Rapid Evidence Product

Adverse Events Associated With COVID-19 Pharmaceutical Treatments

Background and Purpose

The purpose of this rapid review is to determine if COVID treatments authorized for emergency use by the Food and Drug Administration (FDA) are associated with serious harms. The review will be used by the Health Resources & Services Administration (HRSA) Countermeasures Injury Compensation Program to inform a Countermeasures Injury Table (Table). Once a Table and any relevant amendments are published, the Table will be used to make benefits eligibility determinations for covered injuries or deaths. The Agency for Healthcare Research and Quality (AHRQ) commissioned this rapid review using abbreviated methods to provide an assessment of evidence in a compressed timeframe to inform HRSA's work.

Methods

The section contains a summary of the project methods; a full description is available as Appendix A. The protocol is registered in PROSPERO (CRD42023467821). The following pharmaceutical interventions to treat or prevent COVID-19 were reviewed:

- Convalescent plasma (from recovered COVID-19 patients);
- Antivirals: Remdesivir (Veklury), Nirmatrelvir and Ritonavir in combination (Paxlovid), Molnupiravir (Lagevrio);
- Monoclonal antibodies: Bamlanivimab and Etesevimab in combination, Bebtelovimab, Casirivimab and Imdevimab in combination (Regeneron), Sotrovimab (Xevudy), Tixagevimab and Cilgavimab in combination (Evusheld), Tocilizumab (Actemra);

Agency for Healthcare Research and Quality

- Interleukin-1 receptor antagonist: Anakinra (Kineret).

This rapid review was limited to studies of the above listed interventions when used for treatment or prevention of COVID-19. Studies were required to have a placebo, untreated, or usual care comparison group. Having a comparison group that did not receive the intervention provides important information about the background rate of adverse events in its absence, in particular when adverse events are nonspecific. Numerous serious medical problems occur in patients hospitalized with COVID-19, given patients' advanced age, multiple pre-existing medical conditions, and the natural sequalae of COVID-19 infection. A comparison rate is essential for understanding what would be expected to occur naturally in the absence of any intervention. Thus, no case reports, case series, or uncontrolled surveillance studies were included. Head-to-head comparisons of medications were also excluded.

The review was limited to studies that included at least one US site or territory, where populations most likely to file a Countermeasures Injury Compensation Program claim would be included.

In August 2023, we searched PubMed (including litCOVID), clinicaltrials.gov, and the FDA submission database with start date January 2020; the Cochrane Database of Systematic Reviews was searched starting at January 2022. We reference mined the Infectious Disease Society of America guidelines, the international COVID Network Meta-analysis database, and systematic reviews published in 2022 and 2023. Researchers screened abstracts and full texts for inclusion using DistillerSR software.

The rapid review was limited to serious adverse events as defined in U.S. statute 42 CFR 110.3(z):

> "[P]hysical biochemical alterations leading to physical changes and serious functional abnormalities at the cellular or tissue level in any bodily function may, in certain circumstances, will be considered serious injuries. As a general matter, only injuries that warranted hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability (whether or not hospitalization was warranted) will be considered serious injuries."[1]

Most studies used the Common Terminology Criteria for Adverse Events levels in reporting adverse events. We abstracted those at severity level 3, defined as " severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling" or higher. We abstracted follow up timing and categorized adverse events as occurring within either 45 days of initial pharmaceutical administration or greater than 45 days from administration, per HRSA request. We abstracted exact events except pulmonary embolism and deep vein thrombosis, which were grouped as *thrombotic events*; arterial or venous bleeding, grouped as *bleeding events*; and we grouped all serious infections as *infection, including sepsis* per prior work conducted for AHRQ.[2] For applicability, we abstracted data for the dosage authorized by the FDA when available. Adverse events data were converted to rates for intervention and comparison groups; rates were used to compute risk ratios (RRs) to estimate effects.

We assessed risk of bias with respect to adverse events using two items: whether collection was passive (i.e., whether outpatients contacted researchers if they experienced an event rather than the researchers actively contacting each patient and asking about a pre-determined list of events); and whether the authors reported the proportion of patients experiencing each event (e.g., rather than the total number of events because a patient could experience an event more

than once, in which case the proportion of patients would lead to an underestimate of the number of events).

We summarized the risk ratios for each intervention and each event; where possible, we summarized risk ratios for specific populations such as those hospitalized with specific COVID-19 symptoms, pregnant women, and those with pre-existing medical conditions.

Finally, the system below, from the Institute of Medicine 2012 report *Adverse Effects of Vaccines: Evidence and Causality,*[3] was used to assess certainty of evidence.

- *High*: Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect provide high confidence.
- *Moderate*: One study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, that provides moderate confidence.
- *Limited*: One study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.
- *Insufficient*: No epidemiologic studies of sufficient quality.

Evidence Summary

In total, 54 studies met eligibility criteria.[4-57] Serious adverse events were abstracted from peer-reviewed journal articles, clinicaltrials.gov, and submissions for FDA emergency use authorization.

- In patients with hematologic cancers, there is moderate certainty based on one study that administration of convalescent plasma while hospitalized with COVID-19 may cause elevated risk of serious bleeding events and infection, including sepsis, within 30 days. Certainty of evidence is limited for congestive heart failure within 30 days in this population based on the same study.
- Based on four studies, there is limited certainty that convalescent plasma may be associated with serious thrombotic events within 90 days among patients hospitalized for COVID-19.
- We found insufficient evidence of association of any serious adverse events with the antivirals used for COVID-19 (remdesivir, nirmatrelvir and ritonavir combination, molnupiravir).
- We found insufficient evidence of association of any serious adverse events with the SARS-CoV-2 spike protein receptor binding antibodies bamlanivimab/ etesevimab, bebtelovimab, sotrovimab, casirivimab/ imdevimab, and tixagevimab/ cilgavimab.
- There is limited certainty that the monoclonal antibody tocilizumab, an IL-6 inhibitor, may be associated with elevated risk of neutropenia within four weeks in patients hospitalized with COVID-19, based on one study. There is limited certainty that COVID-19 patients on extracorporeal membrane oxygenation for respiratory support or intravenous infusion of a vasopressor or inotrope for cardiovascular support in the intensive care unit are at elevated risk of bleeding events within 90 days, based on another study.
- No studies of Anakinra for COVID-19 met inclusion criteria. FDA emergency use authorization was based on studies conducted overseas.

Evidence Base

After full text review of 320 publicly available documents, 54 studies published in 66 publications met eligibility criteria.[4-69] The primary reasons for exclusion were no US study locations (N = 70) and lack of reporting of adverse events (N = 33) in studies of efficacy or effectiveness. A literature flow diagram is included as Appendix B. The number of included studies per intervention ranges from one (tixagevimab and cilgavimab) to 15 (convalescent plasma). Importantly, we identified no US studies of anakinra that met inclusion criteria; US emergency use authorization was based on studies conducted overseas.

Thirty-one randomized controlled trials (RCTs) and 23 controlled observational studies met inclusion criteria. Fifteen studies compared an intervention to no treatment, 26 were placebo-controlled trials, and 12 studies compared an intervention to usual care. One observational study compared patients who received hydroxychloroquine with a group who received hydroxychloroquine plus tocilizumab.[23] Interventions were administered in an outpatient setting in 23 studies; the remainder involved patients hospitalized with COVID-19. Appendix C, the evidence and risk of bias table, displays details such as design, intervention, comparator, age groups, pre-existing conditions, setting, and patient severity for each study.

It was uncommon for studies to report the exact timing of adverse events; we discuss exact timing in the rare cases where it was provided. Published studies usually provided a table listing all serious adverse events that occurred within a specific number of days from administration. Most clinical trials, via clinicaltrials.gov, provided a table which used MedDRA (Medical Dictionary for Regulatory Activities definitions)[70] terms for adverse events and standard definitions of severity according to the Common Terminology Criteria for Adverse Events (serious being level 3 to 5 on a scale of 1 to 5).[71]

Most studies (N = 37) had low overall risk of bias regarding the collection and reporting of adverse events. Because manufacturers sought Emergency Use Authorization from the FDA, clinical trials carefully monitored and reported adverse events, adhering to expected standards. Twelve studies were rated as moderate or unclear risk of bias; most were observational studies with unclear timing or data collection procedures. These were primarily conducted in hospitals where patients presumably were monitored regularly but we did not make assumptions when this was not stated and classified adverse events collection in these cases as unclear. Five observational studies had high risk of bias; they focused on efficacy or effectiveness and included only statement that certain adverse events (e.g., transfusion-related acute lung injury, and transfusion-associated circulatory overload) did not occur during the study period. Risk of bias was incorporated into our certainty of evidence ratings and is discussed in each section describing findings.

Below we describe the serious adverse events reported for each intervention, followed by available data on populations hospitalized with specific COVID-19 sequalae or with specific pre-existing medical conditions. We intended to provide risk ratios for specific age groups such as adolescents and older adults; however, this was not possible. No studies included children under age twelve. Three studies included adolescents (at least age 12) in addition to adults, but adverse events were not reported separately for the adolescents.[12, 33, 38] All studies but six included adults aged 65 or older; none reported adverse events separately for older adults.

Convalescent Plasma

Adverse Events 45 Days or Less

We identified 11 controlled studies of convalescent plasma that reported serious adverse events within 45 days of administration, with timing from 14 to 30 days.[4, 5, 7, 9, 11, 25, 28, 31, 34, 48, 53] Study data are displayed in Table 1 below.

Six studies reported all-cause mortality; the risk was significantly lower in the intervention group in two studies; one within 28 days from baseline[34] (RR 0.51; confidence interval [CI] 0.29, 0.92) with low risk of bias and one within 30 days from baseline[53] (RR 0.54; CI 0.35, 0.83) with moderate/unclear risk of bias. In contrast, in another study[31] mechanically ventilated patients who received convalescent plasma had significantly increased risk of all-cause mortality (RR 1.74; CI 1.49, 2.04) with low risk of bias. The other three studies of patients with severe COVID-19 reported no significant difference. Thus, there is insufficient certainty of evidence for increased mortality in severely ill patients.

Three studies reported serious bleeding events. A study of hematological cancer patients with moderate/unclear risk of bias[53] showed significantly increased risk of bleeding within 30 days from baseline (RR 1.96; CI 1.14, 3.36); this is discussed in the section on patients with pre-existing conditions. The other two studies reported no significant difference in risk for bleeding.

Five studies reported serious infection including sepsis; the risk was significantly lower in the intervention group in one study with low risk of bias (RR 0.24; CI 0.09, 0.69).[34] In contrast, the study of hematological cancer patients[53] reported an increased risk of infection (RR 1.79; CI 1.41, 2.26). The other three studies reported no significant difference. There were no significant differences in risk of acute kidney injury, anaphylaxis, cardiac arrhythmia, fever, hypotension, cerebrovascular accident, transfusion-associated lung injury, seizure, infection, thrombotic events, and transfusion-associated circulatory overload in the other studies.[4, 9, 11, 28, 48]

Table 1. Serious adverse events, convalescent plasma, 45 days or less

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Begin, 2021[5]	30	12/614	7/307	CONCOR-1	500 ml	RR 0.86; CI 0.34, 2.16	Low
	Korley, 2021[25]	30	1/257	0/254	SIREN-C3PO	200 ml	RR 2.97; CI 0.12, 72.45	Low
	Thompson, 2021[53]	30	37/143	222/823	Convalescent Plasma and hematologic cancers	Not reported	RR 0.96; CI 0.71, 1.29	Moderate /Unclear
All-Cause Mortality	Liu, 2020[28]	14	5/39	8/39	Convalescent Plasma for severe COVID-19	Not reported	RR 0.62; CI 0.22, 1.74	High
	Begin, 2021[5]	30	160/625	70/313	CONCOR-1	500 ml	RR 1.14; CI 0.90, 1.46	Low
	Korley, 2021[25]	30	5/257	1/254	SIREN-C3PO	200 ml	RR 4.94; CI 0.58, 42	Low
	O'Donnell, 2021[34]	28	19/150	18/73	AAAS9924	200 - 250 ml	RR 0.51; CI 0.29, 0.92	Low
	Misset, 2023[31]	28	184/237	106/238	Convalescent Plasma for Covid-19	400-500ml	RR 1.74; CI 1.49, 2.04	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
					Induced ARDS in Mechanically Ventilated Patients			
	Thompson, 2021[53]	30	19/143	204/823	Convalescent Plasma and hematologic cancers	Not reported	RR 0.54; CI 0.35, 0.83	Moderate /Unclear
Anaphylaxis	Korley, 2021[25]	30	1/257	0/254	SIREN-C3PO	200 ml	RR 2.97; CI 0.12, 72.45	Low
Bleeding	Begin, 2021[5]	30	8/614	1/307	CONCOR-1	500 ml	RR 4.00; CI 0.50, 31.84	Low
	Misset, 2023[31]	28	9/237	14/238	Convalescent Plasma for Covid-19 Induced ARDS in Mechanically Ventilated Patients	400-500ml	RR 0.65; CI 0.28, 1.46	Low
	Thompson, 2021[53]	30	16/143	47/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.96; CI 1.14, 3.36	Moderate /Unclear
Cardiac Arrythmia	Begin, 2021[5]	30	0/614	3/307	CONCOR-1	500 ml	RR 0.07; CI 0, 1.38	Low
	Korley, 2021[25]	30	1/257	1/254	SIREN-C3PO	200 ml	RR 0.99; CI 0.06, 15.72	Low
	Thompson, 2021[53]	30	5/143	27/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.07; CI 0.42, 2.72	Moderate /Unclear
Fever	Begin, 2021[5]	30	1/614	0/307	CONCOR-1	500 ml	RR 1.50; CI 0.06, 36.77	Low
	Chauhan, 2022[11]	Unclear, varied	1/188	0/188	Convalescent Plasma for hospitalized patients	100-250 ml	RR 3.00; CI 0.12, 73.18	Moderate /Unclear
Myocardial infarction	Begin, 2021[5]	30	3/614	2/307	CONCOR-1	500 ml	RR 0.75; CI 0.13, 4.46	Low
	Thompson, 2021[53]	30	5/143	26/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.11; CI 0.43, 2.83	Moderate /Unclear
Hypotension	Begin, 2021[5]	30	8/614	0/307	CONCOR-1	500 ml	RR 8.51; CI 0.49, 147.02	Low
	Korley, 2021[25]	30	1/257	0/254	SIREN-C3PO	200 ml	RR 2.97; CI 0.12, 72.45	Low
Infection Including Sepsis	Begin, 2021[5]	30	20/614	10/307	CONCOR-1	500 ml	RR 1.00; CI 0.47, 2.11	Low
	Korley, 2021[25]	30	32/257	40/254	SIREN-C3PO	200 ml	RR 0.79; CI 0.51, 1.22	Low
	O'Donnell, 2021[34]	28	5/147	10/72	AAAS9924	200 - 250 ml	RR 0.24; CI 0.09, 0.69	Low
	Misset, 2023[31]	28	24/237	21/238	Convalescent Plasma for Covid-19 Induced ARDS in Mechanically	400-500ml	RR 1.15; CI 0.66, 2.00	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
					Ventilated Patients			
	Thompson, 2021[53]	30	58/143	187/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.79; CI 1.41, 2.26	Moderate /Unclear
Seizure	Korley, 2021[25]	30	1/257	0/254	SIREN-C3PO	200 ml	RR 2.97; CI 0.12, 72.45	Low
Cerebro-vascular accident	Begin, 2021[5]	30	0/614	2/307	CONCOR-1	500 ml	RR 0.10; CI 0, 2.08	Low
	Misset, 2023[31]	28	1/237	0/238	Convalescent Plasma for Covid-19 Induced ARDS in Mechanically Ventilated Patients	400-500 ml	RR 3.01; CI 0.12, 73.58	Low
Thrombotic Event	Self, 2022[48]	Un-clear	101/487	109/473	Pass It On	500 ml	RR 0.90; CI 0.71, 1.14	Low
	Begin, 2021[5]	30	4/614	2/307	CONCOR-1	500 ml	RR 1; CI 0.18, 5.43	Low
	Korley, 2021[25]	30	3/257	2/254	SIREN-C3PO	200 ml	RR 1.48; CI 0.25, 8.80	Low
	Thompson, 2021[53]	30	15/143	63/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.37; CI 0.80, 2.34	Moderate /Unclear
Transfusion-Associated Lung Injury	Liu, 2020[28]	14	0/39	0/39	Convalescent Plasma for severe COVID-19	Not reported	RR 1; CI 0.02, 49.17	High
	Briggs, 2021[9]	14	0/132	0/132	Early vs late convalescent Plasma for moderate to severe COVID-19	200 ml	RR 1; CI 0.02, 50.03	High
	Self, 2022[48]	Un-clear	0/487	0/473	Pass It On	500 ml	RR 0.97; CI 0.02, 48.85	Low
	Begin, 2021[5]	30	1/614	0/307	CONCOR-1	500 ml	RR 1.50; CI 0.06, 36.77	Low
	Chauhan, 2022[11]	Uncle ar, varied	0/188	0/188	Convalescent Plasma for hospitalized patients	100-250 ml	RR 1; CI 0.02, 50.14	Moderate /Unclear
Transfusion-associated circulatory overload	Liu, 2020[28]	14	0/39	0/39	Convalescent Plasma for severe COVID-19	Not reported	RR 1; CI 0.02, 49.17	High
	Briggs, 2021[9]	14	0/132	0/132	Early vs late convalescent Plasma for moderate to severe COVID-19	200 ml	RR 1; CI 0.02, 50.03	High
	Self, 2022[48]	Un-clear	1/487	0/473	Pass It On	500 ml	RR 2.91; CI 0.12, 71.35	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Chauhan, 2022[11]	Uncle ar, varied	0/188	0/188	Convalescent Plasma for hospitalized patients	100-250 ml	RR 1.00; CI 0.02, 50.14	Moderate /Unclear

Notes: ARDS = acute respiratory distress syndrome, CI = 95% confidence interval, RR = risk ratio

Adverse Events More Than 45 Days

We identified eight controlled studies of convalescent plasma[4, 5, 11, 20, 35, 46, 48, 52] that described serious adverse events which occurred between administration and more than 45 days post-intervention, with timing from 60 to 90 days. Data are displayed in Table 2.

Six studies reported all-cause mortality; the risk was significantly lower in the intervention group in two studies; one (RR 0.27; CI 0.08, 0.88) had moderate/unclear risk of bias[4] and the other (RR 0.47; CI 0.29, 0.76) had high risk of bias.[46] The four other studies reported no significant difference in risk.

There were no significant differences in risk for bleeding, cardiac arrhythmia, headache, myocardial infarction, hypertension, hypotension, transfusion associated lung injury, and infection including sepsis in the studies; the direction of risk (elevated vs decreased) varied. One observational study with high risk of bias[46] reported on serious allergic reaction other than anaphylaxis; risk was elevated but not statistically significant (RR 5.07; CI 0.21, 124.14) based on only one patient experiencing. Certainty of evidence for serious allergic reaction is insufficient due to lack of statistical significance, imprecision, and lack of the event in additional studies.

Results conflicted for risk of acute kidney injury in two studies;[35, 48] neither result was statistically significant. Four studies reported serious thrombotic events;[4, 35, 48, 52] three of the these reported elevated risk (one almost five-fold[52]), but results were not statistically significant. Certainty of evidence is limited due to conflicting results in one of the four studies, lack of statistical significance, and wide confidence intervals. A study of high titer plasma for severe COVID-19[46] showed an elevated but not statistically significant risk of transfusion associated circulatory overload (RR 5.07; CI 0.21, 124.14) based on only one person experiencing; this study had high risk of bias. Certainty of evidence is insufficient due to risk of bias, lack of statistical significance, extremely wide confidence intervals, and lack of other studies reporting this event. One study reported two cases cerebrovascular accident in the intervention group;[35] risk was elevated but not statistically significant (RR 5.05; CI 0.24, 104.97). Risk of bias was low in this clinical trial. Certainty of evidence for cerebrovascular accident is insufficient due to lack of statistical significance, extremely wide confidence intervals, and lack of other studies reporting this event.

Table 2. Serious adverse events, convalescent plasma, more than 45 days

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Self, 2022[48]	90	2/495	10/479	Pass It On	500 ml	RR 4.84; CI 0.23, 100.53	Low
	Ortigoza, 2022[35]	90	16/468	19/473	CONTAIN	250 ml	RR 0.85; CI 0.44, 1.63	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Alanine aminotransferase (ALT) increase	Ortigoza, 2022[35]	90	5/468	3/473	CONTAIN	250 ml	RR 1.68; CI 0.4, 7.01	Low
All-Cause Mortality	Bar, 2021[4]	60	3/40	11/39	PennCCP2	2 units	RR 0.27; CI 0.08, 0.88	Moderate /Unclear
	Self, 2022[48]	90	89/495	80/479	Pass It On	500 ml	RR 1.08; CI 0.82, 1.42	Low
	Sullivan, 2022[52]	90	0/592	3/589	CSSC-004	250 ml	RR 0.14; CI 0.01, 2.75	Low
	Ortigoza, 2022[35]	90	4/468	3/473	CONTAIN	250 ml	RR 1.35; CI 0.30, 5.99	Low
	Salazar, 2021[46]	60	20/351	72/594	High titer Convalescent Plasma for severe COVID-19	300 ml	RR 0.47; CI 0.29, 0.76	High
	Hsue, 2021[20]	90	1/16	1/18	CAPRI	250 ml	RR 1.13; CI 0.08, 16.55	Low
Allergic reaction (not anaphylaxis)	Salazar, 2021[46]	60	1/351	0/594	High titer Convalescent Plasma for severe COVID-19	300 ml	RR 5.07; CI 0.21, 124.14	High
Bleeding	Bar, 2021[4]	60	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate /Unclear
	Ortigoza, 2022[35]	90	35/468	41/473	CONTAIN	250 ml	RR 0.86; CI 0.56, 1.33	Low
Cardiac Arrythmia	Bar, 2021[4]	60	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate /Unclear
	Self, 2022[48]	90	0/495	1/479	Pass It On	500 ml	RR 0.32; CI 0.01, 7.90	Low
	Ortigoza, 2022[35]	90	23/468	16/473	CONTAIN	250 ml	RR 1.45; CI 0.78, 2.71	Low
Cerebrovascular accident	Ortigoza, 2022[35]	90	2/468	0/473	CONTAIN	250 ml	RR 5.05; CI 0.24, 104.97	Low
Headache	Bar, 2021[4]	60	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate /Unclear
	Sullivan, 2022[52]	90	0/592	1/589	CSSC-004	250 ml	RR 0.33; CI 0.01, 8.12	Low
Myocardial infarction	Self, 2022[48]	90	1/495	1/479	Pass It On	500 ml	RR 0.97; CI 0.06, 15.43	Low
	Ortigoza, 2022[35]	90	61/468	70/473	CONTAIN	250 ml	RR 0.88; CI 0.64, 1.21	Low
Hypertension	Sullivan, 2022[52]	90	2/592	1/589	CSSC-004	250 ml	RR 1.99; CI 0.18, 21.89	Low
Hypotension	Bar, 2021[4]	60	0/40	2/39	PennCCP2	2 units	RR 0.20; CI 0.01, 3.94	Moderate /Unclear
	Self, 2022[48]	90	1/495	1/479	Pass It On	500 ml	RR 0.97; CI 0.06, 15.43	Low
	Sullivan, 2022[52]	90	0/592	1/589	CSSC-004	250 ml	RR 0.33; CI 0.01, 8.12	Low
	Ortigoza, 2022[35]	90	38/468	55/473	CONTAIN	250 ml	RR 0.70; CI 0.47, 1.03	Low
Infection including Sepsis	Self, 2022[48]	90	4/495	2/479	Pass It On	500 ml	RR 1.94; CI 0.36, 10.52	Low
	Sullivan, 2022[52]	90	0/592	0/589	CSSC-004	250 ml	RR 0.99; CI 0.02, 50.06	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Ortigoza, 2022[35]	90	36/468	55/473	CONTAIN	250 ml	RR 0.73; CI 0.48, 1.10	Low
Thrombotic Event	Self, 2022[48]	90	1/495	1/479	Pass It On	500 ml/hour	RR 0.97; CI 0.06, 15.43	Low
	Sullivan, 2022[52]	90	2/592	0/589	CSSC-004	250 ml	RR 4.97; CI 0.24, 103.4	Low
	Ortigoza, 2022[35]	90	22/468	14/473	CONTAIN	250 ml	RR 1.59; CI 0.82, 3.07	Low
	Bar, 2021[4]	60	2/40	1/39	PennCCP2	2 units	RR 1.95; CI 0.18, 20.64	Moderate /Unclear
Transfusion-Associated Circulatory Overload	Ortigoza, 2022[35]	90	0/468	0/473	CONTAIN	250 ml	RR 1.01; CI 0.02, 50.83	Low
	Salazar, 2021[46]	60	1/351	0/594	High titer plasma for severe COVID-19	300 ml, titer 1:1350	RR 5.07; CI 0.21, 124.14	High
Transfusion-Associated Lung Injury	Ortigoza, 2022[35]	90	0/468	0/473	CONTAIN	250 ml	RR 1.01; CI 0.02, 50.83	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Antivirals: Remdesivir

Adverse Events 45 Days or Less

We identified three observational studies[22, 38, 47] and one RCT[6] of remdesivir that reported serious adverse events within less than 45 days (see Table 3). Remdesivir was administered in an outpatient setting in one observational study which had moderate risk of bias; the other studies were conducted with hospitalized patients and had low risk of bias. Timing ranged from 7 to 29 days. There were no statistically significant risk differences for serious elevated levels of aspartate aminotransferase, hypotension, transfusion associated lung injury, infection, thrombotic events, and transfusion associated circulatory overload. Risk of cardiac arrythmia was elevated in the RCT (RR 4.85; CI 0.57, 41.37) but this was not statistically significant.[6] There was decreased risk of cardiac arrythmia (also not statistically significant) in an observational study of patients with severe renal disease.[47] Thus, the evidence of risk of cardiac arrythmia is insufficient due to conflicting results, lack of statistical significance, and lack of precision in the RCT.

In one observational study of patients with severe kidney disease[47] the risk of alanine aminotransferase increase and seizure were elevated within seven days of administration, but risk ratios were not statistically significant. This is discussed in the later section on patients with pre-existing conditions.

Table 3. Serious adverse events, remdesivir, 45 days or less

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Beigel, 2020[6]	29	7/532	12/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 0.57; CI 0.22, 1.43	Low
	Kalligeros, 2020[22]	28	12/99	17/125	Remdesivir compared with supportive care in hospitalized patients	200 mg	RR 0.89; CI 0.45, 1.78	Low
Alanine aminotransferase (ALT) increase	Seethapathy, 2022[47]	7	1/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 3.00; CI 0.13, 70.92	Low
	Kalligeros, 2020[22]	28	0/99	13/25	Remdesivir compared with supportive care in hospitalized patients	200 mg	RR 0.18; CI 0.01, 3.44	Low
All-Cause Mortality	Beigel, 2020[6]	29	59/532	77/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 0.74; CI 0.54, 1.02	Low
	Piccicacco, 2021[38]	29	0/82	1/90	Early remdesivir and sotrovimab in highest-risk patients	200mg	RR 0.37; CI 0.02, 8.85	Moderate/ Unclear
	Seethapathy, 2022[47]	7	6/31	7/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.86; CI 0.32, 2.26	Low
	Kalligeros, 2020[22]	28	7/99	17/125	Remdesivir compared with supportive care in hospitalized patients	200 mg	RR 0.52; CI 0.22, 1.20	Low
Aspartate aminotransferase (AST) increase	Seethapathy, 2022[47]	7	1/31	2/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.50; CI 0.05, 5.23	Low
	Kalligeros, 2020[22]	28	0/99	2/125	Remdesivir compared with supportive care in hospitalized patients	200 mg	RR 0.25; CI 0.01, 5.19	Low

Serious Adverse Event	Study ID	Days	n/N Inter-vention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Cardiac Arrythmia	Beigel, 2020[6]	29	5/532	1/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 4.85; CI 0.57, 41.37	Low
	Seethapathy, 2022[47]	7	16/31	21/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.76; CI 0.50, 1.16	Low
Hypotension	Beigel, 2020[6]	29	4/532	7/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 0.55; CI 0.16, 1.88	Low
Infection Including Sepsis	Beigel, 2020[6]	29	8/532	15/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 0.52; CI 0.22, 1.21	Low
Seizure	Seethapathy, 2022[47]	7	1/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 3.00; CI 0.13, 70.92	Low
Thrombotic Event	Beigel, 2020[6]	29	5/532	4/516	ACTT-1	200 mg day 1, 100 mg daily for up to 9 additional days	RR 1.21; CI 0.33, 4.49	Low
Transfusion associated Lung Injury	Seethapathy, 2022[47]	7	0/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 1.00; CI 0.02, 48.87	Low
Transfusion-associated circulatory overload	Seethapathy, 2022[47]	7	0/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 1.00; CI 0.02, 48.87	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Adverse Events More Than 45 Days

An RCT of remdesivir in patients hospitalized with moderate COVID-19 symptoms reported serious adverse events at more than 45 days;[50] timing was unclear resulting in moderate/ unclear risk of bias. The differences between groups for risk of both "any serious adverse event" and all-cause mortality were not statistically significant. (Data not displayed.) Specific serious adverse events were not reported.

Antivirals: Nirmatrelvir and Ritonavir

Table 4 displays serious adverse events reported in studies of nirmatrelvir combined with ritonavir. All studies were conducted in an outpatient setting.

Adverse Events 45 Days or Less

We identified one observational study of nirmatrelvir and ritonavir compared with no treatment reporting serious adverse events within 45 days; patients were solid organ transplant recipients.[18] Intervention patients had a significantly lower risk for acute kidney injury (RR 0.13; CI 0.02, 0.90) at 30 days. The risk of bias in collection and reporting of adverse events was moderate/ unclear.

We also identified two placebo controlled trials;[37, 57] both had low risk of bias. In one trial, intervention patients had a higher risk for cerebrovascular accident (RR 3.02; CI 0.12, 73.96), but this was based on one case and not statistically significant, thus the upper limit of confidence was very high. Thus, the certainty of evidence for cerebrovascular accident is insufficient. The trials reported conflicting non statistically significant results regarding alanine aminotransferase (ALT) increase. Acute kidney injury, bleeding, and serious infection were also reported in the trials; intervention patients had reduced risk that was sometimes statistically significant.

Table 4. Serious adverse events, nirmatrelvir and ritonavir

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Hedvat, 2022[18]	30	1/28	21/75	COVID-19 therapeutics and outcomes in solid organ transplant recipients	Not reported	RR 0.13; CI 0.02, 0.90	Moderate /Unclear
	Pfizer, 2021[57]	28	0/1654	1/634	EPIC-SR	300/100 mg	RR 0.32; CI 0.01, 7.92	Low
Alanine Aminotransferase (ALT) Increase	Pfizer, 2021[37]	34	0/1109	1/1115	EPIC-HR	300/100 mg	RR 0.34; CI 0.01, 8.22	Low
	Pfizer, 2021[57]	28	1/654	0/634	EPIC-SR	300/100 mg	RR 2.91; CI 0.12, 71.26	Low
All-Cause Mortality	Pfizer, 2021[37]	34	0/1109	15/1115	EPIC-HR	300/100 mg	RR 0.03; CI 0, 0.54	Low
	Pfizer, 2021[57]	28	0/654	1/634	EPIC-SR	300/100 mg	RR 0.32; CI 0.01, 7.92	Low
Bleeding	Pfizer, 2021[37]	34	0/1109	1/1115	EPIC-HR	300/100 mg	RR 0.34; CI 0.01, 8.22	Low
Cerebro-vascular Accident	Pfizer, 2021[37]	34	1/1109	0/1115	EPIC-HR	300/100 mg	RR 3.02; CI 0.12, 73.96	Low
Infection including Sepsis	Pfizer, 2021[37]	34	12/1109	57/1115	EPIC-HR	300/100 mg	RR 0.21; CI 0.11, 0.39	Low
	Pfizer, 2021[57]	28	0/654	1/634	EPIC-SR	300/100 mg	RR 0.32; CI 0.01, 7.92	Low

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Thrombotic Event	Pfizer, 2021[37]	34	0/1109	2/1115	EPIC-HR	300/100 mg	RR 0.02; CI 0.00, 0.42	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Antivirals: Molnupiravir

Adverse Events 45 Days or Less

As displayed in Table 5, we identified four RCTs[10, 13, 14, 36] and one observational study[40] of molnupiravir that reported serious adverse events at 45 days or less. Timing ranged from 14 to 30 days; risk of bias was low in three studies, moderate/ unclear in one, and high in one. Route of administration was oral; all studies were conducted in outpatient settings. The differences between groups for risk of all-cause mortality were not statistically significant in any study. Only one study[10] reported specific serious adverse events; there were no statistically significant differences in risk of acute kidney injury, hypertension, infection, or thrombotic events. Risk of bleeding events was elevated but not statistically significant, with wide confidence intervals (RR 2.96; CI 0.12, 72.59). Certainty of evidence for bleeding events is insufficient due to lack of statistical significance, lack of precision (extremely wide confidence intervals) and no report of this adverse event in other studies of the medication.

Adverse Events More Than 45 Days

One RCT that reported at 14 days also reported serious adverse events at 318 days;[10] results are displayed in Table 5. Risk of bias was low. The risk of all-cause mortality was significantly lower in the intervention group; there were no significant differences in risk of acute kidney injury, hypertension, infection, or thrombotic events.

Table 5. Serious adverse events, molnupiravir

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Caraco, 2021[10]	14	0/701	1/701	MK-4482-002	800 mg	RR 0.33; CI 0.01, 8.17	Low
All-Cause Mortality	Painter, 2021[36]	15	0/116	0/30	Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity against SARS-CoV-2	50, 100, 200, 400, 600, 800, 1200, 1600 mg.	RR 0.26; CI 0.01, 13.09	High
	Fischer, 2022[14]	28	0/140	1/62	Phase 2a clinical trial of molnupiravir in patients with COVID-19	200 mg, 400 mg, and 800 mg	RR 0.15; CI 0.01, 3.61	Low

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Fischer, 2021[13]	28	0/55	1/62	Molnupiravir treatment for COVID-19	800 mg	RR 0.38; CI 0.02, 9.02	Low
	Radcliffe, 2022[40]	30	0/49	1/48	COVID-19 therapies in outpatient, solid organ transplant recipients	Not reported	RR 0.14; CI 0.01, 2.64	Moderate /Unclear
Bleeding	Caraco, 2021[10]	14	1/710	0/701	MK-4482-002	800 mg	RR 2.96; CI 0.12, 72.59	Low
Hypertension	Caraco, 2021[10]	14	0/701	1/701	MK-4482-002	800 mg	RR 0.33; CI 0.01, 8.17	Low
Infection Including Sepsis	Caraco, 2021[10]	14	43/710	61/701	MK-4482-002	800 mg	RR 0.70; CI 0.48, 1.01	Low
Thrombotic Event	Caraco, 2021[10]	14	1/710	1/701	MK-4482-002	800 mg	RR 0.99; CI 0.06, 15.75	Low
Acute Kidney Injury	Caraco, 2021[10]	318	0/710	1/701	MK-4482-002	800 mg	RR 0.33; CI 0.01, 8.07	Low
All-Cause Mortality	Caraco, 2021[10]	318	4/716	16/717	MK-4482-002	800 mg	RR 0.25; CI 0.08, 0.75	Low
Hypertension	Caraco, 2021[10]	318	0/710	1/701	MK-4482-002	800 mg	RR 0.33; CI 0.01, 8.07	Low
Infection including Sepsis	Caraco, 2021[10]	318	75/710	102/701	MK-4482-002	800 mg	RR 0.73; CI 0.55, 0.96	Low
Thrombotic Event	Caraco, 2021[10]	318	1/710	2/701	MK-4482-002	800 mg	RR 0.49; CI 0.04, 5.43	Low

Notes: CI = 95% confidence interval; RR = risk ratio; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

Monoclonal Antibodies: Bamlanivimab and Etesevimab Combination (Anti-Spike Protein Receptor Binding Domain of SARS-CoV-2)

Adverse Events 45 Days or Less

We identified two RCTs of bamlanivimab/ etesevimab[12, 29] that reported serious adverse events. Both had low risk of bias for adverse events collection and reporting. Data are displayed in Table 6. In an outpatient trial[12] bamlanivimab/ etesevimab patients had a significantly lower risk for all-cause mortality (RR 0.50; CI 0.0, 0.81) within 29 days from baseline. In an inpatient trial patients had elevated but not statistically significant risk of all-cause mortality;[29] the dosage administered was much higher than eventually authorized by FDA for emergency use. Elevated but not statistically significant risk for acute kidney injury, cardiac arrythmia, myocardial infarction and infection were detected in the outpatient study.[12] There is insufficient certainty

regarding risk of these adverse events due to lack of precision (very wide confidence intervals), lack of statistical significance, and lack of additional studies reporting these events.

Table 6. Serious adverse events, bamlanivimab/etesevimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Dougan, 2021[12]	29	0/513	0/776	BLAZE-1 Phase 3	700/1400 mg	RR 1.51; CI 0.03, 76.06	Low
All-Cause Mortality	Dougan, 2021[12]	29	0/513	15/776	BLAZE-1 Phase 3	700/1400 mg	RR 0.05; CI 0, 0.81	Low
	Lundgren, 2021[29]	5	1/163	0/51	ACTIV-3/ TICO	7000 mg	RR 2.78; CI 0.11, 67.74	Low
Cardiac Arrythmia	Dougan, 2021[12]	29	1/513	0/776	BLAZE-1 Phase 3	700/1400 mg	RR 4.54; CI 0.19, 111.11	Low
Myocardial Infarction	Dougan, 2021[12]	29	0/513	0/776	BLAZE-1 Phase 3	700/1400 mg	RR 1.51; CI 0.03, 76.06	Low
Infection Including Sepsis	Dougan, 2021[12]	29	3/513	1/776	BLAZE-1 Phase 3	700/1400 mg	RR 4.54; CI 0.47, 43.51	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Monoclonal Antibodies: Bebtelovimab (Anti-Spike Protein Receptor Binding Domain of SARS-CoV-2)

Adverse Events More Than 45 Days

We identified a placebo controlled trial of bebtelovimab that reported serious adverse events;[55] risk of bias for adverse events collection and reporting was low. Patients with mild or moderate symptoms were administered the medication intravenously in an outpatient setting. We abstracted data for patients who received 175 mg, as this is the dose authorized by the FDA for emergency use. There were no statistically significant differences between groups in risk for anaphylaxis or serious infection. Risk of cerebrovascular accident (RR 2.07; CI 0.08, 50.50 and thrombotic events (RR 2.07; CI 0.08, 50.50) were elevated but not statistically significant based on only one patient experiencing; there is insufficient certainty of evidence due lack of precision (very wide confidence intervals), lack of statistical significance, and lack of additional studies reporting these events. Data are displayed in Table 7.

Table 7. Serious adverse events, bebtelovimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Anaphylaxis	FDA, 2022[55]	169	0/225	0/155	BLAZE 4	175 mg	RR 0.69; CI 0.01, 34.60	Low
Infection, including Sepsis	FDA, 2022[55]	169	0/225	0/155	BLAZE 4	175 mg	RR 0.69; CI 0.01, 34.60	Low
Cerebro-vascular accident	FDA, 2022[55]	169	1/225	0/155	BLAZE 4	175 mg	RR 2.07; CI 0.08, 50.50	Low
Thrombotic Event	FDA, 2022[55]	169	1/225	0/155	BLAZE 4	175 mg	RR 2.07; CI 0.08, 50.50	Low

Notes: CI = 95% confidence interval; FDA = U.S. Food and Drug Administration; RR = risk ratio

Monoclonal Antibodies: Sotrovimab (Anti-Spike Protein Receptor Binding Domain of SARS-CoV-2)

Adverse Events 45 Days or Less

We identified one RCT[16] of sotrovimab and three observational studies[18, 38, 40] containing a sotrovimab arm that reported serious adverse events at 29 and 30 days post-intervention. All were conducted in an outpatient setting; data are displayed in Table 8. In three studies risk of all-cause mortality was much lower in the intervention group; however, the result was not statistically significant. There was elevated risk of increase in alanine transaminase (RR 3.06; CI 0.12, 74.8) and aspartate aminotransferase (RR 3.06; CI 0.12, 74.8) in the RCT[16] based on only one case of each, so neither were statistically significant. The certainty of evidence is rated insufficient due to lack of precision (very wide confidence intervals), lack of statistical significance, and lack of additional studies reporting these events.

An observational study of organ transplant recipients and showed significant reduction in risk of acute kidney injury[18] in the intervention group (RR 0.35; CI 0.14, 0.87).

Table 8. Serious adverse events, 45 days or less, sotrovimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Hedvat, 2022[18]	30	0/51	2/75	COVID-19 therapeutics and outcomes in solid organ transplant recipients	Not Reported	RR 0.35; CI 0.14, 0.87	Moderate /Unclear
Alanine Transaminase (ALT) Increase	Gupta, 2021[16]	29	1/430	0/438	COMET-ICE	500 mg	RR 3.06; CI 0.12, 74.8	Low
All-Cause Mortality	Piccicacco, 2021[38]	29	0/88	1/90	Early remdesivir and sotrovimab in highest-risk patients	500 mg	RR 0.34; CI 0.01, 8.26	Moderate /Unclear

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Radcliffe, 2022[40]	30	0/24	3/48	COVID-19 therapies in outpatient, solid organ transplant recipients	Not reported	RR 0.28; CI 0.02, 5.21	Moderate /Unclear
	Gupta, 2021[16]	29	0/430	2/438	COMET-ICE	500 mg	RR 0.20; CI 0.01, 4.23	Low
Aspartate Aminotransferase (AST) increase	Gupta, 2021[16]	29	1/430	0/438	COMET-ICE	500 mg	RR 3.06; CI 0.12, 74.8	Low

Notes: CI = 95% confidence interval; RR = risk ratio

Adverse Events More Than 45 Days

The RCT described immediately above[16] also reported serious adverse events within 168 days post intervention. There were no significant differences in risks for acute kidney injury, cardiac arrhythmia, infection, and thrombotic events. Data are displayed in Table 9.

Table 9. Serious adverse events, more than 45 days, sotrovimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Gupta, 2021[16]	168	0/523	2/526	COMET-ICE	500 mg	RR 0.20; CI 0.01, 4.18	Low
All-Cause Mortality	Gupta, 2021[16]	168	0/523	5/526	COMET-ICE	500 mg	RR 0.09; CI 0.01, 1.65	Low
Cardiac Arrythmia	Gupta, 2021[16]	168	1/523	2/526	COMET-ICE	500 mg	RR 0.50; CI 0.05, 5.53	Low
Infection Including Sepsis	Gupta, 2021[16]	168	2/523	3/526	COMET-ICE	500 mg	RR 0.67; CI 0.11, 4.00	Low
Thrombotic Event	Gupta, 2021[16]	168	1/523	2/526	COMET-ICE	500 mg	RR 0.50; CI 0.05, 5.53	Low

Notes: CI = 95% confidence interval; RR = risk ratio

Monoclonal Antibodies: Tocilizumab (IL-6 Inhibitor)

Adverse Events 45 Days or Less

Table 10 displays data for two controlled trials[44, 51] and eight observational studies[8, 17, 19, 21, 23, 24, 41, 43] of tocilizumab; they reported serious adverse events from five to 28 days post baseline and were conducted with hospital patients. Risk of bias was low in four studies, and moderate/ unclear in six studies. In three observational studies[8, 17, 21] patients on tocilizumab had a significantly lower risk for all-cause mortality (RR 0.30; CI 0.68, 0.93; RR 0.71; CI 0.61, 0.83; RR 0.40; CI 0.19, 0.85), while difference was not statistically significant in six other studies.

In one trial patients on tocilizumab had a significantly lower risk for serious infection[51] (RR 0.47; CI 0.23, 0.96) while tocilizumab patients were at significantly higher risk (RR 1.72; CI 1.04, 2.83) in an observational study of patients critically ill with COVID-19.[24] Differences in risk for serious infection events were not significant in eight other studies. There is insufficient certainty of risk due to conflicting results.

Patients on tocilizumab had a significantly higher risk of neutropenia (RR 11.2; CI 1.54, 81.67) within 28 days of baseline in one low bias trial of 243 patients[51] while a smaller observational study reported no cases.[19] Despite the large effect size, certainty is limited due to lack of precision (extremely wide confidence interval), lack of other controlled studies indicating elevated risk, and conflicting results. Elevated but not statistically significant risk for thrombotic events was found in three studies[17, 19, 23] while decreased but not statistically significant risk was found in another.[51] Certainty of risk is insufficient due to lack of statistical significance and conflicting results. Three studies found conflicting results for cerebrovascular accident;[19, 44, 51] none were statistically significant, leading to a rating of insufficient certainty for this event. Other serious adverse events reported in the studies were acute kidney injury, cardiac arrythmia, and myocardial infarction; there were no statistically significant differences in risk of these events in any study.

Table 10. Serious adverse events, tocilizumab, 45 days or less

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Kewan, 2020[23]	10	15/28	13/23	Tocilizumab for severe COVID-19	400 mg	RR 0.95; CI 0.58, 1.56	Low
	Rojas-Marte, 2020[43]	While hospit-alized	22/96	13/97	Severe COVID-19 and tocilizumab: a case-controlled study	8 mg per kg	RR 1.71; CI 0.92, 3.19	Moderate/ Unclear
	Rajendram, 2021[41]	28	18/82	27/82	Tocilizumab in Critical COVID	4-8 mg per kg	RR 0.67; CI 0.40, 1.11	Moderate/ Unclear
Alanine Aminotransferase (ALT) increase	Stone, 2020[51]	28	8/161	4/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 1.02; CI 0.32, 3.28	Low
All-Cause Mortality	Stone, 2020[51]	28	9/161	4/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 1.15; CI 0.36, 3.61	Low
	Kewan, 2020[23]	10	3/28	2/23	Tocilizumab for severe COVID-19	400 mg	RR 1.23; CI 0.22, 6.76	Low
	Biran, 2020[8]	22	102/210	256/420	Tocilizumab for COVID-19 in the intensive care unit	400 mg	RR 0.80; CI 0.68, 0.93	Low
	Gupta, 2021[17]	14	125/433	1419/3491	Early Tocilizumab for Severe COVID	Not reported	RR 0.71; CI 0.61, 0.83	Low
	Rosas, 2021[44]	28	58/295	28/143	COVACTA	8 mg per kg	RR 1; CI 0.67, 1.50	Moderate/ Unclear
	Hill, 2021[19]	14	9/43	15/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 0.63; CI 0.31, 1.28	Moderate/ Unclear
	Rojas-Marte, 2020[43]	While hospit-alized	43/96	55/97	Severe COVID-19 and tocilizumab: a case-controlled study	8 mg per kg	RR 0.79; CI 0.60, 1.05	Moderate/ Unclear

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Rajendram, 2021[41]	28	20/82	29/82	Tocilizumab in Critical COVID	4-8 mg per kg	RR 0.69; CI 0.43, 1.12	Moderate/ Unclear
	Huang, 2021[21]	28	8/55	15/41	Tocilizumab treatment in critically ill patients with COVID-19	400mg	RR 0.40; CI 0.19, 0.85	Moderate/ Unclear
Allergic reaction (not anaphylaxis)	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
Anaphylaxis	Rosas, 2021[44]	28	0/295	1/143	COVACTA	8 mg per kg	RR 0.16; CI 0.01, 3.96	Moderate/ Unclear
Aspartate aminotransferase (AST) increase	Stone, 2020[51]	28	6/161	3/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 1.02; CI 0.26, 3.97	Low
Bleeding	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
	Rosas, 2021[44]	28	13/295	5/143	COVACTA	8 mg per kg	RR 1.26; CI 0.46, 3.47	Moderate/ Unclear
Cardiac Arrythmia	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
	Gupta, 2021[17]	14	63/433	602/3491	Early Tocilizumab for Severe COVID	NA	RR 0.84; CI 0.66, 1.07	Low
Myocardial infarction	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
	Rosas, 2021[44]	28	3/295	2/143	COVACTA	8 mg per kg	RR 0.73; CI 0.12, 4.3	Moderate/ Unclear
	Hill, 2021[19]	14	0/43	0/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 1.05; CI 0.02, 51.55	Moderate/ Unclear
Hypertension	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
Hypotension	Stone, 2020[51]	28	3/161	2/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.76; CI 0.13, 4.48	Low
Infection Including Sepsis	Stone, 2020[51]	28	13/161	14/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.47; CI 0.23, 0.96	Low
	Kewan, 2020[23]	10	5/28	5/23	Tocilizumab for severe COVID-19	400 mg	RR 0.82; CI 0.27, 2.49	Low

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Kimmig, 2020[24]	5	26/54	16/57	Increased secondary infections in critically ill COVID-19 patients	400 mg	RR 1.72; CI 1.04, 2.83	Low
	Biran, 2020[8]	22	18/210	33/420	Tocilizumab for COVID-19 in the intensive care unit	400 mg	RR 1.09; CI 0.63, 1.89	Low
	Gupta, 2021[17]	14	140/433	1085/3491	Early Tocilizumab for Severe COVID	Not reported	RR 1.04; CI 0.90, 1.2	Low
	Rosas, 2021[44]	28	62/295	37/143	COVACTA	8 mg per kg	RR 0.81; CI 0.57, 1.16	Moderate/ Unclear
	Hill, 2021[19]	14	13/43	9/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 1.51; CI 0.72, 3.17	Moderate/ Unclear
	Rojas-Marte, 2020[43]	While hospitalized	12/96	23/97	Severe COVID-19 and tocilizumab: a case-controlled study	8 mg per kg	RR 0.53; CI 0.28, 1.00	Moderate/ Unclear
	Rajendram, 2021[41]	28	21/82	21/82	Tocilizumab in Critical COVID	4-8 mg per kg	RR 1.00; CI 0.59, 1.68	Moderate/ Unclear
Neutropenia	Stone, 2020[51]	28	22/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 11.20; CI 1.54, 81.67	Low
	Hill, 2021[19]	14	0/43	0/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 1.05; CI 0.02, 51.55	Moderate/ Unclear
Seizure	Stone, 2020[51]	28	0/161	1/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.17; CI 0.01, 4.15	Low
Cerebrovascular accident	Stone, 2020[51]	28	2/161	0/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 2.56; CI 0.12, 52.75	Low
	Rosas, 2021[44]	28	3/295	2/143	COVACTA	8 mg per kg	RR 0.73; CI 0.12, 4.30	Moderate/ Unclear
	Hill, 2021[19]	14	0/43	0/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 1.05; CI 0.02, 51.55	Moderate/ Unclear
Thrombotic Event	Stone, 2020[51]	28	4/161	5/82	Tocilizumab for Hospitalized Non-Critically Ill Patients	8 mg per kg	RR 0.41; CI 0.11, 1.48	Low
	Kewan, 2020[23]	10	3/28	2/23	Tocilizumab for severe COVID-19	400 mg	RR 1.23; CI 0.22, 6.76	Low

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	Gupta, 2021[17]	14	46/433	342/3491	Early Tocilizumab for Severe COVID	Not reported	RR 1.08; CI 0.81, 1.45	Low
	Hill, 2021[19]	14	5/43	2/45	Tocilizumab in hospitalized patients with COVID	400 mg	RR 2.62; CI 0.54, 12.77	Moderate/ Unclear

Notes: CI = 95% confidence interval; RR = risk ratio

Adverse Events More Than 45 Days

Three controlled trials of tocilizumab for patients hospitalized for COVID-19 reported serious adverse events at 60 days;[15, 44, 45] data are displayed in Table 11. The risk of bias was low in two studies, and moderate/unclear in the other. There was no significant difference in risk of all-cause mortality in any study. Elevated but not statistically significant risk of alanine transaminase increase was found in one trial[45] certainty of evidence for this event is insufficient. Elevated but not statistically significant risk of aspartate aminotransferase increase was found in another trial;[44] certainty of evidence for this event is also insufficient. Results for bleeding were not statistically significant and in conflicting directions. Intervention patients in one trial[44] had elevated but not statistically significant risk of cardiac arrythmia and myocardial infarction while another showed reduced risk (not statistically significant) for these serious adverse events.[45] Lack of statistical significance and conflicting results lead to a certainty rating of insufficient for these events.

Intervention patients in one trial had elevated but not statistically significant risk of infection[15] while patients in the other two[44, 45] had decreased risk that was not statistically significant. Lack of statistical significance and conflicting results lead to a certainty rating of insufficient for these events. Three studies had non-significant results for thrombotic events in opposing directions. The certainty of evidence is also insufficient for these events. Patients in one trial[44] had elevated but not statistically significant risk for neutropenia (RR 4.38; CI 0.24, 80.77); certainty of evidence was rated insufficient. Risks for acute kidney injury, hypertension, hypotension, seizure, and transfusion-associated lung injury were lower compared to control but the differences were not statistically significant.

Table 11. Serious adverse events, tocilizumab, more than 45 days

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Salama, 2021[45]	60	1/250	3/127	EMPACTA	8 mg per kg	RR 0.17; CI 0.02, 1.61	Low
	Rosas, 2021[44]	60	10/294	4/295	COVACTA	8 mg per kg	RR 1.22; CI 0.39, 3.81	Moderate /Unclear
Alanine Aminotransferase (ALT) increase	Salama, 2021[45]	60	2/250	0/127	EMPACTA	8 mg per kg	RR 2.55; CI 0.12, 52.72	Low
All-Cause Mortality	Rosas, 2021[44]	60	29/295	15/143	COVACTA	8 mg per kg	RR 0.88; CI 0.70, 1.11	Moderate /Unclear
	Salama, 2021[45]	60	116/250	64/127	EMPACTA	8 mg per kg	RR 0.98; CI 0.55, 1.76	Low
Aspartate aminotransferase (AST) increase	Rosas, 2021[44]	60	1/295	0/143	COVACTA	8 mg per kg	RR 1.46; CI 0.06, 35.60	Moderate /Unclear

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Bleeding	Rosas, 2021[44]	60	9/294	4/143	COVACTA	8 mg per kg	RR 1.09; CI 0.34, 3.49	Moderate /Unclear
	Gordon, 2021[15]	90	5/353	4/402	REMAP-CAP	8 mg per kg	RR 1.42; CI 0.39, 5.26	Low
	Salama, 2021[45]	60	0/250	1/127	EMPACTA	8 mg per kg	RR 0.17; CI 0.01, 4.14	Low
Cardiac Arrythmia	Rosas, 2021[44]	60	3/295	1/143	COVACTA	8 mg per kg	RR 1.45; CI 0.15, 13.86	Moderate /Unclear
	Salama, 2021[45]	60	1/250	1/127	EMPACTA	8 mg per kg	RR 0.51; CI 0.03, 8.06	Low
Myocardial Infarction	Rosas, 2021[44]	60	1/295	0/143	COVACTA	8 mg per kg	RR 1.46; CI 0.06, 35.60	Moderate /Unclear
	Salama, 2021[45]	60	0/250	1/127	EMPACTA	8 mg per kg	RR 0.17; CI 0.01, 4.14	Low
Hypertension	Rosas, 2021[44]	60	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate /Unclear
	Salama, 2021[45]	60	0/250	1/127	EMPACTA	8 mg per kg	RR 0.17; CI 0.01, 4.14	Low
Hypotension	Rosas, 2021[44]	60	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate /Unclear
	Salama, 2021[45]	60	0/250	1/127	EMPACTA	8 mg per kg	RR 0.17; CI 0.01, 4.14	Low
Infection including Sepsis	Rosas, 2021[44]	60	90/295	55/143	COVACTA	8 mg per kg	RR 0.79; CI 0.61, 1.04	Moderate /Unclear
	Gordon, 2021[15]	90	1/353	0/402	REMAP-CAP	8 mg per kg	RR 3.42; CI 0.14, 83.57	Low
	Salama, 2021[45]	60	13/250	8/127	EMPACTA	8 mg per kg	RR 0.83; CI 0.35, 1.94	Low
Transfusion related lung Injury	Rosas, 2021[44]	60	0/295	1/143	COVACTA	8 mg per kg	RR 0.16; CI 0.01, 3.96	Moderate /Unclear
Neutropenia	Rosas, 2021[44]	60	4/295	0/143	COVACTA	8 mg per kg	RR 4.38; CI 0.24, 80.77	Moderate /Unclear
Seizure	Rosas, 2021[44]	60	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate /Unclear
Cerebro-vascular accident	Salama, 2021[45]	60	2/250	1/127	EMPACTA	8 mg per kg	RR 1.02; CI 0.09, 11.1	Low
Thrombotic Event	Rosas, 2021[44]	60	6/295	2/143	COVACTA	8 mg per kg	RR 1.45; CI 0.3, 7.12	Moderate /Unclear
	Gordon, 2021[15]	90	0/353	7/402	REMAP-CAP	8 mg per kg	RR 0.08; CI 0, 1.32	Low
	Salama, 2021[45]	60	4/250	1/127	EMPACTA	8 mg per kg	RR 2.03; CI 0.23, 17.99	Low

Notes: CI = 95% confidence interval; RR = risk ratio

Monoclonal Antibodies: Casirivimab and Imdevimab Combination (Anti-Spike Protein Receptor Binding Domain of SARS-CoV-2)

Table 12 displays serious adverse events reported in studies of casirivimab and imdevimab.

Adverse Events 45 Days or Less

We identified an observational study of pregnant patients[26] and two controlled trials.[33, 56] All were conducted in an outpatient setting. The results for pregnant patients are discussed in the section on patients with pre-existing conditions. The trials reported serious adverse events at 28

or 29 days, with low risk of bias. Intervention patients had increased risk of myocardial infarction and serious infection in one trial[33] but the results were not statistically significant. Certainty of evidence for these events is insufficient due to lack of report during the first month in other studies and lack of statistical significance.

Adverse Events More Than 45 Days

Three controlled outpatient trials of casirivimab and imdevimab reported serious adverse events within more than 45 days.[33, 39, 54] Events were reported at 163 and 226 days; risk of bias was low in each study. Serious adverse events reported were acute kidney injury, anaphylaxis, bleeding, cerebrovascular accident, myocardial infarction, infection, seizure, hypertension, hypotension, neutropenia, and thrombotic events. Although there was a non-statistically significant elevated risk for acute kidney injury, all-cause mortality, bleeding events, and myocardial infarction in one trial[33] the other trials reported non-statistically significant reduced risk, leading to a certainty rating of insufficient.

Table 12. Serious adverse events, casirivimab and imdevimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
All-Cause Mortality	O'Brien, 2021[33]	28	2/1311	2/1306	R10933-10987-COV-2069	1200 mg	RR 1.00; CI 0.14, 7.06	Low
Myocardial Infarction	O'Brien, 2021[33]	28	1/1311	0/1306	R10933-10987-COV-2069	1200 mg	RR 2.99; CI 0.12, 73.29	Low
Hypertension	O'Brien, 2021[33]	28	0/1311	1/1306	R10933-10987-COV-2069	1200 mg	RR 0.33; CI 0.01, 8.14	Low
	Weinreich, 2021[56]	29	0/176	1/93	REGN-COV2	2.4 g and 8.0 g	RR 0.18; CI 0.01, 4.30	Low
Infection Including Sepsis	O'Brien, 2021[33]	28	9/1311	4/1306	R10933-10987-COV-2069	1200 mg	RR 2.24; CI 0.69, 7.26	Low
Acute Kidney Injury	O'Brien, 2021[33]	226	1/1627	0/1643	R10933-10987-COV-2069	1200 mg	RR 3.03; CI 0.12, 74.31	Low
	FDA, 2020[54]	169	1/246	4/247	R10933-10987-COV-2066	1200 mg	RR 0.25; CI 0.03, 2.23	Low
All-Cause Mortality	Portal-Celhay, 2021[39]	169	0/325	0/164	R10933-10987-COV-20145	600 mg	RR 0.51; CI 0.01, 25.39	Low
	O'Brien, 2021[33]	226	3/1627	2/1643	R10933-10987-COV-2069	1200 mg	RR 1.51; CI 0.25, 9.05	Low
	FDA, 2020[54]	169	24/246	42/247	R10933-10987-COV-2066	1200 mg	RR 0.57; CI 0.36, 0.92	Low
Anaphylaxis	FDA, 2020[54]	169	0/246	0/247	R10933-10987-COV-2066	1200 mg	RR 1; CI 0.02, 50.40	Low
Bleeding	O'Brien, 2021[33]	226	1/1627	0/1643	R10933-10987-COV-2069	1200 mg	RR 3.03; CI 0.12, 74.31	Low

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
	FDA, 2020[54]	169	0/246	3/247	R10933-10987-COV-2066	1200 mg	RR 0.14; CI 0.01, 2.76	Low
Myocardial Infarction	O'Brien, 2021[33]	226	2/1627	0/1643	R10933-10987-COV-2069	1200 mg	RR 5.05; CI 0.24, 105.09	Low
	FDA, 2020[54]	169	0/246	1/247	R10933-10987-COV-2066	1200 mg	RR 0.33; CI 0.01, 8.18	Low
Hypertension	O'Brien, 2021[33]	226	0/1627	2/1643	R10933-10987-COV-2069	1200 mg	RR 0.20; CI 0.01, 4.2	Low
	FDA, 2020[54]	169	0/246	2/247	R10933-10987-COV-2066	1200 mg	RR 0.20; CI 0.01, 4.16	Low
Hypotension	FDA, 2020[54]	169	0/246	2/247	R10933-10987-COV-2066	1200 mg	RR 0.2; CI 0.01, 4.16	Low
Infection Including Sepsis	Portal-Celhay, 2021[39]	169	0/985	1/164	R10933-10987-COV-20145	600 mg	RR 0.06; CI 0, 1.36	Low
	O'Brien, 2021[33]	226	10/1627	13/1643	R10933-10987-COV-2069	1200 mg	RR 0.78; CI 0.34, 1.77	Low
	FDA, 2020[54]	169	1/246	0/247	R10933-10987-COV-2066	1200 mg	RR 3.01; CI 0.12, 73.58	Low
Neutropenia	FDA, 2020[54]	169	0/246	0/247	R10933-10987-COV-2066	1200 mg	RR 1.00; CI 0.02, 50.4	Low
Seizure	FDA, 2020[54]	169	0/246	1/247	R10933-10987-COV-2066	1200 mg	RR 0.33; CI 0.01, 8.18	Low
Cerebro- vascular accident	FDA, 2020[54]	169	0/246	1/247	R10933-10987-COV-2066	1200 mg	RR 0.33; CI 0.01, 8.18	Low
Thrombotic Event	FDA, 2020[54]	169	0/246	2/247	R10933-10987-COV-2066	1200 mg	RR 0.20; CI 0.01, 4.16	Low

Notes: CI = 95% confidence interval; RR = risk ratio

Monoclonal Antibodies: Tixagevimab and Cilgavimab Combination (Anti-Spike Protein Receptor Binding Domain of SARS-CoV-2)

Adverse Events More Than 45 Days

We identified one outpatient RCT of tixagevimab and cilgavimab that reported serious adverse events (see Table 13).[27] Investigators followed up at 457 days; this long observation period was designed to reflect five half-lives of the medication. Risk of bias was low. Serious adverse events reported were acute kidney injury, bleeding, headache, myocardial infarction, hypertension, joint pain, muscle pain, infection, cerebrovascular accident, and thrombotic events. There were no statistically significant differences between groups in risk for any of these events. However, there was a non-statistically significant trend toward elevated risk of each of these serious events except bleeding and infection. Certainty of evidence is insufficient due to lack of report in other studies, lack of precision (the upper limits of confidence were very high) and lack of statistical significance.

Table 13. Serious adverse events, tixagevimab and cilgavimab

Serious Adverse Event	Study ID	Days	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Levin, 2022[27]	457	2/3461	0/1736	PROVENT	300 mg	RR 2.51; CI 0.12, 52.23	Low
All-Cause Mortality	Levin, 2022[27]	457	4/3461	4/1736	PROVENT	300 mg	RR 0.50; CI 0.13, 2.00	Low
Bleeding	Levin, 2022[27]	457	2/3461	1/1736	PROVENT	300 mg	RR 1.00; CI 0.09, 11.06	Low
Headache	Levin, 2022[27]	457	1/3461	0/1736	PROVENT	300 mg	RR 1.51; CI 0.06, 36.93	Low
Myocardial infarction	Levin, 2022[27]	457	3/3461	0/1736	PROVENT	300 mg	RR 3.51; CI 0.18, 67.96	Low
Hypertension	Levin, 2022[27]	457	2/3461	0/1736	PROVENT	300 mg	RR 2.51; CI 0.12, 52.23	Low
Infection, including Sepsis	Levin, 2022[27]	457	10/3461	5/1736	PROVENT	300 mg	RR 1.00; CI 0.34, 2.93	Low
Joint Pain	Levin, 2022[27]	457	1/3461	0/1736	PROVENT	300 mg	RR 1.51; CI 0.06, 36.93	Low
Muscle Pain	Levin, 2022[27]	457	2/3461	0/1736	PROVENT	300 mg	RR 2.51; CI 0.12, 52.23	Low
Cerebrovascular accident	Levin, 2022[27]	457	1/3461	0/1736	PROVENT	300 mg	RR 1.51; CI 0.06, 36.93	Low
Thrombotic Event	Levin, 2022[27]	457	1/3461	0/1736	PROVENT	300 mg	RR 1.51; CI 0.06, 36.93	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Anakinra (Interleukin-1 Receptor Antagonist)

We identified no studies of anakinra for COVID-19 conducted in the United States or that included U.S. patients that met our inclusion criteria (comparison group required). Authorization for emergency use was based on studies conducted overseas.

Patients With Pre-existing Conditions or Specific COVID-19 Symptomology

COVID-19 Pneumonia

We identified an RCT of convalescent plasma[4] and an RCT of tocilizumab[44] where all subjects were hospitalized with COVID-19 related pneumonia. Other studies included patients with pneumonia but did not stratify adverse events for this specific subset of patients. The risk of bias for adverse events collection and reporting was moderate/unclear in both. Both studies reported adverse events at two months; the tocilizumab trial also reported at four weeks. As displayed in Tables 14 and 15, serious adverse events reported in the convalescent plasma trial were all cause mortality, bleeding events, cardiac arrythmia, acute central nervous system ischemia, headache, hypotension, syncope, and thrombotic events, while the tocilizumab trial reported acute kidney injury, anaphylaxis, transfusion associated lung injury, cardiac arrythmia, aspartate aminotransferase increase, bleeding, infection, neutropenia, hypoglycemia, hypertension, hypotension, thrombotic events, and myocardial infarction. There were no statistically significant differences between intervention and control groups in risk for any of those events. Within 60 days, risk of bleeding events, cardia arrythmia, acute central nervous

system ischemia, headache, and thrombotic events were elevated but not statistically significant in the plasma trial leading to insufficient certainty of evidence. Within 60 days, risk of acute kidney injury, cardiac arrythmia, myocardial infarction and thrombotic events were elevated but not statistically significant in the tocilizumab trial leading to insufficient certainty of evidence.

Although not statistically significant, the tocilizumab trial investigators made note of possible risk for neutropenia (RR 4.38; CI 0.24, 80.77) within 60 days of administration in the FDA submission; this serious adverse event occurred in four of 295 (1.4%) of patients in the tocilizumab arm with no occurrences among 143 patients in the placebo arm. Again, certainty is insufficient due to lack of report in other studies, lack of statistical significance, and lack of precision (extremely wide confidence intervals).

Eight intervention patients and thirteen usual care patients in the convalescent plasma trial experienced dyspnea or respiratory distress (not displayed); the authors considered this event related to COVID-19 – related pneumonia rather than any treatment.

Table 14. Serious adverse events, 45 days or less, patients hospitalized with COVID pneumonia

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
All-Cause Mortality	Rosas, 2021[44]	28	Tocilizumab	58/295	28/143	COVACTA	8 mg per kg	RR 1.00; CI 0.67, 1.5	Moderate/ Unclear
Anaphylaxis	Rosas, 2021[44]	28	Tocilizumab	0/295	1/143	COVACTA	8 mg per kg	RR 0.16; CI 0.01, 3.96	Moderate/ Unclear
Bleeding	Rosas, 2021[44]	28	Tocilizumab	13/295	5/143	COVACTA	8 mg per kg	RR 1.26; CI 0.46, 3.47	Moderate/ Unclear
Myocardial Infarction	Rosas, 2021[44]	28	Tocilizumab	3/295	2/143	COVACTA	8 mg per kg	RR 0.73; CI 0.12, 4.30	Moderate/ Unclear
Infection Including Sepsis	Rosas, 2021[44]	28	Tocilizumab	62/295	37/143	COVACTA	8 mg per kg	RR 0.81; CI 0.57, 1.16	Moderate/ Unclear
Cerebrovascular Accident	Rosas, 2021[44]	28	Tocilizumab	3/295	2/143	COVACTA	8 mg per kg	RR 0.73; CI 0.12, 4.3	Moderate/ Unclear

Notes: CI = 95% confidence interval; RR = risk ratio

Table 15. Serious adverse events, more than 45 days, patients hospitalized with COVID pneumonia

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Rosas, 2021[44]	60	Tocilizumab	10/294	4/143	COVACTA	8 mg per kg	RR 1.22; CI 0.39, 3.81	Moderate/ Unclear
All-Cause Mortality	Bar, 2021[4]	60	Convalescent Plasma	3/40	11/39	PennCCP2	2 units	RR 0.27; CI 0.08, 0.88	Moderate/ Unclear
	Rosas, 2021[44]	60	Tocilizumab	116/295	64/143	COVACTA	8 mg per kg	RR 0.88; CI 0.70, 1.11	Moderate/ Unclear
Aspartate aAinotransferase (AST) increase	Rosas, 2021[44]	60	Tocilizumab	1/295	0/143	COVACTA	8 mg per kg	RR 1.46; CI 0.06, 35.60	Moderate/ Unclear

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Bleeding	Bar, 2021[4]	60	Convalescent Plasma	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate/ Unclear
	Rosas, 2021[44]	60	Tocilizumab	9/294	4/143	COVACTA	8 mg per kg	RR 1.09; CI 0.34, 3.49	Moderate/ Unclear
Cardiac Arrythmia	Bar, 2021[4]	60	Convalescent Plasma	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate/ Unclear
	Rosas, 2021[44]	60	Tocilizumab	3/295	1/143	COVACTA	8 mg per kg	RR 1.45; CI 0.15, 13.86	Moderate/ Unclear
CNS Ischemia (acute)	Bar, 2021[4]	60	Convalescent Plasma	2/40	1/39	PennCCP2	2 units	RR: 1.90; CI 0.18, 20.20	Moderate/ Unclear
Headache	Bar, 2021[4]	60	Convalescent Plasma	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate/ Unclear
Myocardial Infarction	Rosas, 2021[44]	60	Tocilizumab	1/295	0/143	COVACTA	8 mg per kg	RR 1.46; CI 0.06, 35.60	Moderate/ Unclear
Hypertension	Rosas, 2021[44]	60	Tocilizumab	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate/ Unclear
Hypoglycemia	Bar, 2021[4]	60	Convalescent Plasma	0/40	1/39	PennCCP2	2 units	RR:0.32; CI 0.01, 7.95	Moderate/ Unclear
Hypotension	Bar, 2021[4]	60	Convalescent Plasma	0/40	2/39	PennCCP2	2 units	RR 0.20; CI 0.01, 3.94	Moderate/ Unclear
	Rosas, 2021[44]	60	Tocilizumab	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate/ Unclear
Infection including Sepsis	Rosas, 2021[44]	60	Tocilizumab	90/295	55/143	COVACTA	8 mg per kg	RR 0.79; CI 0.61, 1.04	Moderate/ Unclear
Transfusion associated lung injury	Rosas, 2021[44]	60	Tocilizumab	0/295	1/143	COVACTA	8 mg per kg	RR 0.16; CI 0.01, 3.96	Moderate/ Unclear
Neutropenia	Rosas, 2021[44]	60	Tocilizumab	4/295	0/143	COVACTA	8 mg per kg	RR 4.38; CI 0.24, 80.77	Moderate/ Unclear
Seizure	Rosas, 2021[44]	60	Tocilizumab	1/295	1/143	COVACTA	8 mg per kg	RR 0.48; CI 0.03, 7.69	Moderate/ Unclear
Syncope	Bar, 2021[4]	60	Convalescent Plasma	1/40	0/39	PennCCP2	2 units	RR 2.93; CI 0.12, 69.74	Moderate/ Unclear
Thrombotic Event	Bar, 2021[4]	60	Convalescent Plasma	2/40	1/39	PennCCP2	2 units	RR 1.95; CI 0.18, 20.64	Moderate/ Unclear
	Rosas, 2021[44]	60	Tocilizumab	6/295	1/143	COVACTA	8 mg per kg	RR 1.45; CI 0.30, 7.12	Moderate/ Unclear

Notes: CI = 95% confidence interval; RR = risk ratio

Respiratory or Cardiovascular Organ Support in the Intensive Care Unit

We identified an RCT of tocilizumab administered after COVID-19 patients started organ support in the intensive care unit.[15, 63] Patients were on extracorporeal membrane oxygenation (ECMO) for respiratory support or intravenous infusion of a vasopressor or inotrope for cardiovascular support. (Other studies included patients on ECMO but did not stratify adverse events results.) Data are displayed in Table 16. The risk of bias for adverse events collection and reporting was low. Within 90 days, there were no statistically significant risk differences between intervention and usual care for bleeding events and thrombotic events. The risk of infection was elevated (RR 3.42; CI 0.14, 83.57) but this was not statistically significant and based on only one of the 353 intervention patients and none of the 402 usual care patients experiencing infection. The certainty of evidence is insufficient due to lack of other studies providing results specifically for organ support patients, lack of statistical significance, and imprecision (very wide confidence intervals). The risk of bleeding events was elevated but not statistically significant (RR 1.42; CI 0.39, 5.26); certainty of evidence was limited due to lack of additional studies providing stratified data for this specific population.

Table 16. Serious adverse events, patients with COVID-19 on organ support in the intensive care unit

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Bleeding	Gordon, 2021[15]	90	Tocilizumab	5/353	4/402	REMAP-CAP	8 mg per kg	RR 1.42; CI 0.39, 5.26	Low
Infection including Sepsis	Gordon, 2021[15]	90	Tocilizumab	1/353	0/402	REMAP-CAP	8 mg per kg	RR 3.42; CI 0.14, 83.57	Low
Thrombotic Event	Gordon, 2021[15]	90	Tocilizumab	0/353	7/402	REMAP-CAP	8 mg per kg	RR 0.08; CI 0, 1.32	Low

Notes: CI = 95% confidence interval; RR = risk ratio

Hematologic Cancers

We identified a propensity score matched observational study of convalescent plasma for patients with hematologic cancers hospitalized with COVID-19.[53] The risk of bias for adverse events collection and reporting was moderate/unclear. Data are displayed in Table 17. Within 30 days, convalescent plasma patients had a significantly lower risk for all-cause mortality (RR 0.54; CI 0.35, 0.83), but a significantly higher risk for serious bleeding events (RR 1.96; CI 1.14, 3.36) and infection (RR 1.79; CI 1.41, 2.26) than patients receiving usual care. The risk of certainty was rated moderate due to statistical significance and precision. Other serious adverse events reported were cardiac arrythmia, myocardial infarction, and thrombotic events; there were no statistically significant differences in risk. Congestive heart failure was diagnosed in ten of the 143 plasma patients and less than five of the 143 matched patients who received usual care; unfortunately, the risk ratio was not calculable because the authors did not report patient numbers when less than five experienced an adverse event. Risk would be elevated (RR 2.50; CI 0.79, 7.96) in the most conservative scenario, with four usual care patients diagnosed with congestive heart failure. Certainty of evidence is limited due to lack of statistical significance

and risk of bias due to lack of reporting the exact number of patients experiencing the event in the control group.

Table 17. Serious adverse events, patients with hematologic cancers hospitalized with COVID-19

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
Acute Kidney Injury	Thompson, 2021[53]	30	Convalescent Plasma	37/143	222/823	Convalescent Plasma and hematologic cancers	Not reported	RR 0.96; CI 0.71, 1.29	Moderate /Unclear
All-Cause Mortality	Thompson, 2021[53]	30	Convalescent Plasma	19/143	204/823	Convalescent Plasma and hematologic cancers	Not reported	RR 0.54; CI 0.35, 0.83	Moderate /Unclear
Bleeding	Thompson, 2021[53]	30	Convalescent Plasma	16/143	47/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.96; CI 1.14, 3.36	Moderate /Unclear
Cardiac Arrythmia	Thompson, 2021[53]	30	Convalescent Plasma	5/143	27/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.07; CI 0.42, 2.72	Moderate /Unclear
Myocardial Infarction	Thompson, 2021[53]	30	Convalescent Plasma	5/143	26/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.11; CI 0.43, 2.83	Moderate /Unclear
Infection Including Sepsis	Thompson, 2021[53]	30	Convalescent Plasma	58/143	187/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.79; CI 1.41, 2.26	Moderate /Unclear
Thromboti c Event	Thompson, 2021[53]	30	Convalescent Plasma	15/143	63/823	Convalescent Plasma and hematologic cancers	Not reported	RR 1.37; CI 0.80, 2.34	Moderate /Unclear

Notes: CI = 95% confidence interval; RR = risk ratio

Severe Kidney Disease

We identified a propensity score matched cohort study of patients with severe kidney disease who were hospitalized for COVID-19; patients received remdesivir or no treatment.[47] The risk of bias for adverse events collection and reporting was low. Data are displayed in Table 18. At one week, there were no statistically significant differences between groups in risk for aspartate aminotransferase increase, cardiac arrythmia, or transfusion associated lung injury. The risk of alanine aminotransferase increase and seizure were elevated for remdesivir patients but neither risk was statistically significant and the upper confidence limits were very high, leading to insufficient certainty.

Table 18. Serious adverse events, patients with severe kidney disease hospitalized with COVID-19

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
All-Cause Mortality	Seethapathy, 2022[47]	7	Remdesivir	6/31	7/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.86; CI 0.32, 2.26	Low
Alanine Aminotransferase (ALT) increase	Seethapathy, 2022[47]	7	Remdesivir	1/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 3.00; CI 0.13, 70.92	Low
Aspartate Aminotransferase (AST) increase	Seethapathy, 2022[47]	7	Remdesivir	1/31	2/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.50; CI 0.05, 5.23	Low
Cardiac Arrythmia	Seethapathy, 2022[47]	7	Remdesivir	16/31	21/31	Remdesivir in patients with severe kidney disease	Not reported	RR 0.76; CI 0.50, 1.16	Low
Transfusion associated lung injury	Seethapathy, 2022[47]	7	Remdesivir	0/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 1.00; CI 0.02, 48.87	Low
Seizure	Seethapathy, 2022[47]	7	Remdesivir	1/31	0/31	Remdesivir in patients with severe kidney disease	Not reported	RR 3.00; CI 0.13, 70.92	Low

Notes: CI = 95% confidence interval, RR = risk ratio

Organ Transplant

We identified a retrospective cohort study comparing molnupiravir, sotrovimab, and no treatment for COVID-19 outpatients who had undergone solid organ transplant.[40] Two-thirds were kidney transplant recipients. The risk of bias for adverse events collection and reporting was moderate/unclear. Risk for "any serious adverse event" at 30 days was not statistically significant (data not displayed). Specific serious adverse events were not reported.

Pregnancy

We identified two cohort studies of pregnant patients. Data are displayed in Table 19. One compared those who received no treatment for COVID-19 with those who received casirivimab and imdevimab primarily in the outpatient setting.[26] Serious adverse events reported were anaphylaxis, neonatal death, preterm birth, and infection. There were no statistically significant differences between groups in risk for any of these rare events. Timing of adverse events was unclear, resulting in moderate/unclear risk of bias for adverse events collection and reporting. The other observational study[32] compared remdesivir with usual care (antibiotics +/- glucocorticoids) for pregant patients hospitalized with moderate symptoms of COVID-19 (data not displayed). Eight of 24 women on remdesivir experienced elevated transaminases during treatment; in 3 of 24, incidental oligohydramnios (too little amniotic fluid around a fetus) was observed within five days of finishing remdesivir. None of these adverse events led to discontinuation of treatment, implying that investigators felt the events were unrelated to the medication (in the case of oligohydramnios) or not serious. The certainty of evidence is insufficient for these events, as no other studies reported these events in pregnant women, investigators did not specifically mention whether these events occurred in the usual care group, and they did not rate severity.

In addition, two of seven pregnant women enrolled in a Phase 2 dose-ranging outpatient study of casirivimab and imdevimab[39] experienced miscarriage (not displayed). Both received a higher dose than the 600 mg casirivimab and 600 mg imdevimab combination eventually authorized ed for emergency use. No patients receiving placebo experienced miscarriage. The authors did not report the number of pregnant people in each arm, so risk ratio calculation was not possible. Both miscarriages occurred during the first trimester and were considered unrelated to the study drug or COVID-19 by the investigators. Risk of bias was unclear.

Table 19. Serious adverse events, pregnant patients

Serious Adverse Event	Study ID	Days	Intervention	n/N Intervention	n/N Control	Study Name	Dose	Risk Ratio	Risk of Bias
All-Cause Mortality	Levey, 2022[26]	Not reported	Casirivimab and imdevimab	0/36	0/50	Pregnant patients & REGEN-COV	Not reported	RR 1.38; CI 0.03, 67.89	Moderate /Unclear
Anaphylaxis	Levey, 2022[26]	Not reported	Casirivimab and imdevimab	0/36	0/50	Pregnant patients & REGEN-COV	Not reported	RR 1.38; CI 0.03, 67.89	Moderate /Unclear
Neonatal Death	Levey, 2022[26]	Not reported	Casirivimab and imdevimab	1/24	2/47	Pregnant patients & REGEN-COV	Not reported	RR 0.98; CI 0.09, 10.26	Moderate /Unclear
Preterm Birth	Levey, 2022[26]	Not reported	Casirivimab and imdevimab	7/24	14/47	Pregnant patients & REGEN-COV	Not reported	RR 0.98; CI 0.46, 2.10	Moderate /Unclear

Notes: CI = 95% confidence interval; RR = risk ratio

Conclusions

This rapid review found few associations between emergency use authorized pharmaceutical interventions for COVID-19 treatment and serious adverse events.

The associations found included increased risk of infection in one trial of patients with hematologic cancers who received convalescent plasma and in the same trial an increased risk of serious bleeding events. Certainty of evidence was rated moderate. Both increased risk of infection and bleeding events might be expected given the patient population. Adverse events previously reported as associated with convalescent plasma include allergic reactions, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[72] Although those events were reported in the controlled studies we identified, there was no evidence of increased risk. There was limited certainty of the evidence from four studies that convalescent plasma may be associated with serious thrombotic events among patients hospitalized for COVID-19; this is consistent with the product label which notes blood clotting as a potential adverse event.

Our rapid review found no evidence of an association of SARS-CoV-2 antiviral treatment with serious adverse events. This is consistent with a prior network meta-analysis of antiviral agents for COVID-19 treatment which found no increased risk of adverse events when compared with placebo.[73]

While infusion-related reactions ranging from mild to severe are common among recipients of monoclonal antibodies,[74] we found no evidence of elevated risk of these reactions when compared with placebo infusions. The studies of SARS-CoV-2 spike protein receptor binding antibodies (bamlanivimab/etesevimab, bebtelovimab, sotrovimab, casirivimab/ imdevimab, and tixagevimab/cilgavimab) found no association with any serious adverse events. We identified evidence of limited certainty that tocilizumab, an IL-6 inhibitor, may be associated with elevated risk of neutropenia, a previously described adverse effect[75] noted on the product label, and an increased risk of bleeding events. There is also limited certainty that COVID-19 patients on ECMO or intravenous infusion of a vasopressor or inotrope for cardiovascular support in the intensive care unit are at elevated risk of bleeding events within 90 days, based on another study. The tocilizumab label notes the potential for gastrointestinal perforation and thrombocytopenia (reduced platelets which help blood clot) which may be related to our findings on bleeding.

No studies of anakinra for COVID-19 met our inclusion criteria of involving US patients. Due to the prothrombotic effects of anakinra, it was hypothesized that there might be an increase in thrombotic events in patients with COVID-19; however, a meta-analysis of non-US studies[76] found no significant increased risk compared to control.

A serious limitation of this review is the inclusion requirement that studies have at least one US site. Inclusion of studies conducted in other regions could potentially change or strengthen the findings. The certainty of evidence for the findings described above could increase if additional studies showed elevated risk but could decrease if those studies showed no elevated risk. Studies from other regions might also report elevated risks for additional serious adverse events. We also limited to studies with a control group to detect elevated rates of events. This excluded uncontrolled studies that may provide signals that should be investigated further. Another limitation is that although most studies included patients with a number of conditions such as chronic obstructive pulmonary disease, obesity, cardiovascular disease, diabetes, chronic

kidney disease, and cancer, few were limited to patients with a specific pre-existing condition or reported adverse events data stratified by specific pre-existing conditions.

In conclusion, there were no associations of increased risk of serious adverse events of high certainty. The lack of statistically significant association of most serious adverse events with treatments for COVID-19, when compared with no treatment, placebo, or usual care, supports the hypothesis that such events may be the result of COVID-19 itself. Most patients in the hospital studies had multiple pre-existing chronic conditions; these conditions are known to be associated with multiple adverse clinical outcomes.[77]

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Disclaimers

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program is developing a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

The AHRQ EPC Program recognizes that people are struggling with urgent questions on how to address the COVID-19 pandemic. To shorten timelines, reviewers make strategic choices about which review processes to abridge. The adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used and the resulting limitations of the evidence synthesis are extremely important.

Given the rapidly evolving field, the AHRQ EPC Program will update these reviews on a regular basis to keep the medical community and public up to date as more studies are published. If you have comments or have unpublished data to share related to this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov and will be considered in the next version of the report.

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Appendixes

Appendix A. Methods

Key Questions

This Rapid Review addresses the Key Question:

- What are the serious adverse effects or events directly caused by the use or administration of medications authorized by the Food and Drug Administration (FDA) to prevent or treat COVID-19 infection?
- In what timeframe are the adverse effects or events expected to occur (considering elimination half-life, etc.)?

Criteria for Inclusion/Exclusion of Studies in the Review

The inclusion and exclusion criteria for studies, per the Federal Request for Task Order, are listed below.

Table A.1. Eligibility criteria

Domain	Inclusion Criteria	Exclusion Criteria
Population	Pediatric and adult patients with a confirmed SARS-CoV-2 infection (positive Nucleic Acid Amplification Test) and / or symptoms consistent with COVID-19, or in close contact with someone with confirmed COVID-19, requiring medication to prevent or treat COVID-19	Animal studies
Interventions	1. COVID-19 convalescent plasma 2. Anti-viral medications • Remdesivir • Nirmatrelvir and ritonavir • Molnupiravir 3. Monoclonal antibodies • Tocilizumab • Bamlanivimab / Etesevimab • Bebtelovimab • Sotrovimab • Casirivimab and Imdevimab • Tixagevimab and cilgavimab 4. Interleukin Antagonist: Anakinra	Vaccines Use of intervention for reason other than prevention or treatment of COVID-19
Comparators	Placebo, treatment as usual, no treatment	Active comparators
Outcomes	• Serious physical injury that warrants hospitalization (whether or not the person was actually hospitalized) or injuries that led to a significant loss of function or disability • Mortality	Non-major and non-serious adverse events, effectiveness outcomes
Timing	No restriction	Not applicable
Study Design	Randomized controlled trials, controlled clinical trials, observational studies with a comparison group, case-control studies	Uncontrolled studies, case series, case reports
Setting	Inpatient and outpatient studies conducted in the US or studies that include US patients	Conducted solely outside the US

Domain	Inclusion Criteria	Exclusion Criteria
Other Limiters	English language publications	Studies reported in abbreviated format only (e.g., conference abstract rather than in a journal publication) will be excluded, studies only reported in non-English publications

Searching for the Evidence: Strategies for Identification of Relevant Studies

To explore adverse events potentially associated with the included pharmaceuticals, we reviewed the product labels and conducted a search on causality of adverse events associated with the interventions, regardless of medical indication. We retrieved the Infectious Disease Society of America guidelines for COVID-19 treatment for context.

In August 2023 we searched the research databases PubMed (including LitCOVID) and the Cochrane Database of Systematic Reviews to identify existing research studies and syntheses on the topic. Identified systematic reviews were screened for relevancy and reference mined for studies of the interventions. The following search terms were used:

- COVID-19 Treatment (PubMed Filter)
- AND convalescent plasma OR Anti-viral medications OR Remdesivir OR Veklury OR (Nirmatrelvir AND ritonavir) OR Paxlovid OR (Tixagevimab AND cilgavimab) OR Evusheld OR Molnupiravir OR Lagevrio OR Monoclonal antibodies OR Tocilizumab OR (Bamlanivimab AND Etesevimab) OR Bebtelovimab OR Sotrovimab OR (Casirivimab AND Imdevimab) OR REGEN-COV OR Interleukin antagonists OR Anakinra OR Kineret
- NOT editorial[Publication Type] OR comment[Publication Type] OR case reports[Publication Type]
- Language: English
- No date limitation

The searches were updated on October 12, 2023. We also downloaded submissions from the FDA database for interventions that received Emergency Use Authorization and reference mined the international COVID Network Meta-analysis database. Finally, we conducted a search of clinicaltrials.gov.

We used a form containing the eligibility criteria listed above in Table A.1 to screen publications for inclusion. To reduce reviewer errors and bias, all citations and abstracts were reviewed by the project leader.

Each full-text document was independently reviewed for eligibility by two literature reviewers. We maintained a record of studies excluded at the full-text level with reasons for exclusion. Documents reporting on the same study were consolidated into one study record.

Data Abstraction and Data Management

A data abstraction form was created in DistillerSR, an online program for systematic reviews. Forms include detailed guidance to support reviewers to aid both reproducibility and standardization of data collection. One researcher abstracted the data and the project leader checked for accuracy and completeness. Forms were pilot tested with a sample of included articles to ensure that all relevant data elements were captured, and that ambiguity was avoided.

The following data were abstracted:

- Study identifier (author) and publication year
- Study design
  - Randomized Controlled Trial (RCT)
  - Controlled Clinical Trial
  - Retrospective cohort
  - Prospective cohort
  - Case control
  - Other, specify _____
- Setting
  - Inpatient
  - Outpatient
- Interventions
  - Intervention category (Convalescent plasma, Anti-viral, Monoclonal antibodies, Interleukin Antagonist)
  - Specific intervention
  - Dosage
- Comparator
  - Placebo
  - No treatment
  - Usual care
  - Other, specify _____
- Population
  - Pregnant women
  - Elderly (65 years and older)
  - Children & adolescents (up to 18 years old)
  - Co-morbidities
  - COVID-19 severity level (If reported, World Health Organization 8-point scale ranging from asymptomatic (1) to death (8)
- Adverse events
  - Common Terminology Criteria for Adverse Events (CTCAE) severity category[71]
  - CTCAE event name
  - Timing (days since the beginning of treatment)
  - Timing category
    - Less than or equal to 45 days
    - Greater than 45 days
  - Number of participants in each group experiencing each serious adverse event.

For applicability, we abstracted data for the dosage authorized by the FDA when reported. Final abstracted data will be uploaded to SRDR+.

Assessment of Methodological Risk of Bias of Individual Studies

Several study designs were eligible for the review; the evaluation criteria to assess the risk of bias in collection and reporting of adverse events can be applied across all types. We abstracted two items, based on the McHarm instrument. First, if collection was passive (i.e., outpatients contacted researchers if they experienced an event rather than the researchers actively contacting each patient and asking about a predetermined list of events) rather than active, we rated the

study as high risk of bias for collection; if collection/ monitoring methods were not described, we rated as "unclear/moderate. Studies that actively monitored patients were rated as low risk of bias. Secondly, if the authors reported the proportion of patients experiencing each event (e.g., rather than the total number of events) we rated reporting as low risk of bias. If most adverse events were reported this way but some were not, we rated this item as "unclear/moderate" risk of bias. For a study to be rated "overall" as low risk, the study must be rated as low risk on both items.

We incorporated the risk of bias ratings into the rating of evidence certainty.

Data Synthesis

Adverse events data were converted to rates for intervention and comparison groups; rates were used to compute risk ratios to estimate effects (where not reported as effect sizes) for each serious adverse event reported in each study. We summarized the risk ratios for each intervention and each event; where possible, we summarized risk ratios for specific population categories such as children, elderly, those hospitalized for COVID-19, pregnant women, and those with pre-existing medical conditions.

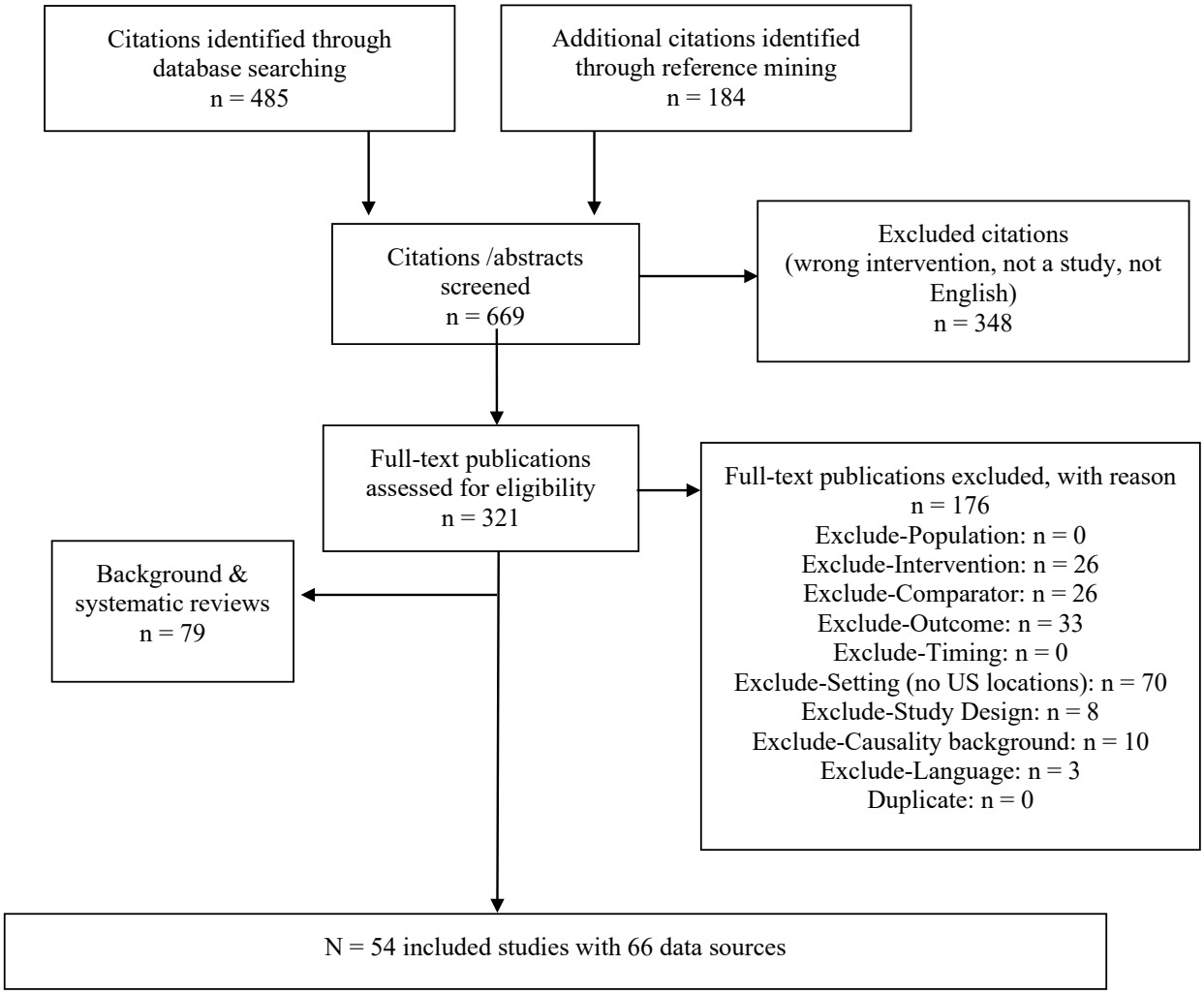
Certainty of Evidence

The system below, from the Institute of Medicine 2012 report *Adverse Effects of Vaccines: Evidence and Causality*[3] was used to assess certainty of evidence.

- *High*: Two or more studies with negligible methodological limitations that are consistent in terms of the direction of the effect provide high confidence.
- *Moderate*: One study with negligible methodological limitations, or a collection of studies generally consistent in terms of the direction of the effect, that provides moderate confidence.
- *Limited*: One study or a collection of studies lacking precision or consistency that provides limited, or low, confidence.
- *Insufficient*: No epidemiologic studies of sufficient quality. We also considered circumstances where the evidence is inconclusive (meaning the preponderance of evidence favors no association despite one or two poor quality or imprecise studies in the opposite direction) as insufficient.

Appendix B. Literature Flow Diagram

Figure B.1. Literature flow diagram



Appendix C. Evidence and Risk of Bias Table

Table C.1. Evidence and risk of bias table

Author, Year **Related Studies** **Trial ID** **Location** **Setting** **Study Design** **Study Size**	**Population** **Preexisting Conditions** **Severity Level**	**Intervention**	**Other Serious Adverse Events** **Risk Factor Analysis**	**Risk of Bias (ROB)**
Bar, 2021[4] NCT04397757 PennCCP2 Article U.S. only Setting: Inpatient RCT N = 80	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, liver disease, immunocompromised, cancer **Special population:** COVID pneumonia **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Severe	**Intervention:** Plasma **Dose:** 2 units **Titer:** low and high **Timing:** 6 days **Control:** Usual care **Cutoff:** 45 days or less: 29, More than 45 days: 60	**Other serious adverse events:** (Tx Arm, Control) Nausea: 0/40, 1/39 RR = 0.33, CI: 0.01, 7.95 Syncope: 1/40, 0/39 RR = 2.93, CI: 0.12, 68.11 Altered mental status: 1/40, 1/39 RR = 0.98; CI: 0.06, 15.05 Neurosensory alteration: 0/40, 1/39 RR = 0.33; CI: 0.01, 7.95 **Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Begin, 2021[5] NCT04348656 CONCOR-1 Article U.S. plus international sites Setting: Inpatient RCT N = 940	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** 500 mL **Titer:** unclear **Timing:** 7.9 days **Control:** Usual care **Cutoff:** 45 days or less: 30	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Beigel, 2020[6] NCT04280705 ACTT-1 Article U.S. plus international sites Setting: Inpatient RCT N = 1062	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, CVD, diabetes, CKD, liver disease, cancer **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Remdesivir **Dose:** 200 mg day 1, 100 mg daily for up to 9 additional days **Timing:** ≤ 6 days **Control:** Placebo **Cutoff:** 45 days or less: 29	**Risk factor analysis:** In both the intervention and control groups, no patients with mild or moderate COVID-19 experienced level 4 (life-threatening) adverse events.	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Bennett-Guerrero, 2021[7] NCT04344535 Stony Brook Medicine COVID Plasma Trial Article U.S. only Setting: Inpatient RCT N = 74	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, Immunocompromised **Severity level:** Hospitalized, not on oxygen, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Plasma **Dose:** 2 units **Titer:** high titer **Timing:** 9 days **Control:** Placebo **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Biran, 2020[8] Ip, 2020[60] NCT04347993 Tocilizumab for COVID-19 in the intensive care unit Article U.S. only Setting: Inpatient Cohort study propensity matched N = 630	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, Stroke, cancer, rheumatological disorder **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 400 mg **Timing:** 19 days **Control:** No intervention **Cutoff:** 45 days or less: 22	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Briggs, 2021[9] Early vs late convalescent plasma for moderate to severe COVID-19 Article U.S. only Setting: Inpatient Cohort study N = 3368	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, CKD, Chronic lung disease **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Plasma **Dose:** 200 mL **Titer:** unclear **Timing:** 6 days **Control:** No intervention **Cutoff:** 45 days or less: 14	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

Caraco, 2021[10] FDA, 2021[67] NCT04575597 MK-4482-002 Article U.S. plus international sites Setting: Outpatient RCT N = 1433	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, Immunocompromise, Active Cancer **Severity level:** Not hospitalized, Mild, Moderate, Severe	**Intervention:** Molnupiravir **Dose:** 800 mg **Timing:** 3 days **Control:** Placebo **Cutoff:** 45 days or less: 14, More than 45 days: 318	**Other serious adverse events:** Intervention N=710 Placebo N=701 Blood and lymphatic system disorders: 1/710, 0/701 RR = 2.96; CI: 0.12, 72.49 Thrombocytopenia: 0/710, 1/701 RR = 0.33; CI: 0.01, 8.08 Cardiac disorders: 0/710, 2/701 RR = 0.20; CI: 0.01, 4.12 Gastrointestinal disorders: 1/710, 1/701 RR = 0.99; CI: 0.06, 15.76 Pancreatitis: 0/710, 1/701 RR = 0.33; 0.01, 8.08 Pancreatitis acute: 1/710, 0/701 RR = 2.96; CI: 0.13, 72.49 General disorders and administration site conditions: 1/710, 0/701	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk:

			RR = 2.96 CI: 0.12, 72.49 Edema peripheral: 1/710, 0/701 RR = 2.96; CI: 0.12, 72.49 Metabolism and nutrition disorders: 1/710, 3/701 RR = 0.43; CI: 0.03, 3.17 Diabetic ketoacidosis: 1/710, 1/701 RR = 0.99; CI:0.06, 15.76 Diabetic metabolic decompensation: 0/710, 1/701 RR = 0.33; CI: 0.01, 8.08 Respiratory, thoracic, and mediastinal disorders: 9/710, 19/701 RR = 0.47; CI: 0.22, 1.04 Acute respiratory failure: 0/710, 2/701 RR = 0.20; CI: 0.01, 4.12 Cough: 0/710, 1/701	

			RR = 0.33; CI: 0.01, 8.08 Dyspnea: 0/710, 1/701 RR = 0.33; CI: 0.01, 8.08 Hypoxia: 1/710, 1/701 RR = 0.99; CI: 0.06, 15.76 Pneumomediastinum: 0/710, 1/701 RR = 0.33; CI: 0.01, 8.08 Pneumothorax: 1/710, 0/701 RR = 2.96; CI: 0.12, 72.49 Respiratory distress: 0/710, 1/701 RR = 0.33; CI: 0.01, 8.08 Respiratory failure: 6/710, 9/701 RR = 0.66; CI: 0.24, 1.85 Vascular disorders: 1/710, 0/701 RR = 2.96; CI: 0.12, 72.49 Peripheral vascular disorder: 0/710, 0/701 Shock: 1/710, 0/701	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
			RR = 2.96; CI: 0.12, 72.49 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Chauhan, 2022[11] Not applicable Convalescent plasma for hospitalized patients Article U.S. only Setting: Inpatient Cohort study propensity score matched N = 376	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, Immunocompromised, Cancer **Severity level:** Not reported	**Intervention:** Plasma **Dose:** 100-250 mL **Titer:** unclear **Timing:** <=7 days **Control:** No intervention **Cutoff:** 45 days or less: Unclear, varied Subjects were observed until time to in-hospital mortality or discharge	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Dougan, 2021[12] Gottlieb, 2021[58]; FDA, 2020[64] NCT04427501 BLAZE-1 Phase 3 Article U.S. only Setting: Outpatient RCT N = 1035	**Population:** Children or adolescents, Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, Immunocompromised **Severity level:** Not hospitalized, Mild, Moderate	**Intervention:** Bamlanivimab / etesevimab **Dose:** 700/1400 **Timing:** 3 days **Control:** Placebo **Cutoff:** 45 days or less: 29	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

FDA, 2020[54] NCT04426695 R10933-10987-COV-2066 FDA filing U.S. only Setting: Outpatient RCT N = 2252	**Population:** Children or adolescents, General population/Adults **Preexisting conditions:** none **Severity level:** Not hospitalized, Mild, Moderate	**Intervention:** Regeneron **Dose:** 1200 mg **Timing:** 3 days **Control:** Placebo **Cutoff:** More than 45 days: 169	**Other serious adverse events:** (Tx arm, Placebo) Hepatic Enzyme Increased: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Anemia: 2/246, 2/247 RR = 1.00; CI: 0.14, 7.07 Hypercoagulation: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Acute left ventricular failure: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Cardiogenic shock: 1/246, 2/247 RR = 0.50; CI: 0.05 to 5.52 Intestinal Obstruction: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Multiple organ dysfunction syndrome: 1/246, 3/247 RR = 0.33; CI: 0.04, 3.22	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

			Acute hepatic failure: 0/246, 1/247 RR = 0.33; CI: 0.01 to 8.21 Pneumonia: 0/246, 2/247 RR = 0.20; CI: 0.01, 4.20 Pyelonephritis acute: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Stomal Hernia: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Hemoglobin decreased: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Hypoglycemia: 0/246, 1/247 RR = 0.33; CI: 0.01 to 8.21 Compartment syndrome: 0/246, 1/247 RR = 0.33 ; CI: 0.01 to 8.21 Encephalopathy: 0/246, 1/247	

			RR = 0.33; CI: 0.01, 8.21 Ischemic stroke: 1/246, 1/247 RR = 1.00; CI: 0.06, 15.96 Seizure: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Mental status changes: 3/246, 1/247 RR = 3.01; CI: 0.31, 28.53 Dyspnea: 3/246, 2/247 RR = 1.51; CI: 0.25, 8.90 Hypoxia: 8/246, 8/247 RR = 1.00; CI: 0.38, 2.63 Acute respiratory distress syndrome: 3/246, 2/247 RR = 1.51; CI: 0.25 to 8.90 Acute respiratory failure: 6/246, 11/247 RR = 0.55; CI: 0.21 to 1.49 Hemoptysis: 0/246, 1/247	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
			RR = 0.33; CI: 0.01, 8.21 Pneumonia aspiration: 0/246, 1/247 RR = 0.33; CI: 0.01, 8.21 Pneumothorax: 1/246, 1/247 RR = 1.00; CI: 0.06, 15.96 Respiratory failure: 7/246, 7/247 RR = 1.00; CI: 0.36, 2.82 Shock: 0/246, 1/247 RR = 0.33; CI: 0.01 to 8.21 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
FDA, 2022[55] NCT04634409 BLAZE 4 FDA filing U.S. only Setting: Outpatient RCT N = 1755	**Population:** Children or adolescents, General population/Adults **Severity level:** Mild, Moderate	**Intervention:** Bebtelovimab **Dose:** 175 mg **Timing:** 3.6 days **Control:** Placebo **3rd arm:** Bamlanivimab / Eteseviimab **3rd arm dose:** 700 mg each **3rd arm timing:** 3.6 **Cutoff:** More than 45 days: 169	**Other serious adverse events:** Meniscus Injury: Tx Arm 1/225, Placebo 0/155, 3rd arm 1/158 Tx Arm vs Placebo: 1/225, 0/155 RR = 2.07; CI: 0.08, 50.28 Tx Arm vs 3rd Arm: 1/225, 1/158 RR = 0.70; CI: 0.04, 11.17 3rd Arm vs Placebo: 1/158, 0/155 RR = 2.94; CI: 0.12 to 71.26 **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Fischer, 2021[13] NCT04405570 Molnupiravir treatment for COVID-19 Article U.S. only Setting: Outpatient RCT N = 202	**Population:** Elderly, General population/Adults **Preexisting conditions:** none **Severity level:** Not applicable, prevention study	**Intervention:** Molnupiravir **Dose:** 800 mg **Timing:** 7 days **Control:** Placebo **3rd arm:** Molnupiravir **3rd arm dose:** 400 mg or 800 mg **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Fischer, 2022[14] NCT04405570 Phase 2a clinical trial of molnupiravir in patients with COVID-19 Article U.S. only Setting: Outpatient RCT N = 202	**Population:** Elderly, General population/Adults **Preexisting conditions:** none **Severity level:** Not reported	**Intervention:** Molnupiravir **Dose:** 200 mg, 400 mg, and 800 mg **Timing:** 4 days **Control:** Placebo **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Gordon, 2021[15] Estcourt, 2021[63] NCT02735707 REMAP-CAP Article U.S. plus international sites Setting: Inpatient RCT N = 755	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, CKD, Immunocompromised **Special population:** organ support in ICU **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 8 mg per kg **Timing:** 2 days **Control:** Usual care **Cutoff:** More than 45 days: 90	**Other serious adverse events:** one deterioration in vision (tocilizumab) **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Gupta, 2021[17] Article U.S. only Setting: Inpatient Cohort study N = 3924	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, CKD, liver disease, active cancer **Severity level:** Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Tocilizumab **Dose:** NA **Timing:** 2 days **Control:** No intervention **Cutoff:** 45 days or less: 14	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Gupta, 2021[16] FDA, 2021[69] NCT04545060 COMET-ICE Article U.S. plus international sites Setting: Outpatient RCT N = 1507	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, diabetes, CKD **Severity level:** Not hospitalized	**Intervention:** Sotrovimab **Dose:** 500 mg **Timing:** ≤5 days **Control:** Placebo **Cutoff:** 45 days or less: 29, More than 45 days: 168	**Other serious adverse events:** Intervention Placebo Gastroesophageal reflux disease: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Obstructive pancreatitis: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Small intestinal obstruction: 1/523, 0/526 RR = 3.02; CI: 0.12, 73.76 Dehydration: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Diabetes mellitus: 1/523, 0/526 RR = 3.02; CI: 0.12 to 73.76 Hypovolaemia: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

			Adenocarcinoma pancreas: 1/523, 0/526 RR = 3.02; CI: 0.12 to 73.76 Non-small cell lung cancer: 1/523, 0/526 RR = 3.02; CI: 0.01, 8.23 Depression: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Acute respiratory failure: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Respiratory distress: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Respiratory failure: 0/523, 1/526 RR = 0.34; CI: 0.01, 8.23 Diabetic foot: 1/523, 0/526 RR = 3.02; CI: 0.12, 73.76 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Hedvat, 2022[18] COVID-19 therapeutics and outcomes in solid organ transplant recipients Article U.S. only Setting: Outpatient Cohort study N = 154	**Population:** General population/Adults **Preexisting conditions:** Organ Transplant, Immunocompromised **Severity level:** Mild, Moderate	**Intervention:** Paxlovid **Dose:** NR **Timing:** 5 days **Control:** No intervention **3rd arm:** Sotrovimab **3rd arm dose:** NR **3rd arm timing:** 10 **Cutoff:** 45 days or less: 30	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Moderate/Unclear **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Hill, 2021[19] Tocilizumab in hospitalized patients with COVID-19 Article U.S. only Setting: Inpatient Cohort study N = 88	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, liver disease, Immunocompromised **Special population:** Cardiovascular disease **Severity level:** Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Tocilizumab **Dose:** 400 mg **Timing:** 2-3 days **Control:** No intervention **Cutoff:** 45 days or less: 14	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Hsue, 2021[20] NCT04421404 CAPRI Trial record U.S. only Setting: Inpatient RCT N = 34	**Population:** Elderly, General population/Adults **Preexisting conditions:** none **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Plasma **Dose:** 250 ml **Titer:** unclear **Timing:** 14 days **Control:** Placebo **Cutoff:** More than 45 days: 90	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Huang, 2021[21] Tocilizumab treatment in critically ill patients with COVID-19 Article U.S. only Setting: Inpatient Cohort study N = 96	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, CVD, diabetes, CKD, Renal failure **Severity level:** Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Severe	**Intervention:** Tocilizumab **Dose:** 400 mg **Timing:** 1 days **Control:** Usual care **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Moderate/Unclear **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Kalligeros, 2020[22] NCT04292899 Remdesivir compared with supportive care in hospitalized patients Article U.S. only Setting: Inpatient Cohort study N = 224	**Population:** General population/Adults **Preexisting conditions:** COPD, obesity, CVD, CKD, liver disease **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Remdesivir **Dose:** 200 mg **Timing:** 8 days **Control:** Usual care **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Kewan, 2020[23] Not applicable Tocilizumab for severe COVID-19 Article U.S. only Setting: Inpatient Cohort study N = 51	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, obstructive sleep apnea, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis **Severity level:** Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 400 mg **Timing:** 8 days **Control:** Hydroxychloroquine, Azithromycin (also received by intervention group) **Cutoff:** 45 days or less: 10	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Kimmig, 2020[24] Increased secondary infections in critically ill COVID-19 patients Article U.S. only Setting: Inpatient Cohort study N = 111	**Population:** Elderly, General population/Adults **Preexisting conditions:** Organ Transplant, COPD, obesity, CVD, diabetes, CKD, liver disease, Connective tissue disorder, cancer, dementia **Severity level:** Severe	**Intervention:** Tocilizumab **Dose:** 400 mg **Timing:** 5 days **Control:** No intervention **Cutoff:** 45 days or less: 5	**Risk factor analysis:** There was a trend toward a higher proportion of patients with diabetes mellitus or organ damage in those with bacterial infection and a higher proportion of patients with past medical history of deep venous thrombosis (DVT) or pulmonary embolism (PE)	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Korley, 2021[25] NCT04355767 SIREN-C3PO Article U.S. only Setting: Outpatient RCT N = 511	**Population:** Elderly, General population/Adults **Preexisting conditions:** Organ Transplant, COPD, obesity, CVD, diabetes, CKD, Immunocompromised, Cancer **Severity level:** Not hospitalized	**Intervention:** Plasma **Dose:** 200 ml **Titer:** high titer **Timing:** 7 days **Control:** Placebo **Cutoff:** 45 days or less: 30	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Levey, 2022[26] Pregnant patients & REGEN-COV Article U.S. only Setting: Primarily Outpatient Cohort study Retrospective N = 86	**Population:** Pregnant Women **Preexisting conditions:** Pregnant, obesity, CVD, diabetes **Special population:** Pregnant **Severity level:**	**Intervention:** Regeneron **Dose:** Not reported **Timing:** 3 days **Control:** No intervention **Cutoff:** 45 days or less: Unspecified	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Levin, 2022[27] FDA, 2021[66] NCT04625725 PROVENT Article U.S. plus international sites Setting: Outpatient RCT N = 5,197	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, liver disease, Immunocompromised **Severity level:** Not applicable, prevention study	**Intervention:** Evusheld **Dose:** 300 mg **Timing:** NR **Control:** Placebo **Cutoff:** More than 45 days: 457 Article supplement also reports events by system categories at 180 days, but not *specific* adverse events	**Other serious adverse events:** Cholecystitis: Intervention 1/3461, Placebo 0/1736 RR = 1.50; CI: 0.06, 36.92 Bell's Palsy: Intervention 1/3461, Placebo 0/1736 RR = 1.50; CI: 0.06, 36.92 Transient Ischemic Attack: Intervention 2/3461, Placebo 0/1736 RR = 2.51; CI: 0.12, 52.20 **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Liu, 2020[28] Convalescent plasma for severe COVID-19 Article U.S. only Setting: Inpatient Cohort study Propensity matched N = 78	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, diabetes, CKD, Immunocompromised, asthma, cancer, stroke, sleep apnea **Severity level:** Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Severe	**Intervention:** Plasma **Titer:** high titer **Timing:** 4 days **Control:** Usual care **Cutoff:** 45 days or less: 14	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Lundgren, 2021[29] FDA, 2021[69] NCT04501978 ACTIV-3/ TICO Article U.S. plus international sites Setting: Inpatient RCT N = 314	**Population:** Elderly, General population/Adults **Preexisting conditions:** **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Bamlanivimab / etesevimab **Dose:** 7000 mg **Timing:** 7 days **Control:** Placebo **Cutoff:** 45 days or less: 5	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
McCreary, 2022[30] Subcutaneous or intravenous casirivimab and imdevimab Article U.S. only Setting: Inpatient, Outpatient Cohort study propensity score matched N = 2,185	**Population:** Children or adolescents, Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, liver disease, Immunocompromised **Severity level:** Not hospitalized, Mild, Moderate	**Intervention:** Regeneron **Dose:** 600 mg each **Timing:** 3 days **Control:** No intervention **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Misset, 2023 [31] NCT04558476 Convalescent Plasma for Covid-19–Induced ARDS in Mechanically Ventilated Patients Article U.S. only Setting: Inpatient RCT N = 475	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, congestive heart failure, asthma, hematologic cancer, solid tumor **Severity level:** Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** 400-500 ml **Titer:** low titer, high titer **Timing:** 12 days **Control:** Usual care **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Nasrallah, 2022[32] Pharmacological treatment in pregnant women with moderate symptoms of COVID-19 Article U.S. only Setting: Inpatient Case-Control N = 35	**Population:** Women **Preexisting conditions:** Pregnant **Severity level:** Hospitalized, on standard-flow supplemental oxygen, Moderate	**Intervention:** Remdesivir **Dose:** 200 mg **Timing:** 2 days **Control:** Usual care **Cutoff:** 45 days or less: 14	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

O'Brien, 2021[33] FDA, 2020[54] NCT04452318 R10933-10987-COV-2069 Article U.S. plus international sites Setting: Outpatient RCT N = 3298	**Population:** Children or adolescents, Elderly, General population/Adults **Preexisting conditions:** obesity, diabetes, CKD, Immunocompromised **Severity level:** Not applicable, prevention study	**Intervention:** Regeneron **Dose:** 1200 mg **Timing:** NA days **Control:** Placebo **Cutoff:** 45 days or less: 28, More than 45 days: 226	**Other serious adverse events:** Intervention/ Placebo: Suicidal ideation: 0/1627, 2/1643 RR = 0.20; CI: 0.01, 4.21 Schizophrenia: 1/1627, 0/1643 RR = 3.03, CI: 0.12, 74.27 Mania: 0/1627, 1/1643 RR = 0.34; CI: 0.01, 8.26 Diabetic foot: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Breast hematoma: 0/1627, 1/1643 RR = 0.34; CI: 0.01, 8.26 Transient ischemic attack: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Invasive ductal breast: 0/1627, 1/1643 RR = 0.34; CI: 0.01, 8.26	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

			Cervix carcinoma recurrent: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Abdominal pain upper: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Pancreatitis acute: 0/1627, 1/1643 RR = 0.34; CI: 0.01, 8.26 Cholecystitis acute: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Cholelithiasis: 0/1627, 1/1643 RR = 0.34; CI: 0.01, 8.26 Cardiac failure congestive: 1/1627, 0/1643 RR = 3.03; CI: 0.12, 74.27 Cardiac arrest: 0/1627, 1/1643 RR = 0.34; CI: 0.01 to 8.26 Cardio-respiratory arrest: 1/1627, 0/1643	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
			RR = 3.03; CI: 0.12, 74.27 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
O'Donnell, 2021[34] NCT04359810 AAAS9924 Article U.S. plus international sites Setting: Outpatient RCT N = 223	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, liver disease **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** single unit of plasma (200–250 milliliters) **Titer:** low and high **Timing:** 7 days **Control:** Placebo **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Ortigoza, 2022[35] NCT04364737 CONTAIN Article U.S. only Setting: Inpatient RCT N = 941	**Population:** Elderly, General population/Adults **Preexisting conditions:** Organ Transplant, COPD, CVD, diabetes, CKD, liver disease, Immunocompromise **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** 250 ml **Titer:** low and high **Timing:** 3 to 7 days **Control:** Placebo **Cutoff:** 45 days or less: 28, More than 45 days: 90	**Other serious adverse events:** Intervention / Placebo Anemia: 9/468, 8/473 RR = 1.14; CI: 0.44, 2.92 **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Painter, 2021[36] NCT04392219 Human Safety, Tolerability, and Pharmacokinetics of Molnupiravir, a Novel Broad-Spectrum Oral Antiviral Agent with Activity against SARS-CoV-2 Article U.S. plus international sites Setting: Outpatient RCT N = 146	**Population:** Children or adolescents, Elderly, General population/Adults **Preexisting conditions:** none **Severity level:** Not hospitalized	**Intervention:** Molnupiravir **Dose:** 50, 100, 200, 400, 600, 800, 1200, 1600 mg **Timing:** unclear **Control:** Placebo **Cutoff:** 45 days or less: 15	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

Pfizer, 2021[37] FDA_Paxlovid, 2021[68] NCT04960202 EPIC-HR Trial record U.S. plus international sites Setting: Outpatient RCT N = 2,246	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, CVD, diabetes **Severity level:** Not hospitalized	**Intervention:** Paxlovid **Dose:** 300/100 mg **Timing:** 5 days **Control:** Placebo **Cutoff:** More than 45 days: 168	**Other serious adverse events:** Intervention / Placebo Anemia: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Palpitations: 1/1109, 0/1115 RR = 3.02; CI: 0.12, 73.90 Chest discomfort: 1/1109, 0/1115 RR = 3.02; CI: 0.12, 73.90 Craniocerebral injury: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Eye injury: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Hand fracture: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Road traffic accident: 0/1109, 1/1115	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

			RR = 0.34; CI: 0.01, 8.23 Wrist fracture: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Creatinine renal clearance decreased: 2/1109, 3/1115 RR = 0.67; CI: 0.11, 4.01 Fibrin D dimer increased: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Hemoglobin decreased: 1/1109, 0/1115 RR = 3.02; CI: 0.12, 73.90 Oxygen saturation decreased: 1/1109, 0/1115 RR = 3.02; 0.12, 73.90 Colon adenoma: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Nervous system disorders	

			Facial paralysis: 1/1109, 0/1115 RR = 3.02; 0.12, 73.90 Acute respiratory failure: 0/1109, 5/1115 RR = 0.09; CI: 0.01, 1.66 Dyspnea: 2/1109, 3/1115 RR = 0.67; CI: 0.11, 4.01 Hypoxia: 0/1109, 2/1115 RR = 0.20; CI: 0.01 to 4.19 Interstitial lung disease: 0/1109, 2/1115 RR = 0.20; CI: 0.01, 4.19 Pneumonitis: 0/1109, 5/1115 RR = 0.09; CI: 0.01, 1.66 Respiratory failure: 0/1109, 1/1115 RR = 0.34; CI: 0.01, 8.23 Nasal obstruction: 1/1109, 0/1115	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
			RR = 3.02; CI: 0.12, 73.90 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Pfizer, 2021[57] NCT05011513 EPIC-SR Trial record U.S. plus international sites Setting: Outpatient RCT N = 1440	**Analysis:** Counts **Population:** General population/Adults **Preexisting conditions:** NR **Severity level:** Not hospitalized, Mild, Moderate	**Intervention:** Paxlovid **Dose:** Nirmatrelvir 300mg + Ritonavir 100mg **Timing:** 4 days **Control:** Placebo **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Piccicacco, 2021[38] Early remdesivir and sotrovimab in highest-risk patients Article U.S. only Setting: Outpatient Cohort study N = 260	**Population:** Children or adolescents, Elderly, General population/Adults **Preexisting conditions:** Organ Transplant, obesity, CVD, diabetes, CKD, Immunocompromised **Severity level:** Not hospitalized	**Intervention:** Remdesivir **Dose:** 200 mg **Timing:** 4 days **Control:** Usual care **3rd arm:** Sotrovimab **3rd arm dose:** 500 mg **3rd arm timing:** 4.4 days **Cutoff:** 45 days or less: 29	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Portal-Celhay, 2021[39] NCT04666441 R10933-10987-COV-20145 Preprint U.S. only Setting: Outpatient RCT N = 1149	**Population:** Elderly, General population/Adults **Preexisting conditions:** none **Special population:** Small subgroup pregnant **Severity level:** Not hospitalized, Mild	**Intervention:** Regeneron **Dose:** 600 mg **Timing:** 1-7 days **Control:** Placebo **Cutoff:** More than 45 days: 169	**Other serious adverse events:** 2 miscarriages reported with higher dose (not FDA authorized); both deemed not related to treatment **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Radcliffe, 2022[40] Not applicable COVID-19 therapies in outpatient, solid organ transplant recipients Article U.S. only Setting: Outpatient Cohort N = 122	**Population:** Elderly, General population/Adults **Preexisting conditions:** Organ Transplant, Immunocompromised **Special population:** Organ transplant **Severity level:** Not hospitalized, Mild, Moderate	**Intervention:** Molnupiravir **Dose:** Not reported **Timing:** Not reported **Control:** No intervention **3rd arm:** Sotrovimab **3rd arm dose:** Not reported **3rd arm timing:** Not reported **Cutoff:** 45 days or less: 30	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Moderate/Unclear **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Rajendram, 2021[41] Tocilizumab in Critical COVID Article U.S. only Setting: Inpatient Cohort study N = 444	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, diabetes, CKD, liver disease, Immunocompromised, cancer **Severity level:** Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 4-8 mg/kg **Timing:** Not reported days **Control:** Usual care **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Razonable, 2021[42] Casirivimab-imdevimab treatment among high-risk patients with mild to moderate coronavirus disease-19 Article U.S. only Setting: Outpatient Case-Control N = 1392	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes, CKD, liver disease, Immunocompromised **Severity level:** Mild, Moderate	**Intervention:** Regeneron **Dose:** 1200 mg **Timing:** 10 days **Control:** No intervention **3rd arm timing:** 28 **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Rojas-Marte, 2020[43] Severe COVID-19 and tocilizumab: a case–controlled study Article U.S. only Setting: Inpatient Case-Control N = 193	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 8 mg/kg **Timing:** days **Control:** Usual care **Cutoff:** 45 days or less: While hospitalized, unclear Unclear follow up period and unclear timing/days symptomatic	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Rosas, 2021[44] FDA, 2021[65] NCT04320615 COVACTA Article U.S. plus international sites Setting: Inpatient RCT N = 438	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD **Special population:** COVID pneumonia **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Tocilizumab **Dose:** 8 mg per **Timing:** NR **Control:** Placebo **Cutoff:** 45 days or less: 28, More than 45 days: 60	**Other serious adverse events:** Tocilizumab (TCZ) Arm / Placebo Arm Blood and lymphatic system disorders Coagulopathy: 1/295, 0/143 RR = 1.46; CI: 0.06, 5.49 Eosinophilia: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Leukocytosis: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Pancytopenia: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Thrombocytopenia: 1/295,1/143 RR = 0.48; CI: 0.03, 7.72 Cardiac Angina unstable: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Atrioventricular block complete: 1/295, 0/143	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

			RR = 1.46; CI: 0.06, 35.49 Bundle branch block right: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Cardio-respiratory arrest: 2/295, 0/143 RR = 2.43; CI: 0.12, 50.00 Left ventricular failure: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Pulseless electrical activity: 2/295, 2/143 RR = 0.48; CI: 0.07, 3.43 Stress cardiomyopathy: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Vascular Hematoma: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Acute respiratory distress syndrome: 4/295, 2/143 RR = 0.97; CI: 0.18, 5.23	

			Acute respiratory failure: 2/295, 2/143 RR = 0.48; CI: 0.07, 3.43 Aspiration: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Hemothorax: 1/295, 0/143 RR = 1.46; CI: 0.06. 35.49 Hypoxia: 0/295, 3/143 RR = 0.07; CI: 0.00, 1.36 Lung consolidation: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Obstructive airways disorder: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Pneumonia aspiration: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Pneumothorax: 4/295, 3/143 RR = 0.65; CI: 0.15, 2.87	

			Pneumothorax spontaneous: 1/295, 0/143 RR = 1.46; CI: 0.06 to 35.49 Respiratory disorder: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Delirium: 2/295, 1/143 RR = 0.97; CI: 0.09, 10.61 Depressed level of consciousness: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Metabolism and nutrition disorders Acidosis: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49 Diabetic ketoacidosis: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Fluid overload: 1/295, 0/143 RR = 1.46; CI: 0.06, 35.49	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
			Hyperglycemia: 0/295, 1/143 RR = 0.16; CI: 0.01 to 3.98 Hyperkalemia: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 hypoglycemia: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 Metabolic acidosis: 0/295, 1/143 RR = 0.16; CI: 0.01, 3.98 **Risk factor analysis:** NR	

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Salama, 2021[45] FDA, 2021[65] NCT04372186 EMPACTA Article U.S. plus international sites Setting: Inpatient RCT N = 389	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, obesity, CVD, diabetes **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen	**Intervention:** Tocilizumab **Dose:** 8 mg per kg **Timing:** NR **Control:** Placebo **Cutoff:** More than 45 days: 60	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Salazar, 2021[46] High titer plasma for severe COVID-19 Article U.S. only Setting: Inpatient Case-Control N = 945	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, Hyperlipidemia, coronary disease **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** 300 mL, titer ≥1:1350 **Titer:** high titer **Timing:** 2 days **Control:** No intervention **Cutoff:** More than 45 days: 60	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Seethapathy, 2022[47] Remdesivir in patients with severe kidney disease Article U.S. only Setting: Inpatient Cohort study Propensity matched N = 62	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, CKD, **Special population:** Kidney failure **Severity level:** Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Remdesivir **Dose:** Not reported **Timing:** 3 days **Control:** No intervention **Cutoff:** 45 days or less: 7	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Self, 2022[48] NCT04362176 Pass It On Article U.S. only Setting: Inpatient RCT N = 960	**Population:** Elderly, General population/Adults **Preexisting conditions:** COPD, CVD, diabetes, CKD, liver disease, cancer **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation, Severe	**Intervention:** Plasma **Dose:** 500 mL/hour **Titer:** unclear **Timing:** 8 days **Control:** Placebo **Cutoff:** More than 45 days Supplement reports at 28 days, but only a few serious adverse events display number of patients with the event. The rest are number of events in each group, so not abstracted. Clinicaltrials.gov reports all events correctly at 90 days.	**Other serious adverse events:** Intervention, Control Colon perforation: 1/495, 0/479 RR = 2.90; CI: 0.12, 70.95 Multi organ failure: 2/495, 0/479 RR = 4.83; CI: 0.23 to 100.13 Guillain-Barre Syndrome Grade 3: 1/495, 0/479 RR = 2.90; CI: 0.12 to 70.95 **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Selvaraj, 2021[49] Remdesivir in COVID-19 patients with end stage renal disease Letter to the editor Setting: Inpatient Cohort study N = 28	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, CVD, diabetes **Severity level:** Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation	**Intervention:** Remdesivir **Dose:** NR **Timing:** NR **Control:** No intervention **Cutoff:** 45 days or less	**Risk factor analysis:** NR	**Assessment RoB:** High risk **Reporting RoB:** High risk **Overall RoB:** High risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Spinner, 2020[50] NCT04292730 Remdesivir (GS-5734™) in Participants With Moderate COVID-19 Article U.S. plus international sites Setting: Inpatient RCT N = 584	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, asthma **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Remdesivir **Dose:** 200 mg **Timing:** 2 days **Control:** Usual care **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Stone, 2020[51] NCT04356937 Tocilizumab to Prevent the Progression of Hypoxemic Respiratory Failure in Hospitalized Non-Critically Ill Patients With COVID-19 Article U.S. only Setting: Inpatient RCT N = 243	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, diabetes **Severity level:** Hospitalized, not on oxygen, Hospitalized, on standard-flow supplemental oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation, Hospitalized and on invasive mechanical ventilation or extracorporeal membrane oxygenation	**Intervention:** Tocilizumab **Dose:** 8 mg per kg **Timing:** 3 days **Control:** Placebo **Cutoff:** 45 days or less: 28	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Sullivan, 2022[52] Sullivan, 2021[62] NCT04373460 CSSC-004 Article U.S. only Setting: Outpatient RCT N = 1181	**Population:** Elderly, General population/Adults **Preexisting conditions:** CVD, diabetes, Immunocompromised **Severity level:** Not hospitalized, Mild	**Intervention:** Plasma **Dose:** 250 ml **Titer:** low and high **Timing:** 6 days **Control:** Placebo **Cutoff:** More than 45 days: 90	**Other serious adverse events:** Intervention/ Placebo Hyperglycemia: 1/592, 0/589 RR = 2.98; CI: 0.12, 73.00 Urinary tract obstruction: 0/592, 1/589 RR = 0.33; CI: 0.01, 8.14 Hypoxia: 0/592, 3/589 RR = 0.14; CI: 0.01, 2.76 Infusion related reaction, unspecified: 0/592, 1 /589 RR = 0.33; CI: 0.01, 8.14 Leukocytosis: 0/592, 1/589 RR = 0.33; CI: 0.01, 8.14 **Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Thompson, 2021[53] Plasma and hematologic cancers Article U.S. only Setting: Inpatient Cohort study N = 966	**Population:** Elderly, General population/Adults **Preexisting conditions:** obesity, CVD, diabetes, CKD, liver disease, hematologic cancers **Special population:** Hematologic cancers **Severity level:** Hospitalized, not on oxygen, Hospitalized and on high-flow oxygen therapy or noninvasive mechanical ventilation; Mild, Moderate, Severe	**Intervention:** Plasma **Dose:** Not reported **Titer:** unclear **Timing:** Not reported **Control:** Usual care **Cutoff:** 45 days or less: 30	**Risk factor analysis:** NR	**Assessment RoB:** Moderate/Unclear **Reporting RoB:** Low risk **Overall RoB:** Moderate/Unclear

Author, Year Related Studies Trial ID Location Setting Study Design Study Size	Population Preexisting Conditions Severity Level	Intervention	Other Serious Adverse Events Risk Factor Analysis	Risk of Bias (ROB)
Weinreich, 2021[56] FDA, 2020[54] NCT04425629 REGN-COV2 Article U.S. only Setting: Outpatient RCT N = 269	**Population:** Elderly, General population/Adults **Preexisting conditions:** diabetes **Severity level:** Not hospitalized	**Intervention:** Regeneron **Dose:** 2.4 g and 8.0 g **Timing:** 7 days **Control:** Placebo **Cutoff:** 45 days or less: 29	**Risk factor analysis:** NR	**Assessment RoB:** Low risk **Reporting RoB:** Low risk **Overall RoB:** Low risk