** Writing – review & editing, Formal analysis. **Mahdi Abdorrashidi:** Writing – review & editing, Methodology. **Amirmohammad Tohidinia:** Methodology. **Mahmood Salesi:** Investigation. **Shahrzad Tajik:** Methodology. **Farnaz Farzaneh Dehkordi:** Visualization. **Hamid Sedighian:** Writing – review & editing, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

The datasets used and/or analyzed during this study are available from the corresponding authors upon reasonable request.

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References

[1] C.-C. Lai, C.-Y. Wang, Y.-H. Wang, P.-R. Hsueh, Global coronavirus disease 2019: What has daily cumulative index taught us? Int. J. Antimicrob. Agents 55 (6) (2020) 106001.
[2] WHO Coronavirus (COVID-19) Dashboard 2021 [Available from: https://covid19.who.int/.
[3] Z. Wang, H. Deng, C. Ou, J. Liang, Y. Wang, M. Jiang, S. Li, Clinical symptoms, comorbidities and complications in severe and non-severe patients with COVID-19: a systematic review and meta-analysis without cases duplication, Medicine 99 (48) (2020).
[4] C.-C. Lai, Y.H. Liu, C.-Y. Wang, Y.-H. Wang, S.-C. Hsueh, M.-Y. Yen, et al., Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths, J. Microbiol. Immunol. Infect. 53 (3) (2020) 404–412.
[5] Organization WH. Overview of public health and social measures in the context of COVID-19: interim guidance, 18 May 2020. World Health Organization; 2020.
[6] C. Zanza, T. Romenskaya, A.C. Manetti, F. Franceschi, R. La Russa, G. Bertozzi et al. Cytokine Storm in COVID-19: Immunopathogenesis and Therapy. Medicina (Kaunas). 2022;58(2).
[7] U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: November 9, 2020. Food and drug administration. 2020 https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update november-9-2020. (Accessed 2 February 2021).
[8] Malik B, Ghatol A. Understanding How Monoclonal Antibodies Work. [Updated 2023 Jun 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572118/.
[9] C. Xu, A. Rafique, T. Potocky, A. Paccaly, P. Nolain, Q. Lu, et al., Differential binding of sarilumab and tocilizumab to IL-6Rα and effects of receptor occupancy on clinical parameters, J Clin Pharmacol. 61 (5) (2021) 714–724.
[10] E.A. Coomes, H. Haghbayan, Interleukin-6 in Covid-19: A systematic review and meta-analysis, Rev Med Virol. 30 (6) (2020) 1–9.
[11] R.S. Cvetkovic, K.G. Anakinra, BioDrugs 16 (4) (2002) 303–311, discussion 13–4.
[12] A. Lyly, A. Laulajainen-Hongisto, P. Gevaert, P. Kauppi, S. Toppila-Salmi, Monoclonal Antibodies and Airway Diseases, Int J Mol Sci. 21 (24) (2020).
[13] F.A. Khan, I. Stewart, L. Fabbri, S. Moss, K. Robinson, A.R. Smyth, G. Jenkins, Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19, Thorax 76 (9) (2021) 907–919.
[14] Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016; 5(1):210.
[15] E. Aromataris, Z. Munn (Eds.), JBI Manual for Evidence Synthesis JBI, 2020.
[16] J.P. Higgins, S.G. Thompson, J.J. Deeks, D.G. Altman, Measuring inconsistency in meta-analyses, BMJ 327 (7414) (2003) 557–560.
[17] J.P. Higgins, S.G. Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med. 21 (11) (2002) 1539–1558.
[18] M. Egger, G. Davey Smith, M. Schneider, C. Minder, Bias in meta-analysis detected by a simple, graphical test, BMJ 315 (7109) (1997) 629–634.
[19] C.B. Begg, M. Mazumdar, Operating characteristics of a rank correlation test for publication bias, Biometrics 50 (4) (1994) 1088–1101.
[20] J.H. Stone, M.J. Frigault, N.J. Serling-Boyd, A.D. Fernandes, L. Harvey, A. S. Foulkes, et al., Efficacy of tocilizumab in patients hospitalized with covid-19, N. Engl. J. Med. 383 (24) (2020) 2333–2344.
[21] O. Hermine, X. Mariette, P.-L. Tharaux, M. Resche-Rigon, R. Porcher, P. Ravaud, C-C. Group, Effect of tocilizumab vs usual care in adults hospitalized With COVID-19 and moderate or severe pneumonia: a randomized clinical trial, JAMA Intern. Med. 181 (1) (2021) 32–40.
[22] C. Salama, J. Han, L. Yau, W.G. Reiss, B. Kramer, J.D. Neidhart, et al., Tocilizumab in patients hospitalized with Covid-19 pneumonia, N. Engl. J. Med. 384 (1) (2020) 20–30.
[23] C. Salvarani, G. Dolci, M. Massari, D.F. Merlo, S. Cavuto, L. Savoldi, et al., Effect of Tocilizumab vs standard care on clinical worsening in patients hospitalized With COVID-19 pneumonia: a randomized clinical trial, JAMA Intern. Med. 181 (1) (2021) 24–31.
[24] A. Sancho-López, A.F. Caballero-Bermejo, B. Ruiz-Antorán, E. Múñez Rubio, M. García Gasalla, J. Buades, et al., Efficacy and Safety of Sarilumab in patients with COVID19 pneumonia: a randomized, phase III clinical trial (SARTRE Study), Infect Dis Ther. 10 (4) (2021) 2735–2748.
[25] V.C. Veiga, J.A.G.G. Prats, D.L.C. Farias, R.G. Rosa, L.K. Dourado, F.G. Zampieri, et al., Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial, BMJ 372 (2021) n84.
[26] A.B. Kharazmi, O. Moradi, M. Haghighi, M. Kouchek, A. Manafi-Rasi, M. Raoufi, et al., A randomized controlled clinical trial on efficacy and safety of anakinra in patients with severe COVID-19, Immun. Inflammation Dis. 10 (2) (2022) 201–208.
[27] A.S. Soin, K. Kumar, N.S. Choudhary, P. Sharma, Y. Mehta, S. Kataria, et al., Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial, Lancet Respir. Med. 9 (5) (2021) 511–521.
[28] O. Abani, A. Abbas, F. Abbas, M. Abbas, S. Abbasi, H. Abbass, et al., Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial, Lancet 397 (10285) (2021) 1637–1645.
[29] P.-L. Tharaux, G. Pialoux, A. Pavot, X. Mariette, O. Hermine, M. Resche-Rigon, et al., Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild-to-moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial, Lancet Respir. Med. 9 (3) (2021) 295–304.
[30] F.-X. Lescure, H. Honda, R.A. Fowler, J.S. Lazar, G. Shi, P. Wung, et al., Sarilumab in patients admitted to hospital with severe or critical COVID-19: a randomised, double-blind, placebo-controlled, phase 3 trial, Lancet Respir. Med. 9 (5) (2021) 522–532.
[31] I.O. Rosas, N. Bräu, M. Waters, R.C. Go, B.D. Hunter, S. Bhagani, et al., Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia, N. Engl. J. Med. 384 (16) (2021) 1503–1516.
[32] I.O. Rosas, G. Diaz, R.L. Gottlieb, S.M. Lobo, P. Robinson, B.D. Hunter, et al., Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial, Intensive Care Med. 47 (11) (2021) 1258–1270.
[33] X. Mariette, O. Hermine, P.-L. Tharaux, M. Resche-Rigon, R. Porcher, P. Ravaud, et al., Sarilumab in adults hospitalised with moderate-to-severe COVID-19 pneumonia (CORIMUNO-SARI-1): An open-label randomised controlled trial, The Lancet Rheumatology. 4 (1) (2022) e24–e232.
[34] A. Audemard-Verger, A. Le Gouge, V. Pestre, J. Courjon, V. Langlois, M.O. Vareil, et al., Efficacy and safety of anakinra in adults presenting deteriorating respiratory symptoms from COVID-19: A randomized controlled trial, PLoS One 17 (8) (2022) e0269065.
[35] N. Merchante, S. Cárcel, J.C. Garrido-Gracia, M. Trigo-Rodríguez, M.Á.E. Moreno, R. León-López, et al., Early Use of Sarilumab in Patients Hospitalized with COVID-19 Pneumonia and Features of Systemic Inflammation: the SARICOR Randomized Clinical Trial, Antimicrob Agents Chemother. 66 (2) (2022) e0210721.
[36] P. Fanlo, B.D.C. Gracia-Tello, E. Fonseca Aizpuru, J. Álvarez-Troncoso, A. Gonzalez, S. Prieto-González, et al., Efficacy and Safety of Anakinra Plus Standard of Care for Patients With Severe COVID-19: A Randomized Phase 2/3 Clinical Trial, JAMA Netw Open. 6 (4) (2023) e237243.
[37] J. Sundén-Cullberg, P. Chen, H. Häbel, P. Skorup, H. Janols, J. Rasmuson, et al., Anakinra or tocilizumab in patients admitted to hospital with severe covid-19 at high risk of deterioration (IMMCoVA): A randomized, controlled, open-label trial, PLoS One 18 (12) (2023) e0295838.
[38] E. Kyriazopoulou, Y. Hasin-Brumshtein, U. Midic, G. Poulakou, H. Milionis, S. Metallidis, et al., Transitions of blood immune endotypes and improved outcome by anakinra in COVID-19 pneumonia: an analysis of the SAVE-MORE randomized controlled trial, Crit Care. 28 (1) (2024) 73.
[39] J.D. Cala-García, J.D. Sierra-Bretón, J.E. Cavelier-Baiz, Á.A. Faccini-Martínez, C. E. Pérez-Díaz, Recovery of COVID-19 acute respiratory distress syndrome with tocilizumab: successful outcome in two critically ill patients, Immunotherapy 12 (15) (2020) 1127–1132.
[40] S. Akioka, Interleukin-6 in juvenile idiopathic arthritis, Mod Rheumatol. 29 (2) (2019) 275–286.
[41] A. Piscoya, A. Parra del Riego, R. Cerna-Viacava, J. Rocco, Y.M. Roman, A. A. Escobedo, et al., Efficacy and harms of tocilizumab for the treatment of COVID-19 patients: A systematic review and meta-analysis, PLoS One 17 (6) (2022) e0269368.
[42] S. Gupta, R.P. Padappayil, A. Bansal, S. Daouk, B. Brown, Tocilizumab in Patients Hospitalized with COVID-19 Pneumonia: Systematic Review and Meta-Analysis of Randomized Controlled Trials, J. Invest. Med. 70 (1) (2022) 55–60.
[43] S.-H. Lan, C.-C. Lai, H.-T. Huang, S.-P. Chang, L.-C. Lu, P.-R. Hsueh, Tocilizumab for severe COVID-19: a systematic review and meta-analysis, Int. J. Antimicrob. Agents 56 (3) (2020) 106103.