Convalescent Plasma

Section last reviewed and updated 2/3/2022

Last literature search conducted 1/31/2022

Recommendation 1: Among patients hospitalized with COVID-19, the IDSA guideline panel recommends against COVID-19 convalescent plasma. (Strong recommendation, Moderate certainty of evidence)

Recommendation 2 (UPDATED): Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)

Remarks:

- In the US, FDA EUA only authorizes use in patients with immunosuppressive disease or receiving immunosuppressive treatment.
- Patients, particularly those who are not immunocompromised, who place a low value on the uncertain benefits (reduction in the need for mechanical ventilation, hospitalization, and death) and a high value on avoiding possible adverse events associated with convalescent plasma would reasonably decline convalescent plasma.

Why is convalescent plasma considered for treatment?

Convalescent plasma has been used as passive immunotherapy for prevention and treatment of infections for over 100 years [1, 2]. The predominant proposed protective mechanism is thought to be pathogen neutralization, although antibody-dependent cellular cytotoxicity and enhanced phagocytosis may also play a role. With the advent of effective antimicrobial therapy (i.e., "the antibiotic era"), convalescent plasma fell out of favor. In recent years, interest in this approach has been revived as a means of addressing viral epidemics such as Ebola, SARS-CoV-1, and MERS. Studies of convalescent plasma derived from people who had recovered from those specific infections showed encouraging results but were typically small, non-randomized, and largely descriptive [3-5]. In the current pandemic, convalescent plasma obtained from individuals who have recovered from COVID-19 has been used in over 100,000 patients with moderate to severe infection as part of an expanded access program [6, 7]. In an analysis of the convalescent plasma expanded access program, higher levels of antibodies were associated with significant improvements in mortality compared to those receiving

convalescent plasma with lower concentrations of neutralizing antibodies [6]. However, there was no placebo group in the study, so this result could be from increased mortality with low antibody titer plasma rather than improved mortality with high antibody titer plasma. Subgroup data from one open-label RCT reporting on plasma with anti-receptor-binding domain ELISA values corresponding to a high antibody titer cutoff resulted in a non-significant relative risk reduction in mortality of 5% (RR: 0.95; 95% CI: 0.73, 1.25) [8]. An additional subgroup analysis suggested unselected convalescent plasma (i.e., not limited to high-titer antibodies) may increase the relative risk for mortality by 49% (RR: 1.42; 95% CI: 0.92, 1.69).

An analysis of the convalescent plasma expanded access program suggests the most benefit is seen when convalescent plasma is given in the first three days from diagnosis [6]. In August 2020, the FDA issued an emergency use authorization (EUA) for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients [9]. In early February 2021, the FDA issued a revision to the EUA to limit the authorization to the use of high-titer COVID-19 convalescent plasma for the treatment of hospitalized patients early in the disease course [10].

Summary of the evidence

Our search identified and was informed by evidence from 21 RCTs and a large (n=20,000), single-arm registry study [1-5, 11-20], as they provided the best available evidence for the outcomes of mortality, need for mechanical ventilation, serious adverse events, and adverse events. Eighteen of those RCTs reported on convalescent plasma infusions for patients hospitalized with COVID-19 (**Table 1**) [1-4, 11-16] and three RCTs [18-20] reported on receipt of convalescent plasma by ambulatory persons with mild COVID-19 disease (**Table 2**) [5].

Eighteen trials randomized 17,232 patients hospitalized with COVID-19 to receive COVID-19 convalescent plasma infusion [1-4, 11-16]. Several trials were open-label and/or had concerns with risk of bias due to lack of adjustment for critical confounders or potential for residual confounding (**Supplementary Table s2a**). Timing of receipt of COVID-19 convalescent plasma during the clinical course of the patients' illness varied across studies (**Supplementary Table s1**). One trial reported on 160 persons who received high-titer convalescent plasma less than 72 hours after the onset of symptoms of COVID-19 (mean age: 77.2 years; standard deviation: ±8.6 years) [5]. In addition, Joyner 2020 reported on safety outcomes of over 20,000 patients enrolled in the same FDA Expanded Access Program for COVID-19 convalescent plasma study.

Benefits

Hospitalized patients

In hospitalized patients, convalescent plasma transfusion appears to have trivial or no effect on mortality based on the body of evidence from RCTs (RR: 0.98; 95% CI: 0.93, 1.03; moderate CoE). Recipients of COVID-19 convalescent plasma may have a greater need for mechanical ventilation (RR: 1.10; 95% CI: 0.94, 1.29; low CoE); however, the evidence is uncertain because of concerns with risk of bias imprecision.

Ambulatory persons

Receipt of COVID-19 convalescent plasma showed a reduction in hospitalization (RR: 0.74; 95% CI: 0.56, 0.98; moderate CoE) and a trend toward a reduction in COVID-19 related hospitalizations or medically-attended visits (emergency room or urgent care; RR 0.79; 95% CI: 0.63 to 1.00; moderate CoE); however, the evidence remains uncertain due to few events reported. Similarly, evidence showed a possible reduction of progression to severe respiratory disease (RR: 0.52; 95% CI: 0.29, 0.94; low CoE); however, the evidence remains uncertain, as oxygenation and respiration rates are surrogate measures of need for ventilation, morbidity, and death, and because of the fragility of the estimate due to the small number of events reported. Convalescent plasma transfusion failed to show or exclude a beneficial effect on all-cause mortality based on the body of evidence from two RCTs (RR: 0.53; 95% CI: 0.14, 1.98; low CoE); however, the evidence is uncertain due to concerns with fragility of the estimate due to the small number of events reported. Additional deaths beyond 15 days were reported in one RCT and included five deaths in the plasma group *versus* one in the placebo arm.

Harms

In the largest safety study (n=20,000), within four hours of completion of convalescent plasma transfusion, authors reported 146 serious adverse events classified as transfusion reactions (<1% of all transfusions) [17]. Of these, 63 deaths were reported (0.3%) with 13 judged as possibly or probably related to the transfusion. The non-mortality serious adverse events include 37 reports of transfusion-associated circulatory overload, 20 cases of transfusion-related acute lung injury, and 26 cases of severe allergic transfusion reactions.

Within seven days of transfusion, 1711 deaths were reported (mortality rate: 8.56%; 95% CI: 8.18, 8.95). In addition, 1136 serious adverse events were reported: 643 cardiac events (569 judged as unrelated to the transfusion), 406 sustained hypotensive events requiring intravenous (IV) pressor support, and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).

Eleven trials among patients hospitalized for COVID-19 suggest increased adverse events among patients receiving convalescent plasma (RR: 1.08; 95% CI: 0.94, 1.26; low CoE); however, the evidence was uncertain due to concerns with lack of blinding. In addition, included studies lacked a standard definition for what met the definition of an adverse event. In ambulatory

patients, serious adverse events were higher in the convalescent plasma group due to serious transfusion reactions requiring treatment or admission (RR 5.95; 95% CI: 0.72, 49.29; low CoE), although the evidence is uncertain due to few events.

Other considerations

Hospitalized patients

The panel agreed that the overall certainty of evidence is moderate due to some remaining imprecision as the 95% CI crossed the threshold of 1% for plausible mortality reduction. The guideline panel recognized that unselected use of convalescent plasma appeared to have trivial to no beneficial effect from the now existing large body of evidence.

Ambulatory persons

The panel agreed that the overall certainty of evidence is low due to concerns with imprecision, which recognized the limited events and concerns with fragility. The guideline panel recognized the inability to exclude a meaningful beneficial or detrimental effect when plasma is given early in the course of COVID-19 disease.

Conclusions and research needs for this recommendation

The guideline panel suggests against COVID-19 convalescent plasma for persons hospitalized with COVID-19. Based on limited studies and mechanistic reasoning, COVID-19 convalescent plasma may be more effective if given at high titers early in course of hospitalization, in patients with undetectable or low levels of anti-SARS-CoV-2 antibodies, or in those with a humoral immune deficiency [21-26]. Current RCTs have not reported outcomes in such pre-specified subpopulations. Future studies in hospitalized patients should focus on patients with humoral immunodeficiencies early in the course of COVID-19. Future studies in hospitalized patients should also consider screening for SARS-CoV-2 neutralizing antibodies in all patients at entry into RCTs and assessing outcomes based on antibody levels.

The guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma in the ambulatory setting for persons with mild-to-moderate COVID-19 at high risk for progression to severe disease, who have no other treatment options. In ambulatory patients, convalescent plasma may be more effective if the product used contains high titers of neutralizing antibodies and is used early in clinical presentation or in subpopulations of patients who do not have an adequate humoral immune response even at later stages of disease [21]. There is a paucity of trials in this specific population of patients. Future studies in ambulatory patients should target these populations.

Additional clinical trials may be needed to also determine whether there is a benefit of treatment with COVID-19 convalescent plasma and at what dose (neutralizing antibody titers), especially for patients early in the disease course of COVID-19.

Table 1. GRADE evidence profile, Recommendation 1

Question: Convalescent plasma compared to no convalescent plasma for hospitalized patients with COVID-19

Last updated 11/4/2021

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
Mortality (RCTs) (follow-up: range 15 days to 60 days)												
18 [1-18]	randomized trials	not serious [a,b]	not serious	not serious	serious [c]	none	2163/9082 (23.8%)	2007/8150 (24.6%)	**RR 0.98** (0.93 to 1.03)	**5 fewer per 1,000** (from 17 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Need for mechanical ventilation												
4 [3,6,9,14]	randomized trials	serious [d]	not serious	not serious	serious [e]	none	184/581 (31.7%)	166/471 (35.2%)	**RR 1.10** (0.94 to 1.29)	**35 more per 1,000** (from 21 fewer to 102 more)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events (transfusion-associated circulatory overload, transfusion-related acute lung injury, severe allergic transfusion reaction) (follow-up: 4 hours)												
1 [19]	observational studies	extremely serious [f]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within first 4 hours, of the SAEs, 63 deaths were reported (0.3% of all transfusions) and 13 of those deaths were judged as possibly or probably related to the transfusion of COVID-19 convalescent plasma. There were 83 non-death SAEs reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion-related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction.				⨁◯◯◯ VERY LOW	CRITICAL
Serious adverse events (mortality, cardiac, thrombotic, sustained hypotensive events requiring intervention) (follow-up: 7 days)												
1 [19]	observational studies	extremely serious [f]	not serious	not serious	not serious	none	SAEs from 20,000 transfused patients: Within 7 days of transfusion, 1711 deaths (8.56%) and 1136 serious adverse events (5.68%) were reported. Non-mortality SAEs included: 643 cardiac events (569 judged as unrelated to the transfusion); 406 sustained hypotensive events requiring intravenous pressor support; and 87 thromboembolic or thrombotic events (55 judged as unrelated to the transfusion).				⨁◯◯◯ VERY LOW	CRITICAL
Any adverse events (RCTs)												

11 3,4,6,8,11-13,15-18	randomized trials	serious [d]	not serious	not serious [g]	serious [h]	none	574/2843 (20.2%)	307/1959 (15.7%)	**RR 1.08** (0.94 to 1.26)	**13 more per 1,000** (from 9 fewer to 41 more)	⨁⨁◯◯ LOW	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **HR:** Hazard ratio; **OR:** Odds ratio; **RCTs:** Randomized controlled trials; **RR:** Risk ratio; **SAEs**: Serious adverse events

Explanations

a. Li 2020 time between symptom onset and randomization was over 14 days for >90% (median 30 days), no adjustment for co-interventions, allocation concealment methods not reported and participants and healthcare professionals not blinded.
b. Many trials had concerns due to open-label trial, allocation concealment not reported, and no adjustments for co-interventions.
c. The 95% CI includes the potential for appreciable benefit; however, cannot exclude the potential for no effect.
d. Concerns include open-label trial design and assessment of outcome.
e. The 95% CI may not include a clinically meaningful reduction in need for mechanical ventilation.
f. No comparative effects available. Some subjectivity in classification of outcomes as transfusion related.
g. Lack standard definition for adverse events. Studies report on mild to severe events.
h. The 95% CI includes the potential for both increased harms, as well as no increased harms. Few events suggests fragility of the estimate.

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Table 2. GRADE evidence profile, Recommendation 2

Question: Convalescent plasma compared to no convalescent plasma for ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease

Last reviewed and updated 1/21/2022

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (follow-up: range 15 days to 28 days) [a]												
3 [1-3]	randomized trials	not serious	not serious	not serious	very serious [b]	none	3/929 (0.3%)	7/923 (0.8%)	**RR 0.53** (0.14 to 1.98)	**4 fewer per 1,000** (from 7 fewer to 7 more)	⨁⨁◯◯ LOW	CRITICAL
COVID-19 related hospitalizations, ED/urgent care visits, or death (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [c]	none	94/849 (11.1%)	118/843 (14.0%)	**RR 0.79** (0.62 to 1.00)	**29 fewer per 1,000** (from 53 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Hospitalizations (all-cause) (follow-up: range 15 days to 28 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [d]	none	73/867 (8.4%)	98/869 (11.3%)	**RR 0.74** (0.56 to 0.98)	**29 fewer per 1,000** (from 50 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Progression to severe respiratory disease (follow-up: 15 days; assessed with: defined as a respiratory rate of ≥30 breaths per minute, SaO_2 < 93% on room air, or both)												
1 [2]	randomized trials	not serious [e]	not serious	serious [f]	serious [g]	none	13/80 (16.3%)	25/80 (31.3%)	**RR 0.52** (0.29 to 0.94)	**150 fewer per 1,000** (from 222 fewer to 19 fewer)	⨁⨁◯◯ LOW	CRITICAL
Serious adverse events: serious transfusion reactions (requiring treatment or admission) (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	very serious [c]	none	5/849 (0.6%)	0/843 (0.0%)	**RR 5.95** (0.72 to 49.29) [h]	**6 more per 1,000** (from 1 more to 11 more) [i]	⨁⨁◯◯ LOW	CRITICAL
Any adverse events (follow-up: 15 days)												
2 [1,3]	randomized trials	not serious	not serious	not serious	serious [c]	none	127/849 (15.0%)	147/843 (17.4%)	**RR 0.86** (0.70 to 1.05)	**24 fewer per 1,000** (from 52 fewer to 9 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Risk of bias: Study limitations
Inconsistency: Unexplained heterogeneity across study findings
Indirectness: Applicability or generalizability to the research question
Imprecision: The confidence in the estimate of an effect to support a particular decision
Publication bias: Selective publication of studies

NB: Certainty ratings may be derived from evidence that includes pre-print articles, which have not been peer reviewed or published.

CI: Confidence interval; **ED:** Emergency department; **RR:** Risk ratio; **SaO_2:** Saturated oxygen

Explanations

a. Deaths beyond 15 days and up to 30 days: an additional 5 deaths occurred in the plasma group and 1 death in placebo (normal saline) group.
b. Only one event.
c. 95% CI includes benefits as well as harms; OIS not met.
d. Few events reported. 95% CI may not include clinically meaningful benefit.
e. Trial was terminated early due to futility.
f. Oxygenation and respiration rates are surrogate measures of need for ventilation, morbidity and death.
g. Few events reported do not meet the optimal information size and suggest fragility of the estimate.
h. Using 0.5 event continuity correction.
i. Zero events in the control group. Absolute risk difference not informed by relative risk.

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Supplementary Materials

Study characteristics

- **Table s1.** Should patients (hospitalized or ambulatory) with COVID-19 receive treatment with convalescent plasma vs. no convalescent plasma?

Forest plots

- **Figure s1a.** Outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized patients
- **Figure s1b.** Outcome of mechanical ventilation for convalescent plasma vs. no convalescent plasma in hospitalized patients
- **Figure s1c.** Outcome of adverse events (mild to severe) for convalescent plasma vs. no convalescent plasma in hospitalized patients
- **Figure s1d.** Outcome of mortality for convalescent plasma vs. no convalescent plasma in ambulatory patients
- **Figure s1e.** Outcome of COVID-19-related hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients
- **Figure s1f.** Outcome of all-cause hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients
- **Figure s1g.** Outcome of serious adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients
- **Figure s1h.** Outcome of adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients

Risk of bias

- **Table s2a.** Randomized control studies (convalescent plasma vs. no convalescent plasma)
- **Table s2b.** Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

Table s1. Should patients (hospitalized or ambulatory) with COVID-19 receive treatment with convalescent plasma vs. no convalescent plasma?

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Agarwal / 2020 [1]	India/ 39 tertiary care hospitals	RCT	464 (235/229)	23.7	Median: 52 (42-60)	Hospitalized patients with moderate disease defined as having PaO_2/FiO_2 between 200-300 mmHg, or respiratory rate >24/min with SpO_2 <94% on RA	CP: 2 units of ABO-compatible CP, 200 mL each, infused 24 hours apart	(1) SoC	Antivirals, broad spectrum antibiotics, immunomodulators, other supportive management per institutional protocol, dictated by best available evidence at the time and guidance issued by Indian government	Composite of progression to severe disease or all-cause mortality at day 28 Symptom resolution Oxygen requirement Duration of respiratory support Clinical status Biomarker levels Adverse events	Indian Council of Medical Research
AlQahtani/ 2021 [2]	Bahrain/ 2 medical centers	RCT	40 (20/20)	20.0	Intervention: Mean of 52.6 (14.9) Control: Mean of 50.7 (12.5)	Hospitalized patients with hypoxia ($SpO_2 \leq$ 92% on air, or $PaO_2 <$ 60 mmHg, or $PaO_2/FiO_2 \leq$ 300 mmHg) and receiving supplemental oxygen Excluded patients receiving invasive	CP: 2 units of ABO-compatible CP, 200 mL each, infused over 2 successive days	(1) SoC	Standard supportive treatment, including antipyretics, antivirals, tocilizumab, and antibacterial medication	Invasive or non-invasive ventilation Duration of ventilation Biomarker levels Adverse events	Ministry of Health Bahrain College of Surgeons in Ireland-Bahrain

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						or non-invasive ventilation					
Avendaño-Solà/ 2021 [3]	Spain/ 14 hospitals	RCT	350 (179/171)	34.6	Median: 62.0 (53.0-75.0)	Hospitalized patients with radiographic evidence of pulmonary infiltrates or clinical evidence plus $SpO_2 \leq 94\%$ on RA Excluded patients on mechanical ventilation or high-flow oxygen	CP: 1 unit, 250-300 mL	(1) SoC	Supportive therapy and specific therapy with off-label marketed medications according to local or national guidelines	Mortality at day 15 and 29 Clinical status at day 15 Length of hospitalization Days free from mechanical ventilation or oxygen support Adverse events	Government of Spain, Ministry of Science and Innovation European Regional Development Fund
Balcells/ 2021 [4]	Single center, Santiago, Chile	RCT	58 (28/30)	50	Mean age: 65.8 (range: 27-92)	Hospitalized patients > 18 years old who are less than 7 days from symptom onset with positive SARS-CoV-2 PCR or pending PCR results with imaging consistent with COVID-19 pneumonia and confirmed COVID-19 close contact and CALL score ≥ 9 points and baseline ECOG	Early convalescent (initiated at enrollment) plasma: 2 units (200ml each) separated by 24 hours	Deferred convalescent plasma only if a pre-specified worsening respirator function (Pa02/Fi02 < 200) or if still in hospital for > 7 days after enrollment; 2 units (200ml each)	Antivirals, antibiotics, heparin thromboprophylaxis, and immunomodulators	Composite of In-hospital mortality, mechanical ventilation, or hospital stay > 14 days 30 day mortality Days of mechanical ventilation, high flow nasal cannula Viral clearance Time to respiratory failure development	Fondo de Adopción Tecnológica SiEmpre, SOFOFA Hub, and Ministerio de Ciencia, Tecnología, Conocimiento e Innovación, Chile

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						performance status of 0-2		separated by 24 hours		Serious adverse events TRAILI	
Bégin/ 2021 [5]	Canada (47 sites) US (3 sites)	RCT	938 (625/313)	40.9	Median: 69 (58-79)	Hospitalized patient with confirmed COVID-19 infection on supplemental oxygen, and within 12 days of symptom onset	1 unit of 500 mL of ABO-compatible CP from one donor, or 2 units of 250 mL of CP from two donors	SoC	None	All-cause mortality within 30 days Intubation or death within 30 days Time to intubation or death Ventilator-free days Length of stay Need for organ support QALY Adverse effects	Canadian Institutes of Health Research Ontario COVID-19 Rapid Research Fund Toronto COVID-19 Action Initiative 2020 Fondation du CHU Ste-Justine Ministére de l'Economie et de l'Innovation du Québec Fonds de Recherche du Québec University Health Network

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Emergent Access Innovation Fund University Health Academic Health Science Centre Alternative Funding Plan Saskatchewan Ministry of Health University of Alberta Hospital Foundation Alberta Health Services COVID-19 Foundation Competition Sunnybrook Health Sciences Centre Foundation Fondation du CHUM

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Ottawa Hospital Academic Medical Organization Ottawa Hospital Foundation COVID-19 Research Fund Sinai Health System Foundation McMaster University
Bennett-Guerrero/ 2021 [6]	US/ Stony Brook University Hospital	RCT	74 (59/15)	40.5	Intervention: Mean of 67 (15.8) Control: Mean of 64 (17.4)	Patients hospitalized with positive SARS-CoV-2 PCR test	2 units of ABO-compatible CP (about 480 mL). Each unit infused over 2-14 hours	2 units of standard plasma	Therapies for COVID-19 treatment at discretion of providers, including glucocorticoids, remdesivir, hydroxychloroquine, tocilizumab, sarilumab	All-cause mortality at 90 days Ventilator-free days at day 28 WHO clinical severity scale Antibody levels Adverse effects	Stony Brook Medicine

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Gharbharan/ 2021 [9]	Netherlands/ 14 secondary and academic hospitals	RCT	86 (43/43)	28	Median: 63 (56-74)	Eligible patients were at least 18 years, admitted to a study site for COVID-19 and had clinical COVID-19 disease proven by a positive SARS-CoV-2 reverse transcriptase polymerase chain reaction (RT-PCR) test in the previous 96 hours	CP: 300ml of plasma with anti-SARS-CoV-2 neutralizing antibody titers of at least 1:80; "Patients without a clinical response and a persistently positive RT-PCR could receive a second plasma unit after five days."	(1) SoC	Off-label use of EMA-approved drugs (e.g., chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra)	Mortality Improvement in WHO COVID-19 disease severity score on day 15 Time to discharge Hazard ratio/95% CI	Erasmusfoundation
Joyner, Senefeld, et al/ 2020 [10]	USA/2807 acute care facilities in the US and territories	Open-label, Expanded Access Program	35,322	39.7	N/A	Hospitalized with a laboratory confirmed diagnosis of infection with SARS-CoV-2, and had (or were judged by a healthcare provider to be at high risk of progression to) severe or life-	IV Minimum of one unit approximately 200 mL = one unit (Low IgG, Medium IgG and High IgG)	N/A	angiotensin receptor blocker, ACE inhibitor, AZ, remdesivir, steroids, chloroquine, HCQ	Mortality at Day 7 (Days to Transfusion ≤3 days and 4+ Days) Mortality at Day 30 (Days to Transfusion ≤3 days and 4+ Days)	Department of Health and Human Services Office of the Assistant Secretary Preparedness and Response Biomedical Advanced

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						threatening COVID-19					Research and Development National Center for Advancing Translational Sciences (NCATS) grant National Heart, Lung, and Blood Institute (NHLBI) National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Natural Sciences and Engineering Research Council of Canada (NSERC) National Institute of Allergy and Infectious

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Disease (NIAID) National Heart Lung and Blood Institute National Institute on Aging (NIA) Schwab Charitable Fund (Eric E Schmidt, Wendy Schmidt donors) United Health Group National Basketball Association (NBA) Millennium Pharmaceuticals Octapharma USA, Inc

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											The Mayo Clinic
Joyner, Wright, et al/ 2020 [11]	USA/ Over 2,000 acute care facilities registered	Retrospective cohort	5000	36.5	Median: 62.3 (18.5-97.8)	Severe or life-threatening COVID-19 or judged by a healthcare provider to be at high risk of progression to severe or life-threatening COVID-19 Severe or life-threatening COVID-19 is defined by one or more of the following: dyspnea, respiratory frequency ≥ 30 breaths/min, SpO_2 ≤ 93%, lung infiltrates >50% within 24-28h of enrollment, respiratory failure, septic shock, and multiple organ dysfunction or failure	IV 200-500 mL ABO-compatible COVID-19 CP	N/A	N/A	Mortality over first 7 days after CP transfusion Adverse events	Mayo Clinic Biomedical Advanced Research and Development Authority National Center for Advancing Translational Sciences National Heart, Lung, and Blood Institute National Institute of Diabetes and Digestive and Kidney Diseases Natural Sciences and Engineering Research Council

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											National Institute of Allergy and Infectious Diseases Schwab Charitable Fund United Health Group National Basketball Association (NBA) Millennium Pharmaceuticals, Octopharma USA, Inc
Kirenga/ 2021 [12]	Uganda/ Mulago National Referral Hospital	RCT	136 (69/67)	28.7	Median: 50 (38.5-62)	Patients with positive SARS-CoV-2 PCR test	2 units of ABO-compatible CP infused over 2-3 hours at a rate of 1.4 to 2 mL/min, with 3 hours between infusions.	SoC (Ugandan National Guidelines)	Most recent Uganda National Treatment Guidelines available (last updated April 2020) include hydroxychloroquine, vitamin C, zinc, thiamine, empiric antibiotics,	Time to viral clearance Time to symptom resolution Clinical status on WHO ordinal scale Progression to severe/critical condition (SpO_2	Makerere University Research and Innovation Fund

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
									heparin, and statins	<93% or needing supplemental O_2) Adverse events	
Korley/ 2021 [13]	USA/ 48 Emergency departments across 21 states	RCT	511 (257/254)	54	Median: 54 (41-62)	Positive SARS-CoV-2 NAAT, symptom onset within 7 days of enrollment, and either greater than 50 years old or have at least 1 risk factor for disease progression	1 unit of high-titer ABO-compatible CP	Placebo	None	All-cause mortality within 30 days Disease progression within 15 days WHO illness severity scale Time until worsening of symptoms Hospital-free days within 15 days Adverse events	National Heart, Lung, and Blood Institute National Institute of Neurological Disorders and Stroke Biomedical Advanced Research and Development Authority Operation Warp Speed
Körper/ 2021 [14]	Germany (13 hospitals)	RCT	105 (53/52)	26.7	Median: 60 (53-66)	Patients with a positive SARS-CoV-2 PCR test between 18-75 years old, with severe COVID-19 disease (RR ≥30 on ambient air, requirement of any respiratory	One unit of CP given on day 1, 3, and 5. CP collected from donors had a 50% plaque reduction neutralization	SoC	Other antiviral treatments and/or supportive treatments according to institutional protocols	Mortality Treatment success day 21 (survival, no ventilation support, no ICU treatment, and RR <30) Time to clinical improvement of ≥2	German Federal Ministry of Health

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						support, or need of ICU treatment)	test titer of at least 1:20.			points on an ordinal severity scale Duration of ventilatory support Length of hospitalization Time to ICU discharge Time until negative SARS-CoV-2 PCR Adverse events	
Li/ 2020 [15]	China/ 7 medical centers	RCT	103 (52/51)	41.7	Median: 70 (62-78)	Hospitalized patients with severe and/or life-threatening COVID-19: Severe: respiratory distress (≥30 breaths/min; in resting state, SpO_2 of 93% or less on room air; or PaO_2/FIO_2 of 300 or less; Life-threatening: respiratory failure requiring	CP: transfusion dose approximately 4 to 13 mL/kg; approximately 10 mL for the first 15 minutes, which was then increased to approximately 100 mL per hour with close monitoring	(1) SoC	Possible treatments included antiviral medications, antibacterial medications, steroids, human immunoglobulin , Chinese herbal medicines, and other medications	Mortality at day 28 Clinical improvement at day 28 Time to clinical improvement (days) Time from hospitalization to discharge Adverse events	Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences Nonprofit Central Research Institute Fund of Chinese Academy of Medical Sciences

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						mechanical ventilation; shock; or other organ failure (apart from lung) requiring ICU monitoring					
Liu/ 2020 [16]	USA/ The Mount Sinai Hospital	Retrospective cohort with matching	39	36.0	Mean: 55 (13)	Hospitalized patients; disease severity assessed by O_2 supplementation required and laboratory parameters	CP 2 units of ABO-type matched CP once, each unit 250mL infused over 1 to 2 hrs	(1) SoC	Antimicrobial agents (AZ), broad spec antibiotics, HCQ; investigational antivirals); therapeutic anticoagulation; anti-inflammatory agents	Mortality Worsened clinical condition by day 14 Follow-up time Hazard ratio for plasma	N/A
Libster/ 2021 [17]	Argentina / 13 centers	RCT	160 (80/80)	62.5%	77.2 (8.6)	Ambulatory patients 65 or older with at least one of each sign or symptom in the following two categories for less than 48 hours: temp >37.5, unexplained sweating, or chills; and dry cough, dyspnea, fatigue, myalgia, anorexia, sore throat,	Convalescent Plasma 250 ml with IgG titer >1:1000 against SARS-CoV-2 x 1 dose	Placebo	None	Mortality Development of severe respiratory disease at day 15 Life-threatening respiratory disease Critical systemic illness	Bill and Melinda Gates Foundation Fundación INFANT Pandemic Fund

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
						dysgeusia, anosmia, or rhinorrhea.					
O'Donnell/ 2021 [18]	5 hospitals in New York City (USA) and Rio de Janeiro (Brazil)	RCT	223 (150/73)	34	Median age: 61 years	Hospitalize d patients ≥ 18 years with positive SARS-CoV-2 within 14 days of randomization, with infiltrates on chest imaging and oxygen saturation ≤ 94% on RA on oxygen, mechanical ventilation, or ECMO	A single unit of convalescent plasma given over 2 hours	Control	Patients could receive steroids, remdesivir, hydroxychloroquine, and antibacterial agents	Time to clinical improvement Clinical status at day 28 Adverse events through day 28	Amazon Foundation
Pouladzadeh/ 2021 [19]	Iran/ Ravi Hospital, Ahvaz	RCT	60 (30/30)	45	Intervention: Mean of 53.5 (10.3) Control: Mean of 57.2 (17)	Patients with a positive SARS-CoV-2 PCR test, positive changes on CT scan, were within 7 days of symptom onset, SpO2 <94% on room air, and WHO severity score > 4	One unit of CP given within 4 hours of admission. Second unit given at discretion of physician if no improvement	SoC	SoC included chloroquine phosphate and lopinavir/ritonavir	2-month mortality Length of hospitalization Improvement in WHO severity score Change in cytokine levels Adverse effects	Ahvaz University of Medical Sciences

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
Ray/ 2020 [20]	India/ ID & BG Hospital, Kolkata	RCT	80 (40/40)	28.8	Female: Mean of 61.4 (11.3) Male: Mean of 61.4 (12.2)	Hospitalized patients with severe disease (fever or suspected respiratory infection plus one of the following: respiratory rate >30/min, severe respiratory distress, or SpO_2 <90% on RA) with mild-moderate ARDS (PaO_2/FiO_2 100-300mmHg) not on mechanical ventilation	CP: 2 units of ABO-matched CP, 200 mL each, administered on 2 successive days	(1) SoC	Most patients received hydroxychloroquine for 5 days, azithromycin for 5 days, ivermectin for 5 days, and doxycycline for 10 days. Standard of care at trial site for patients with ARDS also included: corticosteroids and anticoagulation in addition to indicated supportive therapy. Several patients also received remdesivir and one patient received tocilizumab.	30-day mortality SpO_2/FiO_2 ratio over 10 days Length of hospitalization Biomarker levels	Council of Scientific Industrial Research, Government of India Fondation Botnar
RECOVERY Collaborative Group	United Kingdom/ National Health Service	RCT	N= 11558 (5795/5763)	36	Mean: 63.5 (14.7)	Hospitalized patients of any age with clinical suspected or laboratory	Usual care plus convalescent plasma, first unit of 275ml convalescent	Usual care	Co-interventions according to main randomization and use of steroids were	Mortality at day 28 Time to hospital discharge	UK Research and Innovation (Medical Research Council) and

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
(Horby)/ 2021 [21]	(NHS) hospitals					confirmed SARS-CoV-2	plasma given as soon as possible after randomization and a second unit of 275ml the following day (at least 12 hours after the first)		permitted; 93% of participants in the CP arm received steroids vs 92% of usual care participants	Receipt of mechanical ventilation or death Transfusion elated adverse events at 72 hours Cause-specific mortality Major cardiac arrhythmia	National Institute of Health Research
Sekine/ 2021 [22]	Brazil/ Hospital de Clínicas de Porto Alegre	RCT	160 (80/80)	41.9	Median: 60.5 (48-68)	Patients with positive SARS-CoV-2 PCR test and within 15 days of symptom onset, with severe disease (RR > 30 breaths/min, SpO2 ≤ 93% in RA, PaO2/FIO2 ≤ 300, supplemental oxygen)	2 infusions 48 hours apart of 300 mL of CP	SoC	Glucocorticoids, "other immunomodulators", antibiotics, antivirals	All-cause mortality at 14 and 28 days Proportion with clinical improvement at 28 days RT-PCR for SARS-CoV-2 Clinical status using a 6-level ordinal scale Time to hospital discharge Days free from oxygen support	Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul Fundação de Amparo à Pesquisa do Estado de São Paulo Instituto Cultural Floresta

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
										SOFA and NEWS 2 scores Length of ventilator support Adverse events	
Simonovich/ 2021 [23]	Argentina / 12 clinical sites	RCT	334 (228/105)	32.3	Median: 62 (52-72)	Hospitalized patients with at least one of the following: SaO_2 < 93% on RA, PaO_2/FiO_2 < 300 mmHg, SOFA or mSOFA score 2 or more points above baseline status Excluded patients on mechanical ventilation or multiorgan failure	CP: IV 5-10 mL/kg with limit of 400 mL for those with body weight < 70 kg and limit of 600 mL for those with body weight > 70 kg SARS-CoV-2 IgG antibody titer > 1:800	(1) SoC	Allowed to receive antiviral agents, glucocorticoids, or other therapies for COVID-19 according to standard of care at institution	Clinical status at day 7, 14, and 30 (including mortality) Time to hospital discharge Time to discharge from ICU Adverse events	Research Council of the Hospital Italiano de Buenos Aires
Sullivan 2021	US/23 sites	RCT	1225 (592/589)	57%	CP: 42 (31.5-54) Control: 44 (33-55)	Adult patients who were positive for SARS CoV-2 who within 8 days of symptom onset	Convalescent plasma with minimum titers of ≥ 1:320	Control plasma	Allowed to receive steroids. Monoclonals prior to plasma were not permitted however were allowed after plasma receipt.	COVID-19 related hospitalization at day 28 Mortality SAEs	US Department of Defense Defense Health Agency Bloomberg Philanthropies

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											State of Maryland NIH/NIAID NCATS Moriah Fund Octapharma HealthNetwork Foundation Shear Family Foundation
Writing Committee for the REMAP-CAP Investigators (Estcourt), et al/ 2021 [24]	Australia, Canada, UK, US	RCT	1987 (1078/909)	32.3	CP: Median 61 (52-69) SoC: 61 (52-70)	Adult, hospitalized patient with confirmed SARS-CoV-2 infection with moderate or severe illness	CP: High titer, ABO compatible	SoC	Standard of care at trial site, could also be randomized to another domain of investigational treatment in REMAP-CAP. 94% of patients were treated with glucorticoids	In hospital mortality, day 28 and 90 day mortality, Respiratory and cardiovascular organ-free support days by day 21 Progression to invasive mechanical ventilation, ECMO, or death	Monash University Utrececht Medical Center St. Michaels Hospital Global Coalition for Adaptive Research Platform for European

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
									45% of patients received remdesivir	ICU and hospital length of stay WHO ordinal scale at day 14 VTE at day 90 and SAEs	Preparedness Against (Re-) emerging Epidemics Australian National Health and Medical Research Council Health Research Council of New Zealand Canadian Institute of Health National Institute For Health Research The EU programme Emergency Support Instrument UPMC Learning While Doing Program Breast Cancer

Study/ year	Country/ Hospital	Study design	N subjects (intervention/ comparator)	% female	Age mean (SD) / Median (IQR)	Severity of disease	Intervention (study arms)	Comparator	Co-interventions	Outcomes reported	Funding source
											Research Foundation French Ministry of Health Minderoo Foundation Wellcome Trust

Figure s1a. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma in hospitalized patients

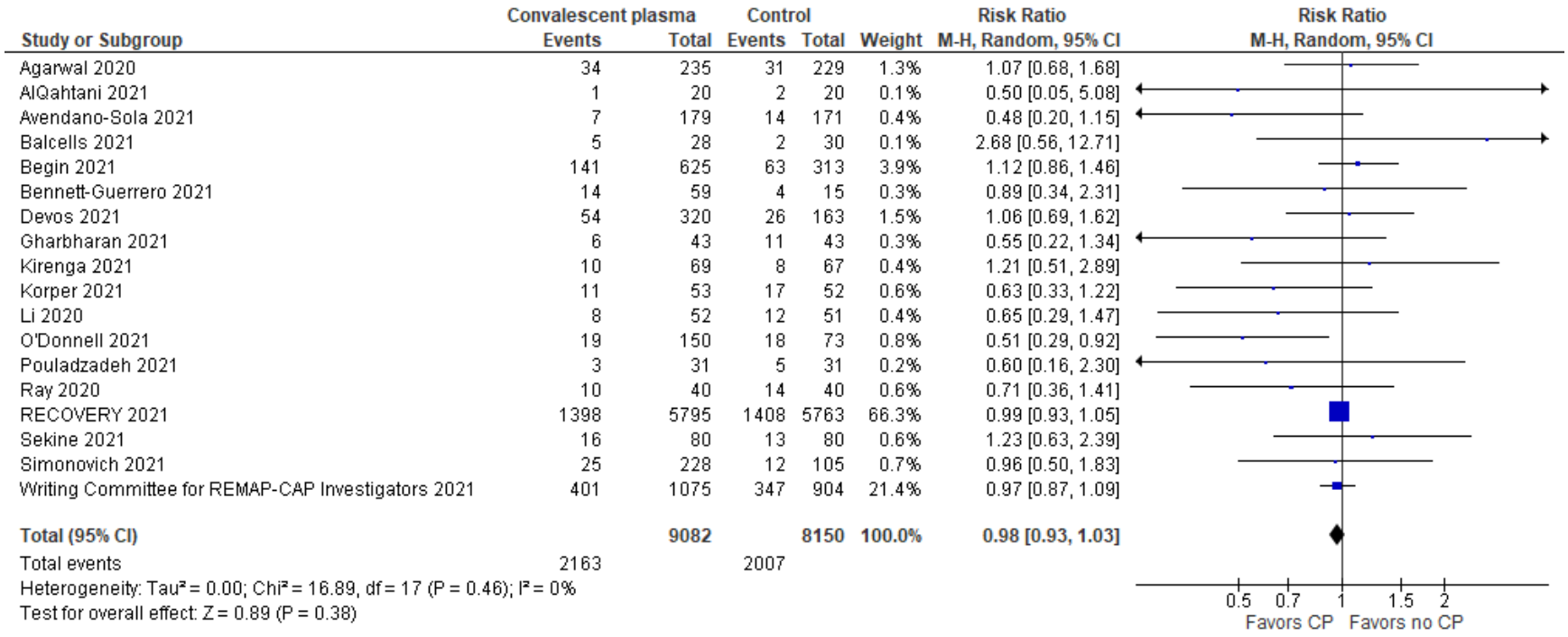

Figure s1b. Forest plot for the outcome of mechanical ventilation for convalescent plasma vs. no convalescent plasma in hospitalized patients

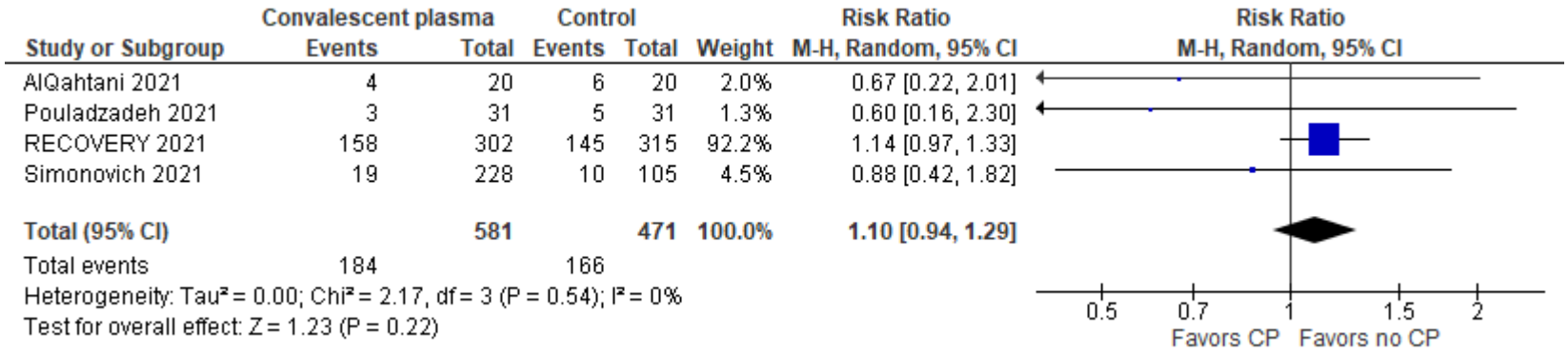

Figure s1c. Forest plot for the outcome of adverse events (mild to severe) for convalescent plasma vs. no convalescent plasma in hospitalized patients

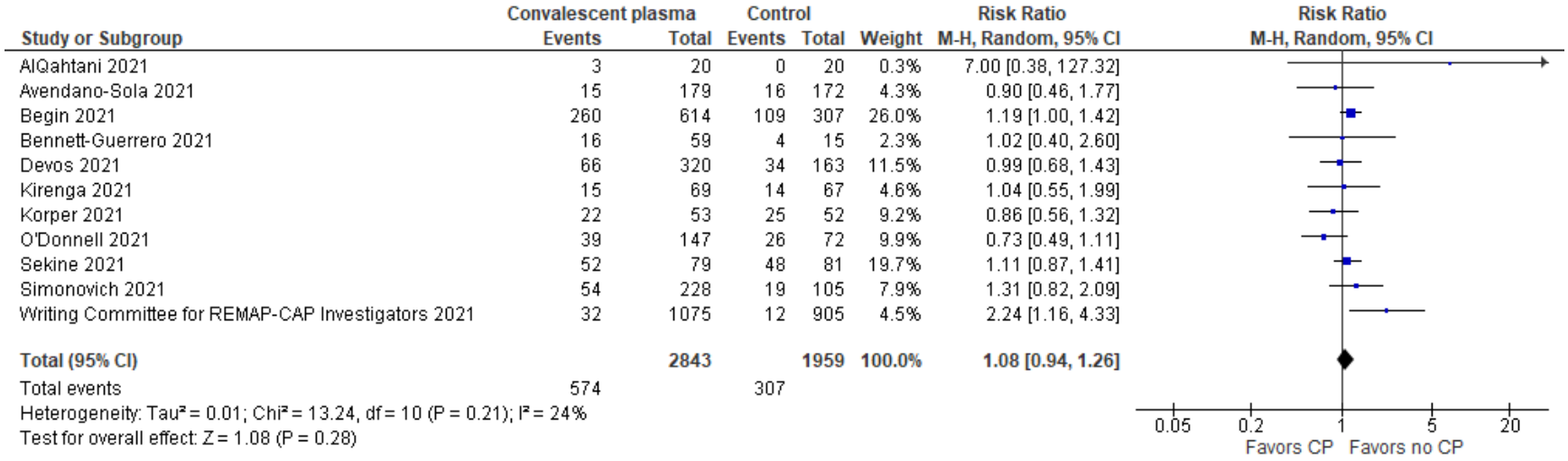

Figure s1d. Forest plot for the outcome of mortality for convalescent plasma vs. no convalescent plasma in ambulatory patients

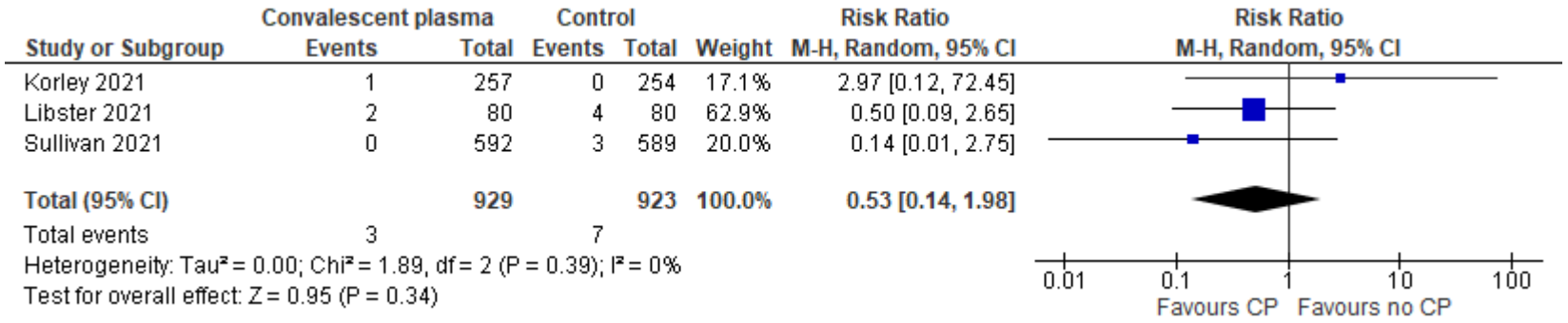

Figure s1e. Forest plot for the outcome of COVID-19-related hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients

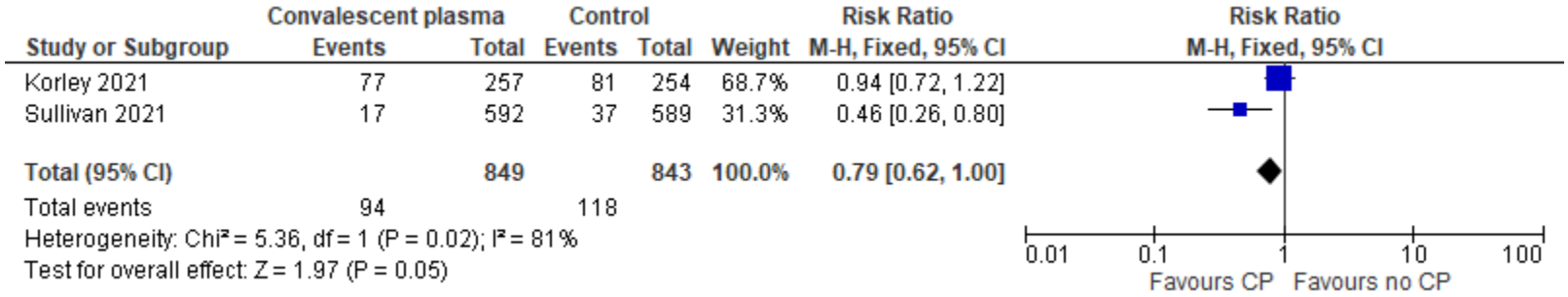

Figure s1f. Forest plot for the outcome of all-cause hospitalizations for convalescent plasma vs. no convalescent plasma in ambulatory patients

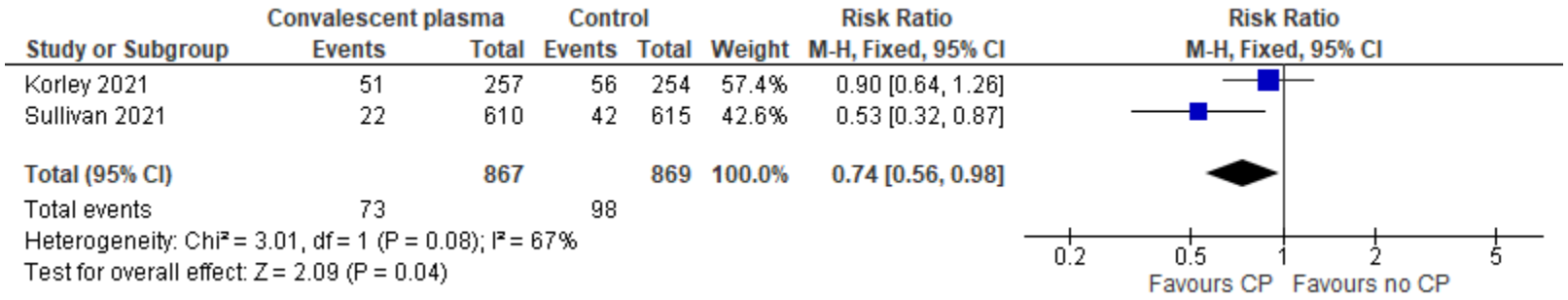

Figure s1g. Forest plot for the outcome of serious adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients

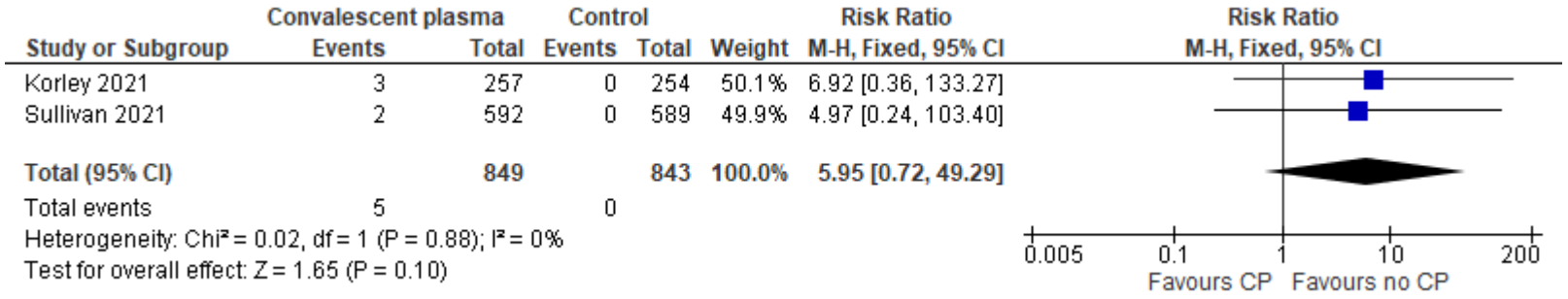

Figure s1h. Forest plot for the outcome of adverse events for convalescent plasma vs. no convalescent plasma in ambulatory patients

Table s2a. Risk of bias for randomized controlled studies (convalescent plasma vs. no convalescent plasma)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Agarwal 2020 [1]							
AlQahtani 2021 [2]							
Avendaño-Solà 2021 [3]							
Balcells 2021 [4]							
Bégin 2021 [5]							
Bennett-Guerrero 2021 [6]							
Devos 2021 [7]							
Gharbharan 2021 [9]							
Kirenga 2021 [12]							
Korley 2021 [13]							
Körper 2021 [14]							
Li 2020 [15]							
Libster 2021 [17]							
O'Donnell 2021 [18]							
Pouladzadeh 2021 [19]							
Ray 2020 [20]							
RECOVERY Collaborative Group (Horby) 2021 [21]							

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Sekine 2021 [22]							
Simonovich 2021 [23]							
Sullivan 2021 [24]							
Writing Committee for the REMAP-CAP Investigators (Estcourt) 2021 [25]							

Low	High	Unclear

Table s2b. Risk of bias for non-randomized studies (convalescent plasma vs. no convalescent plasma)

Study	Bias due to confounding	Selection bias	Bias in classification of interventions	Bias due to deviations from interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported results
Duan 2020 [8]							
Joyner, Senefeld, et al 2020 [10]							
Joyner, Wright, et al 2020 [11]							
Liu 2020 [16]							

Low	Moderate	Serious	Critical

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