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CLINICAL RESEARCH STUDY

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Beneficial and Harmful Effects of Monoclonal Antibodies for the Treatment and Prophylaxis of COVID-19: Systematic Review and Meta-Analysis

Adrian V. Hernandez, MD, PhD,[a,b] Alejandro Piscoya, MD, MPH,[b] Vinay Pasupuleti, MD, PhD,[c] Mi T. Phan, BS,[a] Sreya Julakanti, PharmD,[a] Phirin Khen, PharmD,[a] Yuani M. Roman, MD, MPH,[a] César O. Carranza-Tamayo, MD, PhD,[d] Angel A. Escobedo, MD, PhD,[e] C. Michael White, PharmD[a]

[a]Health Outcomes, Policy and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT; [b]Unidad de Revisiones Sistemáticas y Meta-análisis (URSIGET), Vicerrectorado de Investigación, Universidad San Ignacio de Loyola (USIL), Lima, Peru; [c]Cello Health, Yardley, PA; [d]Faculdade de Medicina, Universidade Católica de Brasilia, Brasília, Brazil; [e]Epidemiology Unit, National Institute of Gastroenterology, La Habana, Cuba.

ABSTRACT

BACKGROUND: We systematically assessed beneficial and harmful effects of monoclonal antibodies for coronavirus disease 2019 (COVID-19) treatment, and prophylaxis in individuals exposed to severe acute respiratory syndrome coronavirus 2.

METHODS: We searched 5 engines and 3 registries until November 3, 2021 for randomized controlled trials evaluating monoclonal antibodies vs control in hospitalized or non-hospitalized adults with COVID-19, or as prophylaxis. Primary outcomes were all-cause mortality, COVID-19-related death, and serious adverse events; hospitalization for non-hospitalized; and development of symptomatic COVID-19 for prophylaxis. Inverse variance random effects models were used for meta-analyses. Grading of Recommendations, Assessment, Development, and Evaluations methodology was used to assess certainty of evidence.

RESULTS: Twenty-seven randomized controlled trials were included: 20 in hospitalized patients (n = 8253), 5 in non-hospitalized patients (n = 2922), and 2 in prophylaxis (n = 2680). In hospitalized patients, monoclonal antibodies slightly reduced mechanical ventilation (relative risk [RR] 0.74; 95% confidence interval [CI], 0.60-0.9; I^2 = 20%, low certainty of evidence) and bacteremia (RR 0.77; 95% CI, 0.64-0.92; I^2 = 7%, low certainty of evidence); evidence was very uncertain about the effect on adverse events (RR 1.31; 95% CI, 1.02-1.67; I^2 = 77%, very low certainty of evidence). In non-hospitalized patients, monoclonal antibodies reduced hospitalizations (RR 0.30; 95% CI, 0.17-0.53; I^2 = 0%, high certainty of evidence) and may slightly reduce serious adverse events (RR 0.47; 95% CI, 0.22-1.01; I^2 = 33%, low certainty of evidence). In prophylaxis studies, monoclonal antibodies probably reduced viral load slightly (mean difference −0.8 $\log_{10}$; 95% CI, −1.21 to −0.39, moderate certainty of evidence). There were no effects on other outcomes.

CONCLUSIONS: Monoclonal antibodies had limited effects on most of the outcomes in COVID-19 patients, and when used as prophylaxis. Additional data are needed to determine their efficacy and safety.

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KEYWORDS: COVID-19; Meta-analysis; Monoclonal antibodies; Prophylaxis; Treatment

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Requests for reprints should be addressed to Adrian V. Hernandez, MD, PhD, Health Outcomes, Policy and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, 69 N Eagleville Rd U-3092, Storrs, CT 06269.

E-mail address: adrian.hernandez-diaz@uconn.edu

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INTRODUCTION

By March 28, 2022, approximately 1 million and 6.2 million deaths had been reported due to coronavirus disease 2019 (COVID-19) in the United States and the world, respectively.[1] Several therapies have received emergency use authorization to prevent hospitalizations or death in COVID-19 patients or to prevent high-risk people from becoming infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Convalescent plasma, a therapy based on neutralizing SARS-CoV-2 virus with a previously infected person's antibodies, was given emergency authorization; however, it did not demonstrate significant clinical benefits in systematic reviews.[2,3]

Monoclonal antibodies against the SARS-CoV-2 virus have a theoretical advantage over convalescent plasma in that selective antibodies against the SARS-CoV-2 virus can be created and administered to patients.[4] While the anti-SARS-CoV-2 monoclonal antibody products containing casirivimab + imdevimab, bamlanivimab + etesevimab, and sotrovimab have emergency authorizations for treating mild to moderate COVID-19 infections, current use is not recommended against the omicron subvariant of SARS-CoV-2.[5] However, the anti-SARS-CoV-2 monoclonal antibody bebtelovimab can be used to treat patients with mild to moderate COVID-19 disease, and tixagevimab + cilgavimab can be used to prevent COVID-19 infection in high-risk patients, even in regions with high omicron subvariant prevalence.[5]

There are also monoclonal antibodies used to impede the inflammatory response to COVID-19, such as interleukin, complement, surface glycoprotein, and granulocyte-monocyte colony-stimulating factor inhibitors. Many of these anti-inflammatory monoclonal antibodies have studies assessing their efficacy or safety in COVID-19 patients, but the only one with emergency authorization is tocilizumab.[5]

Monoclonal antibodies have not been systematically evaluated for their efficacy and safety for the treatment of, or prophylaxis against, COVID-19. We conducted a systematic review with meta-analyses of randomized controlled trials assessing the efficacy and safety of monoclonal antibodies for the treatment or prevention of COVID-19.

CLINICAL SIGNIFICANCE

- In hospitalized patients, monoclonal antibodies slightly reduced mechanical ventilation and bacteremia.
- In non-hospitalized patients, monoclonal antibodies reduced hospitalization, and may slightly reduce serious adverse events.
- In individuals exposed to serious acute respiratory syndrome coronavirus 2, monoclonal antibodies probably reduced viral load slightly.
- There were no effects of monoclonal antibodies on all-cause mortality or COVID-19-related mortality.

MATERIALS AND METHODS

Searches

We conducted a comprehensive literature search in PubMed, Web of Science, Scopus, Embase, and Cochrane Library on November 3, 2021. Also, we searched for ongoing randomized controlled trials at www.clinicaltrials.gov, www.who.int/clinical-trials-registry-platform, and www.clinicaltrialsregister.eu/ctr-search/search. There was no time or language limitation. The PubMed strategy is available in the Supplementary Material.

Study Selection

Three reviewers (AP, VP, AVH) searched engines and websites and collected records in myendnoteweb.com. Three independent reviewers (AP, COC-T, AAE) assessed titles and abstracts for eligibility; discrepancies were resolved by discussion. We included randomized controlled trials evaluating one or more monoclonal antibody vs control, conducted in adults who were either hospitalized or non-hospitalized with polymerase chain reaction (PCR)-confirmed COVID-19 (active treatment) or in adults at high risk of developing COVID-19 due to close contact to people with PCR-confirmed COVID-19 (prophylaxis). Monoclonal antibodies of interest included anti-inflammatory (tocilizumab, sarilumab, meplazumab, canakinumab, mavrilimumab, itolizumab) and anti-spike protein of SARS-CoV-2 (bamlanivimab, bamlanivimab + etesevimab, sotrovimab, and casirivimab + imdevimab). Controls of interest were placebo, standard of care, or an active treatment. Studies were excluded if conducted in individuals <18 years old, did not report on at least one outcome, or included individuals with hepatitis B or human immunodeficiency virus infection.

Outcomes

Primary outcomes were all-cause mortality, COVID-19-related death, and serious adverse events for all populations; hospitalization for non-hospitalized individuals, and development of symptomatic COVID-19 for prophylaxis studies. Secondary outcomes included hospital stay, invasive mechanical ventilation, viral load, adverse events, and bacteremia. We used definitions provided by authors.

Data Extraction

Data extraction was completed by 2 independent reviewers (SY, PK) in a predefined Excel format (Microsoft Corporation, Redmond, Wash). Disagreements were resolved with a third reviewer (AVH). Extracted data included: 1) first author and year of publication; 2) number of participants; 3) countries involved; 4) population (hospitalized, non-hospitalized, prophylaxis); 5) monoclonal antibody type, dose, and duration; 6) control type, dose, and duration; 7) follow-up

time; 8) median age; 9) male proportion; 10) comorbidities prevalence (ie, diabetes, hypertension, obesity, coronary artery disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease); 11) concomitant treatments for both monoclonal antibody and control arms; 12) primary outcomes per arm; and 13) secondary outcomes per arm.

Risk of Bias Assessment

Two reviewers (SJ, PK) independently evaluated risk of bias (RoB) of randomized controlled trials using the Cochrane risk of bias tool RoB2.0.[6] A third reviewer (AVH) resolved discrepancies. The RoB2.0 tool assesses 5 domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Judgements of bias per domain can be "low" or "high", or can express "some concerns". The presence of high RoB in at least one domain means the study is at high RoB; the presence of some concerns in at least one domain without a single domain at high RoB means the study has some concerns of bias.

Statistical Analyses

This systematic review was reported according to 2020 PRISMA guidelines.[7] We primarily stratified our analyses by type of population: hospitalized and non-hospitalized COVID-19 patients, and high risk of COVID-19 infection (prophylaxis). We performed random effects meta-analyses using the inverse variance method, the Paule-Mandel method to calculate the between-study variance tau,[2] and the Hartnung-Knapp method to adjust 95% confidence intervals (CIs).[8,9] Effects were reported as relative risks (RR) with their 95% CIs for dichotomous outcomes, and mean differences with their 95% CIs for continuous outcomes. Heterogeneity of effects was quantified with the I^2 statistic, with an I^2 >60 defined as high heterogeneity.[10] Three sets of subgroup analyses were prespecified: by type of drug (tocilizumab vs other) in hospitalized patients; by type of control (placebo, standard of care, active) in hospitalized patients; and by type of control in hospitalized patients of tocilizumab studies. A P for interaction < .1 was considered statistically significant for a given subgroup. We evaluated only small study effects with the

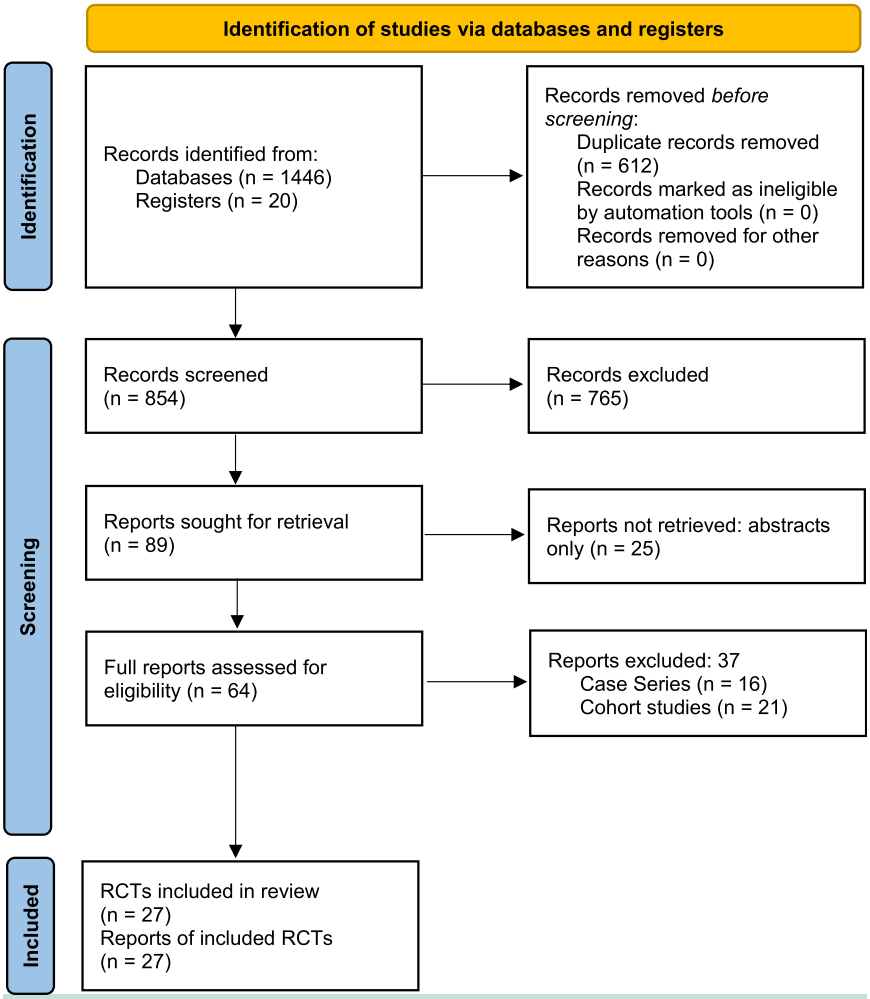

Figure 1 PRISMA 2020 flowchart.

Table 1 Characteristics of 27 Included Randomized Controlled Trials

First Author, Year,[reference] Acronym	Country(ies)	Population, % Vaccination	Sample Size	Monoclonal Antibody, Duration and Total Dose	Control	Mean Age, Years (SD)	Male (%)	Hypertension (%)	Diabetes (%)	Heart Disease (%)	Reported Outcomes	Follow-Up Days
Bian, 2021[11]	China	Hospitalized, vaccination NA	28	Meplazumab, 5 days, 30 mg	Standard of care	56.5 (15.1)	57.1	32.1	10.7	10.7	Time to viral clearance, elevated aspartate aminotransferase or alanine transaminase	28
Caricchio, 2021[12]	USA, Europe	Hospitalized, vaccination NA	454	Canakinumab, 1 day, 660 mg	Placebo	58.5 (14.1)	58.8	55.7	36.1	20.3	All-cause mortality, serious adverse events, adverse events, COVID-19-related death, bacteremia	28
Cremer, 2021[13]	USA	Hospitalized, vaccination NA	40	Mavrilimumab, 1 day, 420 mg	Placebo	56.2 (15.7)	65.0	55.0	42.5	NA	All-cause mortality, serious adverse events, mechanical ventilation, length of stay	28
Gordon, 2021[14] REMAP-CAP	Australia, New Zealand, UK, Belgium, Thailand, Sri Lanka, USA, Canada, Northern Ireland, Netherlands	Hospitalized, vaccination NA	895	Tocilizumab, 1-2 days, 560-1120 mg Sarilumab, 1 day, 400 mg	Standard of care	61.3 (12.7)	72.1	NA	36.4	10.8	All-cause mortality, serious adverse events, mechanical ventilation, bacteremia	21
Hamed, 2021[15]	United Arab Emirates	Hospitalized, vaccination NA	49	Tocilizumab, 1 day, 400 mg	Active	48.5 (11.3)	81.6	22.4	42.9	NA	All-cause mortality, COVID-19-related death, mechanical ventilation, length of stay	45
Hermine, 2021[16]	France	Hospitalized, vaccination NA	131	Tocilizumab, 1-3 days, 560-960 mg	Standard of care	64.4 (12.0)	67.7	NA	33.6	31.3	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia	28
Horby, 2021[17] RECOVERY	UK	Hospitalized, vaccination NA	4116	Tocilizumab; 1-2 days; 600-1200 mg	Standard of care	63.6 (13.7)	67.3	NA	28.4	22.6	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia	28
Kumar, 2021[18]	India	Hospitalized, vaccination NA	30	Itolizumab, 7-30 days, 280 mg	Standard of care	49.1 (13.0)	86.7	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia	30
Lescure, 2021[19]	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain	Hospitalized, vaccination NA	416	Sarilumab, 1 day, 400 mg	Placebo	58.6 (12.9)	62.7	42.5	26.4	9.9	All-cause mortality, serious adverse events, adverse events, bacteremia	29
Lundgren, 2021[20] ACTIV-3/TICO LY-CoV555	USA, Denmark Singapore	Hospitalized, vaccination NA	314	Bamlanivimab, 1 day, 7000 mg	Placebo	60.7 (16.7)	58.0	49.0	28.7	4.1	All-cause mortality, adverse events, bacteremia	90
Rashad, 2021[21]	Egypt	Hospitalized, vaccination NA	149	Tocilizumab, 1-2 days, 560-1120 mg	Active	61.8 (12.8)	56.9	47.7	28.4	12.8	All-cause mortality, mechanical ventilation	14
Rosas, 2021[22]	USA, UK, Spain	Hospitalized, vaccination NA	438	Tocilizumab, 1 day, 560 mg	Placebo	60.8 (14.3)	69.9	62.1	38.1	28.1	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia, length of stay	28
Salama, 2021[23]	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized, vaccination NA	389	Tocilizumab, 1 day, 560 mg	Placebo	55.9 (14.5)	59.2	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia, length of stay.	28
Salvarani, 2021[24]	Italy	Hospitalized, vaccination NA	126	Tocilizumab, 1 day, 800 mg	Standard of care	61.6 (12.0)	61.1	44.4	15.1	NA	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia	14
Soin, 2021[25]	India	Hospitalized, vaccination NA	180	Tocilizumab, 1-7 days, 480-960 mg	Standard of care	54.5 (13.4)	84.9	84.9	84.9	15.1	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia	28
Stone, 2020[26]	USA	Hospitalized, vaccination NA	243	Tocilizumab, 1 day, 560 mg	Placebo	58.7 (17.3)	58.3	48.8	31.0	18.6	All-cause mortality, serious adverse events, mechanical ventilation, bacteremia	28

Table 1 (*Continued*)

First Author, Year,[reference] Acronym	Country(ies)	Population, % Vaccination	Sample Size	Monoclonal Antibody, Duration and Total Dose	Control	Mean Age, Years (SD)	Male (%)	Hypertension (%)	Diabetes (%)	Heart Disease (%)	Reported Outcomes	Follow-Up Days
Veiga, 2021[27]	Brazil	Hospitalized, vaccination NA	129	Tocilizumab, 1 day, 560 mg	Standard of care	57.4 (14.6)	68.2	49.6	32.6	10.9	All-cause mortality, serious adverse events, adverse events, mechanical ventilation, bacteremia, length of stay	28
Vlaar, 2020[28]	Netherlands	Hospitalized, vaccination NA	30	Vilobelimab, 15-22 days, 800 mg	Placebo	60.5 (8.7)	73.3	30.0	26.7	NA	All-cause mortality, serious adverse events, COVID-19-related death, bacteremia,	28
Wang, 2021[29]	China	Hospitalized, vaccination NA	65	Tocilizumab, 1-2 days, 500 mg	Standard of care	63.2 (10.3)	50.8	30.8	15.4	NA	Serious adverse events, adverse events, length of stay	14
Zhao H, 2021[30]	China	Hospitalized, vaccination NA	31	Tocilizumab, 7 days, 400 mg	Active	67.0 (33.3)	52.4	42.9	9.5	14.3	Serious adverse events, adverse events, mechanical ventilation	14
Chen, 2021[31]	USA	Non-hospitalized, vaccination NA	452	Bamlanivimab, 1 day, 3486 mg	Placebo	48 (48.3)	44.9	NA	NA	NA	Viral load	29
Dougan, 2021[32]	USA	Non-hospitalized, vaccination NA	1035	Bamlanivimab + etesevimab, 1 day, 5600 mg	Placebo	53.8 (16.8)	48%	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, COVID-19-related death, bacteremia, viral load, length of stay, COVID-19-related hospitalization	29
Gottlieb, 2021[33]	USA	Non-hospitalized, vaccination NA	577	Bamlanivimab, 1 day, 3486 mg; Bamlanivimab + etesevimab, 1 day, 5600 mg	Placebo	44.5 (18.5)	45.4	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, COVID-19-related death, mechanical ventilation, viral load, COVID-19-related hospitalization or emergency department visit*	29
Gupta, 2021[34]	USA, Canada, Brazil, Spain	Non-hospitalized, vaccination NA	275	Sotrovimab, 1 day, 500 mg	Placebo	53.9 (54.9)	45.6	NA	22.6	0.7	All-cause mortality, serious adverse events, adverse events, mechanical ventilation	29
Weinreich, 2021[35]	USA	Non-hospitalized, vaccination NA	583	Casirivimab + imdevimab, 1 day, 5169 mg	Placebo	43.7 (13.4)	48.7	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, COVID-19-related death, viral load	29
Cohen, 2021[36]	USA	Prophylaxis, vaccination 0%	1175	Bamlanivimab, 1 day, 4200 mg	Placebo	53.5 (47.3)	25.3	NA	NA	NA	All-cause mortality, serious adverse events, adverse events, COVID-19-related death, bacteremia, viral load	29
O'Brien, 2021[37]	USA, Romania Moldova	Prophylaxis, vaccination 0%	1505	Casirivimab + imdevimab, 1 day, 1200 mg	Placebo	46.9 (57.5)	45.9	NA	6.8	NA	Serious adverse events, adverse events, bacteremia	28

NA = Not available.

*12 of 15 (80%) COVID-19-related hospitalizations or emergency department visits were hospitalizations.

Egger's test when there were 10 or more studies. All analyses were performed in R 4.1.2 (www.r-project.org).

The certainty of evidence was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology (www.gradeworkinggroup.org). The certainty of evidence per outcome was based on the evaluation of 5 aspects: RoB, inconsistency, imprecision, indirectness, and publication bias. Description of certainty of evidence was presented in summary of findings tables using GRADEpro software (McMaster University and Evidence Prime, 2021; www.gradepro.org/).

RESULTS

Selection of Studies

We identified 1446 citations from databases and 20 from registries (Figure 1). After removing duplicates and title, abstract, and full text reviews, 27 randomized controlled trials met our inclusion criteria. Twenty studies were conducted in hospitalized COVID-19 patients,[11-30] 5 studies in non-hospitalized COVID-19 patients,[31-35] and 2 studies in individuals at high risk of developing COVID-19.[36,37] Two trials evaluated 2 different monoclonal antibodies: Gordon et al[14] evaluated tocilizumab and sarilumab, and Gottlieb et al[33] evaluated bamlanivimab and bamlanivimab + etesevimab.

Characteristics of Included Randomized Controlled Trials

Table 1[11-37] displays features of the 20 trials in hospitalized COVID-19 patients.[11-30] Nine, eight, and three of the studies had monoclonal antibodies compared with standard of care, placebo, and active control, respectively. Nineteen of the 20 studies assessed anti-inflammatory monoclonal antibodies (13 tocilizumab, 2 sarilumab, and one each meplazumab, canakinumab, mavrilimumab, itolizumab, and vilobelimab) while one assessed an anti-SARS-CoV-2 virus monoclonal antibody (bamlanivimab). Nineteen trials were 2-group comparisons (monoclonal antibody vs control) while one trial[14] had 3 arms (tocilizumab or sarilumab vs standard of care). The follow-up ranged from 14 to 90 days,

Table 2 Summary of Findings Table of Effects of Monoclonal Antibodies in Hospitalized COVID-19 Patients

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants (Studies)	Certainty of the Evidence (GRADE)
	Risk with Standard of Care, Active Therapy or Placebo	Risk with Monoclonal Antibodies			
All-cause mortality follow-up: range 14-90 days	26 per 100	25 per 100 (21-29)	RR 0.94 (0.80-1.11)	7800 (18 RCTs)	⊕⊕OO Low†
COVID-19-related death follow-up: range 28-45 days	8 per 100	5 per 100 (2-14)	RR 0.65 (0.25-1.72)	524 (3 RCTs)	⊕⊕OO Low‡,§
Invasive mechanical ventilation follow-up: range 14-45 days	19 per 100	14 per 100 (11-17)	RR 0.74 (0.60-0.92)	5807 (14 RCTs)	⊕⊕OO Low‖
Length of hospital stay assessed with: days follow-up: range 14-45 days	The mean length of hospital stay was 18.1 days	MD 1.86 days lower (6.1 lower to 2.38 higher)	—	1098 (6 RCTs)	⊕OOO Very low¶,**,††
Any adverse events follow-up: range 14-90 days	22 per 100	29 per 100 (23-37)	RR 1.31 (1.02-1.67)	6628 (13 RCTs)	⊕OOO Very low‡‡,§§
Serious adverse events follow-up: range 14-45 days	6 per 100	6 per 100 (5-7)	RR 0.93 (0.80-1.08)	7831 (17 RCTs)	⊕⊕OO Low‖
Bacteremia follow-up: range 14-90 days	5 per 100	4 per 100 (3-5)	RR 0.77 (0.64-0.92)	7789 (14 RCTs)	⊕⊕OO Low‖‖

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MD = mean difference; RCT = randomized controlled trial; RR = relative risk.

†RoB: Three RCTs were at high risk of bias, and 8 RCTs had some concerns of bias.

‡RoB: Vlaar et al[28] RCT was at high risk of bias in the selection of the reported results.

§Imprecision: 95% CI of RR 0.25-1.72.

‖RoB: Three RCTs were at high risk of bias, and 7 RCTs had some concerns of bias.

¶RoB: Two RCTs (Rosas et al,[22] Salama et al[23]) had some concerns of bias, and one RCT (Veiga et al[27]) was at high risk of bias.

**Inconsistency: I^2 was 79%.

††Imprecision: 95% CI of MD from −6.1-2.4 days.

‡‡RoB: Two RCTs (Zhao et al[30] and Veiga et al[27]) were at high risk of bias, and 6 RCTs had some concerns of bias.

§§Inconsistency: I^2 was 77%.

‖‖RoB: Two RCTs (Veiga et al[27] and Vlaar et al[28]) were at high risk of bias, and 8 RCTs had some concerns of bias.

with 4 trials at 14 days, one at 21 days, 13 at 28-30 days, and 2 at >30 days.

Table 1 displays features of the 5 trials in non-hospitalized COVID-19 patients.[31-35] All trials assessed anti-SARS-CoV-2 monoclonal antibodies (2 bamlanivimab, 2 bamlanivimab + etesevimab, one sotrovimab, one casirivimab + imdevimab). Four studies had 2-group comparisons (monoclonal antibody vs placebo) while one had 3 arms (bamlanivumab or bamlanivumab + etesevimab vs placebo). All of the trials had 29 days of follow-up.

There were only 2 trials[36,37] assessing the prophylactic impact of anti-SARS-CoV-2 monoclonal antibodies in high-risk patients vs placebo (Table 1). Studies assessed bamlanivimab or casirivimab + imdevimab, and had follow-up times of 29 or 28 days, respectively.

Supplementary Figure 1 (available online) shows RoB assessments of the 27 randomized trials, and 12 were found to have low RoB, 9 some concerns of bias, and 6 high RoB. The selection of the reporting result was the item most likely to receive a high risk of bias in this literature set. There was no evidence of small study effects for all meta-analyses. Effects of monoclonal antibodies on primary and secondary outcomes are shown in Figures 2 to 4, and in Supplementary Figures 2 to 9, available online. Effects of monoclonal antibodies for pre-specified subgroups are described in the Supplement, available online, and shown in Supplementary Figures 10A1 to 10A7, 10B1 to 10B7, and 10C1 to 10C6, available online.

Effects of Monoclonal Antibodies in Hospitalized Patients

Table 2[22,23,27,28] shows the certainty of evidence of monoclonal antibody effects in hospitalized patients. There were no differences between monoclonal antibody and controls (standard of care, placebo, or active treatment) for all-cause

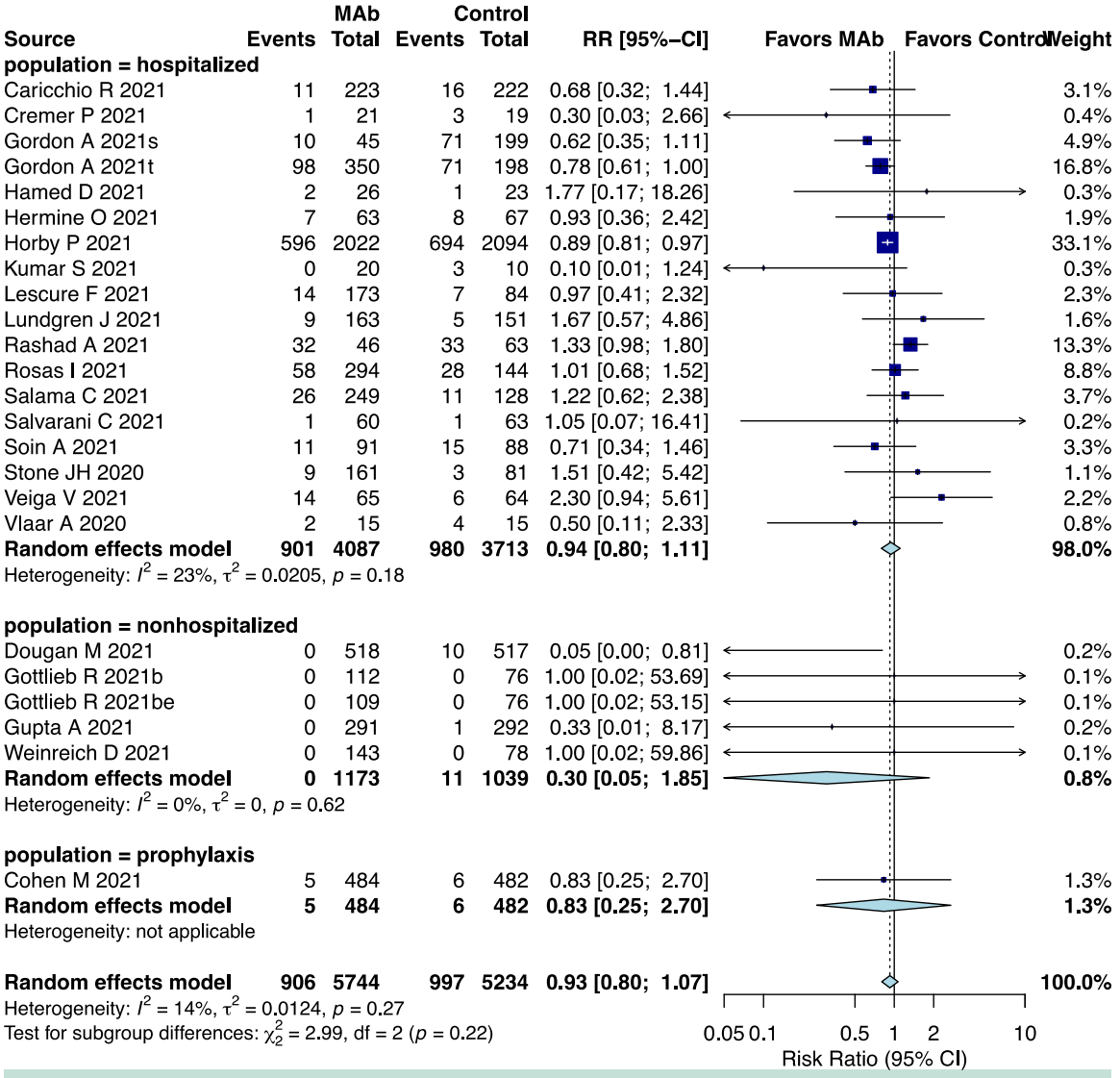

Figure 2 Effects of monoclonal antibodies on all-cause mortality stratified by type of COVID-19 patients.

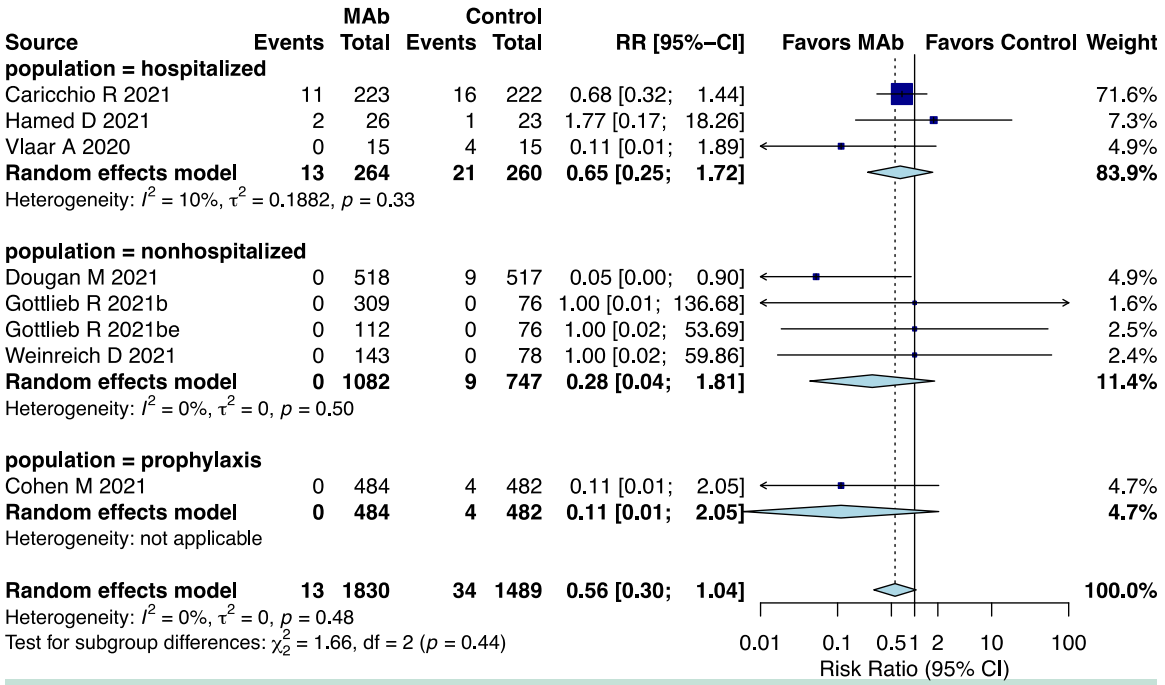

Figure 3 Effects of monoclonal antibodies on COVID-19-related death stratified by type of COVID-19 patients.

mortality (Figure 2), COVID-19-related death (Figure 3), or serious adverse events (Figure 4), with low certainty of evidence for these outcomes. For the secondary outcomes, length of stay was not different between monoclonal antibodies and controls, with very low certainty of evidence (Supplementary Figure 2, available online). Monoclonal antibodies slightly reduced mechanical ventilation (RR 0.74; 95% CI, 0.60-0.90; I^2 = 20%, low certainty of evidence, Supplementary Figure 3, available online) and bacteremia (RR 0.77; 95% CI, 0.64-0.92; I^2 = 7%, low certainty of evidence, Supplementary Figure 6, available online) vs controls; the evidence was very uncertain about the effect of monoclonal antibodies on adverse events (RR 1.31; 95% CI, 1.02-1.67; I^2 = 77%, very low certainty of evidence, Supplementary Figure 5 [available online], Table 2). Subgroup analyses in hospitalized COVID-19 patients showed differential effects for mechanical ventilation when comparing tocilizumab vs non-tocilizumab effects, and for all-cause mortality when comparing monoclonal antibody effects vs types of controls and tocilizumab effects vs types of controls (Supplementary Material, available online).

Effects of Monoclonal Antibodies in Non-Hospitalized Patients

Table 3[34,35] shows the certainty of evidence of monoclonal antibody effects in non-hospitalized patients. Monoclonal antibodies reduced hospitalizations vs placebo (RR 0.30; 95% CI, 0.17-0.53; I^2 = 0%, high certainty of evidence, Supplementary Figure 7, available online) and may slightly reduce serious adverse events vs placebo (RR 0.47; 95% CI, 0.22-1.01; I^2 = 33%, low certainty of evidence, Figure 4). All-cause mortality, COVID-19-related death, mechanical ventilation, length of stay, viral load, bacteremia, and adverse events were not different between monoclonal antibodies and placebo, with certainty of evidence ranging from very low to moderate (Figures 2 and 3, Supplementary Figures 2 to 6, available online).

Effects of Monoclonal Antibodies in Prophylaxis Against COVID-19

Table 4[37] shows the certainty of evidence of monoclonal antibody effects in trials of prophylaxis. Symptomatic COVID-19, positive SARS-CoV-2 PCR test, all-cause mortality, COVID-19-related death, adverse events, serious adverse events, and bacteremia were not different between monoclonal antibodies and placebo, with certainty of evidence ranging from very low to moderate (Supplementary Figures 5, 6, 9 and 9 [available online] and Figures 2-4). Monoclonal antibodies probably reduced viral load slightly vs placebo (mean difference −0.8 $\log_{10}$; 95% CI, −1.21 to −0.39, one trial, moderate certainty of evidence).

DISCUSSION

Our systematic review suggests that monoclonal antibodies had limited effects on most of the outcomes in hospitalized and non-hospitalized COVID-19 patients, and in individuals exposed to SARS-CoV-2, with certainty of evidence ranging from very low to moderate for most outcomes. In particular, there were no effects of monoclonal antibodies on all-cause mortality or COVID-19-related mortality across trials. In 20

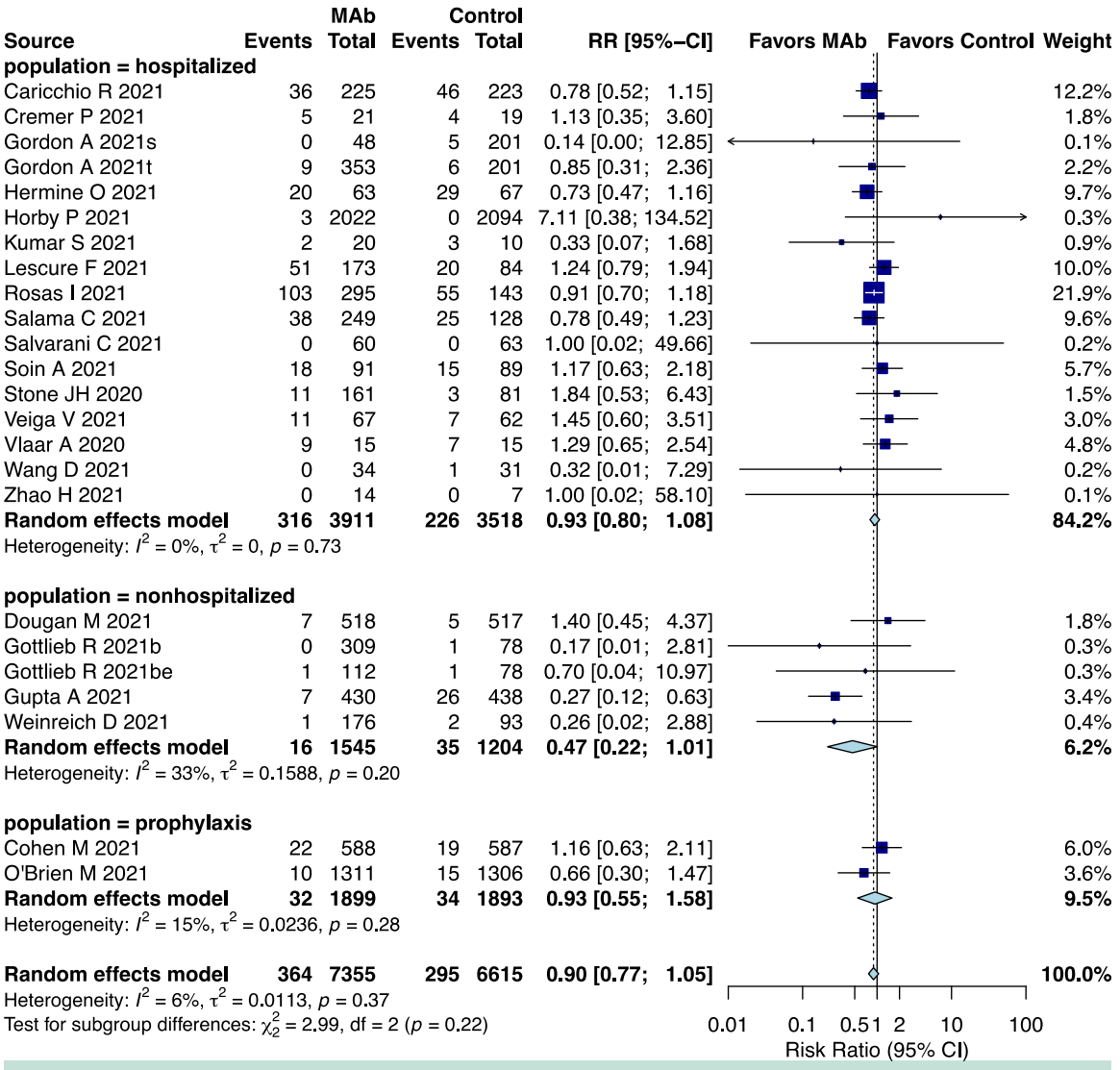

Figure 4 Effects of monoclonal antibodies on serious adverse events stratified by type of COVID-19 patients.

trials of hospitalized COVID-19 patients, monoclonal antibodies slightly reduced mechanical ventilation and bacteremia, and the evidence was very uncertain about the effect on adverse events. In 5 placebo-controlled trials of non-hospitalized COVID-19 patients, monoclonal antibodies reduced COVID-19-related hospitalization, and may slightly reduce serious adverse events. In 2 placebo-controlled prophylaxis trials of individuals exposed to SARS-CoV-2, monoclonal antibodies probably reduced viral load slightly.

The anti-inflammatory monoclonal antibodies in our systematic review included inhibitors of interleukin-6 (tocilizumab, sarilumab), interleukin-1 (canakinumab), complement-5 (vilobelimab), surface glycoprotein CD-6 (itolizumab), CD-147 (meplazumab), and granulocyte-monocyte colony-stimulating factor (mavrilimumab). While more robust reductions in all-cause mortality were seen for non-tolicizumab anti-inflammatory monoclonal antibodies vs control as compared with tolicizumab vs control, whether alternative mechanisms of blocking inflammation provide superior benefits needs future verification in randomized trials. Finding a smaller magnitude of benefit for some outcomes in hospitalized patients receiving monoclonal antibodies vs standard of care than when monoclonal antibodies were compared vs placebo may suggest that the weaknesses in blinding when standard of care is used might have biased the results.

The use of anti-SARS-CoV-2 monoclonal antibodies in hospitalized COVID-19 patients has been evaluated in only one trial[20] and the results were not promising. Unfortunately, this trial evaluated bamlanivimab alone, where the emergency authorization-approved product now contains bamlanivimab + etesevimab, so the monoclonal antibodies assessed might have been suboptimal. It is pharmacologically plausible that suppressing excessive inflammation is more important than suppressing viral replication in hospitalized patients.[38]

In non-hospitalized COVID-19 patients, anti-inflammatory monoclonal antibodies have not been assessed and

Table 3 Summary of Findings Table of Effects of Monoclonal Antibodies in Non-Hospitalized COVID-19 Patients

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants (Studies)	Certainty of the Evidence (GRADE)
	Risk with Placebo	Risk with Monoclonal Antibodies			
COVID-19-related hospitalization follow-up: median 29 days	6 per 100	2 per 100 (1-3)	RR 0.30 (0.17-0.53)	1612 (2 RCTs)	⊕⊕⊕⊕ High
All-cause mortality follow-up: median 29 days	1 per 100	0 per 100 (0-2)	RR 0.30 (0.05-1.85)	2212 (4 RCTs)	⊕OOO Very low[†,‡]
COVID-19-related death follow-up: median 29 days	1 per 100	0 per 100 (0-2)	RR 0.28 (0.04-1.81)	1829 (3 RCTs)	⊕OOO Very low[§,‖]
Invasive mechanical ventilation follow-up: median 29 days	1 per 100	0 per 100 (0-3)	RR 0.20 (0.01-4.16)	583 (1 RCT)	⊕OOO Very low[¶,**]
Length of hospital stay assessed with: days follow-up: median 29 days	The mean length of hospital stay was 11.2 days	MD 3.9 days lower (9.02 lower to 1.22 higher)	—	44 (1 RCT)	⊕⊕OO Low[††]
Viral load reduction from baseline assessed with: log_{10} follow-up: median 29 days	The mean viral load reduction from baseline was −1.2 log_{10}	MD 0.44 log_{10} lower (1.4 lower to 0.52 higher)	—	1941 (4 RCTs)	⊕OOO Very low[§,‡‡,§§]
Any adverse events follow-up: median 29 days	16 per 100	14 per 100 (12-17)	RR 0.90 (0.75-1.09)	2749 (4 RCTs)	⊕⊕⊕O Moderate[†]
Serious adverse events follow-up: median 29 days	3 per 100	1 per 100 (1-3)	RR 0.47 (0.22-1.01)	2749 (4 RCTs)	⊕⊕OO Low[†,‖‖]
Bacteremia follow-up: median 29 days	1 per 100	1 per 100 (0-3)	RR 1.33 (0.30-5.92)	1035 (1 RCT)	⊕⊕OO Low[¶¶]

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MD = mean difference; RR = relative risk.
†Risk of bias (RoB): Weinreich et al[35] was at high risk of bias; Gupta et al[34] had some concerns of bias.
‡Imprecision: 95% CI was 0.05-1.85.
§RoB: Weinreich et al[35] was at high risk of bias.
‖Imprecision: 95% CI was 0.04-1.81.
¶RoB: Gupta et al[34] had high risk of bias.
**Imprecision: 95% CI was 0.01-4.16.
††Imprecision: 95% CI of MD was −9.02-1.22 days.
‡‡Inconsistency: I^2 = 91%.
§§Imprecision: 95% CI of MD was −1.4-0.52 log_{10}.
‖‖Imprecision: 95% CI, 0.22-1.01.
¶¶Imprecision: 95% CI, 0.30-5.92.

there is pharmacologic reason to believe that they would not be effective.[38] At this stage of the disease, the suppression of viral replication may be more effective because excessive inflammation is not commonly seen in non-hospitalized patients. In our study, we found that the anti-SARS-CoV-2 monoclonal antibodies reduced COVID-19-related hospitalization, with no significant effects on all-cause mortality, COVID-19-related death, mechanical ventilation, and length of stay, but the literature base has only 5 randomized trials. Importantly, there were no increases in adverse events or serious adverse events in our systematic review, which is very promising.

In patients at high risk of developing COVID-19, the patient population assessing the impact of anti-SARS-CoV-2 monoclonal antibodies on patient outcomes is small. That means that the promising reductions in viral load, and the absence of effects on developing symptomatic or asymptomatic COVID-19 disease, all-cause mortality, COVID-19-related deaths, and bacteremia with anti-SARS-CoV-2 monoclonal antibodies are underpowered to show statistical significance. Further research in this area is encouraged, as these potential benefits could occur without increases in adverse events or serious adverse events.

In Winter 2022, the omicron variant became the dominant subvariant (99%) in the United States.[39] The anti-SARS-CoV-2 monoclonal antibodies casirivimab + imdevimab, bamlanivimab + etesevimab, and sotrovimab were not effective against the omicron subvariant in vitro, and therapy with these drugs was therefore discouraged by the US Food and Drug Administration.[5] This suggests that anti-SARS-CoV2 monoclonal antibodies will be even less effective than what we found in our systematic review when the omicron variant or other resistant subvariants predominate. Our literature search was through November 3, 2021, and would not have included predominant omicron subvariant patient populations. However, the efficacy of the anti-

Table 4 Summary of Findings Table of Effects of Monoclonal Antibodies in Individuals Exposed to SARS-CoV-2 (Prophylaxis)

Outcomes	Anticipated Absolute Effects (95% CI)		Relative Effect (95% CI)	Number of Participants (Studies)	Certainty of the Evidence (GRADE)
	Risk with Placebo	Risk with Monoclonal Antibodies			
Symptomatic COVID-19 assessed with: positive PCR test plus COVID-19 symptoms follow-up: median 28 days	7 per 100	5 per 100 (2-10)	RR 0.75 (0.36-1.54)	2471 (2 RCTs)	⊕OOO Very low[†,‡,§]
Symptomatic and asymptomatic COVID-19 assessed with: Positive PCR test with or without COVID-19 symptoms follow-up: median 28 days	18 per 100	9 per 100 (4-21)	RR 0.52 (0.23-1.17)	2471 (2 RCTs)	⊕OOO Very low[†,‖,¶]
All-cause mortality follow-up: median 28 days	1 per 100	1 per 100 (0-3)	RR 0.83 (0.25-2.70)	966 (1 RCT)	⊕⊕OO Low**
COVID-19-related death follow-up: median 28 days	1 per 100	0 per 100 (0-2)	RR 0.11 (0.01-2.05)	966 (1 RCT)	⊕⊕OO Low††
Viral load reduction from baseline assessed with: $\log_{10}$ follow-up: median 28 days	The mean viral load reduction from baseline was −0.39 $\log_{10}$	MD 0.8 $\log_{10}$ lower (1.21 lower to 0.39 lower)	—	132 (1 RCT)	⊕⊕⊕O Moderate‡‡
Any adverse events follow-up: median 28 days	26 per 100	22 per 100 (14-33)	RR 0.85 (0.56-1.28)	3792 (2 RCTs)	⊕OOO Very low[†,‡‡]
Serious adverse events follow-up: median 28 days	2 per 100	2 per 100 (1-3)	RR 0.93 (0.55-1.58)	3792 (2 RCTs)	⊕⊕⊕O Moderate[†]
Bacteremia follow-up: median 28 days	2 per 100	1 per 100 (1-2)	RR 0.70 (0.37-1.33)	2680 (2 RCTs)	⊕⊕⊕O Moderate[†]

CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MD = mean difference; PCR = polymerase chain reaction; RR = relative risk.

†Risk of bias (RoB): O'Brien et al[37] at high risk of bias due to measurement of the outcome and selection of the reported result.

‡Inconsistency: $I^2 = 60\%$.

§Imprecision: 95% CI, 0.36-1.54.

‖Inconsistency: $I^2 = 93\%$.

¶Imprecision: 95% CI, 0.23-1.17.

**Imprecision: 95% CI, 0.25-2.70.

††Imprecision: 95% CI, 0.01-2.05.

‡‡Imprecision: 95% CI, −1.21 to −0.39 $\log_{10}$.[§§]Inconsistency: $I^2 = 89\%$.

inflammatory monoclonal antibodies would be less likely than the anti-SARS-CoV-2 monoclonal antibodies to vary given the circulating subvariant at the time. The anti-SARS-CoV-2 monoclonal antibody bebtelovimab received an emergency authorization from the Food and Drug Administration on February 11, 2022 for the treatment of mild to moderate COVID-19, as it retained activity against the omicron variant.[5,40] With the progress of research on pathogenesis of SARS-CoV-2 infection, new monoclonal antibodies (such as anti-inflammasomes or monocyte/macrophage entry inhibitors[41]) should be evaluated in randomized trials to assess their efficacy and safety.

The increase in vaccination against SARS-CoV-2 could support earlier and more robust creation of a patient's own antibody response to COVID-19 infection. Whether this attenuates some of the benefits of providing monoclonal antibody therapy is unknown. Importantly, there was no reporting on the proportion of fully vaccinated individuals in our included randomized controlled trials. This potential confounding factor should be assessed in future studies.

Our study had some limitations. First, most of the randomized trials were conducted in hospitalized COVID-19 patients, and effects for non-hospitalized and prophylaxis randomized trials were less conclusive. Second, certainty of evidence was low or very low for most of the outcomes in the 3 populations. Third, we did not assess effects of individual monoclonal antibodies on outcomes in non-hospitalized and prophylaxis due to the scarcity of studies; we did evaluate the effects of tocilizumab vs other monoclonal antibodies for hospitalized patients. Fourth, randomized trial data for hospitalized patients were comprised almost entirely of anti-inflammatory monoclonal antibodies, while for non-hospitalized patients and those at high risk of developing COVID-19, only anti-SARS-CoV-2 monoclonal antibody data were available. Finally, all monoclonal antibodies in non-hospitalized and prophylaxis were evaluated against placebo, but no active treatment or standard of care.

CONCLUSIONS

Monoclonal antibodies had limited effects on most of the outcomes in hospitalized and non-hospitalized COVID-19 patients, and in individuals exposed to SARS-CoV-2. There were no effects of monoclonal antibodies on all-cause mortality or COVID-19-related mortality. In hospitalized COVID-19 patients, monoclonal antibodies slightly reduce mechanical ventilation and bacteremia, and the evidence was very uncertain on adverse events. In non-hospitalized COVID-19 patients, monoclonal antibodies reduced COVID-19-related hospitalization, and may slightly reduce serious adverse events. In randomized trials of individuals exposed to SARS-CoV-2, monoclonal antibodies probably reduced viral load slightly.

Anti-inflammatory monoclonal antibodies in hospitalized COVID-19 patients and anti-SARS-CoV-2 monoclonal antibodies in non-hospitalized COVID-19 patients or those at high risk of developing COVID-19 are promising, but additional data are needed to determine their efficacy and safety.

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SUPPLEMENTARY MATERIALS

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2022.06.019.

SUPPLEMENTARY MATERIAL

1. PubMed search strategy

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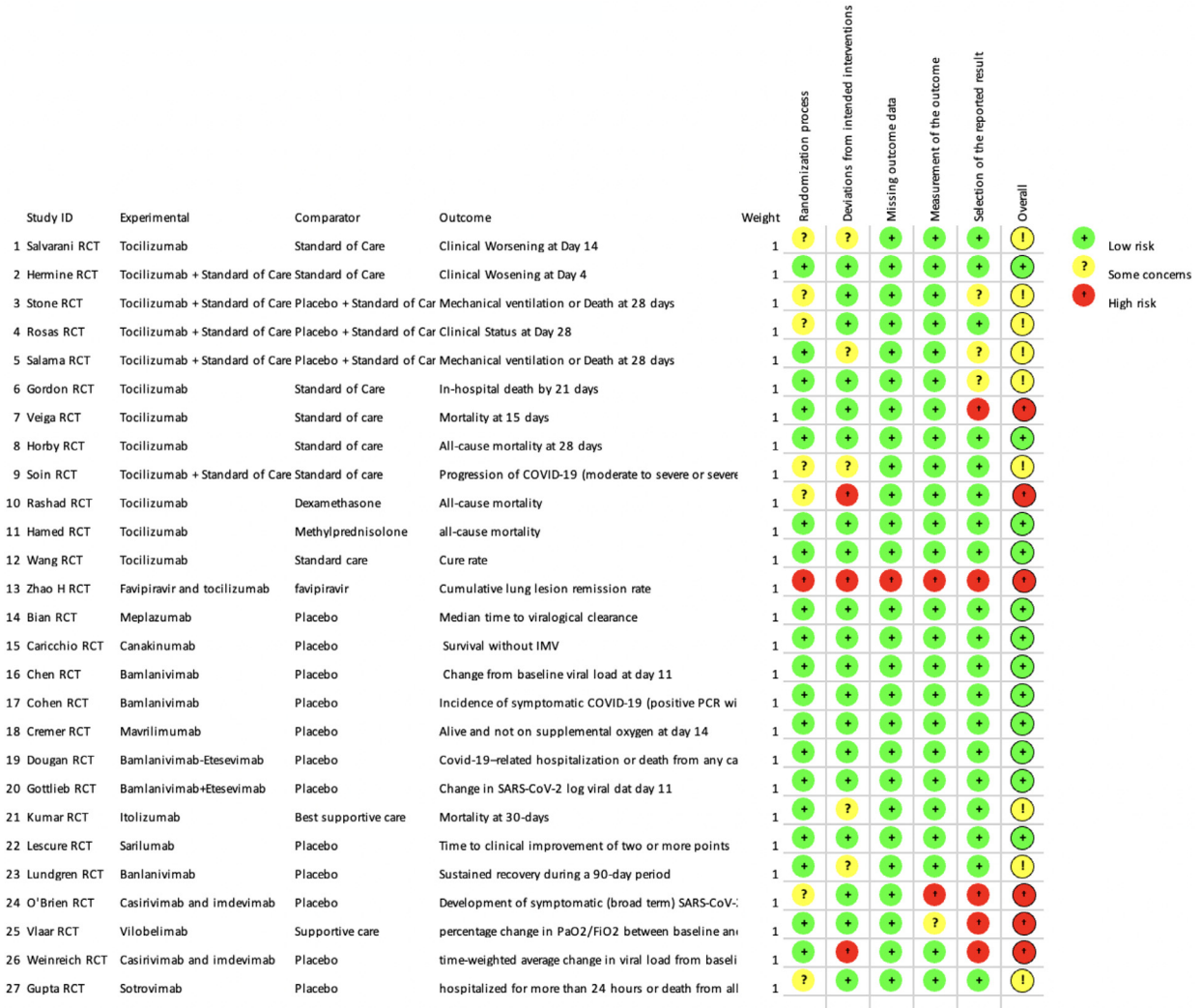
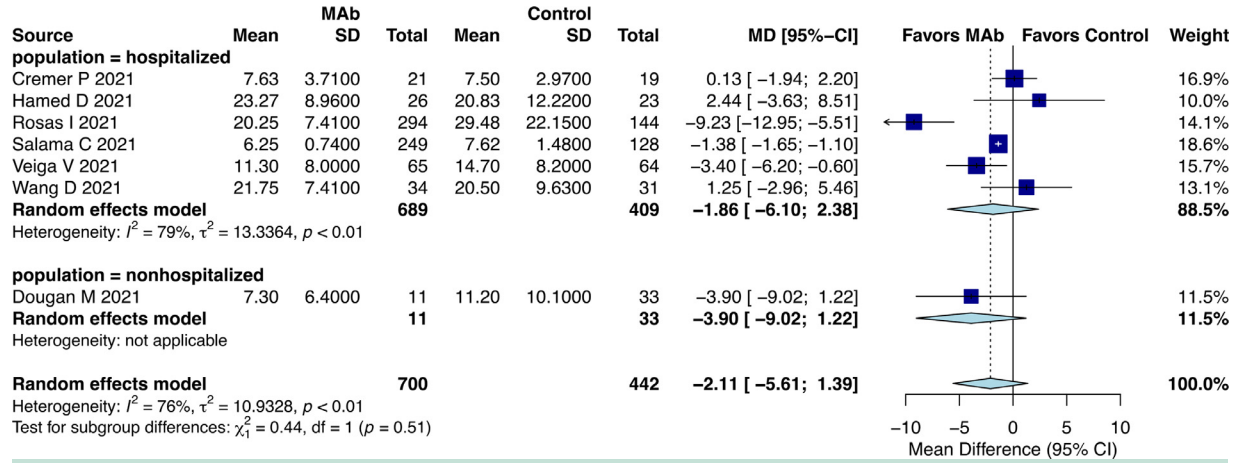


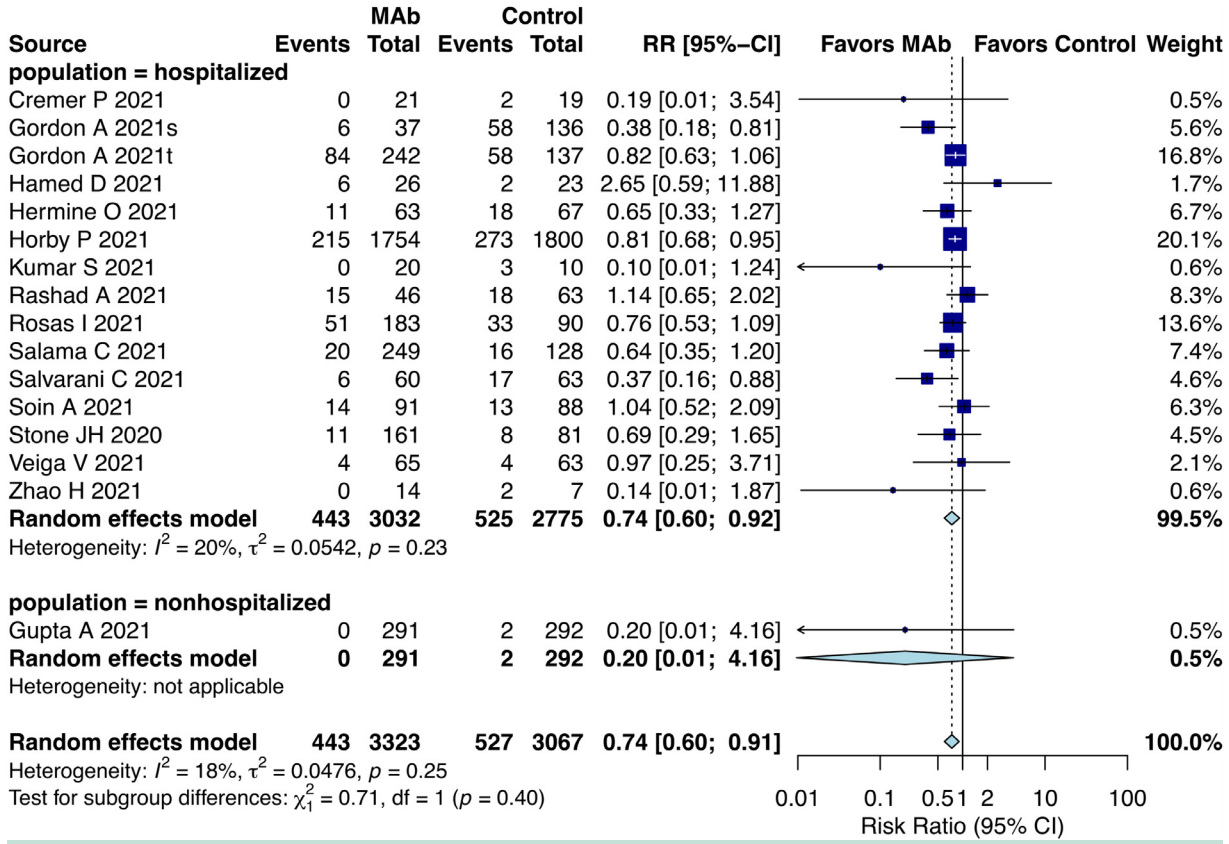
	Study ID	Experimental	Comparator	Outcome	Weight
1	Salvarani RCT	Tocilizumab	Standard of Care	Clinical Worsening at Day 14	1
2	Hermine RCT	Tocilizumab + Standard of Care	Standard of Care	Clinical Wosening at Day 4	1
3	Stone RCT	Tocilizumab + Standard of Care	Placebo + Standard of Car	Mechanical ventilation or Death at 28 days	1
4	Rosas RCT	Tocilizumab + Standard of Care	Placebo + Standard of Car	Clinical Status at Day 28	1
5	Salama RCT	Tocilizumab + Standard of Care	Placebo + Standard of Car	Mechanical ventilation or Death at 28 days	1
6	Gordon RCT	Tocilizumab	Standard of Care	In-hospital death by 21 days	1
7	Veiga RCT	Tocilizumab	Standard of care	Mortality at 15 days	1
8	Horby RCT	Tocilizumab	Standard of care	All-cause mortality at 28 days	1
9	Soin RCT	Tocilizumab + Standard of Care	Standard of care	Progression of COVID-19 (moderate to severe or severe	1
10	Rashad RCT	Tocilizumab	Dexamethasone	All-cause mortality	1
11	Hamed RCT	Tocilizumab	Methylprednisolone	all-cause mortality	1
12	Wang RCT	Tocilizumab	Standard care	Cure rate	1
13	Zhao H RCT	Favipiravir and tocilizumab	favipiravir	Cumulative lung lesion remission rate	1
14	Bian RCT	Meplazumab	Placebo	Median time to viralogical clearance	1
15	Caricchio RCT	Canakinumab	Placebo	Survival without IMV	1
16	Chen RCT	Bamlanivimab	Placebo	Change from baseline viral load at day 11	1
17	Cohen RCT	Bamlanivimab	Placebo	Incidence of symptomatic COVID-19 (positive PCR wi	1
18	Cremer RCT	Mavrilimumab	Placebo	Alive and not on supplemental oxygen at day 14	1
19	Dougan RCT	Bamlanivimab-Etesevimab	Placebo	Covid-19–related hospitalization or death from any ca	1
20	Gottlieb RCT	Bamlanivimab+Etesevimab	Placebo	Change in SARS-CoV-2 log viral dat day 11	1
21	Kumar RCT	Itolizumab	Best supportive care	Mortality at 30-days	1
22	Lescure RCT	Sarilumab	Placebo	Time to clinical improvement of two or more points	1
23	Lundgren RCT	Banlanivimab	Placebo	Sustained recovery during a 90-day period	1
24	O'Brien RCT	Casirivimab and imdevimab	Placebo	Development of symptomatic (broad term) SARS-CoV-	1
25	Vlaar RCT	Vilobelimab	Supportive care	percentage change in PaO2/FiO2 between baseline an	1
26	Weinreich RCT	Casirivimab and imdevimab	Placebo	time-weighted average change in viral load from baseli	1
27	Gupta RCT	Sotrovimab	Placebo	hospitalized for more than 24 hours or death from all	1

Supplementary Figure 1 Risk of bias of included randomized controlled trials (RCTs).

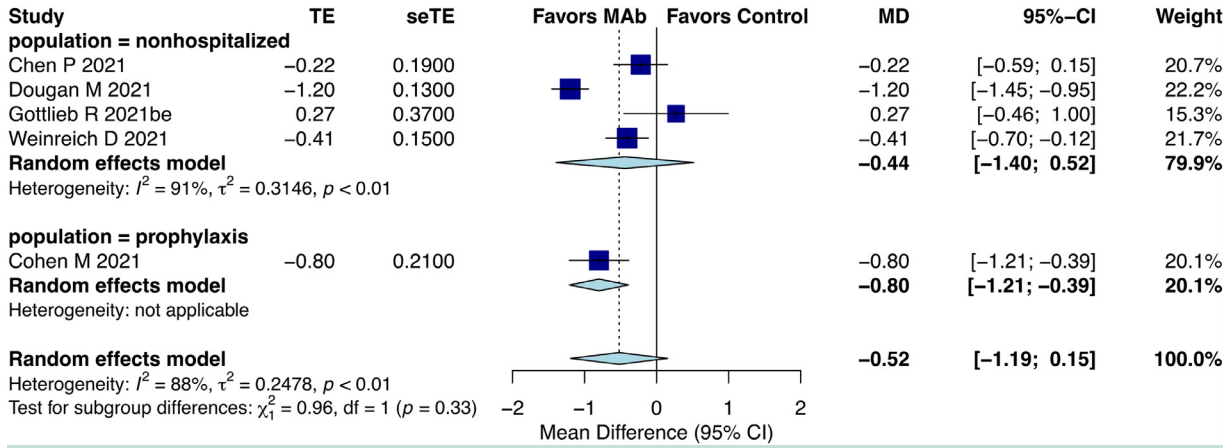


Source	MAb Mean	MAb SD	MAb Total	Control Mean	Control SD	Control Total	MD [95%–CI]	Weight
population = hospitalized								
Cremer P 2021	7.63	3.7100	21	7.50	2.9700	19	0.13 [−1.94; 2.20]	16.9%
Hamed D 2021	23.27	8.9600	26	20.83	12.2200	23	2.44 [−3.63; 8.51]	10.0%
Rosas I 2021	20.25	7.4100	294	29.48	22.1500	144	−9.23 [−12.95; −5.51]	14.1%
Salama C 2021	6.25	0.7400	249	7.62	1.4800	128	−1.38 [−1.65; −1.10]	18.6%
Veiga V 2021	11.30	8.0000	65	14.70	8.2000	64	−3.40 [−6.20; −0.60]	15.7%
Wang D 2021	21.75	7.4100	34	20.50	9.6300	31	1.25 [−2.96; 5.46]	13.1%
Random effects model			**689**			**409**	**−1.86 [−6.10; 2.38]**	**88.5%**
Heterogeneity: I^2 = 79%, τ^2 = 13.3364, p < 0.01								
population = nonhospitalized								
Dougan M 2021	7.30	6.4000	11	11.20	10.1000	33	−3.90 [−9.02; 1.22]	11.5%
Random effects model			**11**			**33**	**−3.90 [−9.02; 1.22]**	**11.5%**
Heterogeneity: not applicable								
Random effects model			**700**			**442**	**−2.11 [−5.61; 1.39]**	**100.0%**
Heterogeneity: I^2 = 76%, τ^2 = 10.9328, p < 0.01								
Test for subgroup differences: χ^2_1 = 0.44, df = 1 (p = 0.51)								

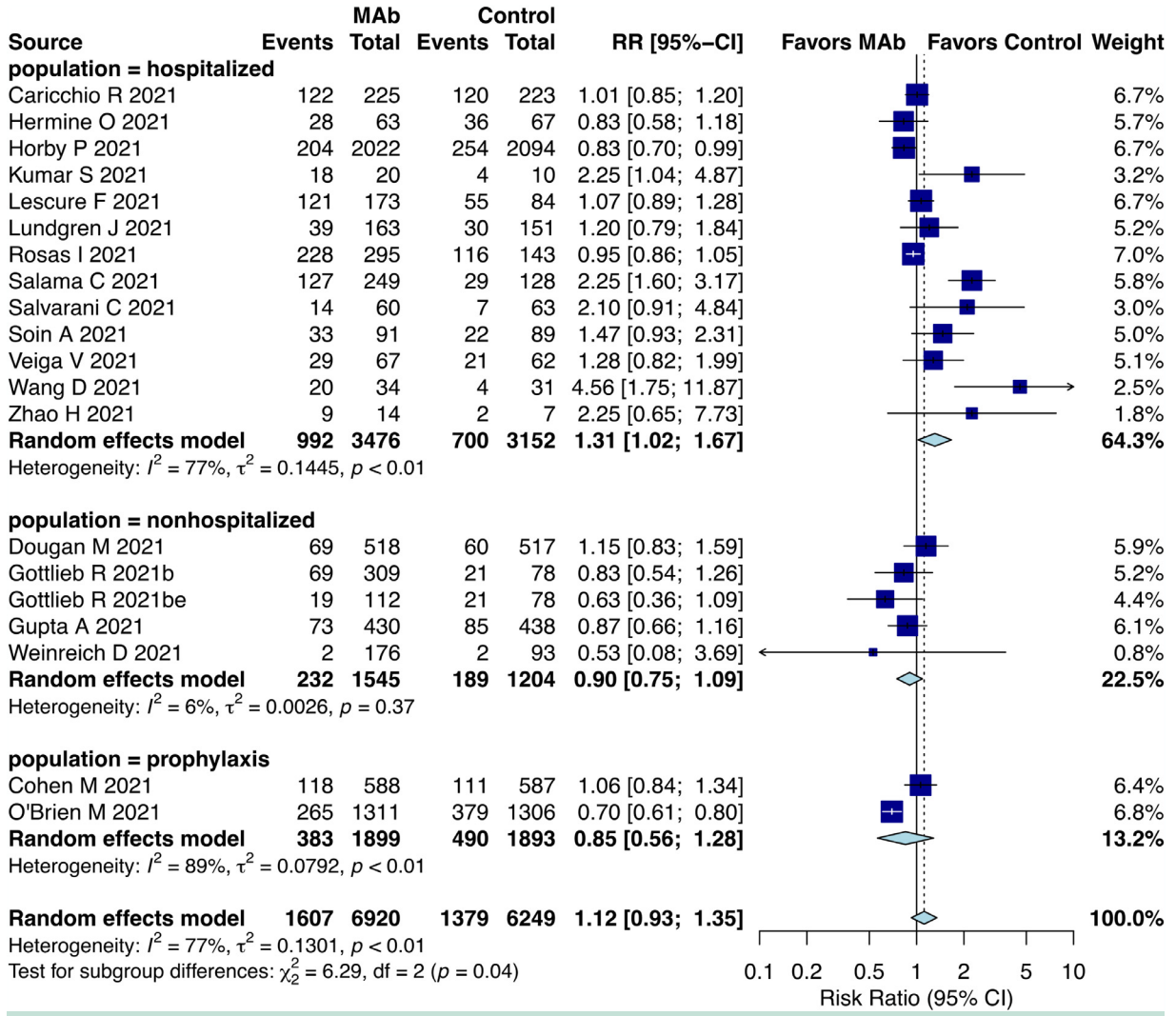
Supplementary Figure 2 Effects of monoclonal antibodies on length of hospital stay stratified by type of COVID-19 patients.



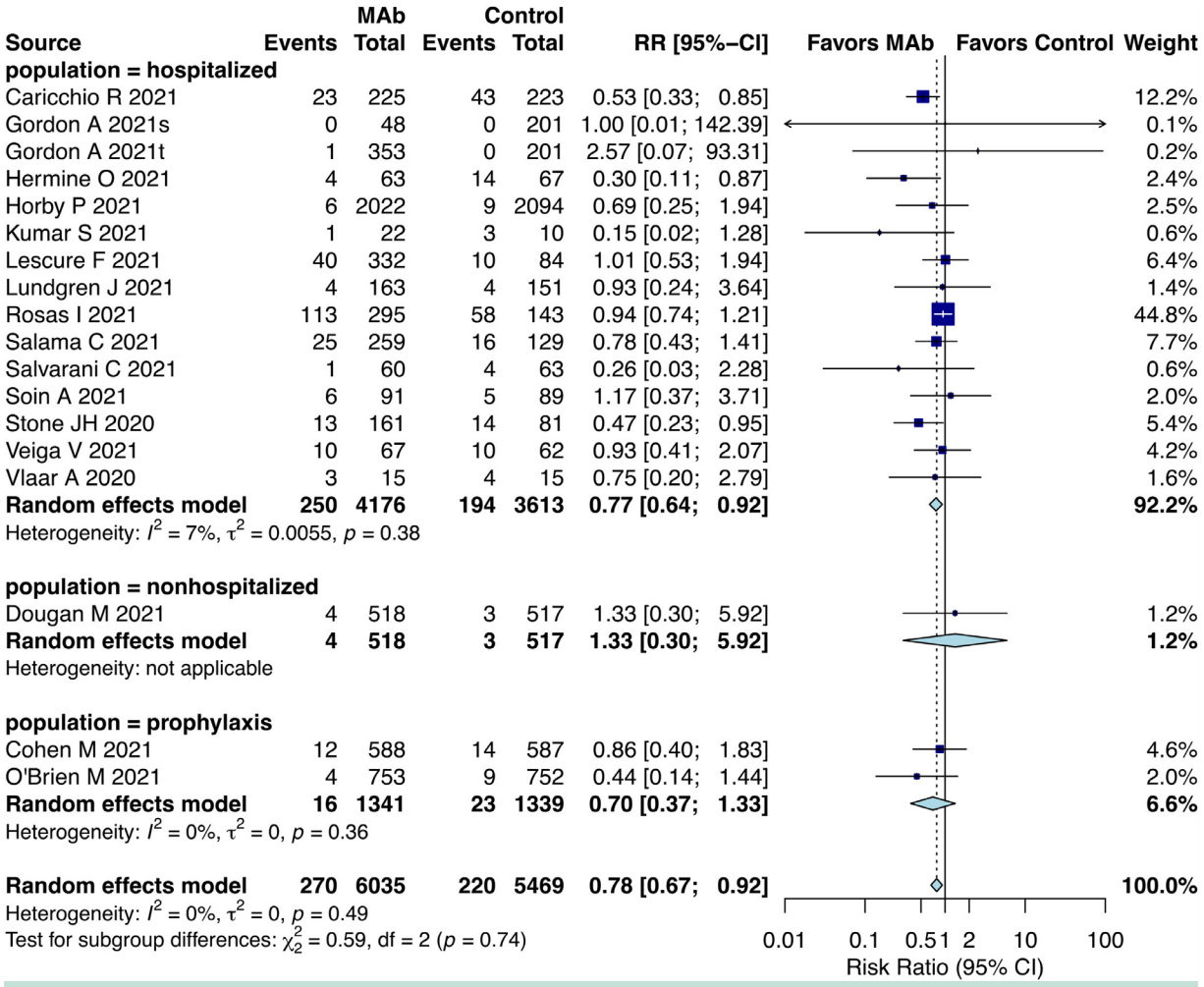
Supplementary Figure 3 Effects of monoclonal antibodies on invasive mechanical ventilation stratified by type of COVID-19 patients.



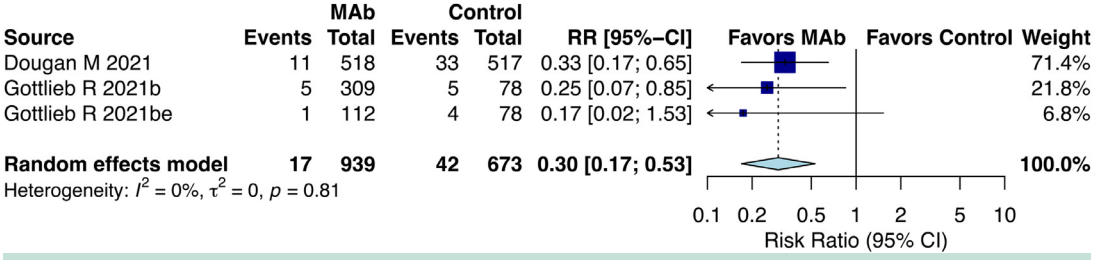
Supplementary Figure 4 Effects of monoclonal antibodies on viral load stratified by type of COVID-19 patients.



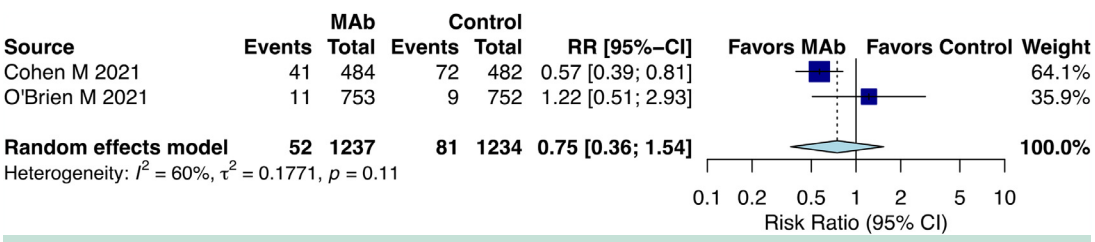
Supplementary Figure 5 Effects of monoclonal antibodies on adverse events stratified by type of COVID-19 patients.



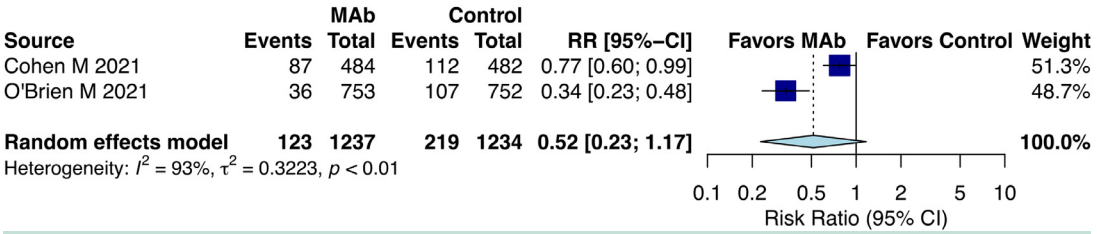
Supplementary Figure 6 Effects of monoclonal antibodies on bacteremia stratified by type of COVID-19 patients.



Supplementary Figure 7 Effects of monoclonal antibodies on COVID-19-related hospitalization in non-hospitalized RCTs



Supplementary Figure 8 Effects of monoclonal antibodies on symptomatic COVID-19 incidence in prophylaxis RCTs

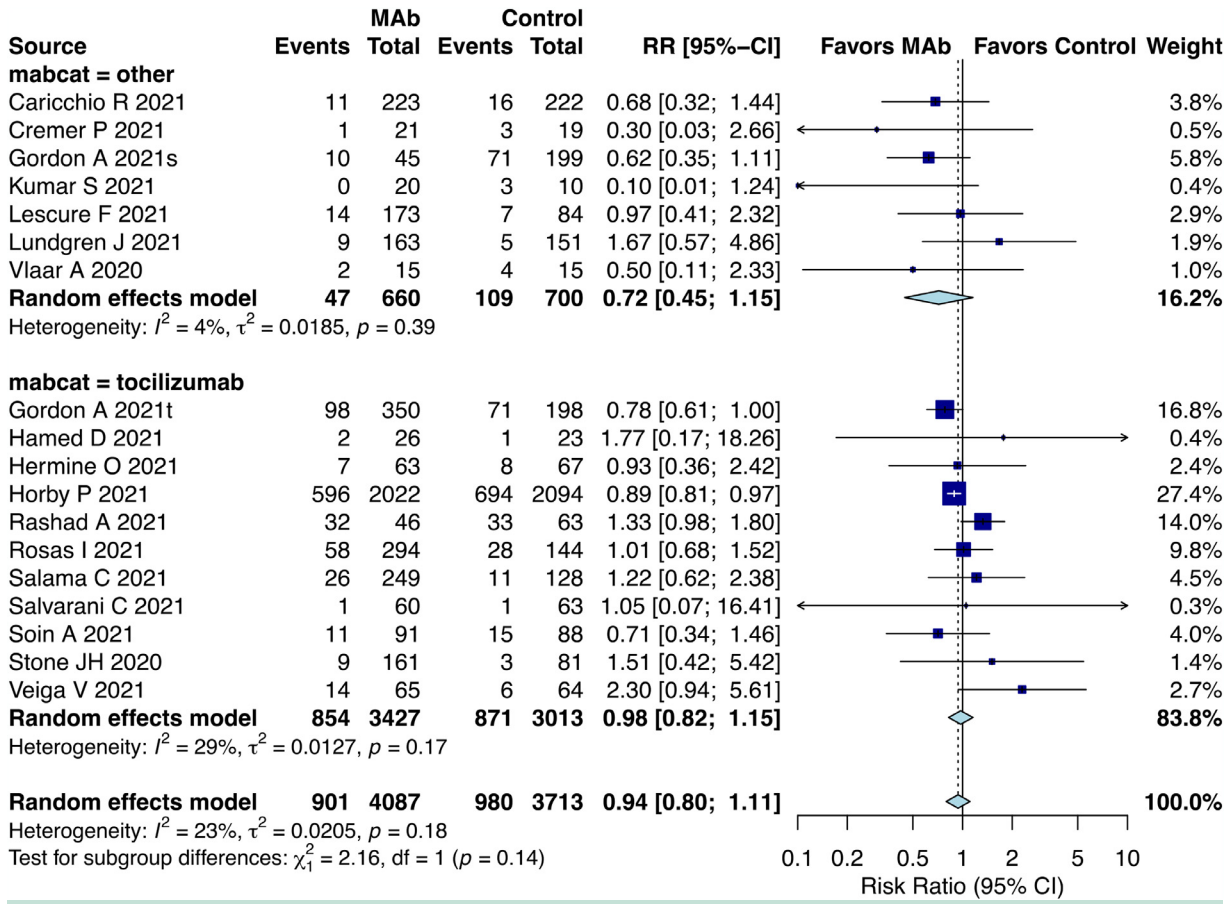


Supplementary Figure 9 Effects of monoclonal antibodies on symptomatic or asymptomatic COVID-19 incidence in prophylaxis RCTs

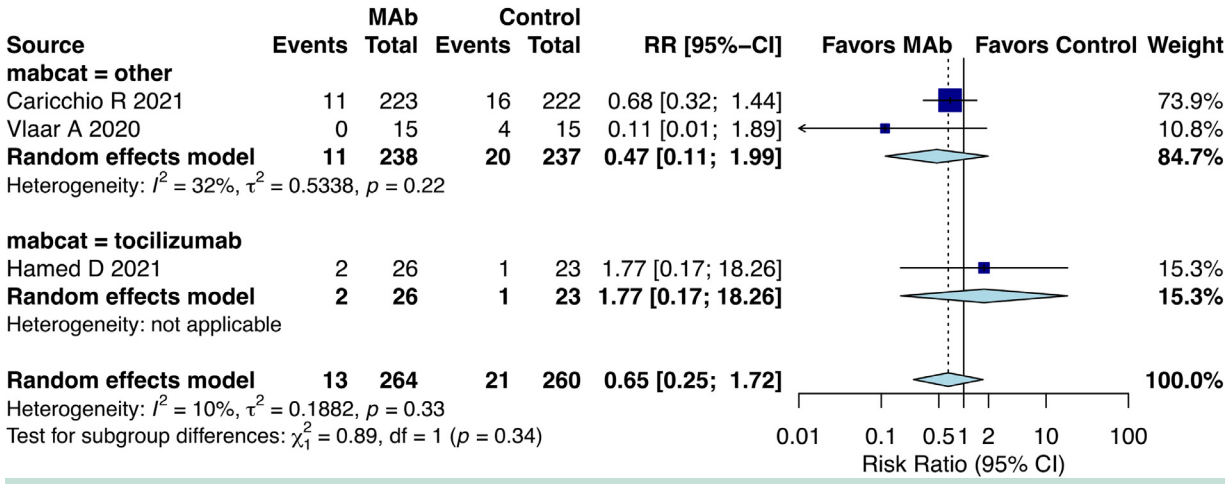
11. Subgroup analyses

Effects of monoclonal antibodies on outcomes across pre-defined subgroups are shown in Supplementary Figures 10A1 to 10A7 (by type of drug [tocilizumab vs other monoclonal antobody] in hospitalized patients), Figures 10B1 to 10B7 (by type of control in hospitalized patients), and Figures 10C1 to 10C6 (by type of control in hospitalized patients receiving tocilizumab), all available online. In subgroup analyses of hospitalized patients, we were unable to find any significant reductions associated with tocilizumab vs control therapy for any primary or secondary outcome aside from mechanical ventilation (**A5**), which was reduced by 20% (RR 0.80; 95% CI, 0.70-0.91, I^2 = 0%, P for interaction < .01). When we assessed monoclonal antibodies other than tolicizumab vs controls, the magnitude of the reductions was larger for all-cause mortality (**A1**), COVID-19-related death (**A2**), mechanical ventilation (**A5**), and bacteremia (**A7**) than what was seen with tocilizumab vs controls, but none of the non-tocilizumab vs control assessments were significantly different (all P for interaction >0.1). However, when tocilizumab trials and the single bamlanivimab trial by Lundgren et al[20] were removed, the trials of other anti-inflammatory monoclonal antibodies did significantly reduce all-cause mortality vs control (RR 0.64; 95% CI, 0.42-0.98, I^2 = 0%).

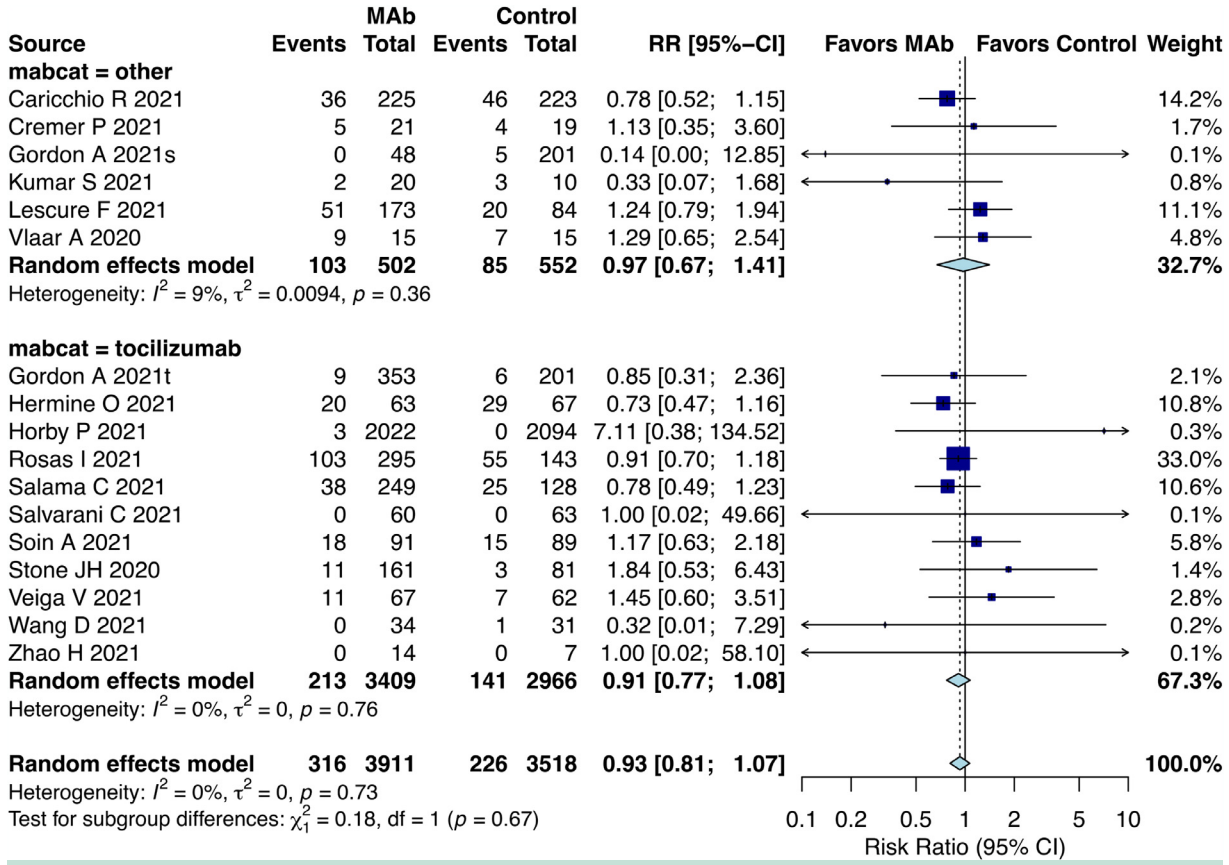
In subgroup analyses by control group (**B1-B7**), monoclonal antibodies had differential effects on all-cause mortality according to the type of control, although none of the subgroup effects was significant (**B1**, P for interaction < .01). Subgroup analyses for other outcomes did not show differential effects of monoclonal antibodies vs types of controls (**B2 to B7**, all P for interaction > .1). In subgroup analyses by type of control in tocilizumab-only trials (**C1-C6**), monoclonal antibodies had differential effects on all-cause mortality according to the type of control, although none of the subgroup effects was significant (**Figure C1**, P for interaction < .01). Subgroup analyses for other outcomes did not show differential effects of monoclonal antibodies vs types of controls (**C2 to C6**, all P for interaction > .1).



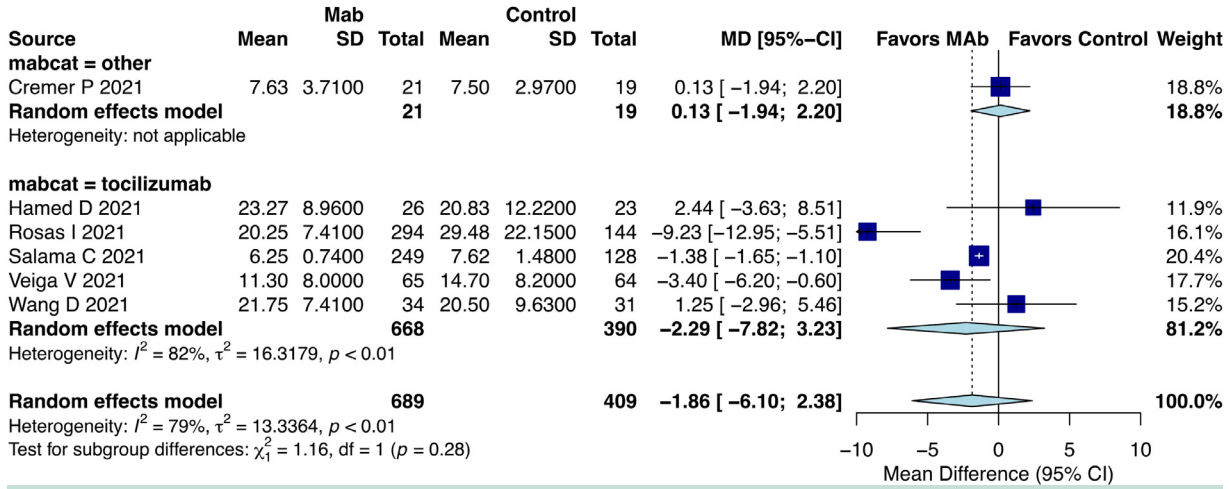
Supplementary Figure 10A Subgroup analyses by type of drug: tocilizumab vs. other MAbs in hospitalized patients
Supplementary Figure 10A1 All-cause mortality.



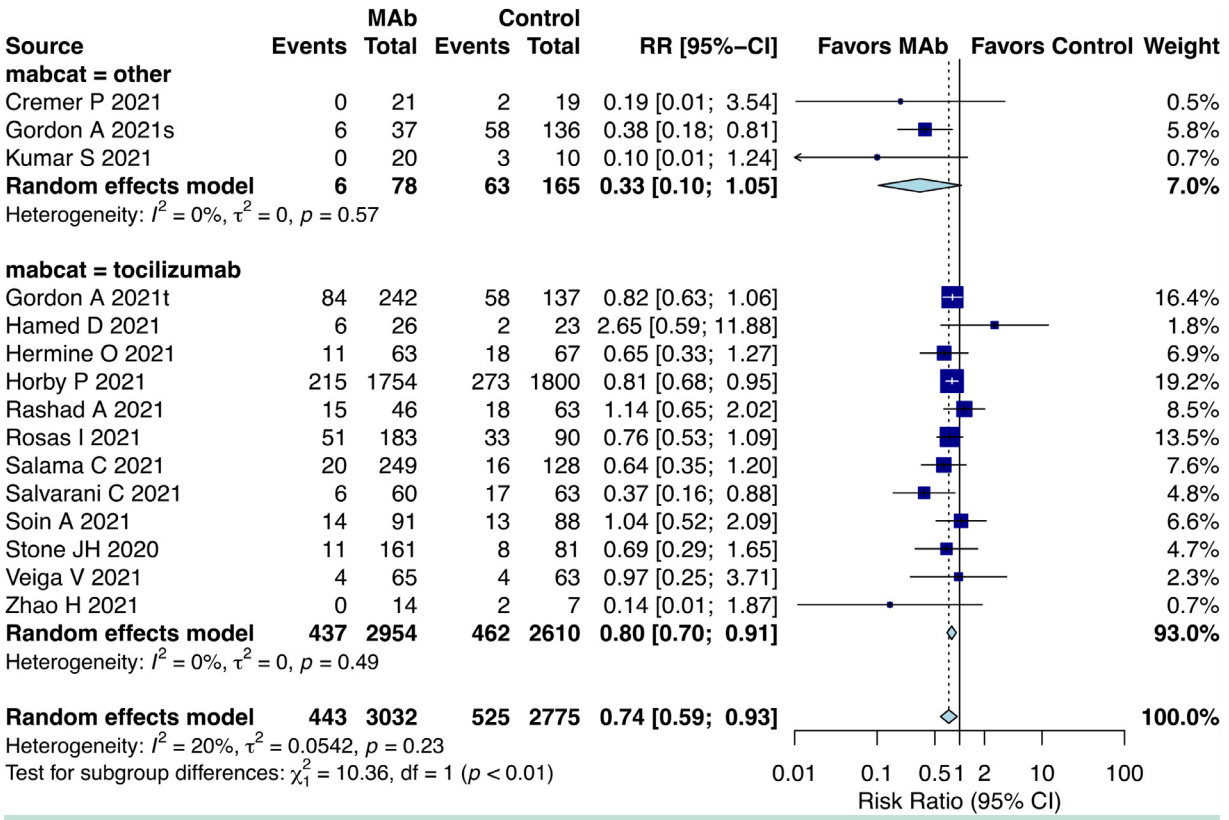
Supplementary Figure 10A2 COVID-19-related death .



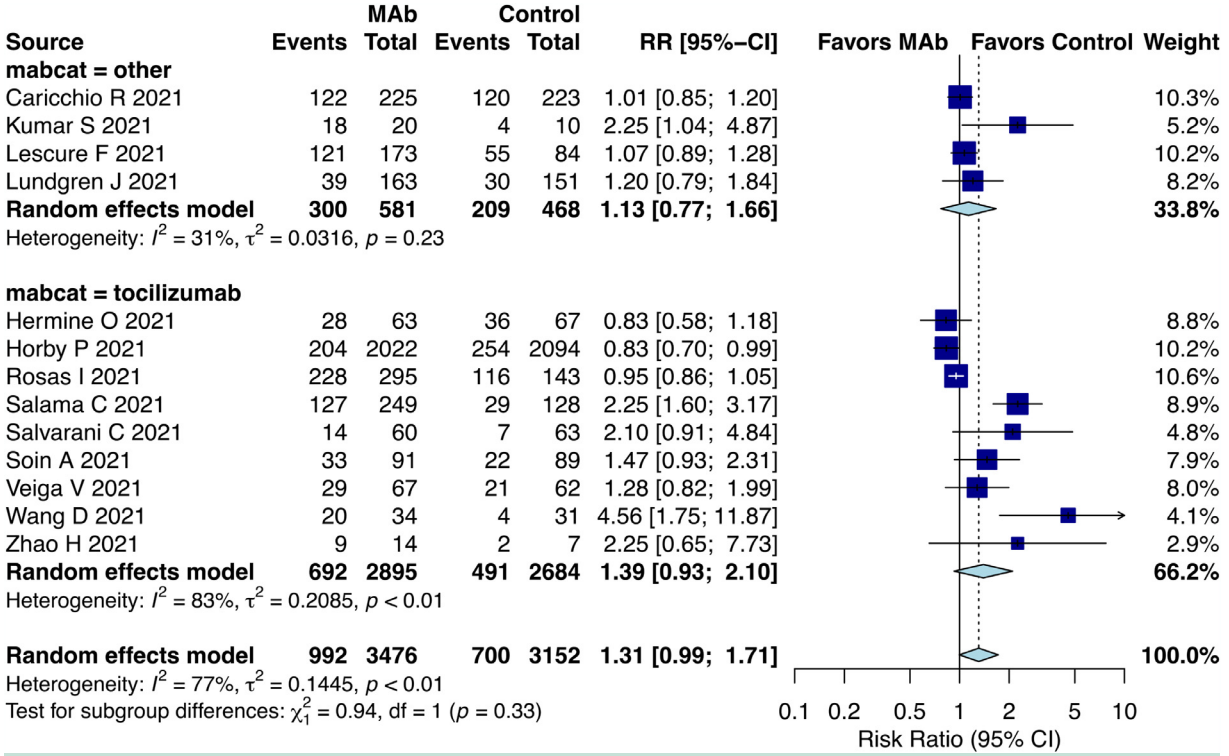
Supplementary Figure 10A3 Serious adverse events.



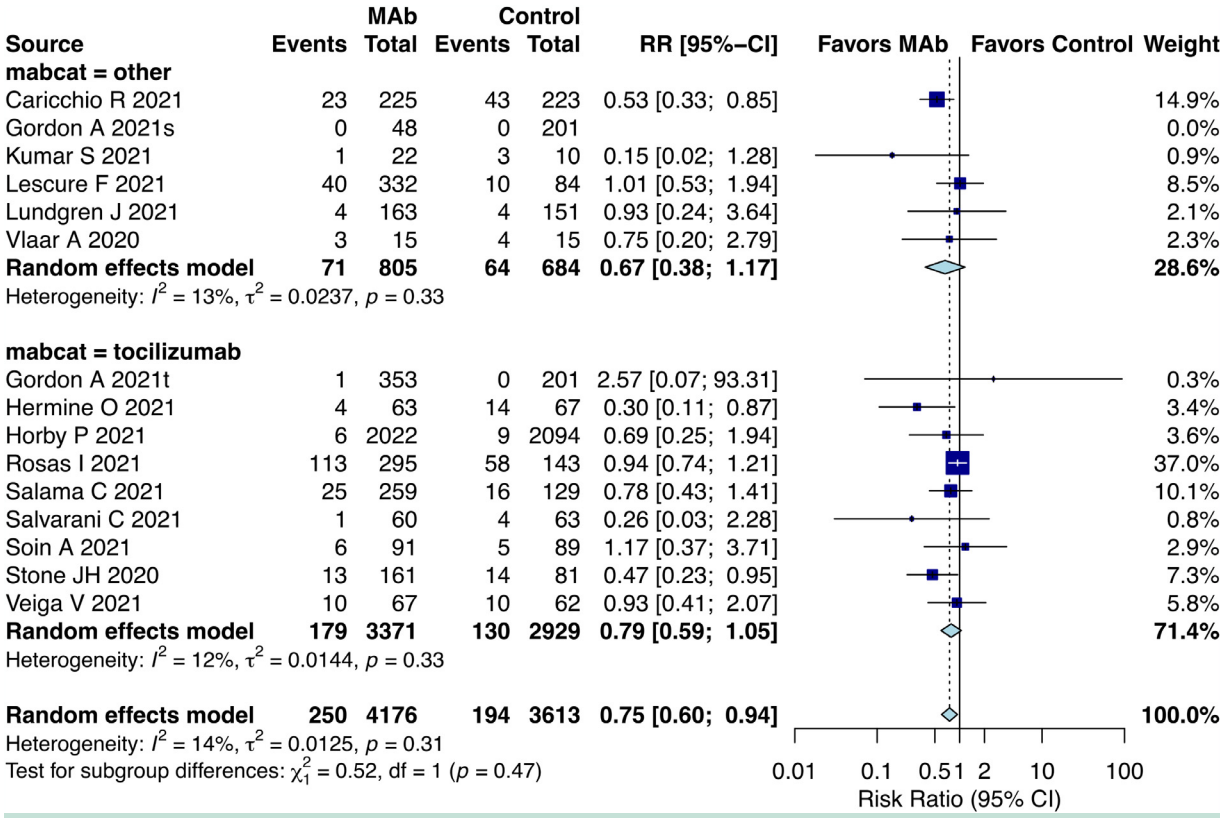
Supplementary Figure 10A4 Length of hospital stay.



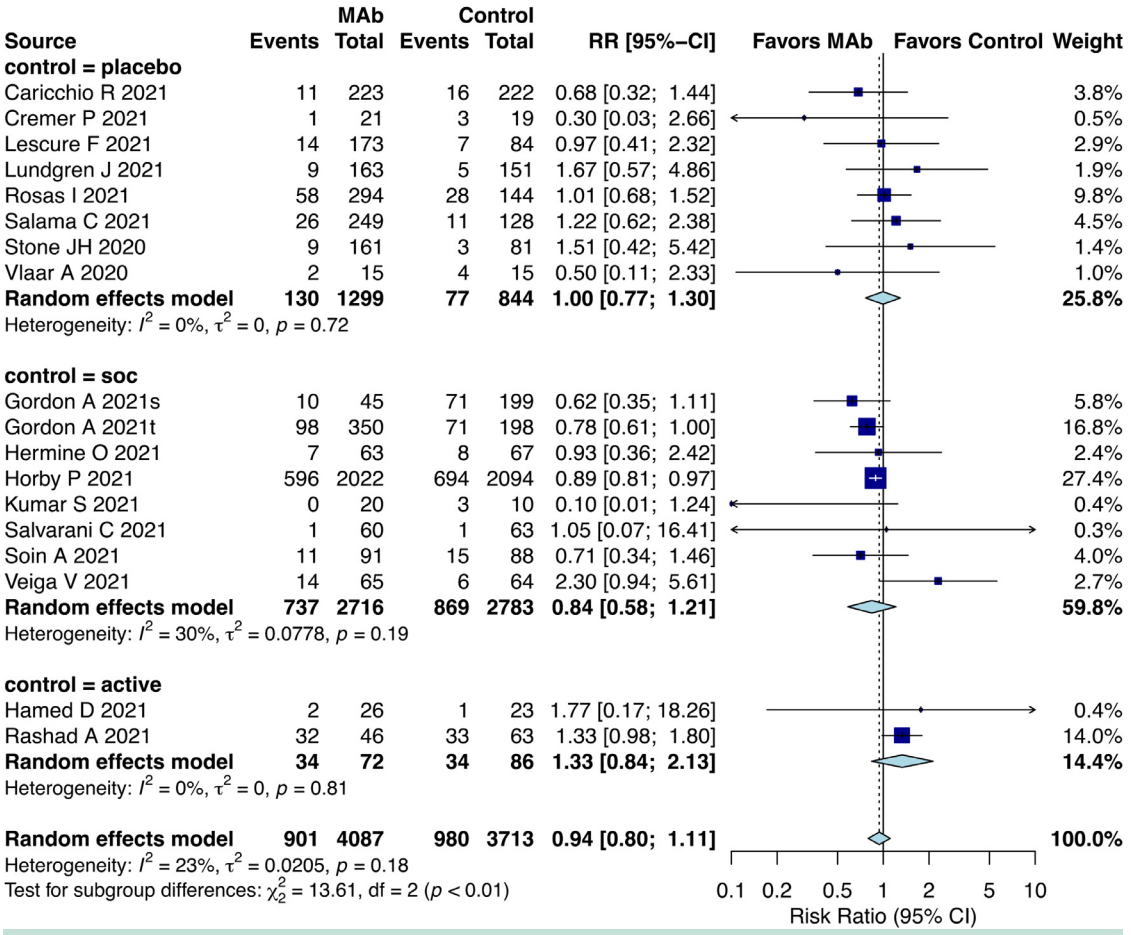
Supplementary Figure 10A5 Invasive mechanical ventilation.



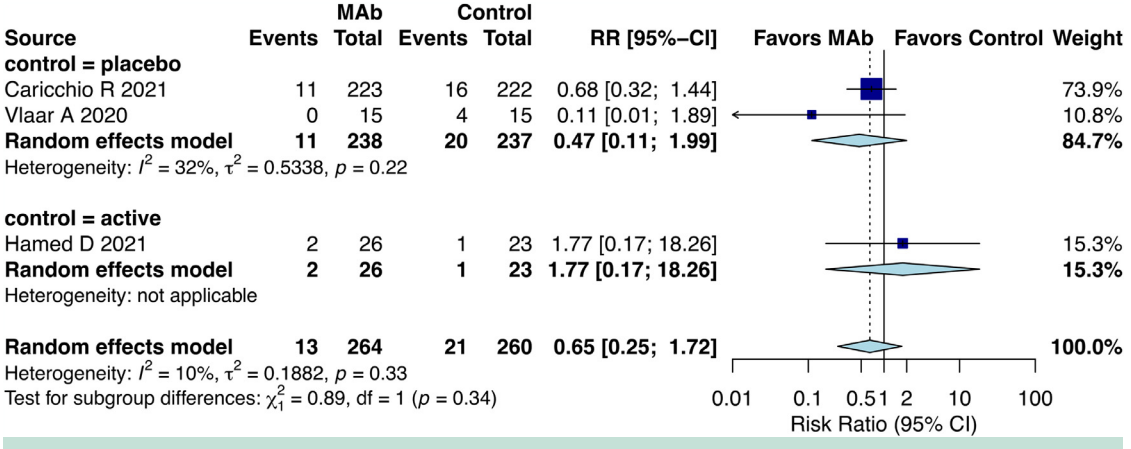
Supplementary Figure 10A6 Adverse events.



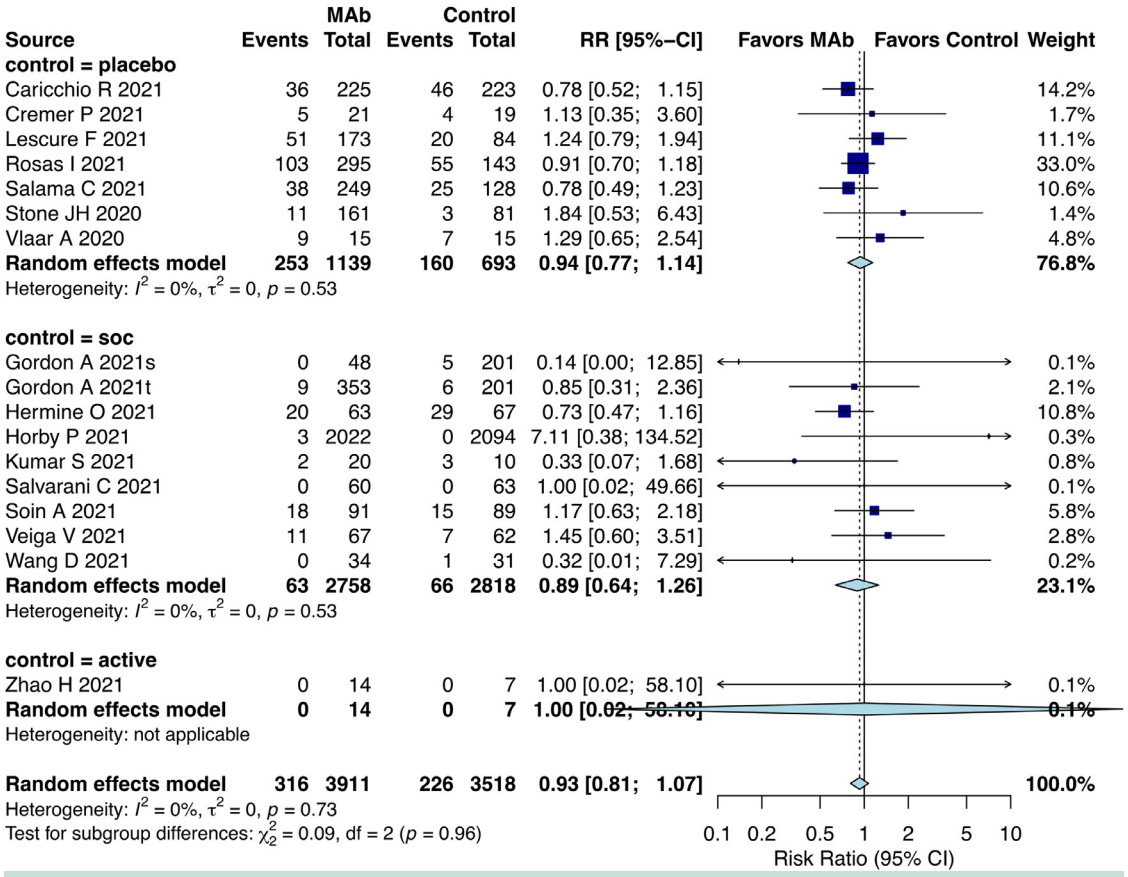
Supplementary Figure 10A7 Bacteremia



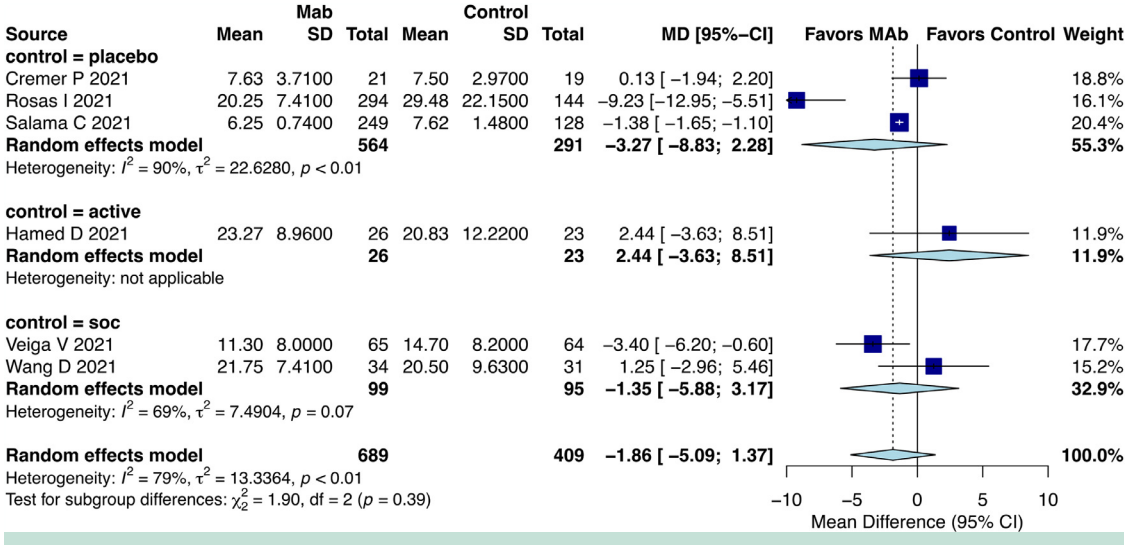
Supplementary Figure 10B Subgroup analyses by type of control in hospitalized patients.
Supplementary Figure 10B1 All-cause mortality.



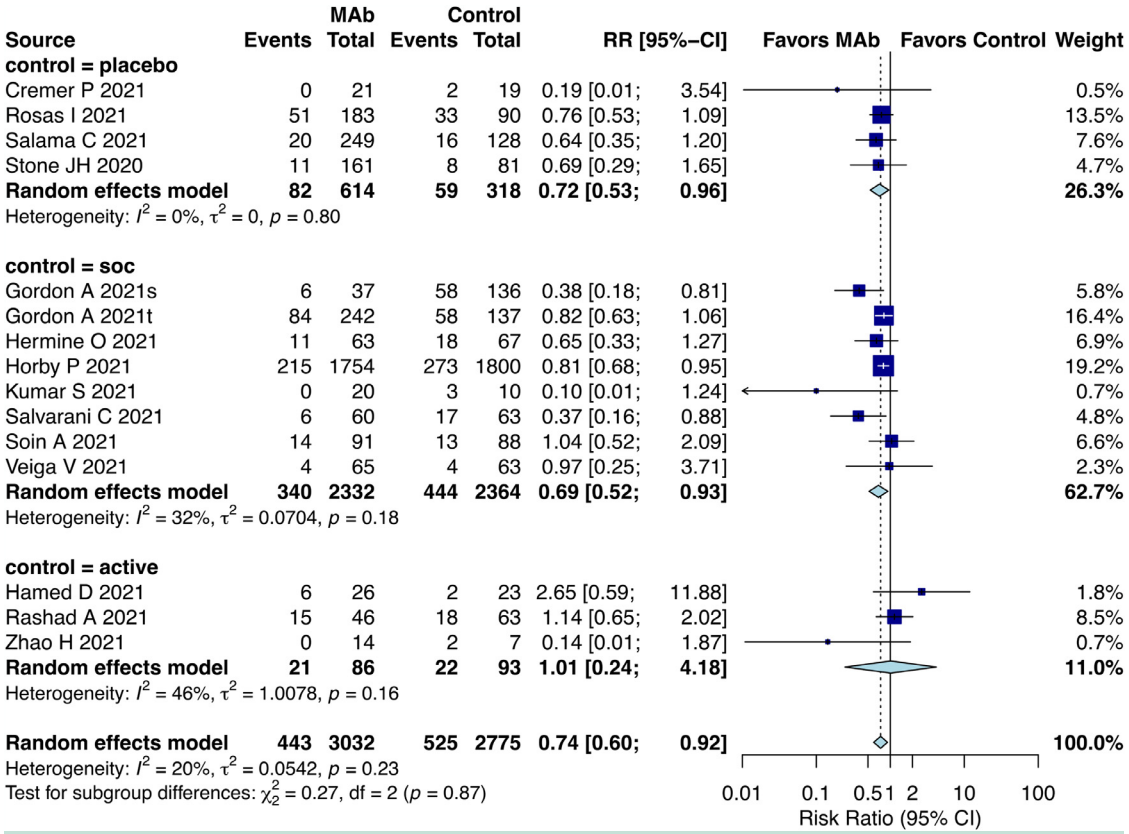
Supplementary Figure 10B2 COVID-19-related death



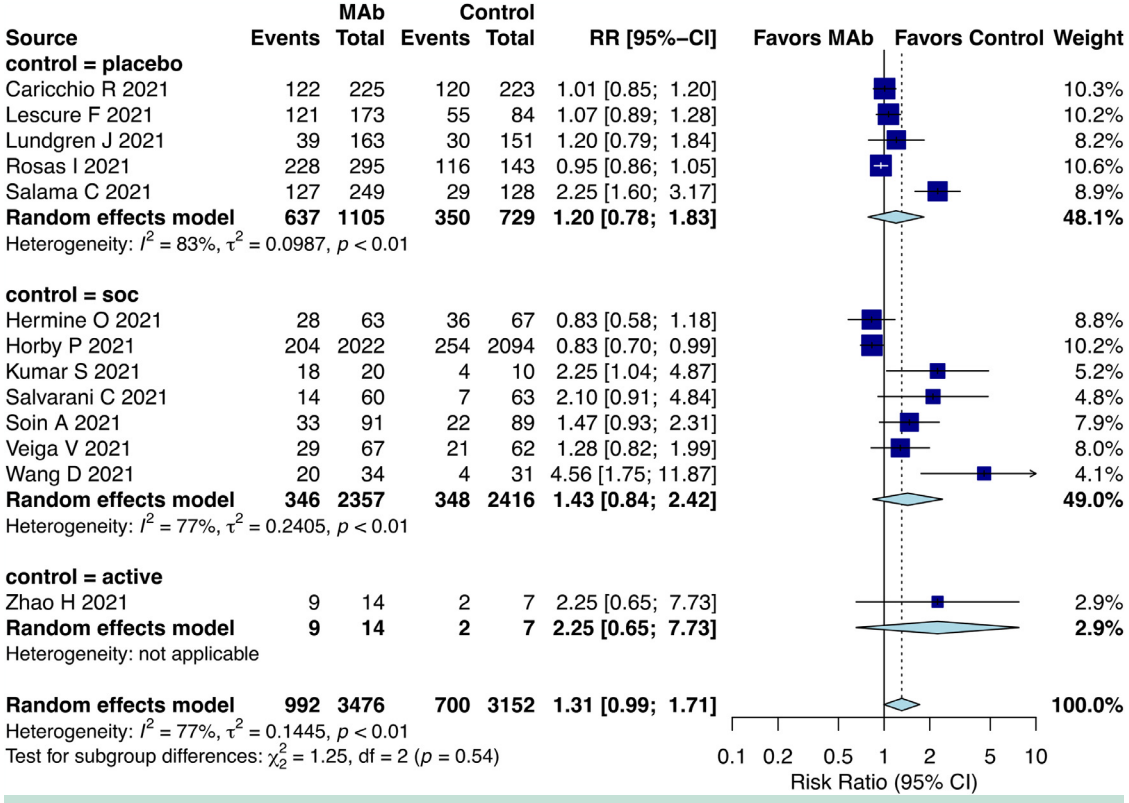
Supplementary Figure 10B3 Serious adverse events.



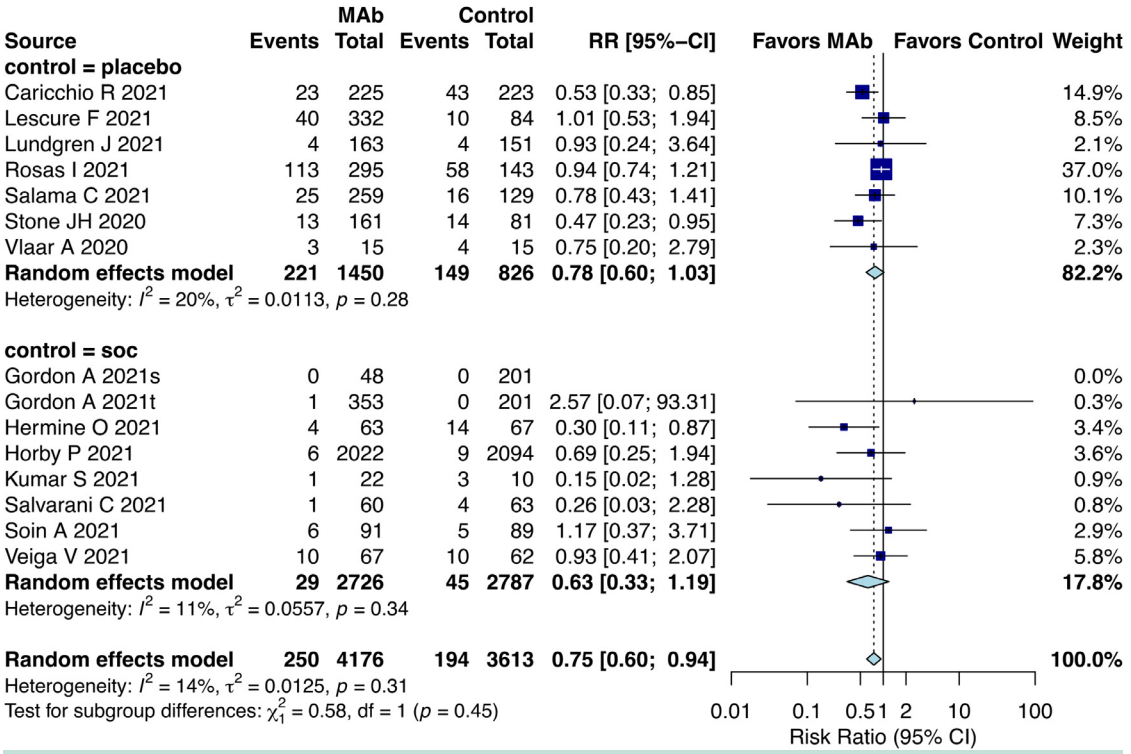
Supplementary Figure 10B4 Length of hospital stay.



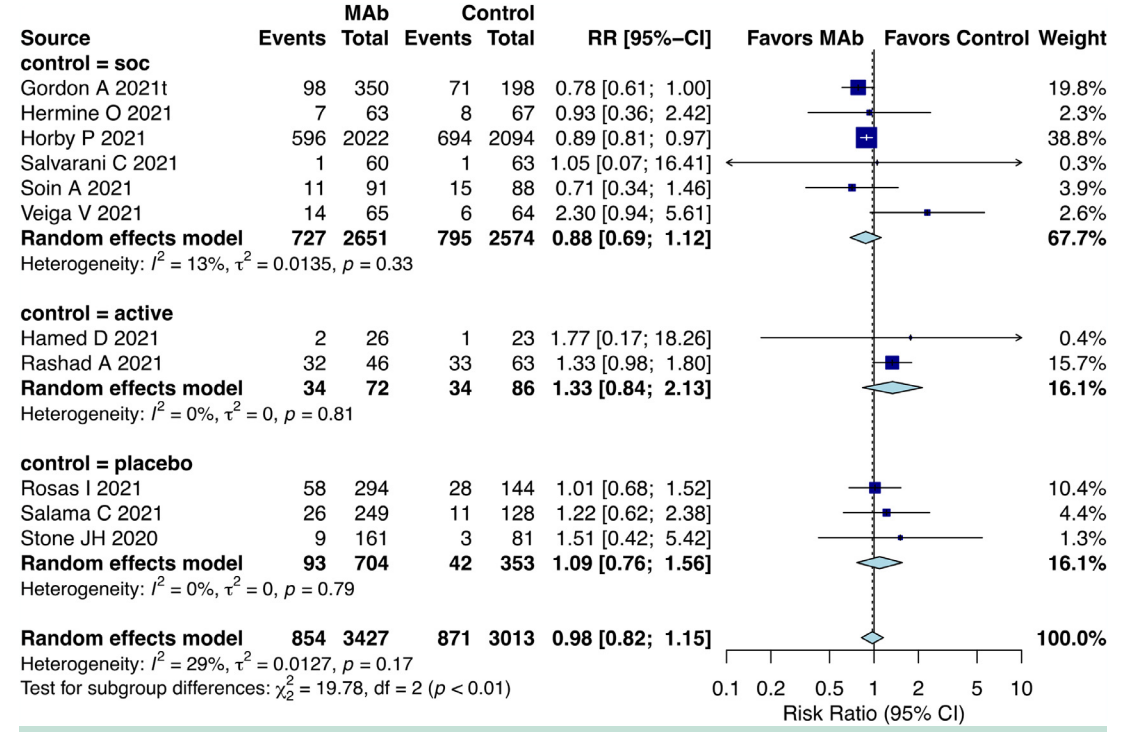
Supplementary Figure 10B5 Invasive mechanical ventilation.



Supplementary Figure 10B6 Adverse events.

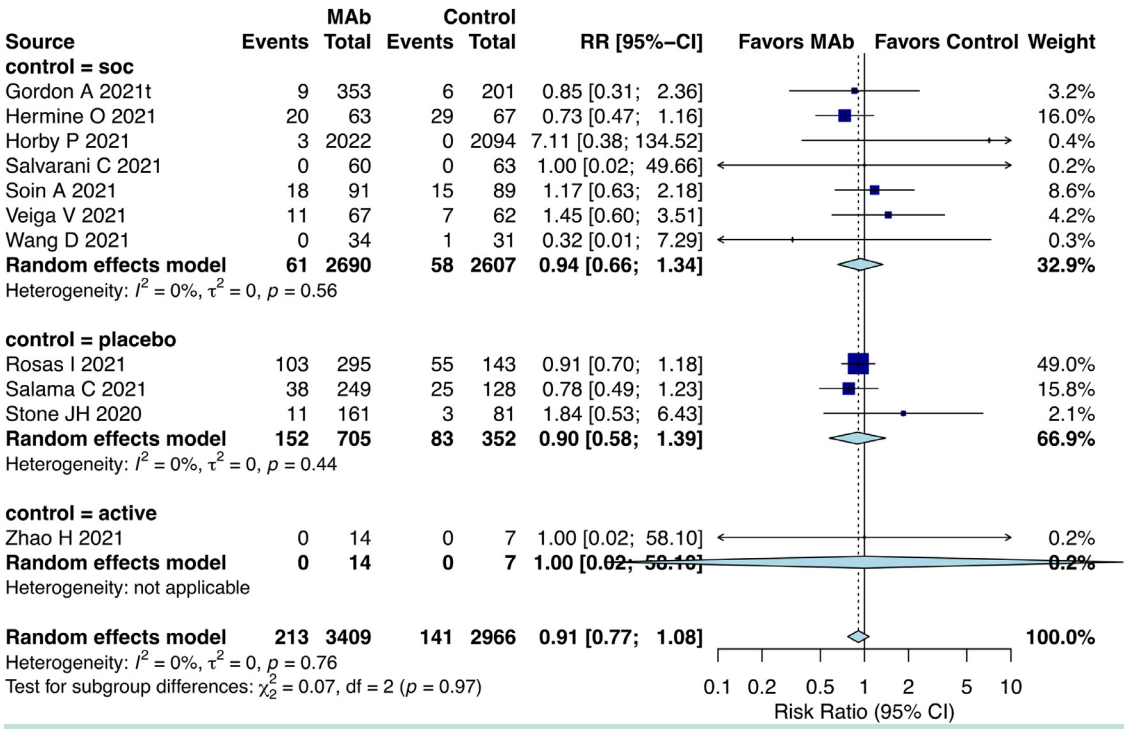


Supplementary Figure 10B7 Bacteremia.

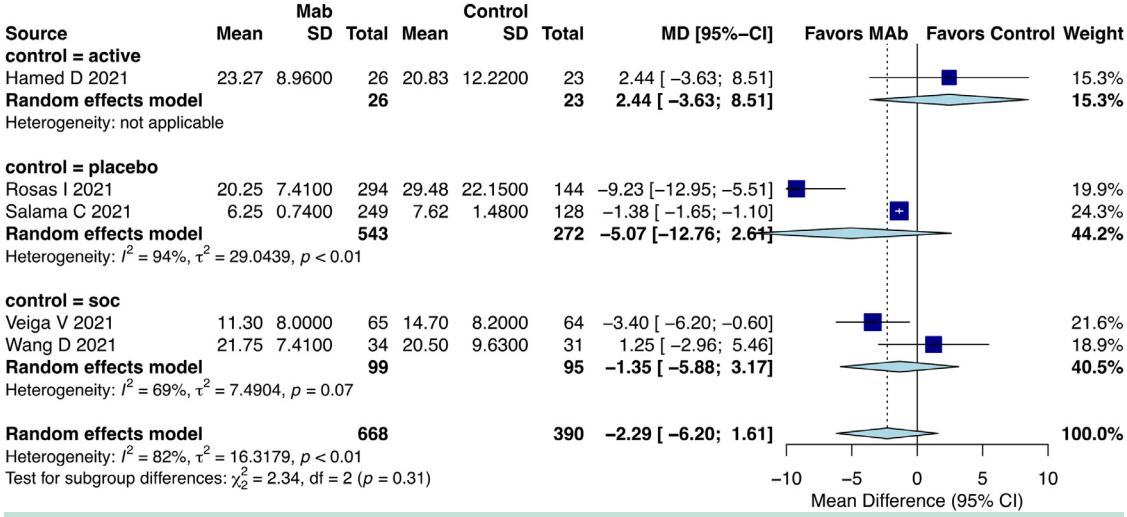


Supplementary Figure 10C Subgroup analyses by type of control in hospitalized patients receiving tocilizumab.

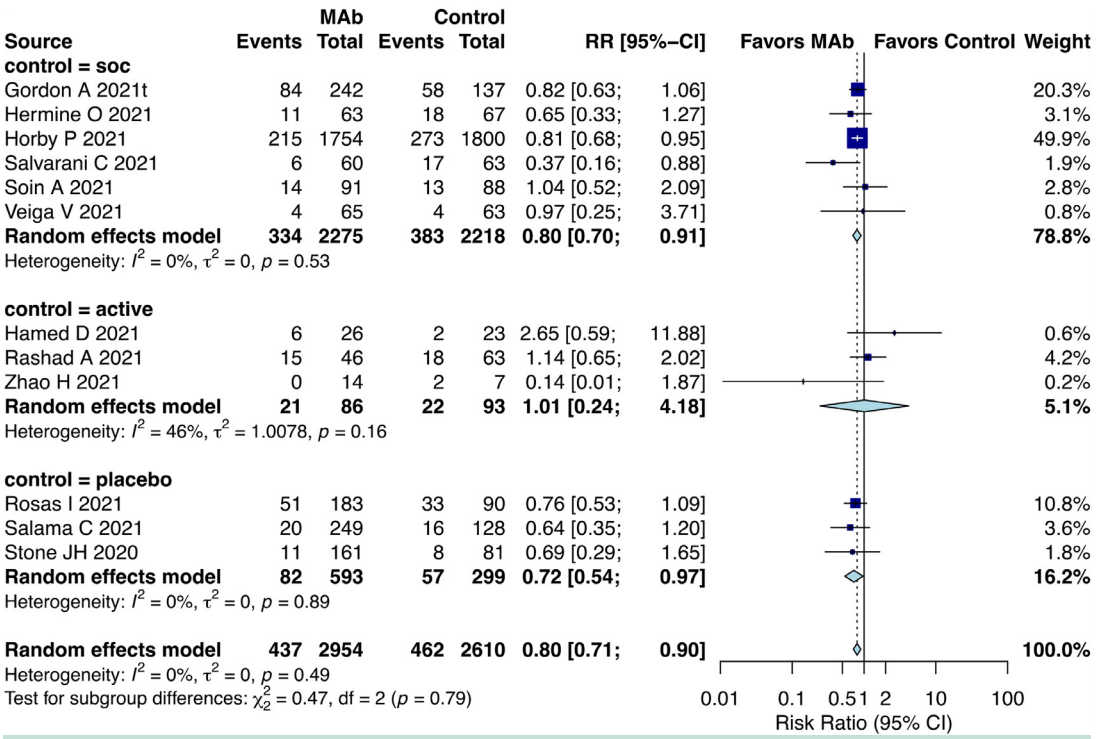
Supplementary Figure S10C1 All-cause mortality.



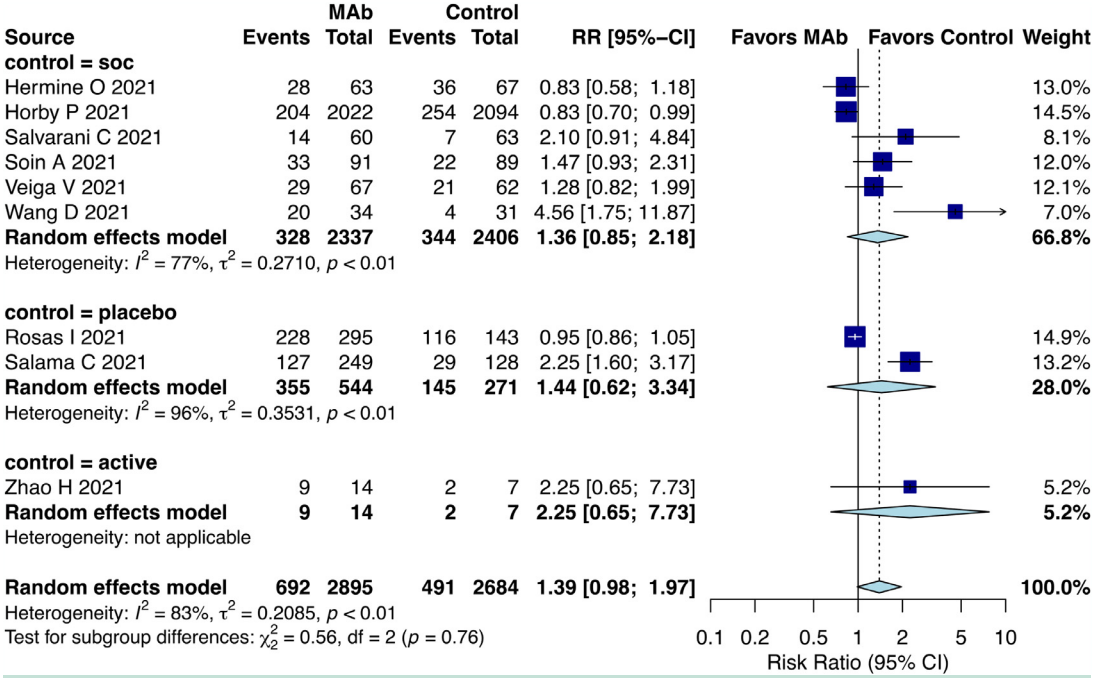
Supplementary Figure 10C2 Serious adverse events.



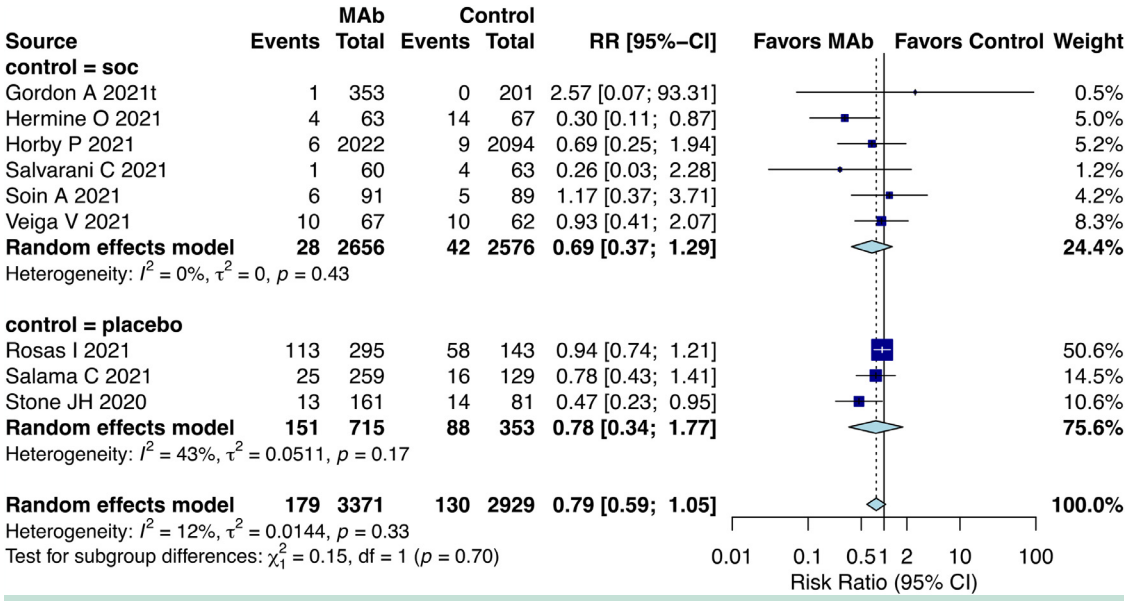
Supplementary Figure 10C3 Length hospital stay.



Supplementary Figure 10C4 Invasive mechanical ventilation.



Supplementary Figure 10C5 Adverse events.



Supplementary Figure 10C6 Bacteremia.