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

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#### 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. © 2022 Elsevier Inc. All rights reserved. • The American Journal of Medicine (2022) 135:1349–1361

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

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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.<sup>1</sup> 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.<sup>2,3</sup>

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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>5</sup>

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.<sup>5</sup>

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.

## 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.

## **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.

## 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 (pro-

phylaxis). Monoclonal antibodies of interest included antiinflammatory (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-19related 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.<sup>6</sup> 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**

systematic review was reported This according to 2020 PRISMA guidelines.<sup>7</sup> 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,<sup>2</sup> and the Hartnung-Knapp method to adjust 95% confidence intervals (CIs).<sup>8,9</sup> 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.<sup>10</sup> 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



## Table 1 Characteristics of 27 Included Randomized Controlled Trials

First Author, Year, <sup>reference</sup> 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 <sup>11</sup>	China	Hospitalized, vac-	28	Meplazumab, 5 days, 30	Standard of	56.5 (15.1)	57.1	32.1	10.7	10.7	Time to viral clearance, elevated aspartate	28
Caricchio, 2021 <sup>12</sup>	USA, Europe	cination NA Hospitalized, vac- cination NA	454	mg Canakinumab, 1 day, 660 mg	care Placebo	58.5 (14.1)	58.8	55.7	36.1	20.3	aminotransrerase or alanine transaminase All-cause mortality, serious adverse events, adverse events, COVID-19-related death, bacteremia	28
Cremer, 2021 <sup>13</sup>	USA	Hospitalized, vac- cination 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 <sup>14</sup> REMAP-CAP	Australia, New Zealand, UK, Bel- gium, Thailand, Sri Lanka, USA, Canada, Northern Ireland, Netherlands	Hospitalized, vac- cination NA	895	Tocilizumab, 1-2 days, 560-1120 mg Sarilu- mab, 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 <sup>15</sup>	United Arab Emirates	Hospitalized, vac- cination 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 <sup>16</sup>	France	Hospitalized, vac- cination 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 <sup>17</sup> RECOVERY	UK	Hospitalized, vac- cination 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 <sup>18</sup>	India	Hospitalized, vac- cination 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 <sup>19</sup>	Argentina, Brazil, Canada, Chile, France, Germany, Israel, Italy, Japan, Russia, and Spain	Hospitalized, vac- cination 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 <sup>20</sup> ACTIV-3/TICO LY-CoV555	USA, Denmark Singapore	Hospitalized, vac- cination 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 <sup>21</sup>	Egypt	Hospitalized, vac- cination 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 <sup>22</sup>	USA, UK, Spain	Hospitalized, vac- cination 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, bac- teremia. length of stav	28
Salama, 2021 <sup>23</sup>	USA, Mexico, Kenya, South Africa, Peru, Brazil	Hospitalized, vac- cination 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, bac- teremia. length of stav.	28
Salvarani, 2021 <sup>24</sup>	Italy	Hospitalized, vac- cination 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 <sup>25</sup>	India	Hospitalized, vac- cination 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 <sup>26</sup>	USA	Hospitalized, vac- cination 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 (Con	tinued)											
First Author, Year, <sup>reference</sup> 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 <sup>27</sup>	Brazil	Hospitalized, vac- cination 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, bac- teremia. length of stav	28
Vlaar, 2020 <sup>28</sup>	Netherlands	Hospitalized, vac- cination 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 <sup>29</sup>	China	Hospitalized, vac- cination 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 <sup>30</sup>	China	Hospitalized, vac- cination NA	31	Tocilizumab, 7 days, 400	Active	67.0 (33.3)	52.4	42.9	9.5	14.3	Serious adverse events, adverse events, mechanical ventilation	14
Chen, 2021 <sup>31</sup>	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 <sup>32</sup>	USA	Non-hospitalized, vaccination NA	1035	Bamlanivimab + etesevi- mab, 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 <sup>33</sup>	USA	Non-hospitalized, vaccination NA	577	Bamlanivimab, 1 day, 3486 mg; Bamlanivi- mab + 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 <sup>34</sup>	USA, Canada, Brazil, Spain	Non-hospitalized, vaccination NA	275	Sotrovimab, 1 day, 500	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 <sup>35</sup>	<sup>5</sup> 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 <sup>36</sup>	USA	Prophylaxis, vac- cination 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
0'Brien, 2021 <sup>37</sup>	USA, Romania Moldova	Prophylaxis, vac- cination 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,<sup>11-30</sup> 5

studies in non-hospitalized COVID-19 patients,<sup>31-35</sup> and 2 studies in individuals at high risk of developing COVID-19.<sup>36,37</sup> Two trials evaluated 2 different monoclonal antibodies: Gordon et al<sup>14</sup> evaluated tocilizumab and sarilumab, and Gottlieb et al<sup>33</sup> evaluated bamlanivimab and bamlanivimab + etesevimab.

## Characteristics of Included Randomized Controlled Trials

Table 1<sup>11-37</sup> displays features of the 20 trials in hospitalized COVID-19 patients.<sup>11-30</sup> 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<sup>14</sup> 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 Absolu	te Effects (95% CI)	Relative Effect (95% CI)	Number of Participants (Studies)	Certainty of the Evidence (CRADE)
	Risk with Standard of Care, Active Therapy or Placebo	Risk with Monoclonal Antibodies		(Studies)	(UKADL)
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 <sup>†</sup>
COVID-19-related death	8 per 100	5 per 100	RR 0.65	524	$\oplus \oplus 00$
follow-up: range 28-45 days		(2-14)	(0.25-1.72)	(3 RCTs)	Low <sup>‡,§</sup>
Invasive mechanical ventilation	19 per 100	14 per 100	RR 0.74	5807	$\oplus \oplus 00$
follow-up: range 14-45 days		(11-17)	(0.60-0.92)	(14 RCTs)	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)	<u> </u>	1098 (6 RCTs)	⊕000 Very low <sup>¶,</sup> **' <sup>††</sup>
Any adverse events	22 per 100	29 per 100	RR 1.31	6628	⊕000
follow-up: range 14-90 days		(23-37)	(1.02-1.67)	(13 RCTs)	Very low <sup>‡‡,§§</sup>
Serious adverse events	6 per 100	6 per 100	RR 0.93	7831	⊕⊕00
follow-up: range 14-45 days		(5-7)	(0.80-1.08)	(17 RCTs)	Low
Bacteremia	5 per 100	4 per 100	RR 0.77	7789	$\oplus \oplus 00$
follow-up: range 14-90 days		(3-5)	(0.64-0.92)	(14 RCTs)	Low

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

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

‡RoB: Vlaar et al<sup>28</sup> 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.

 $\P$ RoB: Two RCTs (Rosas et al,<sup>22</sup> Salama et al<sup>23</sup>) had some concerns of bias, and one RCT (Veiga et al<sup>27</sup>) was at high risk of bias.

\*\*Inconsistency: I<sup>2</sup> was 79%.

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

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

§§Inconsistency: I<sup>2</sup> was 77%.

|||RoB: Two RCTs (Veiga et al<sup>27</sup> and Vlaar et al<sup>28</sup>) 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.<sup>31-35</sup> 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<sup>36,37</sup> 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 metaanalyses. 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<sup>22,23,27,28</sup> 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.



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

		MAb	C	ontrol				
Source E	vents	Total	Events	Total	RR [95%	–CI]	Favors MAb F	avors Control Weight
population = hospitalized								
Caricchio R 2021	36	225	46	223	0.78 [0.52;	1.15]		12.2%
Cremer P 2021	5	21	4	19	1.13 [0.35; 3	3.60]		— 1.8%
Gordon A 2021s	0	48	5	201	0.14 [0.00; 12	2.85] ←		0.1%
Gordon A 2021t	9	353	6	201	0.85 [0.31; 2	2.36]		- 2.2%
Hermine O 2021	20	63	29	67	0.73 [0.47;	1.16]		9.7%
Horby P 2021	3	2022	0	2094	7.11 [0.38; 134	4.52]		→ 0.3%
Kumar S 2021	2	20	3	10	0.33 [0.07;	1.68]		0.9%
Lescure F 2021	51	173	20	84	1.24 [0.79; <sup>-</sup>	1.94]	-	10.0%
Rosas   2021	103	295	55	143	0.91 [0.70; <sup>-</sup>	1.18]		21.9%
Salama C 2021	38	249	25	128	0.78 [0.49;	1.23]	-	9.6%
Salvarani C 2021	0	60	0	63	1.00 [0.02; 49	9.66]		0.2%
Soin A 2021	18	91	15	89	1.17 [0.63; 2	2.18]		- 5.7%
Stone JH 2020	11	161	3	81	1.84 [0.53; 6	5.43]		<b>1.5</b> %
Veiga V 2021	11	67	7	62	1.45 [0.60; 3	3.51]	- <del> </del> -	— 3.0%
Vlaar A 2020	9	15	7	15	1.29 [0.65; 2	2.54]		- 4.8%
Wang D 2021	0	34	1	31	0.32 [0.01;	7.29] -	•	
Zhao H 2021	0	14	0	7	1.00 [0.02; 58	3.10] ·		0.1%
Random effects model	316	3911	226	3518	0.93 [0.80; 1	1.08]	¢	84.2%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0$	, p = 0.	73						
population = nonhospitali	zed							
Dougan M 2021	7	518	5	517	1.40 [0.45; 4	4.37]		— 1 <u>.</u> 8%
Gottlieb R 2021b	0	309	1	78	0.17 [0.01; 2	2.81] —	•	- 0.3%
Gottlieb R 2021be	1	112	1	78	0.70 [0.04; 10	0.97]		0.3%
Gupta A 2021	7	430	26	438	0.27 [0.12; 0	0.63]		3.4%
Weinreich D 2021	1	176	2	93	0.26 [0.02; 2	2.88]		- 0.4%
Random effects model	16	1545	35	1204	<b>0.47 [0.22</b> ; 1	1.01]	$\sim$	6.2%
Heterogeneity: $I^2 = 33\%$ , $\tau^2 =$	0.1588	, <i>p</i> = 0.2	20					
population = prophylaxis								
Cohen M 2021	22	588	19	587	1.16 [0.63; 2	2.11]		- 6.0%
O'Brien M 2021	10	1311	15	1306	0.66 [0.30;	1.47]		3.6%
Random effects model	32	1899	34	1893	0.93 [0.55; 1	1.58]	$\sim$	9.5%
Heterogeneity: $I^2 = 15\%$ , $\tau^2 =$	0.0236	, p = 0.2	28					
Development of the state of the		7055	005	0045	0 00 10 77	053		100 001
Handom effects model	364	/355	295	6615	0.90 [0.77; 1	1.05]		100.0%
Heterogeneity: $I^{-} = 6\%$ , $\tau^{-} = 0$	2, 2	p = 0.37				0.01		0 10 100
rest for subgroup differences:	$\chi_2^- = 2.$	99, df =	2(p = 0.2)	22)		0.01	0.1 0.51 2	2 10 100
							HISK HATIO (	95% UI)

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 granulocytemonocyte 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<sup>20</sup> 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.<sup>38</sup>

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

Outcomes	Anticipated Absolu	ute Effects (95% CI)	Relative Effect	Number of Participants	Certainty of the Evidence
	Risk with Placebo	Risk with Monoclonal Antibodies	(95% (1)	(Studies)	(GRADE)
COVID-19-related hospitalization	6 per 100	2 per 100	RR 0.30	1612	$\oplus \oplus \oplus \oplus$
follow-up: median 29 days		(1-3)	(0.17-0.53)	(2 RCTs)	High
All-cause mortality	1 per 100	0 per 100	RR 0.30	2212	⊕000
follow-up: median 29 days	-	(0-2)	(0.05-1.85)	(4 RCTs)	Very low <sup>†,‡</sup>
COVID-19-related death	1 per 100	0 per 100	RR 0.28	1829	⊕000
follow-up: median 29 days		(0-2)	(0.04-1.81)	(3 RCTs)	Very low <sup>§,  </sup>
Invasive mechanical ventilation	1 per 100	0 per 100	RR 0.20	583	⊕000
follow-up: median 29 days	-	(0-3)	(0.01-4.16)	(1 RCT)	Very low <sup>¶,</sup> **
Length of hospital stay	The mean length of	MD 3.9 days lower	_	44	$\oplus \oplus 00$
assessed with: days	hospital stay was	(9.02 lower to 1.22		(1 RCT)	Low <sup>††</sup>
follow-up: median 29 days	11.2 days	higher)			
Viral load reduction from baseline	The mean viral load	MD 0.44 log <sub>10</sub> lower	-	1941	⊕000
assessed with: log <sub>10</sub>	reduction from base-	(1.4 lower to 0.52		(4 RCTs)	Very low <sup>§,‡‡,§§</sup>
follow-up: median 29 days	line was $-1.2 \log_{10}$	higher)			
Any adverse events	16 per 100	14 per 100	RR 0.90	2749	$\oplus \oplus \oplus O$
follow-up: median 29 days		(12-17)	(0.75-1.09)	(4 RCTs)	Moderate <sup>†</sup>
Serious adverse events	3 per 100	1 per 100	RR 0.47	2749	$\oplus \oplus 00$
follow-up: median 29 days		(1-3)	(0.22-1.01)	(4 RCTs)	Low <sup>†,    </sup>
Bacteremia	1 per 100	1 per 100	RR 1.33	1035	$\oplus \oplus 00$
follow-up: median 29 days		(0-3)	(0.30-5.92)	(1 RCT)	Low

#### CI = confidence interval; GRADE = Grading of Recommendations, Assessment, Development, and Evaluations; MD = mean difference; RR = relative risk. †Risk of bias (RoB): Weinreich et $a1^{35}$ was at high risk of bias; Gupta et $a1^{34}$ had some concerns of bias.

‡Imprecision: 95% CI was 0.05-1.85.

§RoB: Weinreich et al<sup>35</sup> was at high risk of bias.

||Imprecision: 95% CI was 0.04-1.81.

**¶**RoB: Gupta et al<sup>34</sup> had high risk of bias.

\*\*Imprecision: 95% CI was 0.01-4.16.

††Imprecision: 95% CI of MD was -9.02-1.22 days.

 $\ddagger \ddagger Inconsistency: I^2 = 91\%.$ 

§§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.<sup>38</sup> 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.<sup>39</sup> 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.<sup>5</sup> 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 Absolı	ute Effects (95% CI)	Relative Effect	Number of Participants (Studios)	Certainty of the Evidence (GRADE)	
	Risk with Placebo	Risk with Monoclonal Antibodies	(95 % CI)	(Studies)		
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 <sup>†,‡,§</sup>	
Symptomatic and asymptomatic COVID-19 assessed with: Positive PCR test with or without COVID-19 symptoms	18 per 100	9 per 100 (4-21)	RR 0.52 (0.23-1.17)	2471 (2 RCTs)	⊕OOO Very low <sup>†,∥,¶</sup>	
All-cause mortality	1 per 100	1 per 100	RR 0.83	966	⊕⊕OO	
follow-up: median 28 days		(0-3)	(0.25-2.70)	(1 RCT)	Low**	
COVID-19-related death	1 per 100	0 per 100	RR 0.11	966	⊕⊕OO	
follow-up: median 28 days		(0-2)	(0.01-2.05)	(1 RCT)	Low <sup>††</sup>	
Viral load reduction from baseline assessed with: log <sub>10</sub> follow-up: median 28 days	The mean viral load reduction from base- line was —0.39 log <sub>10</sub>	MD 0.8 log <sub>10</sub> lower (1.21 lower to 0.39 lower)	_	132 (1 RCT)	⊕⊕⊕O Moderate <sup>‡‡</sup>	
Any adverse events	26 per 100	22 per 100	RR 0.85	3792	⊕000	
follow-up: median 28 days		(14-33)	(0.56-1.28)	(2 RCTs)	Very low <sup>†,‡‡</sup>	
Serious adverse events	2 per 100	2 per 100	RR 0.93	3792	$\oplus \oplus \oplus O$	
follow-up: median 28 days		(1-3)	(0.55-1.58)	(2 RCTs)	Moderate <sup>†</sup>	
Bacteremia	2 per 100	1 per 100	RR 0.70	2680	⊕⊕⊕O	
follow-up: median 28 days		(1-2)	(0.37-1.33)	(2 RCTs)	Moderate <sup>†</sup>	

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<sup>37</sup> at high risk of bias due to measurement of the outcome and selection of the reported result. ±Inconsistency: I<sup>2</sup> = 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.

 $^{11}$ Imprecision: 95% CI, -1.21 to -0.39 log<sub>10</sub>.<sup>§§</sup>Inconsistency: I<sup>2</sup> = 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.<sup>5,40</sup> With the progress of research on pathogenesis of SARS-CoV-2 infection, new monoclonal antibodies (such as anti-inflammasomes or monocyte/macrophage entry inhibitors<sup>41</sup>) 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 antiinflammatory 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.

- 1. PubMed search strategy
- 2. Supplementary Figure 1. Risk of bias of included randomized controlled trials (RCTs).
- 3. Supplementary Figure 2. Effects of monoclonal antibodies on length of hospital stay stratified by type of coronavirus disease 2019 (COVID-19) patients.
- 4. Supplementary Figure 3. Effects of monoclonal antibodies on invasive mechanical ventilation stratified by type of COVID-19 patients.
- 5. Supplementary Figure 4. Effects of monoclonal antibodies on viral load stratified by type of COVID-19 patients.
- 6. Supplementary Figure 5. Effects of monoclonal antibodies on adverse events stratified by type of COVID-19 patients.
- 7. 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 nonhospitalized RCTs.
- 9. Supplementary Figure 8. Effects of monoclonal antibodies on symptomatic COVID-19 incidence in prophylaxis RCTs.
- 10. Supplementary Figure 9. Effects of monoclonal antibodies on symptomatic or asymptomatic COVID-19 incidence in prophylaxis RCTs.
- 11. Supplementary Figure 10: Subgroup analyses.
- 11.1.**Supplementary Figure 10A**: Subgroup analyses by type of drug: tocilizumab vs other monoclonal antibodies in hospitalized patients.
  - A1. All-cause mortality
  - A2. COVID-19-related death
  - A3. Serious adverse events
  - A4. Length of hospital stay
  - **A5.** Invasive mechanical ventilation
  - A6. Adverse events
  - A7. Bacteremia
- 11.2 **Supplementary Figure 10B:** Subgroup analyses by type of control in hospitalized patients
  - **B1.** All-cause mortality
  - **B2.** COVID-19-related death
  - **B3.** Serious adverse events
  - B4. Length hospital stay
  - **B5.** Invasive mechanical ventilation

- **B6.** Adverse events
- **B7.** Bacteremia
- 11.3 **Supplementary Figure 10C:** Subgroup analyses by type of control in hospitalized patients receiving tocilizumab
  - C1. All-cause mortality
  - C2. Serious adverse events
  - C3. Length hospital stay
  - C4. Invasive mechanical ventilation
  - C5. Adverse events
  - C6. Bacteremia

#### 1. PubMed search strategy

("antibodies, monoclonal"[MeSH OR Terms] ("antibodies" [All Fields] AND "monoclonal" [All Fields]) OR "monoclonal antibodies" [All Fields] OR ("monoclonal" [All Fields] AND "antibodies" [All Fields]) OR ("antibodies, neutralizing" [MeSH Terms] OR ("antibodies" [All Fields] AND "neutralizing" [All Fields]) OR "neutralizing antibodies" [All Fields] OR ("neutralizing" [All Fields] AND "antibodies" [All Fields])) OR ("bamlanivimab" [Supplementary Concept] OR "bamlanivimab" [All Fields]) OR ("etesevimab" [Supplemen-"etesevimab" [All tary Concept] OR Fields]) OR ("sotrovimab" [Supplementary Concept] OR "sotrovimab" [All Fields]) OR ("meplazumab" [Supplementary Concept] OR "meplazumab" [All Fields]) OR ("itolizumab" [Supplementary Concept] OR "itolizumab" [All Fields]) OR ("sarilumab" [Supplementary Concept] OR "sarilumab"[All Fields]) OR (("casirivimab" [Supplementary Concept] OR "casirivimab" [All Fields]) AND ("imdevimab" [Supplementary Concept] OR "imdevimab" [All Fields])) OR ("tocilizumab" [Supplementary Concept] OR "tocilizumab"[All Fields])) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines" [All Fields] OR "covid 19 vaccines" [MeSH Terms] OR "covid 19 serotherapy" [All Fields] OR "covid 19 serotherapy" [Supplementary Concept] OR "covid 19 nucleic acid testing" [All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing" [All Fields] OR "covid 19 serological testing" [MeSH Terms] OR "covid 19 testing" [All Fields] OR "covid 19 testing" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2" [MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov" [All Fields] OR (("coronavirus" [MeSH Terms] OR "coronavirus" [All Fields] OR "cov" [All Fields])

AND 2019/11/01:3000/12/31[Date - Publication]) OR ("coronavirus" [MeSH Terms] OR "coronavirus" [All Fields] OR "coronaviruses" [All Fields]) OR (("coronavirus" [MeSH Terms] OR "coronavirus" [All Fields] OR "coronaviruses" [All Fields]) AND ("disease" [MeSH Terms] OR "disease" [All Fields] OR "diseases" [All Fields] OR "disease s" [All Fields] OR "diseased" [All Fields])) OR ("covid 19" [MeSH Terms] OR "covid 19" [All Fields] OR "coronavirus disease 19"[All Fields]) OR ("severe acute respiratory syndrome" [MeSH Terms] OR ("severe" [All Fields] AND "acute" [All Fields] AND "respiratory" [All Fields] AND "syndrome" [All Fields]) OR "severe acute respiratory syndrome" [All Fields]) OR ("sars cov 2" [MeSH Terms] OR "sars cov 2" [All Fields] OR "sars cov 2"[All Fields])) AND ("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "random" [All Fields] OR "randomization" [All Fields] OR

"randomized" [All Fields] OR "randomisation" [All Fields] OR "randomisations" [All Fields] OR "randomise" [All Fields] OR "randomised" [All Fields] OR "randomising" [All Fields] OR "randomizations" [All Fields] OR "randomize" "randomizes" [All [All Fields] OR Fields] OR "randomizing" [All Fields] OR "randomness" [All Fields] OR "randoms" [All Fields] OR ("random allocation" [MeSH Terms] OR ("random" [All Fields] AND "allocation" [All Fields]) OR "random allocation" [All Fields] OR "random" [All Fields] OR "randomization" [All Fields] OR "randomized" OR [All Fields] "randomisation" [All Fields] OR "randomisations" [All Fields] OR "randomise" [All Fields] OR "randomised" [All Fields] OR "randomising" [All Fields] OR "randomizations" [All Fields] OR "randomize" [All Fields] "randomizes" [All Fields] OR "randomizing" [All OR Fields] OR "randomness" [All Fields] OR "randoms" [All Fields]))

Study ID	Experimental	Comparator	Outcome	Weight	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall		
1 Salvarani RCT	Tocilizumab	Standard of Care	Clinical Worsening at Day 14	1	?	?	•	•	•		•	Low risk
2 Hermine RCT	Tocilizumab + Standard of Can	e Standard of Care	Clinical Wosening at Day 4	1	•	•	•	•	•	•	?	Some concerns
3 Stone RCT	Tocilizumab + Standard of Car	e Placebo + Standard of Ca	r Mechanical ventilation or Death at 28 days	1	?	•	•	•	?	1	•	High risk
4 Rosas RCT	Tocilizumab + Standard of Can	e Placebo + Standard of Ca	r Clinical Status at Day 28	1	?	•	•	•	•	1		
5 Salama RCT	Tocilizumab + Standard of Can	e Placebo + Standard of Ca	r Mechanical ventilation or Death at 28 days	1	•	?	•	•	?	1		
6 Gordon RCT	Tocilizumab	Standard of Care	In-hospital death by 21 days	1	•	•	•	•	?	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 Car	e Standard of care	Progression of COVID-19 (moderate to severe or sever	e 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	•	•	•	•	•	$\mathbf{\bullet}$		
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 with the symptometry of the symptometry o	i 1	•	•	•		•	•		
18 Cremer RCT	Mavrilimumab	Placebo	Alive and not on supplemental oxygen at day 14	1	•		•		•	$\mathbf{\bullet}$		
19 Dougan RCT	Bamlanivimab-Etesevimab	Placebo	Covid-19-related hospitalization or death from any ca	a 1	•		•			$\mathbf{\bullet}$		
20 Gottlieb RCT	Bamlanivimab+Etesevimab	Placebo	Change in SARS-CoV-2 log viral dat day 11	1		•				$\mathbf{\bullet}$		
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		•	•			$\mathbf{\mathbf{e}}$		
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 basel	i 1								
27 Gupta RCT	Sotrovimab	Placebo	hospitalized for more than 24 hours or death from a	1	•	•	•	•	•	•		

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

Source	Mean	MAb SD	Total	Mean	Control SD	Total	MD [95%–CI]	Favors MAb	Favors Control	Weight
population = hospitalized	d							1		5
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]	← <b></b>		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: $I^2 = 79\%$ , $\tau^2 =$	= 13.3364	, <i>p</i> < 0.01								
population = nonhospita	lized									
Dougan M 2021	7.30	6.4000	11	11.20	10.1000	33	-3.90 [ -9.02; 1.22]		_	11.5%
Random effects model Heterogeneity: not applicable	•		11			33	-3.90 [ -9.02; 1.22]		-	11.5%
Random effects model	40.000		700			442	–2.11 [ –5.61; 1.39]		>	100.0%
Heterogeneity: $I^{-} = 76\%$ , $\tau^{-} =$	= 10.9328	p < 0.01	0 51)					10 5 0	F 10	
rest for subgroup differences	$\chi_1 = 0.4$	14, 01 = 1 (p)	r = 0.51					– 10 –5 0 Mean Differer	5 IU 10e (95% CI)	

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

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [959	%–CI]	Favors MAb	Favors Cont	trol Weight
population = hospitalize	ed								
Cremer P 2021	0	21	2	19	0.19 [0.01;	3.54]			0.5%
Gordon A 2021s	6	37	58	136	0.38 [0.18;	0.81]			5.6%
Gordon A 2021t	84	242	58	137	0.82 [0.63;	1.06]	-		16.8%
Hamed D 2021	6	26	2	23	2.65 [0.59;	11.88]	÷		1.7%
Hermine O 2021	11	63	18	67	0.65 [0.33;	1.27]	-	-	6.7%
Horby P 2021	215	1754	273	1800	0.81 [0.68;	0.95]	+		20.1%
Kumar S 2021	0	20	3	10	0.10 [0.01;	1.24]	<	-	0.6%
Rashad A 2021	15	46	18	63	1.14 [0.65;	2.02]	÷	-	8.3%
Rosas I 2021	51	183	33	90	0.76 [0.53;	1.09]	-	·	13.6%
Salama C 2021	20	249	16	128	0.64 [0.35;	1.20]	-	-	7.4%
Salvarani C 2021	6	60	17	63	0.37 [0.16;	0.88]			4.6%
Soin A 2021	14	91	13	88	1.04 [0.52;	2.09]		<b>-</b>	6.3%
Stone JH 2020	11	161	8	81	0.69 [0.29;	1.65]		_	4.5%
Veiga V 2021	4	65	4	63	0.97 [0.25;	3.71]			2.1%
Zhao H 2021	0	14	2	7	0.14 [0.01;	1.87]	• • •		0.6%
Random effects model	443	3032	525	2775	0.74 [0.60;	0.92]	¢		99.5%
Heterogeneity: $I^2 = 20\%$ , $\tau^2$	= 0.0542	, <i>p</i> = 0.2	23						
population = nonhospit	alized								
Gupta A 2021	0	291	2	292	0.20 [0.01;	4.16]	<		0.5%
Random effects model	0	291	2	292	0.20 [0.01;	4.16]			0.5%
Heterogeneity: not applicab	le								
Random effects model	443	3323	527	3067	0.74 [0.60;	0.91]			100.0%
Heterogeneity: $I^2 = 18\%$ , $\tau^2$	= 0.0476	, p = 0.2	25				1 1 1		I
Test for subgroup difference	es: $\chi_1^2 = 0.$	71, df =	1 (p = 0.4)	10)		0	.01 0.1 0.5	12 10	100
							Risk Ratio	o (95% CI)	

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

Study	TE	seTE	Favo	ors MAb	Favo	ors Cont	rol	MD	95%-CI	Weight
population = nonhospitaliz	zed									
Chen P 2021	-0.22	0.1900		÷-	+			-0.22	[-0.59; 0.15]	20.7%
Dougan M 2021	-1.20	0.1300		-				-1.20	[-1.45; -0.95]	22.2%
Gottlieb R 2021be	0.27	0.3700				_		0.27	[-0.46; 1.00]	15.3%
Weinreich D 2021	-0.41	0.1500		-	-			-0.41	[-0.70; -0.12]	21.7%
Random effects model			-					-0.44	[-1.40; 0.52]	79.9%
Heterogeneity: $I^2 = 91\%$ , $\tau^2 = 0$	0.3146, <i>p</i> < 0	0.01								
population = prophylaxis										
Cohen M 2021	-0.80	0.2100	-					-0.80	[–1.21; –0.39]	20.1%
Random effects model			-	$\checkmark$				-0.80	[-1.21; -0.39]	20.1%
Heterogeneity: not applicable										
Dan dama affa ata ma dal								0.50	[ 1 10, 0 15]	100.00/
Random effects model				$\sim$	7		_	-0.52	[-1.19; 0.15]	100.0%
Heterogeneity: $I^2 = 88\%$ , $\tau^2 = 0$	0.2478, p < 0	0.01		1		1				
Test for subgroup differences: ;	$\chi_1^2 = 0.96$ , df	= 1 ( <i>p</i> = 0.33)	-2	-1	0	1	2			
			Mea	an Differ	ence (9	95% CI)				

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

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95	%–CI]	Favors MAb	Favors Con	trol Weight
population = hospitalize	d								
Caricchio R 2021	122	225	120	223	1.01 [0.85;	1.20]	-		6.7%
Hermine O 2021	28	63	36	67	0.83 [0.58;	1.18]		<u>·</u>	5.7%
Horby P 2021	204	2022	254	2094	0.83 [0.70;	0.99]			6.7%
Kumar S 2021	18	20	4	10	2.25 [1.04;	4.87]			3.2%
Lescure F 2021	121	173	55	84	1.07 [0.89;	1.28]	-		6.7%
Lundgren J 2021	39	163	30	151	1.20 [0.79;	1.84]	_	<del>                                     </del>	5.2%
Rosas I 2021	228	295	116	143	0.95 [0.86;	1.05]	-		7.0%
Salama C 2021	127	249	29	128	2.25 [1.60;	3.17]			5.8%
Salvarani C 2021	14	60	7	63	2.10 [0.91;	4.84]	-		3.0%
Soin A 2021	33	91	22	89	1.47 [0.93;	2.31]	-		5.0%
Veiga V 2021	29	67	21	62	1.28 [0.82;	1.99]	-		5.1%
Wang D 2021	20	34	4	31	4.56 [1.75;	11.87			→ 2.5%
Zhao H 2021	9	14	2	7	2.25 [0.65]	7.73			- 1.8%
Random effects model	992	3476	700	3152	1.31 [1.02;	1.671		$\sim$	64.3%
Heterogeneity: $I^2 = 77\%$ , $\tau^2 = 77\%$	= 0.1445	. <i>p</i> < 0.0	01		,				
		, -							
population = nonhospita	lized								
Dougan M 2021	69	518	60	517	1.15 [0.83:	1.591	_		5.9%
Gottlieb R 2021b	69	309	21	78	0.83 [0.54:	1.26]		<u>.</u>	5.2%
Gottlieb R 2021be	19	112	21	78	0.63 [0.36:	1.091			4.4%
Gupta A 2021	73	430	85	438	0.87 [0.66:	1.16]		÷	6.1%
Weinreich D 2021	2	176	2	.93	0.53 [0.08:	3,691	← <b></b>		0.8%
Random effects model	232	1545	189	1204	0.90 [0.75:	1.091	<	Ļ.	22.5%
Heterogeneity: $l^2 = 6\% \tau^2 =$	0.0026	n = 0.37	7		0.00 [0.10,		•		2210 /0
	0.0020,	p = 0.07							
population = prophylaxie									
Cohen M 2021	118	588	111	587	1 06 [0 84.	1 341		·	6 4%
O'Brien M 2021	265	1311	379	1306	0 70 [0 61:	0.801			6.8%
Bandom effects model	383	1899	490	1893	0.85 [0.56]	1 281			13.2%
Heterogeneity: $l^2 = 80\% \tau^2$ .	- 0 0792	n < 0	11	1000	0.00 [0.00,	1.20]	<u> </u>		10.2 /0
Therefore the second s	- 0.0732	, p < 0.0							
Bandom effects model	1607	6920	1379	6249	1 12 [0 93.	1 351			100.0%
Heterogeneity: $I^2 = 77^{\circ}/_{\sim} \tau^2$	- 0 1301	n < 0	1079	52-15		]			
Test for subgroup differences	$x^2 = 6$	,μ⊂0.0 29 df –	2(n = 0)	)4)		0	1 0 2 0 5	1 2 5	10
lost for subgroup unerences	$J_{1} = 0.$	, ui	= (p = 0.0)	/-/		0	Rick Patio	(95% CI)	10
							Thor Talle		

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

	MAb	C	ontrol						
Source	Events	Total	Events	Total	RR [95	% <b>-CI</b> ]	Favors MAb	<b>Favors Contro</b>	Weight
population = hospitalize	ed								
Caricchio R 2021	23	225	43	223	0.53 [0.33;	0.85]			12.2%
Gordon A 2021s	0	48	0	201	1.00 [0.01; 14	42.39]	<		0.1%
Gordon A 2021t	1	353	0	201	2.57 [0.07; 9	93.31]			0.2%
Hermine O 2021	4	63	14	67	0.30 [0.11;	0.87]			2.4%
Horby P 2021	6	2022	9	2094	0.69 [0.25;	1.94]		<u> </u>	2.5%
Kumar S 2021	1	22	3	10	0.15 [0.02;	1.28]		-	0.6%
Lescure F 2021	40	332	10	84	1.01 [0.53;	1.94]	-	-	6.4%
Lundgren J 2021	4	163	4	151	0.93 [0.24;	3.64]			1.4%
Rosas I 2021	113	295	58	143	0.94 [0.74;	1.21]	<b>E</b>		44.8%
Salama C 2021	25	259	16	129	0.78 [0.43;	1.41]		-	7.7%
Salvarani C 2021	1	60	4	63	0.26 [0.03;	2.28]			0.6%
Soin A 2021	6	91	5	89	1.17 [0.37;	3.71]	<u> </u>	•	2.0%
Stone JH 2020	13	161	14	81	0.47 [0.23;	0.95]			5.4%
Veiga V 2021	10	67	10	62	0.93 [0.41;	2.07]		<u> </u>	4.2%
Vlaar A 2020	3	15	4	15	0.75 [0.20;	2.79]			1.6%
Random effects model	250	4176	194	3613	0.77 [0.64;	0.92]	$\diamond$		92.2%
Heterogeneity: $I^2 = 7\%$ , $\tau^2 =$	0.0055,	p = 0.38	В		_	-			
population = nonhospita	alized								
Dougan M 2021	4	518	3	517	1.33 [0.30;	5.92]		•	1.2%
Random effects model	4	518	3	517	1.33 [0.30;	5.92]	$\sim$	>	1.2%
Heterogeneity: not applicable	le								
population = prophylaxi	S								
Cohen M 2021	12	588	14	587	0.86 [0.40;	1.83]		_	4.6%
O'Brien M 2021	4	753	9	752	0.44 [0.14;	1.44]		_	2.0%
Random effects model	16	1341	23	1339	0.70 [0.37;	1.33]	$\langle$	>	6.6%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	= 0, p = 0.	36							
Random effects model	270	6035	220	5469	0.78 [0.67;	0.92]	ò		100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	= 0, p = 0.	49							
Test for subgroup difference	$s: \chi_2^2 = 0.$	59, df =	2(p = 0.7)	74)		0	.01 0.1 0.5	12 10 10	0
	_						Risk Ratio	o (95% CI)	

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

		MAb	C	ontrol				
Source	Events	Total	Events	Total	RR [95%–CI]	Favors MAb	Favors Contr	ol Weight
Dougan M 2021	11	518	33	517	0.33 [0.17; 0.65]			71.4%
Gottlieb R 2021b	5	309	5	78	0.25 [0.07; 0.85]	← ■		21.8%
Gottlieb R 2021be	1	112	4	78	0.17 [0.02; 1.53]	← ■	+	6.8%
Random effects model	17	939	42	673	0.30 [0.17; 0.53]		 	100.0%
Heterogeneity: $T^{-} = 0\%$ , $\tau^{-}$ :	= 0, p = 0.	81			(	0.1 0.2 0.5 Risk Rati	1 2 5 o (95% Cl)	10

**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



#### 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<sup>20</sup> 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 allcause 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).

		MAb	C	ontrol				
Source	Events	Total	Events	Total	RR [95%–CI]	Favors MAb	Favors Cont	rol Weight
mabcat = other								
Caricchio R 2021	11	223	16	222	0.68 [0.32; 1.44]		<u> </u>	3.8%
Cremer P 2021	1	21	3	19	0.30 [0.03; 2.66]	<		0.5%
Gordon A 2021s	10	45	71	199	0.62 [0.35; 1.11]		-	5.8%
Kumar S 2021	0	20	3	10	0.10 [0.01; 1.24]	K	-	0.4%
Lescure F 2021	14	173	7	84	0.97 [0.41; 2.32]			2.9%
Lundgren J 2021	9	163	5	151	1.67 [0.57; 4.86]			1.9%
Vlaar A 2020	2	15	4	15	0.50 [0.11; 2.33]			1.0%
Random effects model	47	660	109	700	0.72 [0.45; 1.15]	$\sim$	>	16.2%
Heterogeneity: $I^2 = 4\%$ , $\tau^2 =$	= 0.0185,	p = 0.39	)					
mabcat = tocilizumab	× 3	0. 0		0 B		_		8.55
Gordon A 2021t	98	350	71	198	0.78 [0.61; 1.00]			16.8%
Hamed D 2021	2	26	1	23	1.77 [0.17; 18.26]		•	→ 0.4%
Hermine O 2021	7	63	8	67	0.93 [0.36; 2.42]			2.4%
Horby P 2021	596	2022	694	2094	0.89 [0.81; 0.97]	-		27.4%
Rashad A 2021	32	46	33	63	1.33 [0.98; 1.80]			14.0%
Rosas I 2021	58	294	28	144	1.01 [0.68; 1.52]	-		9.8%
Salama C 2021	26	249	11	128	1.22 [0.62; 2.38]		•	4.5%
Salvarani C 2021	1	60	1	63	1.05 [0.07; 16.41]	<	•	→ 0.3%
Soin A 2021	11	91	15	88	0.71 [0.34; 1.46]		<u> </u>	4.0%
Stone JH 2020	9	161	3	81	1.51 [0.42; 5.42]		•	1.4%
Veiga V 2021	14	65	6	64	2.30 [0.94; 5.61]	ł		2.7%
Random effects model	854	3427	871	3013	0.98 [0.82; 1.15]	<	>	83.8%
Heterogeneity: $I^2 = 29\%$ , $\tau^2$	= 0.0127	, <i>p</i> = 0.1	7					
		400-		0740				100.004
Handom effects model	901	4087	980	3713	0.94 [0.80; 1.11]		>	100.0%
Heterogeneity: $I^2 = 23\%$ , $\tau^2$	= 0.0205	, <i>p</i> = 0.1	8		-			'
lest for subgroup difference	es: χ <sub>1</sub> <sup>-</sup> = 2.	16, df =	1 (p = 0.1)	4)	C	0.1 0.2 0.5	1 2 5	10
						Risk Ratio	o (95% CI)	

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

		MAb	C	ontrol				
Source	Events	Total	Events	Total	RR [95%–Cl]	Favors MAb	<b>Favors Contro</b>	I Weight
mabcat = other								
Caricchio R 2021	11	223	16	222	0.68 [0.32; 1.44]		-	73.9%
Vlaar A 2020	0	15	4	15	0.11 [0.01; 1.89]	← ■	<u> </u>	10.8%
Random effects model	11	238	20	237	0.47 [0.11; 1.99]		>	84.7%
Heterogeneity: $I^2 = 32\%$ , $\tau^2$	= 0.5338	, <i>p</i> = 0.2	22					
mabcat = tocilizumab								
Hamed D 2021	2	26	1	23	1.77 [0.17; 18.26]		-	15.3%
Random effects model	2	26	1	23	1.77 [0.17; 18.26]			15.3%
Heterogeneity: not applicab	le							
<b>Random effects model</b> Heterogeneity: $I^2 = 10\%$ , $\tau^2$	<b>13</b> = 0.1882	<b>264</b> . p = 0.3	<b>21</b> 33	260	0.65 [0.25; 1.72]			100.0%
Test for subgroup difference	es: $\chi_1^2 = 0$ .	89, df =	1 ( <i>p</i> = 0.3	34)	0.0	01 0.1 0.5 <sup>-</sup> Risk Ratio	1 2 10 10 0 (95% CI)	00
							. ,	

Supplementary Figure 10A2 COVID-19-related death .

		MAb	С	ontrol					
Source	Events	Total	Events	Total	RR [95%	∕₀–CI]	Favors MAb	Favors Contr	ol Weight
mabcat = other									
Caricchio R 2021	36	225	46	223	0.78 [0.52;	1.15]		+	14.2%
Cremer P 2021	5	21	4	19	1.13 [0.35;	3.60]		•	1.7%
Gordon A 2021s	0	48	5	201	0.14 [0.00; 1	2.85]	< +		→ 0.1%
Kumar S 2021	2	20	3	10	0.33 [0.07;	1.68]	<	<u></u>	0.8%
Lescure F 2021	51	173	20	84	1.24 [0.79;	1.94]	_		11.1%
Vlaar A 2020	9	15	7	15	1.29 [0.65;	2.54]	_		4.8%
Random effects model	103	502	85	552	0.97 [0.67;	1.41]	<	>	32.7%
Heterogeneity: $I^2 = 9\%$ , $\tau^2 =$	= 0.0094,	p = 0.30	6						
mabcat = tocilizumab									
Gordon A 2021t	9	353	6	201	0.85 [0.31;	2.36]			2.1%
Hermine O 2021	20	63	29	67	0.73 [0.47;	1.16]		+	10.8%
Horby P 2021	3	2022	0	2094	7.11 [0.38; 13	84.52]		+	→ 0.3%
Rosas I 2021	103	295	55	143	0.91 [0.70;	1.18]		₽	33.0%
Salama C 2021	38	249	25	128	0.78 [0.49;	1.23]		<u> </u>	10.6%
Salvarani C 2021	0	60	0	63	1.00 [0.02; 4	9.66]	<		→ 0.1%
Soin A 2021	18	91	15	89	1.17 [0.63;	2.18]	_		5.8%
Stone JH 2020	11	161	3	81	1.84 [0.53;	6.43]			1.4%
Veiga V 2021	11	67	7	62	1.45 [0.60;	3.51]			2.8%
Wang D 2021	0	34	1	31	0.32 [0.01;	7.29]	<+		0.2%
Zhao H 2021	0	14	0	7	1.00 [0.02; 5	8.10]	<		→ 0.1%
Random effects model	213	3409	141	2966	0.91 [0.77;	1.08]	<	>	67.3%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	= 0, p = 0	.76							
Random effects model	316	3911	226	3518	0.93 [0.81;	1.07]	<	<u>}</u>	<b>100.0%</b>
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	=0, p = 0	.73							1
lest for subgroup difference	es: χ <sub>1</sub> = 0.	18, df =	1 (p = 0.6)	57)		0	.1 0.2 0.5	1 2 5	10
							Risk Ratio	ט (95% Cl)	
C	<b>•••</b>		1						

Supplementary Figure 10A3 Serious adverse events.

		Mab			Control						
Source	Mean	SD	Total	Mean	SD	Total	MD [95	%–CI]	Favors MAb	Favors (	<b>Control Weight</b>
mabcat = other											
Cremer P 2021	7.63	3.7100	21	7.50	2.9700	19	0.13 [ -1.94;	2.20]	-	<b>-</b>	18.8%
Random effects model			21			19	0.13 [ -1.94;	2.20]		$\geq$	18.8%
Heterogeneity: not applicab	ble										
mabcat = tocilizumab											
Hamed D 2021	23.27	8.9600	26	20.83	12.2200	23	2.44 [ -3.63;	8.51]			— 11.9%
Rosas I 2021	20.25	7.4100	294	29.48	22.1500	144	-9.23 [-12.95;	-5.51]	<del>(+</del>		16.1%
Salama C 2021	6.25	0.7400	249	7.62	1.4800	128	-1.38 [ -1.65;	-1.10]	+		20.4%
Veiga V 2021	11.30	8.0000	65	14.70	8.2000	64	-3.40 [ -6.20;	-0.60]	— <b>—</b>		17.7%
Wang D 2021	21.75	7.4100	34	20.50	9.6300	31	1.25 [ -2.96;	5.46]			15.2%
Random effects model			668			390	-2.29 [ -7.82;	3.23]		-	81.2%
Heterogeneity: $I^2 = 82\%$ , $\tau^2$	<sup>2</sup> = 16.31	179, <i>p</i> < 0	0.01								
Random effects model			689			409	–1.86 [ –6.10;	2.38]		<u> </u>	100.0%
Heterogeneity: $I^2 = 79\%$ , $\tau^2$	<sup>2</sup> = 13.33	364, <i>p</i> < 0	0.01					ſ	I		
Test for subgroup difference	es: χ <sub>1</sub> <sup>2</sup> =	1.16, df =	1 (p =	0.28)				-1	0 -5 (	) 5	10
									wean Differe	nce (95%	01)

**Supplementary Figure 10A4** Length of hospital stay.

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [959	%–CI]	Favors MAb	Favors (	Control Weight
mabcat = other									
Cremer P 2021	0	21	2	19	0.19 [0.01;	3.54]			0.5%
Gordon A 2021s	6	37	58	136	0.38 [0.18;	0.81]			5.8%
Kumar S 2021	0	20	3	10	0.10 [0.01;	1.24]	<	+	0.7%
Random effects model	6	78	63	165	0.33 [0.10;	1.05]		ł	7.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0.	57							
mabcat = tocilizumab									
Gordon A 2021t	84	242	58	137	0.82 [0.63;	1.06]			16.4%
Hamed D 2021	6	26	2	23	2.65 [0.59; -	1.88]	÷	-	1.8%
Hermine O 2021	11	63	18	67	0.65 [0.33;	1.27]	-	+	6.9%
Horby P 2021	215	1754	273	1800	0.81 [0.68;	0.95]	+		19.2%
Rashad A 2021	15	46	18	63	1.14 [0.65;	2.02]	+	-	8.5%
Rosas I 2021	51	183	33	90	0.76 [0.53;	1.09]	-		13.5%
Salama C 2021	20	249	16	128	0.64 [0.35;	1.20]		ł	7.6%
Salvarani C 2021	6	60	17	63	0.37 [0.16;	0.88]	-		4.8%
Soin A 2021	14	91	13	88	1.04 [0.52;	2.09]	-	-	6.6%
Stone JH 2020	11	161	8	81	0.69 [0.29;	1.65]		<b>—</b>	4.7%
Veiga V 2021	4	65	4	63	0.97 [0.25;	3.71]		•	2.3%
Zhao H 2021	0	14	2	7	0.14 [0.01;	1.87]		<u> </u>	0.7%
Random effects model	437	2954	462	2610	0.80 [0.70;	0.91]	Ó		93.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0.	49							
Random effects model	443	3032	525	2775	0.74 [0.59;	0.93]	¢		100.0%
Heterogeneity: $I^2 = 20\%$ , $\tau^2$	= 0.0542	p = 0.2	23						I
Test for subgroup difference	$es: \chi_1^2 = 10$	).36, df	= 1 ( <i>p</i> < 0	.01)		0	.01 0.1 0.5	12 10	100
							Risk Ratio	o (95% CI)	)

**Supplementary Figure 10A5** Invasive mechanical ventilation.

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95%	–CI]	Favors MAb	Favors Cor	ntrol Weight
mabcat = other									
Caricchio R 2021	122	225	120	223	1.01 [0.85;	1.20]	-		10.3%
Kumar S 2021	18	20	4	10	2.25 [1.04;	4.87]			5.2%
Lescure F 2021	121	173	55	84	1.07 [0.89;	1.28]	-		10.2%
Lundgren J 2021	39	163	30	151	1.20 [0.79;	1.84]	-		8.2%
Random effects model	300	581	209	468	1.13 [0.77;	1.66]	<	$\rightarrow$	33.8%
Heterogeneity: $I^2 = 31\%$ , $\tau^2$	= 0.0316	, p = 0.3	23						
mabcat = tocilizumab									
Hermine O 2021	28	63	36	67	0.83 [0.58;	1.18]		┡─┊	8.8%
Horby P 2021	204	2022	254	2094	0.83 [0.70;	0.99]			10.2%
Rosas I 2021	228	295	116	143	0.95 [0.86;	1.05]	-		10.6%
Salama C 2021	127	249	29	128	2.25 [1.60;	3.17]			8.9%
Salvarani C 2021	14	60	7	63	2.10 [0.91;	4.84]			4.8%
Soin A 2021	33	91	22	89	1.47 [0.93;	2.31]			7.9%
Veiga V 2021	29	67	21	62	1.28 [0.82;	1.99]	_		8.0%
Wang D 2021	20	34	4	31	4.56 [1.75; 1	1.87]			→ 4.1%
Zhao H 2021	9	14	2	7	2.25 [0.65;	7.73]		-	- 2.9%
Random effects model	692	2895	491	2684	1.39 [0.93; 2	2.10]		$\sim$	66.2%
Heterogeneity: $I^2 = 83\%$ , $\tau^2$	= 0.2085	, <i>p</i> < 0.	01						
Random effects model	992	3476	700	3152	1.31 [0.99;	1.71]		$\diamond$	100.0%
Heterogeneity: $I^2 = 77\%$ , $\tau^2$	= 0.1445	, <i>p</i> < 0.	01						
Test for subgroup difference	es: $\chi_1^2 = 0$ .	94, df =	1 (p = 0.3)	33)		0.1	0.2 0.5	125	10
							Risk Ratio	o (95% CI)	
Supplementary Figure 10A6 Adverse events.									

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95%-	-CI] Fa	vors MAb F	avors Contr	ol Weight
mabcat = other									
Caricchio R 2021	23	225	43	223	0.53 [0.33; 0	.85]			14.9%
Gordon A 2021s	0	48	0	201					0.0%
Kumar S 2021	1	22	3	10	0.15 [0.02; 1	.28] —			0.9%
Lescure F 2021	40	332	10	84	1.01 [0.53; 1	.94]			8.5%
Lundgren J 2021	4	163	4	151	0.93 [0.24; 3	.64]			2.1%
Vlaar A 2020	3	15	4	15	0.75 [0.20; 2	.79]		_	2.3%
Random effects model	71	805	64	684	0.67 [0.38; 1	.17]	$\stackrel{\cdot}{\checkmark}$		28.6%
Heterogeneity: $I^2 = 13\%$ , $\tau^2$	Heterogeneity: $l^2 = 13\%$ , $\tau^2 = 0.0237$ , $p = 0.33$								
mabcat = tocilizumab									
Gordon A 2021t	1	353	0	201	2.57 [0.07; 93	.31]		+	- 0.3%
Hermine O 2021	4	63	14	67	0.30 [0.11; 0	.87]			3.4%
Horby P 2021	6	2022	9	2094	0.69 [0.25; 1	.94]	<b>•</b>	-	3.6%
Rosas I 2021	113	295	58	143	0.94 [0.74; 1	.21]			37.0%
Salama C 2021	25	259	16	129	0.78 [0.43; 1	.41]	- <b>#</b> -		10.1%
Salvarani C 2021	1	60	4	63	0.26 [0.03; 2	.28] -	•   -	_	0.8%
Soin A 2021	6	91	5	89	1.17 [0.37; 3	.71]			2.9%
Stone JH 2020	13	161	14	81	0.47 [0.23; 0	.95]	- <b>-</b>		7.3%
Veiga V 2021	10	67	10	62	0.93 [0.41; 2	.07]		-	5.8%
Random effects model	179	3371	130	2929	0.79 [0.59; 1	.05]	$\diamond$		71.4%
Heterogeneity: $I^2 = 12\%$ , $\tau^2$	= 0.0144	, <i>p</i> = 0.3	33						
					and a sold server to and the				
Random effects model	250	4176	194	3613	0.75 [0.60; 0	.94]	<b>◇</b>		_ 100.0%
Heterogeneity: $I^2 = 14\%$ , $\tau^2$	= 0.0125	, p = 0.3	31				1 1 1		1
Test for subgroup difference	$s: \chi_1^2 = 0.$	52, df =	1 (p = 0.4)	17)		0.01	0.1 0.51	2 10 1	100
							HISK HATIO (S	95% CI)	

Supplementary Figure 10A7 Bacteremia

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		MAb	С	ontrol				
Source	Events	Total	Events	Total	RR [95%–Cl	] Favors MAb	Favors Cont	rol Weight
control = placebo								
Caricchio R 2021	11	223	16	222	0.68 [0.32; 1.44]	]	+	3.8%
Cremer P 2021	1	21	3	19	0.30 [0.03; 2.66]	]    •	+	0.5%
Lescure F 2021	14	173	7	84	0.97 [0.41; 2.32]	]	+	2.9%
Lundgren J 2021	9	163	5	151	1.67 [0.57; 4.86	j —		1.9%
Rosas I 2021	58	294	28	144	1.01 [0.68; 1.52	j —	÷	9.8%
Salama C 2021	26	249	11	128	1.22 [0.62; 2.38	j —		4.5%
Stone JH 2020	9	161	3	81	1.51 [0.42; 5.42	i —		1.4%
Vlaar A 2020	2	15	4	15	0.50 [0.11; 2.33	i		1.0%
Random effects model	130	1299	77	844	1.00 [0.77; 1.30	] <	÷	25.8%
Heterogeneity: $l^2 = 0\%, \tau^2 = 0, p = 0.72$								
0								
control = soc								
Gordon A 2021s	10	45	71	199	0.62 [0.35: 1.11]	1	+	5.8%
Gordon A 2021t	98	350	71	198	0.78 0.61; 1.00	i -	÷	16.8%
Hermine O 2021	7	63	8	67	0.93 0.36: 2.42	i —		2.4%
Horby P 2021	596	2022	694	2094	0.89 0.81: 0.97	i -	+	27.4%
Kumar S 2021	0	20	3	10	0.10 [0.01; 1.24		<del>.</del>	0.4%
Salvarani C 2021	1	60	1	63	1.05 [0.07: 16.41	]		→ 0.3%
Soin A 2021	11	91	15	88	0.71 [0.34: 1.46	i —•	<u> </u>	4.0%
Veiga V 2021	14	65	6	64	2.30 [0.94; 5.61	1		2.7%
Random effects model	737	2716	869	2783	0.84 [0.58: 1.21]	i <	\$	59.8%
Heterogeneity: $I^2 = 30\%$ , $\tau^2$	$^{2} = 0.0778$	p = 0.7	19		• /			
······		, <b>r</b> -						
control = active								
Hamed D 2021	2	26	1	23	1.77 [0.17: 18.26]	ı ——		→ 0.4%
Rashad A 2021	32	46	33	63	1.33 [0.98: 1.80]	1		14.0%
Random effects model	34	72	34	86	1.33 [0.84: 2.13]	í.		14.4%
Heterogeneity: $l^2 = 0\% \tau^2$ :	$= 0 \ n = 0$	81	• •					
	= 0, p = 0.	0.						
Bandom effects model	901	4087	980	3713	0.94 [0.80: 1.11]	1 <	4	100.0%
Heterogeneity: $l^2 = 23\% \tau^2$	$^{2} = 0.0205$	n = 0	18	50		•		
Test for subgroup difference	$rac{1}{2}$ = 13	3.61. df	= 2(p < 0)	.01)		01 02 05	1 2 5	10
	$12. \sqrt{2} = 10$	, ar	- (,, , 0	,		Bisk Bati	o (95% CI)	
						i liok i lat		

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

		MAb	C	ontrol				
Source	Events	Total	Events	Total	RR [95%–CI]	Favors MAb	Favors Con	trol Weight
control = placebo								
Caricchio R 2021	11	223	16	222	0.68 [0.32; 1.44]		+	73.9%
Vlaar A 2020	0	15	4	15	0.11 [0.01; 1.89]	← ■	<u> </u>	10.8%
Random effects model	11	238	20	237	0.47 [0.11; 1.99]		>	84.7%
Heterogeneity: $I^2 = 32\%$ , $\tau^2$	= 0.5338	, <i>p</i> = 0.3	22					
control = active								
Hamed D 2021	2	26	1	23	1.77 [0.17; 18.26]		-	15.3%
Random effects model	2	26	1	23	1.77 [0.17; 18.26]			15.3%
Heterogeneity: not applicab	le							
Random effects model Heterogeneity: $l^2 = 10\% \tau^2$	<b>13</b> - 0 1882	<b>264</b>	21	260	0.65 [0.25; 1.72]			100.0%
Test for subgroup difference	$s: \chi_1^2 = 0.$	, p = 0 89, df =	1 ( <i>p</i> = 0.3	34)	0.0	01 0.1 0.5 <sup>-</sup> Risk Ratio	l 2 10 0 (95% CI)	100
							,,	

Supplementary Figure 10B2 COVID-19-related death

		MAb Control								
Source	Events	Total	Events	Total	RR [95%–CI]	Favors MAb Favors Control Weight				
control = placebo										
Caricchio R 2021	36	225	46	223	0.78 [0.52; 1.15]	14.2%				
Cremer P 2021	5	21	4	19	1.13 [0.35; 3.60]	<b>———</b> 1.7%				
Lescure F 2021	51	173	20	84	1.24 [0.79; 1.94]	11.1%				
Rosas I 2021	103	295	55	143	0.91 [0.70; 1.18]	33.0%				
Salama C 2021	38	249	25	128	0.78 [0.49; 1.23]	<b>————</b> 10.6%				
Stone JH 2020	11	161	3	81	1.84 [0.53; 6.43]	<b>—</b> 1.4%				
Vlaar A 2020	9	15	7	15	1.29 [0.65; 2.54]	4.8%				
Random effects model	253	1139	160	693	0.94 [0.77; 1.14]	÷ 76.8%				
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0	.53								
control = soc										
Gordon A 2021s	0	48	5	201	0.14 [0.00; 12.85]	↔ 0.1%				
Gordon A 2021t	9	353	6	201	0.85 [0.31; 2.36]	2.1%				
Hermine O 2021	20	63	29	67	0.73 [0.47; 1.16]	<b>10.8%</b>				
Horby P 2021	3	2022	0	2094	7.11 [0.38; 134.52]	→ 0.3%				
Kumar S 2021	2	20	3	10	0.33 [0.07; 1.68]	←				
Salvarani C 2021	0	60	0	63	1.00 [0.02; 49.66]	← → 0.1%				
Soin A 2021	18	91	15	89	1.17 [0.63; 2.18]	5.8%				
Veiga V 2021	11	67	7	62	1.45 [0.60; 3.51]	2.8%				
Wang D 2021	0	34	1	31	0.32 [0.01; 7.29]	← → 0.2%				
Random effects model	63	2758	66	2818	0.89 [0.64; 1.26]	23.1%				
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0	.53								
control = active										
Zhao H 2021	0	14	0	7	1.00 [0.02; 58.10]	← 0.1%				
Random effects model	0	14	0	7	1.00 [0.02; 58.10]	0.1%				
Heterogeneity: not applicat	ole									
Random effects model	316	3911	226	3518	0.93 [0.81; 1.07]	4 100.0%				
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0	.73								
Test for subgroup difference	$es: \chi_2^2 = 0.$	09, df =	2(p = 0.9)	96)		0.1 0.2 0.5 1 2 5 10				
						Risk Ratio (95% CI)				
						. ,				

Supplementary Figure 10B3 Serious adverse events.

		Mab			Control						
Source	Mean	SD	Total	Mean	SD	Total	MD [95%	%–CI]	Favors MAb	Favors Contro	ol Weight
control = placebo											
Cremer P 2021	7.63	3.7100	21	7.50	2.9700	19	0.13 [ -1.94;	2.20]	-	<b>-</b>	18.8%
Rosas I 2021	20.25	7.4100	294	29.48	22.1500	144	-9.23 [-12.95; -	-5.51] 🖶			16.1%
Salama C 2021	6.25	0.7400	249	7.62	1.4800	128	-1.38 [ -1.65; -	-1.10]	+		20.4%
Random effects model			564			291	-3.27 [ -8.83;	2.28]		<b>—</b>	55.3%
Heterogeneity: $I^2 = 90\%$ , $\tau^2$	2 = 22.62	280, <i>p</i> < 0	0.01								
control - active											
Hamed D 2021	23 27	8 9600	26	20.83	12 2200	23	2 44 [ -3 63	8 5 1 1			11 9%
Bandom effects model	20.21	0.3000	20	20.00	12.2200	23	2.44 [ -3.63	8 511			11 0%
Heterogeneity: not applicab	le		20			20	2.44 [ -0.00,	0.01]			11.570
control = soc									_		
Veiga V 2021	11.30	8.0000	65	14.70	8.2000	64	–3.40 [ –6.20; –	-0.60]			17.7%
Wang D 2021	21.75	7.4100	34	20.50	9.6300	31	1.25 [ –2.96;	5.46]			15.2%
Random effects model			99			95	–1.35 [ –5.88;	3.17]		$\geq$	32.9%
Heterogeneity: $I^2 = 69\%$ , $\tau^2$	= 7.490	04, p = 0.0	07								
Random effects model			689			409	-1.86 [ -5.09:	1.371			100.0%
Heterogeneity: $I^2 = 79\%$ , $\tau^2$	<sup>2</sup> = 13.33	364, $p < 0$	0.01					·····, L		<u> </u>	7
Test for subgroup difference	$es: \chi_2^2 =$	1.90, df =	2(p =	0.39)				-10	) –5 (	) 5	10
	- *2			,					Mean Differe	nce (95% CI)	

**Supplementary Figure 10B4** Length of hospital stay.

		MAb	C	ontrol							
Source	Events	Total	Events	Total	RR [9	95%–CI]	Favors MAb Favo	ors Control Weight			
control = placebo											
Cremer P 2021	0	21	2	19	0.19 [0.01;	3.54] -	•	0.5%			
Rosas I 2021	51	183	33	90	0.76 [0.53;	1.09]		13.5%			
Salama C 2021	20	249	16	128	0.64 [0.35;	1.20]		7.6%			
Stone JH 2020	11	161	8	81	0.69 [0.29;	1.65]		4.7%			
Random effects model	82	614	59	318	0.72 [0.53;	0.96]	$\diamond$	26.3%			
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0	80				-					
control = soc											
Gordon A 2021s	6	37	58	136	0.38 [0.18;	0.81]		5.8%			
Gordon A 2021t	84	242	58	137	0.82 [0.63;	1.06]		16.4%			
Hermine O 2021	11	63	18	67	0.65 [0.33;	1.27]	- <b>#</b> +	6.9%			
Horby P 2021	215	1754	273	1800	0.81 [0.68;	0.95]	+	19.2%			
Kumar S 2021	0	20	3	10	0.10 [0.01;	1.24	•	0.7%			
Salvarani C 2021	6	60	17	63	0.37 [0.16;	0.88]	<b>_</b>	4.8%			
Soin A 2021	14	91	13	88	1.04 [0.52;	2.09]		6.6%			
Veiga V 2021	4	65	4	63	0.97 0.25	3.71		2.3%			
Random effects model	340	2332	444	2364	0.69 [0.52:	0.931	$\diamond$	62.7%			
Heterogeneity: $I^2 = 32\%$ , $\tau^2$	= 0.0704	p = 0.7	18								
, , , , , , , , , , , .		, <b>F</b>									
control = active											
Hamed D 2021	6	26	2	23	2.65 [0.59;	11.88]	÷ -	— 1.8%			
Rashad A 2021	15	46	18	63	1.14 [0.65;	2.02]	÷.	8.5%			
Zhao H 2021	0	14	2	7	0.14 [0.01;	1.87		0.7%			
Random effects model	21	86	22	93	1.01 [0.24;	4.18]		11.0%			
Heterogeneity: $I^2 = 46\%$ , $\tau^2$	= 1.0078	p = 0.7	16		•	-					
<b>3 ,</b> ,											
Random effects model	443	3032	525	2775	0.74 [0.60:	0.921	$\diamond$	100.0%			
Heterogeneity: $I^2 = 20\%$ , $\tau^2$	= 0.0542	p = 0.2	23								
Test for subaroup difference	es: $\gamma_{0}^{2} = 0$ .	27. df =	2(p = 0.8)	37)		0.0	01 0.1 0.51 2	10 100			
5.00F	~2	,	- N	/		0.0	Risk Ratio (95%	CI)			

**Supplementary Figure 10B5** Invasive mechanical ventilation.

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95	%–CI]	Favors MAb	Favors Co	ntrol Weight
control = placebo									
Caricchio R 2021	122	225	120	223	1.01 [0.85;	1.20]	-		10.3%
Lescure F 2021	121	173	55	84	1.07 [0.89;	1.28]	-		10.2%
Lundgren J 2021	39	163	30	151	1.20 [0.79;	1.84]	-	+	8.2%
Rosas I 2021	228	295	116	143	0.95 [0.86;	1.05]	-		10.6%
Salama C 2021	127	249	29	128	2.25 [1.60;	3.17]		- <b></b> -	8.9%
Random effects model	637	1105	350	729	1.20 [0.78;	1.83]	<	÷	48.1%
Heterogeneity: $I^2 = 83\%$ , $\tau^2$	= 0.0987	, <i>p</i> < 0.0	01			-			
control = soc									
Hermine O 2021	28	63	36	67	0.83 [0.58;	1.18]		H	8.8%
Horby P 2021	204	2022	254	2094	0.83 [0.70;	0.99]			10.2%
Kumar S 2021	18	20	4	10	2.25 [1.04;	4.87]			5.2%
Salvarani C 2021	14	60	7	63	2.10 [0.91;	4.84]		<u>  - ∎</u> -	4.8%
Soin A 2021	33	91	22	89	1.47 [0.93;	2.31]	3	+=	7.9%
Veiga V 2021	29	67	21	62	1.28 [0.82;	1.99]	-		8.0%
Wang D 2021	20	34	4	31	4.56 [1.75;	11.87]			→ 4.1%
Random effects model	346	2357	348	2416	1.43 [0.84;	2.42]	-	$\leftarrow$	49.0%
Heterogeneity: $I^2 = 77\%$ , $\tau^2$	= 0.2405	, <i>p</i> < 0.0	01						
control = active				_					
Zhao H 2021	9	14	2	7	2.25 [0.65;	7.73]			— 2.9%
Random effects model	9	14	2	7	2.25 [0.65;	7.73]			- 2.9%
Heterogeneity: not applicab	le								
Bandom offecto model	002	2476	700	2152	1 21 [0 00.	1 711			100.0%
Hotorogonoity: $l^2 = 77^{\circ/2} = 2^{\circ/2}$	-01445	34/0	100	3152	1.31 [0.99;				100.0%
Test for subgroup difference	= 0.1445	p < 0.0	$\frac{1}{2}(n-0)$	54)		0.1	0.2 0.5	1 0 5	10
rescior subgroup difference	$x_2 = 1.$	20, ui =	2(p = 0.5)	)4)		0.1	U.2 U.3 Rick Pati		10
							hisk hall	5 (35 /8 01)	

Supplementary Figure 10B6 Adverse events.

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95%–	Cl] Fav	vors MAb	Favors Co	ntrol Weight
control = placebo									
Caricchio R 2021	23	225	43	223	0.53 [0.33; 0.8	85]			14.9%
Lescure F 2021	40	332	10	84	1.01 [0.53; 1.9	94]		-	8.5%
Lundgren J 2021	4	163	4	151	0.93 [0.24; 3.6	64]			2.1%
Rosas I 2021	113	295	58	143	0.94 [0.74; 1.2	21]			37.0%
Salama C 2021	25	259	16	129	0.78 [0.43; 1.4	41]	-	_	10.1%
Stone JH 2020	13	161	14	81	0.47 [0.23; 0.9	95]			7.3%
Vlaar A 2020	3	15	4	15	0.75 [0.20; 2.]	79]			2.3%
Random effects model	221	1450	149	826	0.78 [0.60; 1.0	03]	$\diamond$		82.2%
Heterogeneity: $I^2 = 20\%$ , $\tau^2$	= 0.0113	, p = 0.3	28						
control = soc									
Gordon A 2021s	0	48	0	201					0.0%
Gordon A 2021t	1	353	0	201	2.57 [0.07; 93.3	31]		•	0.3%
Hermine O 2021	4	63	14	67	0.30 [0.11; 0.8	87]			3.4%
Horby P 2021	6	2022	9	2094	0.69 [0.25; 1.9	94]			3.6%
Kumar S 2021	1	22	3	10	0.15 [0.02; 1.2	28] —		_	0.9%
Salvarani C 2021	1	60	4	63	0.26 [0.03; 2.2	28] –	•		0.8%
Soin A 2021	6	91	5	89	1.17 [0.37; 3.]	71]			2.9%
Veiga V 2021	10	67	10	62	0.93 [0.41; 2.0	07]		<u> </u>	5.8%
Random effects model	29	2726	45	2787	0.63 [0.33; 1.1	19]	$\sim$	•	17.8%
Heterogeneity: $I^2 = 11\%$ , $\tau^2$	= 0.0557	p = 0.3	34						
Random effects model	250	4176	194	3613	0.75 [0.60; 0.9	94]	\$		100.0%
Heterogeneity: $I^2 = 14\%$ , $\tau^2$	= 0.0125	, p = 0.3	31				1 11	1 1	
Test for subgroup difference	es: $\chi_1^2 = 0$ .	58, df =	1 (p = 0.4	15)		0.01	0.1 0.51	2 10	100
							<b>Risk Ratio</b>	(95% CI)	

## Supplementary Figure 10B7 Bacteremia.

		MAb	C	ontrol					
Source	Events	Total	Events	Total	RR [95%	6–CI]	Favors MAb	<b>Favors Control</b>	Weight
control = soc									
Gordon A 2021t	98	350	71	198	0.78 [0.61;	1.00]			19.8%
Hermine O 2021	7	63	8	67	0.93 [0.36;	2.42]			2.3%
Horby P 2021	596	2022	694	2094	0.89 [0.81;	0.97]			38.8%
Salvarani C 2021	1	60	1	63	1.05 [0.07; 1	6.41] ←			0.3%
Soin A 2021	11	91	15	88	0.71 [0.34;	1.46]			3.9%
Veiga V 2021	14	65	6	64	2.30 [0.94;	5.61]	+		2.6%
Random effects model	727	2651	795	2574	0.88 [0.69;	1.12]	4	•	67.7%
Heterogeneity: $I^2 = 13\%$ , $\tau^2$	= 0.0135	, <i>p</i> = 0.3	33						
control = active									
Hamed D 2021	2	26	1	23	1.77 [0.17; 1	8.26]		>	0.4%
Rashad A 2021	32	46	33	63	1.33 [0.98;	1.80]	ł	-	15.7%
Random effects model	34	72	34	86	1.33 [0.84;	2.13]	4	$\diamond$	16.1%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	= 0, p = 0	.81							
control - placebo									
Bosas I 2021	58	294	28	144	1 01 [0 68.	1 521		<b>—</b>	10.4%
Salama C 2021	26	249	11	128	1.01 [0.00,	2.381			4 4%
Stone JH 2020	9	161		81	1.51 [0.62;	5 421			1.3%
Bandom effects model	93	704	42	353	1.09 [0.76:	1.56]	4	>	16.1%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 =$	= 0, p = 0	79		000					10.170
	-, p								
Random effects model	854	3427	871	3013	0.98 [0.82;	1.15]	4	>	100.0%
Heterogeneity: $I^2 = 29\%$ , $\tau^2$	= 0.0127	p = 0.	17		-				
Test for subgroup difference	es: $\chi^2_2 = 19$	9.78, df	= 2 (p < 0	.01)		0.1	0.2 0.5 1	2 5 10	)
							Risk Ratio	(95% CI)	

**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.

		MAb	C	ontrol				
Source	Events	Total	Events	Total	RR [9	95%–CI]	Favors MAb Favors Co	ontrol Weight
control = soc								
Gordon A 2021t	84	242	58	137	0.82 [0.63;	1.06]	<del>4</del>	20.3%
Hermine O 2021	11	63	18	67	0.65 [0.33;	1.27]		3.1%
Horby P 2021	215	1754	273	1800	0.81 [0.68;	0.95]		49.9%
Salvarani C 2021	6	60	17	63	0.37 [0.16;	0.88]	<b>•</b> _;	1.9%
Soin A 2021	14	91	13	88	1.04 [0.52;	2.09]		2.8%
Veiga V 2021	4	65	4	63	0.97 [0.25;	3.71]		0.8%
Random effects model	334	2275	383	2218	0.80 [0.70;	0.91]	\$	78.8%
Heterogeneity: $I^2 = 0\%$ , $\tau^2 = 0\%$	= 0, p = 0	.53						
control = active								
Hamed D 2021	6	26	2	23	2.65 [0.59;	11.88]	÷ <b> </b> •	0.6%
Rashad A 2021	15	46	18	63	1.14 [0.65;	2.02]		4.2%
Zhao H 2021	0	14	2	7	0.14 [0.01;	1.87] -		0.2%
Random effects model	21	86	22	93	1.01 [0.24;	4.18]		5.1%
Heterogeneity: $I^2 = 46\%$ , $\tau^2$	= 1.0078	p = 0.	16		-	_		
control = placebo								
Rosas I 2021	51	183	33	90	0.76 [0.53;	1.09]		10.8%
Salama C 2021	20	249	16	128	0.64 [0.35;	1.20]		3.6%
Stone JH 2020	11	161	8	81	0.69 [0.29;	1.65]		1.8%
Random effects model	82	593	57	299	0.72 [0.54;	0.97	ò	16.2%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$ :	= 0, p = 0	.89			• /	-		
0								
Random effects model	437	2954	462	2610	0.80 [0.71;	0.90]	\$	100.0%
Heterogeneity: $I^2 = 0\%$ , $\tau^2$ :	= 0, p = 0	.49			- /	<b>Г</b>		
Test for subgroup difference	es: $\chi_2^2 = 0$ .	47, df =	2(p = 0.7)	79)		0.0	01 0.1 0.51 2 10	100
5	, <u>, 2</u>						Risk Ratio (95% CI)	

**Supplementary Figure 10C4** Invasive mechanical ventilation.



