Efficacy and harms of convalescent plasma for the treatment of COVID-19 patients: a systematic review and meta-analysis

Supplementary material

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1. Supplementary Appendix S1: Pubmed search strategy

("convalesce"[All Fields] OR "convalesced"[All Fields] OR "convalescence"[MeSH Terms] OR "convalescence"[All Fields] OR "convalescences"[All Fields] OR "convalescent"[All Fields] OR "convalescents"[All Fields] OR "convalescing"[All Fields]) AND ("plasma"[MeSH Terms] OR "plasma"[All Fields] OR "plasmas"[All Fields] OR "plasma s"[All Fields]) AND ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR "covid 19"[All Fields] OR "sars cov 2"[All Fields] OR (("coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields])) OR ("covid 19"[Supplementary Concept] OR "covid 19"[All Fields] OR "coronavirus disease 19"[All Fields]) OR ("severe acute respiratory syndrome"[MeSH Terms] OR ("severe"[All Fields] AND "acute"[All Fields] AND "respiratory"[All Fields] AND "syndrome"[All Fields]) OR "severe acute respiratory syndrome"[All Fields]) OR ("severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields]))

2. Supplementary Appendix S2: Detailed description of included RCTs and cohorts evaluating convalescent plasma

RCTs

The RCT by Li et al.[19] (ChiCTR2000029757) assessed intravenous (IV) convalescent plasma 4 to 13mL/kg of recipient body weight vs. standard of care (SOC) based on Chinese national COVID-19 treatment guidelines and hospital practice in hospitalized, confirmed RT-PCR SARS-CoV-2 infection, adult patients with severe or life-threatening COVID-19. The primary outcome was time to clinical improvement within 28 days, defined as patient discharge or a reduction of two points on a 6-point disease severity scale. Secondary outcomes were 28-day all-cause mortality, duration of hospitalization, and conversion of nasopharyngeal swab viral PCR results. This study was terminated early due to pandemic containment in Wuhan, and no new cases were reported for seven consecutive days after March 24th 2020, enrolling their last patient (103 out of 200 required) on March 27th. There was no significant difference in time to clinical improvement within 28 days (HR 1·40, 95% CI 0·79 to 2·49) and in 28-day mortality (OR 0·59, 95% CI 0·22 to 1·59). Li et al. RCT reported 1·9% of serious adverse events, and 3·9% of overall adverse events, both patients coming from the CP arm. Rash was reported in 1·9%, and transfusion reactions in 3·9% of patients. The SOC arm did not report any adverse events. Also, they reported a median of 41 days (CP) vs. 53 days (SOC) of hospital stay, 1·9% vs 0% of treatment discontinuation, and a median of 28 days vs. indeterminate of time to clinical improvement.

The RCT by Gharbharan et al.[20] (NCT04342182) assessed 300mL of IV convalescent plasma, and a repeat dose after 5 days if there was no clinical response vs. SOC based on the Dutch COVID-19 treatment guidelines in hospitalized, PCR-confirmed COVID-19 patients who were not in mechanical ventilation for more than 96 hours and without IgA deficiency. The primary outcome was 15-day all-cause mortality. Secondary outcomes were undefined improvement of 8-point WHO disease severity scale at 15 days, length of hospital stay, and adverse events. This trial was stopped prematurely when 86 out the 426 required were included, as most of COVID-19 patients had neutralizing antibodies at baseline. The adjusted odds ratio (OR) for mortality was OR 0·95 (95% CI 0·20 to 4·67), and for undefined improvement was OR 1·30 (95% CI 0·52 to 3·32). There was no association with a shorter

time to discharge from hospitalization (HR 0·88, 95%CI 0·49 to 1·60), and there were no adverse events reported.

The RCT by Avendaño-Solà et al.[21] (NCT04345523) assessed one unit of 250-300 mL of IV convalescent plasma vs. SOC according to local or national guidelines in hospitalized, PCR-confirmed COVID-19 patients with either radiographic or clinical evidence plus SpO2≤94% on room air, and within 12 days from the onset of symptoms. Authors excluded patients on mechanical ventilation (invasive or non-invasive) and high-flow oxygen devices. Their primary outcome was proportion of patients in categories 5, 6 or 7 at day 15 using a 7-point category ordinal COVID-19 severity scale. Secondary outcomes were time to clinical improvement of one category; mean change on the ordinal severity scale from baseline to 3, 5, 8, 11, 15 and 29 days; proportion of patients in categories 5, 6, or 7 at day 29; all-cause mortality at day 15 and 29; duration of hospital stay; numbers of days alive and free from oxygen; and numbers of days alive from mechanical ventilation. This trial was stopped early (81 out of 278 required) due to the lack of new patients. Progression to categories 5-7 was 0/38 (0%) in the CP group vs. 6/43 (17%) in the control group (RD -14%, 95%CI -24·3% to -3·6%). All-cause mortality at 15 days was not decreased with CP in comparison to SOC (RR 0·13, 95% CI 0·01 to 2·26). Six patients out of 38 from CP group had SAE vs. seven out of 43 from the SOC group.

The RCT by Agarwal et al.[22] (CTRI/2020/04/024775) assessed two doses of 200 mL of IV CP, transfused 24 hours apart, vs. SOC in hospitalized PCR-confirmed moderate adult COVID-19 with either PaO_2/FiO_2 200 to 300 or respiratory rate >24/min with SpO2≤93% on room air; authors excluded critically ill patients (PaO_2/FiO_2<200 or shock). Their primary outcome was a composite measure of progression to severe disease (i.e. PaO_2/FiO_2 <100 any time within 28 days) or all-cause mortality at 28 days. Secondary outcomes were clinical improvement and symptom resolution on day 7; variation in FiO_2 on days 1, 3, 5, 7 and 14; total duration of respiratory support during hospitalization and post-enrollment duration of respiratory support until day 28 or discharge whichever was earlier; negative conversion of SARS-CoV-2 viral RNA on days 3 and 7; levels of biomarkers on days 3 and 7 post enrolment compared to baseline; requirement of vasopressor support; and clinical improvement on WHO ordinal scale on day 0, 1, 3, 5, 7, 14, and 28 days. Safety outcomes

were frequency of minor and serious adverse events within 6 hours of CP transfusion. All-cause mortality at 28 days was found in 34/235 (14·5%) with CP vs. 31/229 (13·5%) with SOC (RR 1·07; 95%CI 0·68 to 1·68), and progression to severe disease was found in 17/235 (7·2%) with CP vs. 17/229 (7·4%) with SOC (RR 0·97, 95%CI 0·51 to 1·86). Composite outcome was found in 44 (18·7%) with CP and 41 (17·9%) with SOC (adjusted OR 1·09; 95% CI 0·67 to 1·77). Six patients in each arm had minor adverse events such as local pain in infusion site, chills, dizziness, fever, tachycardia and dyspnea. Mortality was assessed as possibly related to CP transfusion in 3 patients (1·3%).

The RCT by Simonovich et al.[23] (NCT04383535) assessed IV convalescent plasma 5 to 10 mL/kg of recipient body weight vs. placebo (normal saline) in addition to SOC. Patients were allowed to receive antivirals, glucocorticoids according to the SOC at the provider health care institution. The primary outcome was clinical status 30 days after intervention measured by an adapted 6-point WHO ordinal scale. Secondary outcomes were clinical status on the ordinal scale at days 7 and 14 and at the time to discharge, time to discharge from ICU, time to improvement in at least two categories on the ordinal scale, time to death, time to full functional recovery, adverse and serious adverse events. At day 30, there was no significant difference between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (OR 0.81 95% CI 0.52-1.35). The 30-day all-cause mortality was 25 out of 228 (11%) in the convalescent plasma group and 12 out of 105 (11.4%) in the placebo group. No significance difference was seen in the ordinal scale at days 7 and days 14. No significant differences were found in the overall incidence of adverse and serious adverse events. Eleven out of 228 patients presented infusion-related adverse events in the plasma group vs. 2 out of 105 patients in the placebo group (OR 2.62 95% CI 0.57-12.04). Five patients in the plasma group had nonhemolytic febrile reactions.

Cohort studies

Hegerova et al.[24] was matched cohort that assessed 20 severe or critically-ill patients receiving one unit of ABO compatible plasma and 20 patients receiving SOC. The primary outcome was clinical improvement at days 7 and 14 measured with the WHO 8-point ordinal scale. Median WHO scale was 5 at CP infusion which improved to 4·5 at day 7 and 3·5 at day 14, almost identical to controls where median WHO scale improved from 5 to 4·5 at day

7 and 3 at day 14. No adverse events with CP were reported. At 7 days of follow-up, 25% of patients were discharged, while 10% had died, no additional deaths occurred by day 14.

Liu et al.[25] was a matched cohort that assessed 39 severe or critically-ill patients receiving 2 units of 250 mL CP vs 156 controls. The primary outcome, O_2 supplementation requirement, was considered to have worsened if it changed from a lower to a higher severity category compared to day 0. Four categories were included: room air, low flow oxygen delivery, high-flow oxygen delivery and mechanical ventilation. Oxygen worsening occurred in 18% of CP patients and 24·3% of control (OR 0·86, 95% CI 0·75 to 0·98). Mortality was 12·8% in the CP group vs. 24·3% in the control group (RR 0·53, 95% CI 0·22 to 1·25).

Rasheed et al.[26] was a matched cohort that assessed 21 severe or critically-ill patients receiving an unspecified volume of highly elevated SARS-COV-2 IgG and 28 patients receiving SOC. They evaluated safety of CP within three hours, time to PCR seroconversion and survival or death rate. Only one patient developed an allergic reaction and the mortality risk in CP group (4·8%) was lower than in control group (28·6%) (RR 0·16, 95%CI 0·02 to 1·23).

Zeng et al.[27] was an unmatched cohort that assessed six severe or critically-ill patients receiving 300 mL of CP and 15 patients receiving SOC. The primary outcome evaluated was death or recovery/discharge. Mortality occurred in 83·3% in CP group vs. 93·3% in controls (RR 0·89, 95% CI 0·61 to 1·31).

Abolghasemi et al.[28] was a matched cohort that assessed 115 severe COVID-19 patients receiving 500 mL of CP over 4 hours vs. 74 SOC patients. Their primary outcome, hospital length of stay was significantly lower (9·54 days) in convalescent plasma group compared with control group (12·88 days) (MD -3·34 days, 95% CI -5·10 to -1·58). Also, all-cause mortality was not significantly lower in the CP group (14·8%) vs the control group (24·3%) (RR 0·61, 95% CI 0·34 to 1·10).

Salazar et al.[29] was a propensity-matched cohort. A secondary propensity score matching was done based on ventilation status at day 0. This study included 484 severe and or life-

threatening COVID-19 patients from which 136 received CP and 251 received SOC. Their primary outcome, all-cause mortality, was not significantly lower in the CP group (37%) vs. the control group (7·6%) (RR 0·49, 95% CI 0·19 to 127).

3. Supplementary Appendix S3: References of case series studies

S1. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ. Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea. *J Korean Med Sci*. 2020 Apr;35(14):e149. DOI: https://doi.org/110.3346/jkms.2020.35.e149.

S2. Abdullah HM, Hama-Ali HH, Ahmed SN, Ali KM, Karadakhy KA, Mahmood SO. Severe refractory COVID-19 patients responding to convalescent plasma; A case series. *Annals of Medicine and Surgery*. 2020; 56: 125-127. DOI: https://doi.org/10.1016/j.amsu.2020.06.018.

S3. Bobek I, Gopcsa L, Reti M, Beko G, Hancz L, Lakatos B. Successful administration of convalescent plasma in critically ill COVID-19 patients in Hungary: The first two cases. *Orvosi Hetilap*. 2020; 161(27): 1111-21. DOI: https://doi.org/10.1556/650.2020.31901

S4. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. *PNAS.* 2020; 117(17): 9490-96. DOI: https://doi.org/10.1073/pnas.2004168117

S5. Erkurt MA, Sarici A, Berber I, Kuku I, Kaya E, Ozgul M. Life-saving effect of convalescent plasma treatment in COVID-19 disease: Clinical trial from Eastern Anatolia. *Transfusion and Apheresis Medicine*. 2020. DOI: https://doi.org/10.1016/j.transci.2020.102867

S6. Hartmann W, Hess AS, Connor JP. Hospitalized COVID-19 patients treated with Convalescent Plasma in a mid-size city in the midwest. [Pre-Print] *medRxiv*. 2020. 06.19.20135830. DOI: https://doi.org/10.1101/2020.06.19.20135830

S7. Jin C, Gu J, Youshu Y, Long Q, Zhang Q, Zhou H. Treatment of Six COVID-19 Patients with Convalescent Plasma [Pre-Print] *medRxiv*. 2020.05.21.20109512. DOI: https://doi.org/10.1101/2020.05.21.20109512

S8. Martinez-Resendez MF, Castilleja-Leal F, Torres-Quintanilla A, Rojas-Martinez A, Garcia-Rivas G, Ortiz-Lopez R. Initial experience in Mexico with convalescent plasma in COVID-19 patients with severe respiratory failure, a retrospective case series. [Pre—Print] *medRxiv*. 2020.07.14.20144469. DOI: https://doi.org/10.1101/2020.07.14.20144469

S9. Olivarez-Gazca JC, Priesca-Martin JM, Ojeda-Laguna M, Garces-Eisele J, Soto-Olivera S, Palacios-Alonso A. Infusion of Convalescent Plasma is associated with Clinical

Improvement in Critically Ill Patients with COVID-19: A Pilot Study. *Rev Invest Clin*. 2020; 72(3):159-64. DOI: https://doi.org/10.24875/RIC.20000237

S10. Pei S, Yuan X, Zhang ZZ, Yao RR, Xie Y, Shen MM. Convalescent Plasma to Treat COVID-19: Chinese Strategy and Experiences. [Pre-Print] *medRxiv.* 2020.04.07.20056440. DOI: https://doi.org/10.1101/2020.04.07.20056440

S11. Perotti C, Baldanti F, Bruno R, Delfante C, Seminari E, Casari S. Mortality reduction in 46 severe Covid-19 patients treated with hyperimmune plasma. A proof of concept single arm multicenter interventional trial. [Pre-Print] *medRxiv.* 2020.05.26.20113373. DOI: https://doi.org/10.1101/2020.05.26.20113373

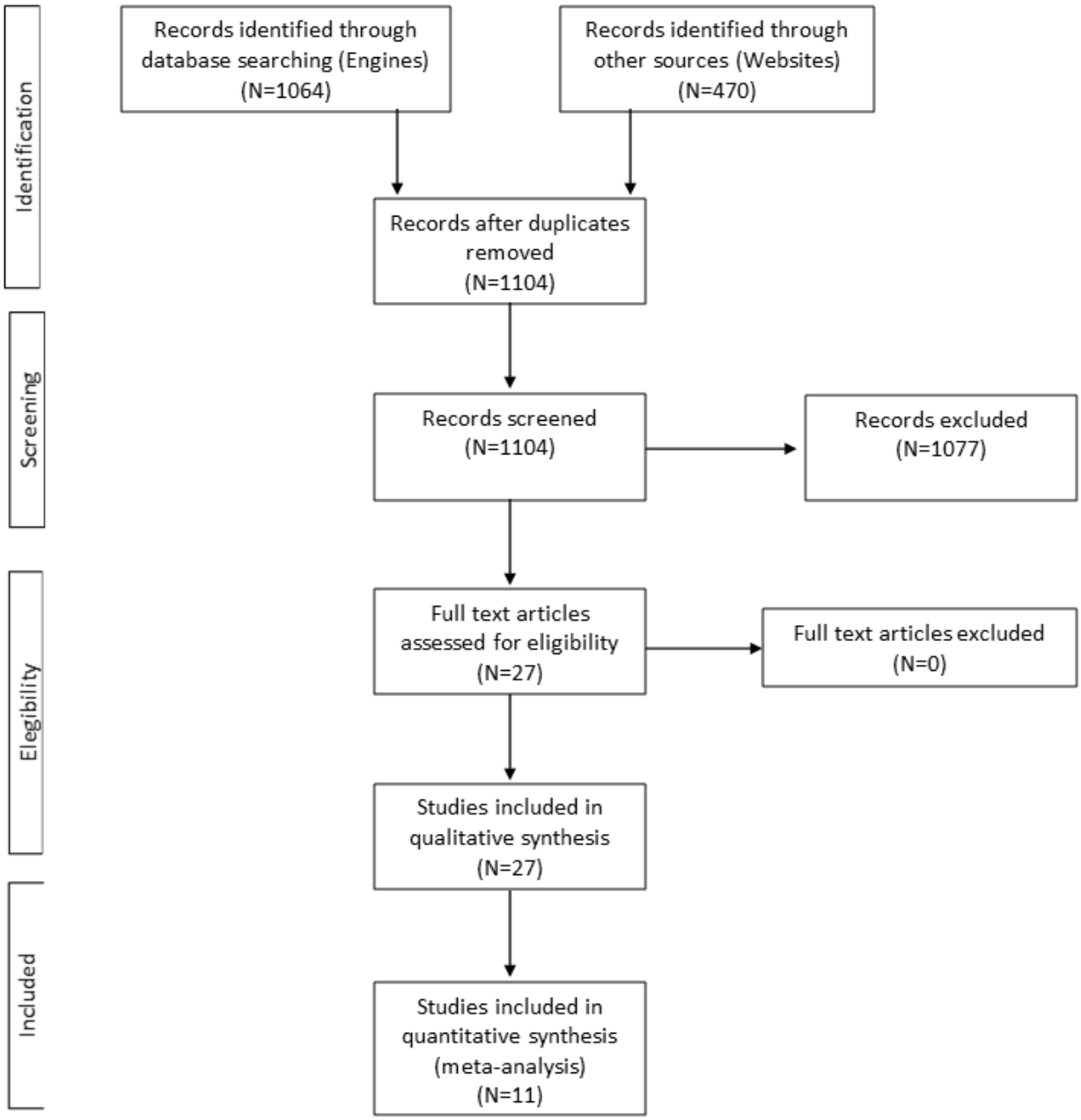
S12. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA. Treatment of Coronavirus Disease 2019 (COVID-19) patients with Convalescent Plasma. *The American Journal of Pathology*. 2020; 190(8): 1680-90. DOI: https://doi.org/10.1016/j.ajpath.2020.05.014

S13. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA*. 2020;323(16):1582–1589. DOI: https://doi.org/10.1001/jama.2020.4783

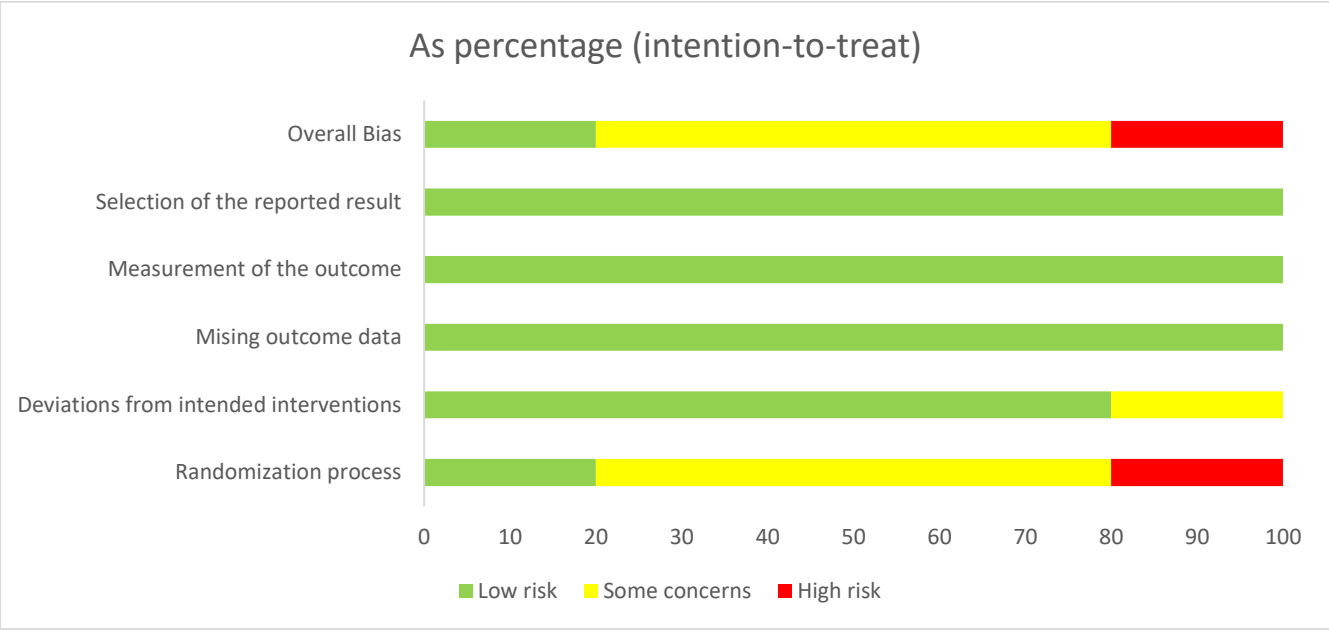
S14. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F. Treatment with Convalescent Plasma for COVID-19 patients in Wuhan, China. *Journal of Medical Virology*. 2020: 1-12. DOI: https://doi.org/10.1002/jmv.25882

S15. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen Y. Treatment with Convalescent Plasma for Critically Ill Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *Chest*. 2020;158(1): e9-e13. DOI: https://doi.org/10.1016/j.chest.2020.03.039

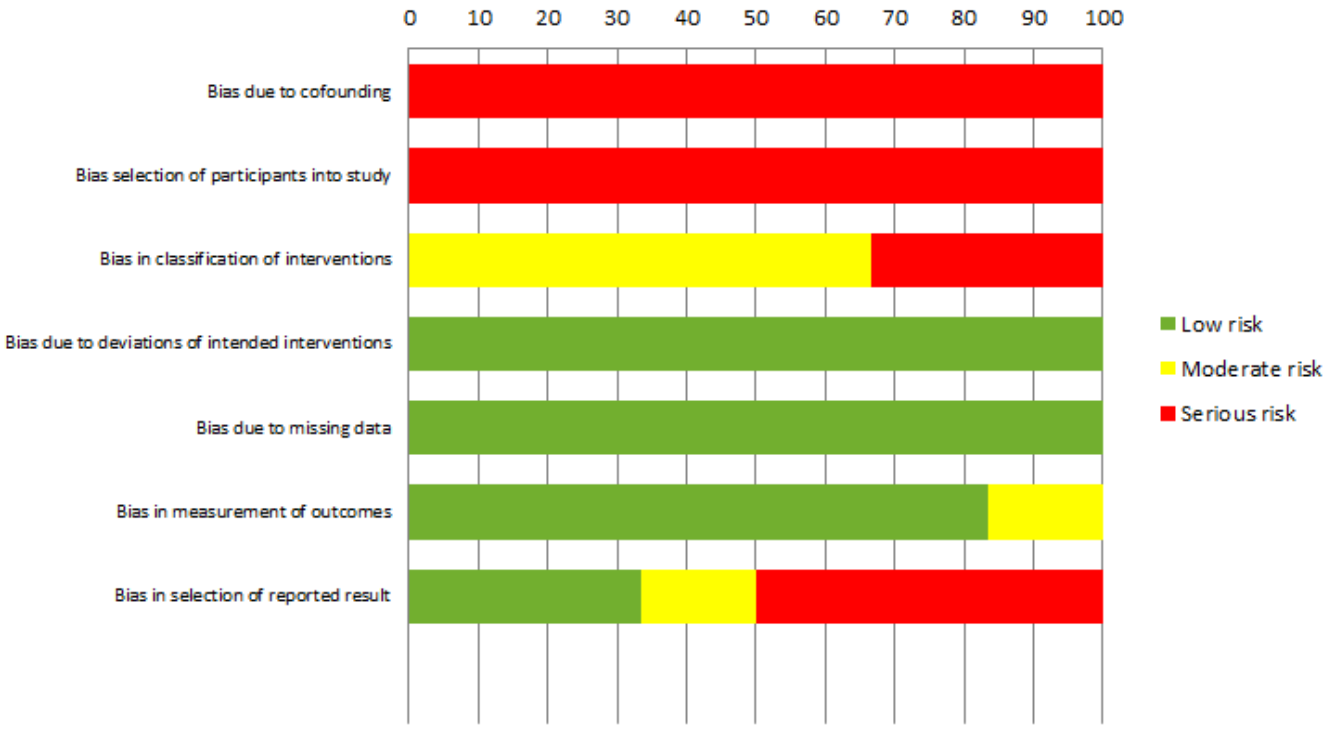
4. Supplementary Figure S1: PRISMA flowchart diagram



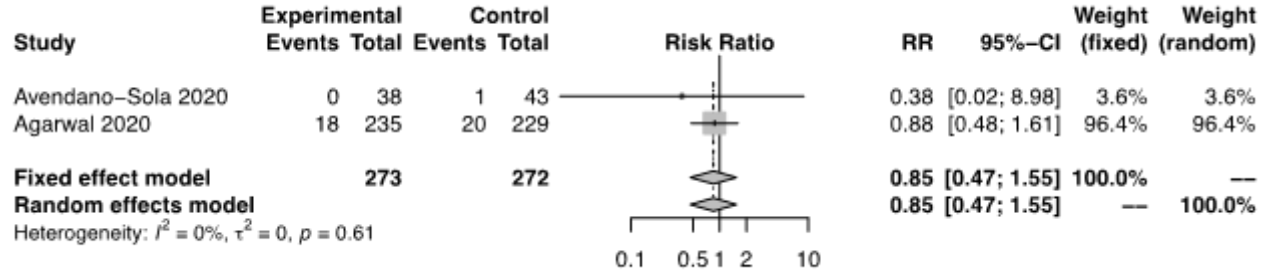
5. Supplementary Figure S2: Cochrane Risk of Bias 2·0. Tool of included randomized controlled trials



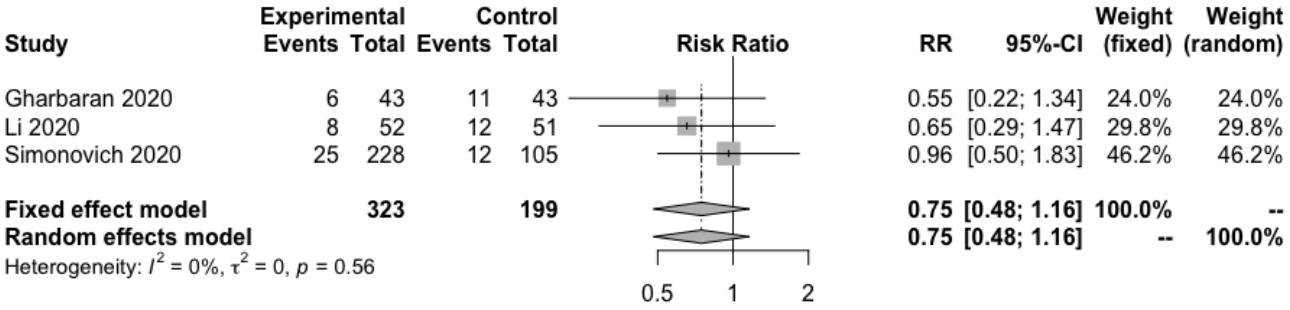
6. Supplementary Figure S3: ROBINS-I Risk of Bias Tool figure of included cohort studies



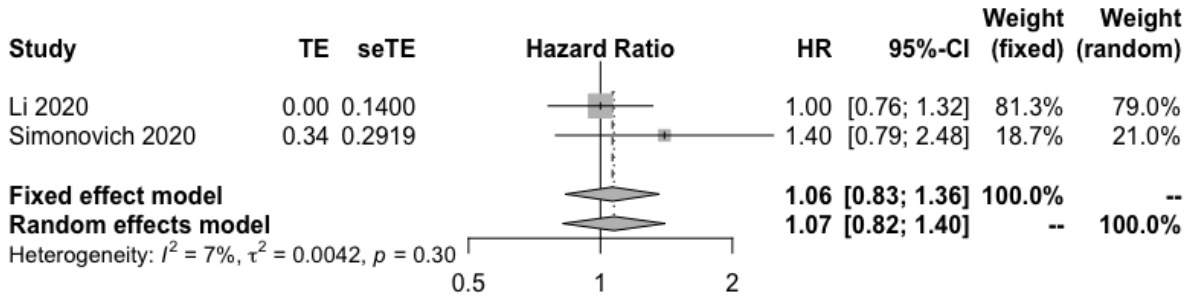
7. **Supplementary Figure S4: Effect of convalescent plasma on need of invasive ventilation in RCT of moderate COVID-19 patients**



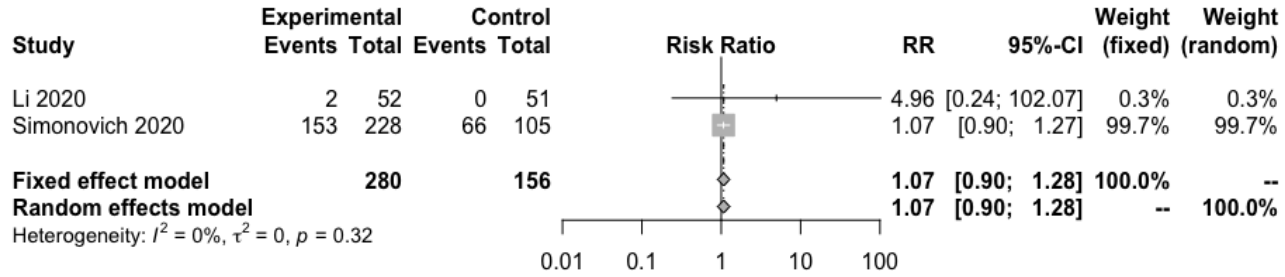
8. **Supplementary Figure S5: Effect of convalescent plasma on all-cause mortality compared to control (placebo plus standard of care) in RCTs of severe COVID-19 patients**



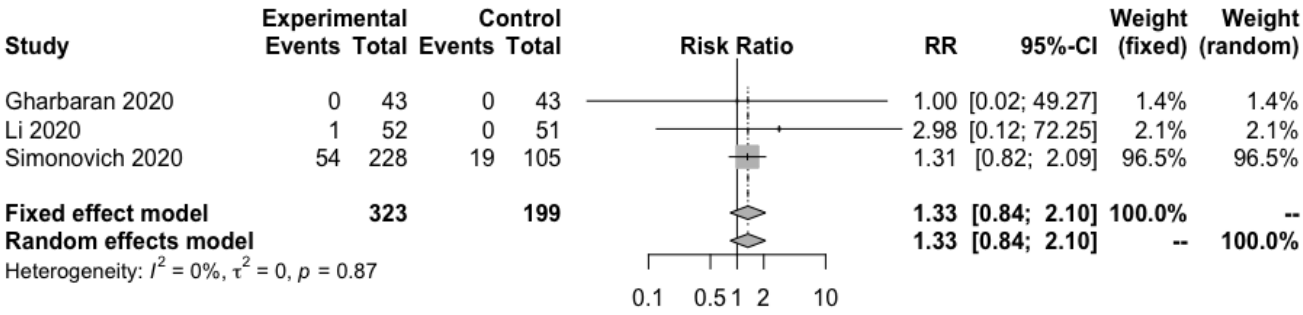
9. **Supplementary Figure S6: Effect of convalescent plasma on clinical improvement compared to control (placebo plus standard of care) in RCTs of severe COVID-19 patients**



10. Supplementary Figure S7: Effect of convalescent plasma on adverse events compared to control (placebo plus standard of care) in RCTs of severe COVID-19 patients



11. Supplementary Figure S8: Effect of convalescent plasma on serious adverse events compared to control (placebo plus standard of care) in RCTs of severe COVID-19 patients



12. Supplementary Table SI: Timing of convalescent plasma administration from symptom appearance, antibody titers in donors, and positivity of antibodies at baseline positivity in randomized patients across RCTs

RCT	Agarwal et al.[22]	Avendaño-Solà et al.[21]	Gharbaran et al.[20]	Li et al.[19]	Simonovich et al.[23]
Timing of plasma administration since symptom appearance to randomization (range)	41 days (31-51)*	8 days (6-9)	10 days (6-15)	30 days (20-39)	8 days (5-10)
Antibody titers in donors	Total titers: At least >1:20 (63.6% of donors) (Median titer: 1:40)	IgG titers: >1:80 (Median titer: 1:292)	Total titers: at least >1:80 (Median titer: 1:640)	IgG titers: at least >1:640	Total titers: at least >1:400 (Median titer: 1:3200)
Positivity of antibodies at baseline in randomized patients	Intervention: 163/229 (80.3%) Control: 185/235 (86.1%) were positive for neutralizing SARS-CoV-2 antibodies	Intervention: 21/38 (55.3%) Control: 19/43 (44.2%) were positive for anti-SARS-CoV-2 IgG antibodies	All: 53/66 (80.3%) patients were positive for anti-SARS-CoV-2 antibodies	0% positive. 17/148 (11.5%) of eligible patients were positive for anti-SARS-CoV-2 IgG antibodies (>1:640) and excluded from randomization.	Intervention: 80/145 (55.2%) Control: 36/70 (51.4%) positive for total anti-SARS-CoV-2 antibodies

*From COVID-19 diagnosis.

13. Supplementary Table SII: Description of outcomes of included studies

	Hegerova et al.[24]		Liu et al.[25]		Rasheed et al.[26]		Zeng et al.[27]		Abolghasemi et al.[28]		Salazar et al.[29]		Gharbharan et al.[20]		Li et al.[19]		Avendaño-Solà et al.[21]		Agarwal et al.[22]		Simonovich et al[23]	
	CP	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**	**CP**	**C**
	(n= 20)	**(n= 20)**	**(n= 39)**	**(n= 156)**	**(n= 21)**	**(n= 28)**	**(n= 6)**	**(n= 15)**	**(n= 115)**	**(n= 74)**	**(n= 136)**	**(n= 251)**	**(n= 43)**	**(n= 43)**	**(n= 52)**	**(n= 51)**	**(n= 38)**	**(n= 43)**	**(n= 235)**	**(n= 229)**	**(n= 228)**	**(n= 105)**
All-cause Mortality, n (%)	7d: 2 (10); 14d: 2 (10)	7d: 5 (25); 14d:6 (30)	5 (12.8)	38 (24.4)	1 (4.8)	8 (28.6)	5 (83.3)	14 (93.3)	17 (14.8)	18 (24.3)	5 (3.7)	19 (7.6)	6 (14)	11 (26)	28d: 8 (15.7)	28d: 12 (24)	15d: 0 (0)	15d: 4 (9.3)	28d: 34 (13.6)	28d: 31 (14.6)	30d: 25 (11)	30d: 12 (11.4)
Clinical Improvement, mean (SD), median (IQR), or n (%)	B:5 (4 - 6.3) 14d: 3.5 (0 -6)[a]	B: 5 (4-7) 14: 3 (0-8)[a]	NA	NA	NA	NA	1 (16.7)	1 (6.7)	NA	NA	NA	NA	25 (58)[b]	25 (58)[b]	7d: 5 (9.6) 14d: 17 (33); 28d: 27 (52)[c]	7d: 5 (9.8); 14d: 9 (18); 28d: 22 (43)[c]	NA	NA	NA	NA	NA	NA
Adverse Events	0 (20)	NA	NA	NA	1 (2.04)	NA	0 (0)	0 (0)	1 (0.87)	NA	NA	NA	NA	NA	2 (3.85)	0 (0)	NA	NA	6 (2.6)	6 (2.6)	153 (67.1)	66 (62.9)
-Rash, n (%)	0 (0)	NA	NA	NA	1 (2.04)	NA	NA	NA	NA	NA	NA	NA	NA	NA	1 (1.92)	0 (0)	1(2.63)	0(0)	NA	NA	1 (0.4)	1 (1)
Serious Adverse Events[d], n (%)	0 (0)	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	NA	NA	NA	0 (0)	0 (0)	1 (1.92)	0 (0)	6 (15.8)	7 (16.3)	NA	NA	54 (23.7)	19 (18.1)

CP: Convalescent plasma; C: Control; B: Baseline; d: day; NA: Not Applicable.

[a] Median (IQR) from baseline of WHO 8-point Ordinal Scale: Category 0 = No clinical or virologic evidence of infection, 1 = No limitations of activities, 2 = Limitations of activities, 3 = Hospitalized, no oxygen therapy, 4 = Hospitalized, oxygen therapy by nasal cannula or mask, 5 = High-flow oxygen therapy or Non-invasive mechanical ventilation, 6 = Mechanical ventilation, 7 = Mechanical ventilation plus additional organ support (vasopressors, RRT, ECMO), 8 = Death.

[b] Undefined improvement in WHO 8-point ordinal scale and reported as n (%).

[c] Clinical improvement defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale (Category 6 = Death, 5= Hospitalization plus ECMO or invasive mechanical ventilation, 4=Hospitalization plus non-invasive ventilation or high-flow supplemental oxygen, 3=Hospitalization plus supplemental oxygen (not high-flow or noninvasive ventilation), 2=Hospitalization with no supplemental oxygen, 1=Hospital discharge). Reported as n (%).
[d] Pulmonary edema, severe allergic reaction, anaphylactic shock, or grade 3-4 per CTCAE v5.0

14. Supplementary Table SIII: Summary of Findings table of convalescent plasma compared to control (placebo or standard of care) in hospitalized, severe COVID-19 patients

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo plus standard of care	**Risk with convalescent plasma**			
All-cause mortality follow up: range 15 days to 30 days	18 per 100	**13 per 100** (8 to 20)	**RR 0.75** (0.48 to 1.16)	522 (3 RCTs)	⨁⨁◯◯ LOW [a,b]
Clinical improvement assessed with: Patient discharge alive or improvement of two categories on a 6-point severity scale [1=discharge, 6=death] follow up: range 28 days to 30 days	0 per 100	**NaN per 100** (NaN to NaN)	**HR 1.07** (0.82 to 1.40)	436 (2 RCTs)	⨁⨁◯◯ LOW [c,d]
Adverse events follow up: range 28 days to 30 days	42 per 100	**45 per 100** (38 to 54)	**RR 1.07** (0.90 to 1.28)	436 (2 RCTs)	⨁⨁◯◯ LOW [c,e]
Severe adverse events assessed with: pulmonary edema, severe allergic reaction, anaphylactic shock or grade 3-4 AEs per CTCAE v5.0 follow up: range 28 days to 30 days	10 per 100	**13 per 100** (8 to 20)	**RR 1.33** (0.84 to 2.10)	522 (3 RCTs)	⨁⨁◯◯ LOW [a,f]

Explanations

a. RoB 2.0: Gharbaran et al. had some concerns of bias in the randomization process; Li et al. had some concerns of bias in the randomization process and deviations from the intended interventions; Somonovich had some concerns of bias in the randomization process.
b. Imprecision: 95%CI of the effect was 0.48 to 1.16
c. RoB 2.0: Li et al. had some concerns of bias in the randomization process and deviations from the intended interventions; Somonovich had some concerns of bias in the randomization process.
d. Imprecision: 95%CI of the effect was 0.82 to 1.40
e. Imprecision: 95%CI of the effect was 0.90 to 1.28, and 95%CI of Li et al. effect was very broad.
f. Imprecision: 95%CI of the effect was 0.84 to 2.10, and 95%CIs of Li et al. and Gharbaran et al. were very broad.

15. Supplementary Table SIV: Ongoing RCTs evaluating Convalescent Plasma on COVID-19 patients

Trial ID	Title	Country	Type of Patient	Comparator	Completion Date
NCT04397757	An Open-Label, Controlled, Phase 1, Safety and Exploratory Efficacy Study of Convalescent Plasma for Severely Ill, Hospitalized Participants With COVID-19 Pneumonia Caused by SARS-CoV-2.	United States	Hospitalized with pneumonia and abnormal respiratory status (ordinal scale 5,6,7)	Standard of care	September 13, 2020
NCT04415086	Treatment of Patients With COVID-19 With Convalescent Plasma Transfusion: a Multicenter, Open-labeled, Randomized and Controlled Study	Brazil	Presence of COVID-19 pneumonia, need for> 3L of O2 in the catheter / mask or respiratory distress syndrome	Standard of care	April 20, 2022
NCT04418518	CONCOR-1: A Randomized Open-Label Trial of CONvalescent Plasma for Hospitalized Adults With Acute COVID-19 Respiratory Illness	United States	COVID-19 respiratory illness, receiving supplemental oxygen	Standard of care	June 2021
NCT04372979	Evaluation of Efficacy Of COVID-19 Convalescent Plasma Versus Standard Plasma In The Early Care Of	France	COVID-19 confirmed case, showing respiratory symptoms with risk of deterioration	Standard plasma	October 2020

	COVID-19 Patients Hospitalized Outside Intensive Care Units.				
NCT04442191	Infusion of Convalescent Plasma for the Treatment of Patients Infected with Severe Acute Respiratory Syndrome-Coronavirus-2 (COVID-19): A Double-blinded, Placebo-controlled, Proof-of-concept Study	United States	Symptomatic infection, need for supplemental oxygen	Fresh frozen plasma	May 5, 2021
NCT04421404	A Randomized Controlled Adaptive Study Comparing COVID-19 Convalescent Plasma (CCP) to Non-immune Plasma to Limit Coronavirus-associated Complications in Hospitalized Patients	United States	Hospitalized with COVID-19, pulmonary infiltrates on chest imaging, oxygenation of <95% on room air	Standard fresh frozen plasma,	April 30, 2021
NCT04438057	Evaluating the Efficacy of Convalescent Plasma in Symptomatic Outpatients Infected With COVID-19	United States	Laboratory confirmed diagnosis of infection with SARS-CoV-2, symptoms of COVID -19, O2 saturation of >93%	Standard of care therapy.	July 6, 2021
NCT04345991	Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in	France	Onset of COVID19 functional signs <8 days, mild severity.	Standard of care	May 15, 2020

	COVID-19 Patients - CORIMUNO-CORIPLASM : EFFICACY OF CONVALESCENT PLASMA TO TREAT SARS-COV2 INFECTED PATIENTS				
NCT04388410	Phase 2b/3 Trial to Evaluate the Safety and Efficacy of Plasma Transfusion from Convalescent Patients With SARS-CoV-2 Infection on Severity and Mortality of COVID-19 in Hospitalized Patients.	Mexico	Confirmed SARS-CoV2 infection, hospitalized, severe or risk for severe disease.	Normal saline solution	October 31, 2020
NCT04355767	Clinical-trial of COVID-19 Convalescent Plasma in Outpatients	United States	Symptoms of COVID-19 illness and laboratory-confirmed SARS-CoV-2 infection, at least one study defined risk factor for severe COVID-19 illness	Saline with multivitamin	December 2022
NCT04433910	A Randomized, Prospective, Open Label Clinical Trial on the Use of Convalescent Plasma Compared to Best Supportive Care in Patients With Severe COVID-19	Germany	SARS-CoV-2 severe infection confirmed by PCR.	Best supportive care	December 2020
NCT04390503	A Phase 2 Randomized, Double-blinded Trial to Evaluate the	United Stated	Infection by nasopharyngeal swab PCR, high risk for severe COVID-	Albumin (Human) 5%	April 2021

	Efficacy and Safety of Human Anti-SARS-CoV-2 Plasma in Close Contacts of COVID-19 Cases		19, no symptoms or no more than 5 days of mild symptoms.		
NCT04374526	Early transfusion of COVID-19 Convalescent Plasma in Elderly COVID-19 Patients to Prevent Disease Progression.	Italy	Age ≥ 65, pneumonia at CT scan, PaO2/FiO2 ≥300 mmHg, presence of one or more comorbidities.	Standard therapy	September 30, 2020
NCT04391101	Efficacy of Convalescent Plasma for the Treatment of Severe SARS-CoV-2 Infection: A Randomized, Open Label Clinical Trial	Colombia	SARS-CoV-2 infection confirmed by PCR, hospitalized in the ICU due to shock or respiratory failure, with less than 24 hours after entering the ICU	Support treatment	June 2021
NCT04405310	Plasma From Convalescent Donors With Covid-19 for the Management of Patients With SARS-COV-2 Fase II and III, a Doble Center Randomized Doble Blind Trial	Mexico	Serious or critically ill patients confirmed for SARS-CoV-2 disease.	Albumin 20% in 250cc of Hartmann solution	June 20, 2020
NCT04428021	Effectiveness of Adding Standard Plasma or COVID-19 Convalescent Plasma to Standard Treatment, Versus Standard Treatment Alone, in	Italy	Confirmed SARS-Cov-2, respiratory failure onset or progression within 5 days	Standard therapy protocol (STP)	June 15, 2021

	Patients With Recent Onset of COVID-19 Respiratory Failure. A Randomized, Three-arms, Phase 2 Trial				
NCT04374487	A Phase II, Open Label, Randomized Controlled Trial to Assess the Safety and Efficacy of Convalescent Plasma to Limit COVID-19 Associated Complications	India	Patients admitted with RT-PCR confirmed COVID-19, severe or immediately life-threatening COVID-19.	Standard Care Therapy	August 9, 2021
NCT04425837	Effectiveness and Safety of Convalescent Plasma in Patients With High-risk COVID-19: A Randomized, Controlled Study CRI-CP (Coronavirus Investigation - Convalescent Plasma)	Colombia	Patients diagnosed with COVID-19 infection by RT-PCR technique, 14 days, high risk of progression or critically ill patients	Standard care alone	February 2021
NCT04348656	A Randomized Open-Label Trial of CONvalenscent Plasma for Hospitalized Adults With Acute COVID-19 Respiratory Illness (CONCOR-1)	United States, Canada,	Admitted to hospital with confirmed COVID-19 respiratory illness, receiving supplemental oxygen	Standard of care	October 31, 2020
NCT04395170	A Randomized, Multicenter Clinical Trial to Evaluate the Efficacy and Safety of the Use of Convalescent Plasma (PC) and Human Intravenous Anti COVID-19	Colombia	Patients with laboratory-confirmed SARS-CoV-2 infection, requiring hospitalization for COVID-19 without mechanical ventilation (invasive or	Standard of care	December 2020

	Immunoglobulin (IV Anti COVID-19 IgG) in Patients Hospitalized for COVID-19.		non-invasive, including an oxygen mask with reserve bag)		
NCT04385199	The Use of Convalescent Plasma for Patients Hospitalized With COVID-19 Disease	United States	Age > 18 with one or more of the following: dyspnea, Respiratory rate >= 30 breaths/min, Oxygen saturation <=93%, PaO2/FiO2 <300, Bilateral airspace opacities on chest radiograph at 24 to 48 hours.	Standard therapy	August 1, 2020
NCT04364737	Convalescent Plasma to Limit Coronavirus Associated Complications: a Randomized Blinded Phase 2 Study Comparing the Efficacy and Safety of Anti-SARS-CoV2 Plasma to Placebo in COVID-19 Hospitalized Patients	United States	Hospitalized with laboratory confirmed COVID-19, one or more respiratory signs, on supplemental oxygen, non-invasive ventilation or high-flow oxygen	Lactated ringer's solution or sterile saline solution	January 31, 2023
NCT04356534	Use of Convalescent Plasma Therapy for COVID-19 Patients With Hypoxia: a Prospective Randomized Trial	Bahrain	COVID-19 diagnosis, patient requiring oxygen therapy	Local standard of care	June 15, 2020
NCT04403477	Convalescent Plasma Transfusion Therapy in Severe COVID-19 Patients- a	Bangladesh	Respiratory rate > 30 breaths/min; PLUS, Severe respiratory distress, PLUS Radiological	Standard supportive treatment	July 20, 2020

	Tolerability, Efficacy and Dose-response Phase II RCT		evidence of bilateral lung infiltrate.		
NCT04393727	Transfusion of Convalescent Plasma for the Early Treatment of pneumonIa Due to SARSCoV2: a Multicenter Open Label Randomized Control Trial	Italy	Virological diagnosis of SARS-CoV-2 infection (real-time PCR), hospitalized due to clinical instrumental diagnosis of pneumonia, PaO2/FiO2 ratio 200-350	Standard therapy	September 30, 2020
NCT04373460	Comparison of the Efficacy and Safety of Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune) Plasma Among Outpatients With Symptomatic COVID-19.	United States	Positive RNA test for presence of SARS-CoV-2, Experiencing any symptoms, ≤ 8 days since the first symptoms	Standard Control plasma	December 21, 2022
NCT04441424	The Therapeutic Potential of Convalescent Plasma Therapy on Treating Critically-ill COVID-19 Patients Residing in Respiratory Care Units in Hospitals in Baghdad, Iraq	Iraq	Critically-ill COVID-19 patient	Conventional therapy	June 1, 2020
NCT04362176	A Randomized, C ontrolled Clinical Trial to Test the Safety and Efficacy of Convalescent Donor Plasma to Treat COVID-19 in	United States	Currently hospitalized, symptoms of acute respiratory infection.	Lactate Ringers containing multivitamins	April 2021

	Hospitalized Adults				
NCT04346446	Efficacy of Convalescent Plasma Therapy in Severely Sick COVID-19 Patients: A Pilot Randomized Controlled Trial	India	Severe COVID -19 infections	Random Donor Plasma+Supportive Care	May 30, 2020
NCT04385186	Inactivated Convalescent Plasma as a Therapeutic Alternative in Hospitalized Patients CoViD-19	Colombia	Confirmed laboratory diagnosis for qRT-PCR to SARS-CoV-2, hospitalized with: Pneumonia, Severe pneumonia, Acute Respiratory Distress Syndrome (moderate or severe), Sepsis or Septic shock	Support treatment	November 30, 2020
NCT04425915	Efficacy of Convalescent Plasma Therapy in Patients With COVID-19: A Randomized Control Trial	India	Patients with severe COVID-19	Standard of Care	May 30, 2021
NCT04359810	A Phase 2, Randomized Clinical Trial to Evaluate the Efficacy and Safety of Human Anti-SARS-CoV-2 Convalescent Plasma in Severely Ill Adults With COVID-19	United States	Evidence of SARS-CoV-2 infection by PCR, (SpO2) ≤ 94%or requiring supplemental oxygen	Standard plasma	December 2020
NCT04380935	Effectiveness and Safety of Convalescent Plasma Therapy on COVID-19	Indonesia	COVID-19 confirmed by RT-PCR, severe pneumonia, PAO2 / FIO2	Standard of care	August 31, 2020

	Patients with Acute Respiratory Distress Syndrome in Referral Hospitals in Indonesia		<300, using mechanical ventilation		
NCT04332835	Convalescent Plasma for Patients With COVID-19: A Randomized, Open Label, Parallel, Controlled Clinical Study	Colombia	Hospitalized participants with diagnosis of COVID 19, moderate cases, CURB-65) >= 2. (SOFA) < 6.	Standard therapy	August 31, 2020
NCT04429854	A Randomized, Open-label, Adaptive, Proof-of-concept Clinical Trial of Donated Antibodies Working Against With COVID-19: DAWN-PLASMA	Belgium	Confirmed diagnosis of SARS-CoV-2 infection, hospitalized with infiltrates, Sp02≤ 94% or use of oxygen.	Standard of Care	November 2, 2021
NCT04344535	Convalescent Plasma to Reduce Complications Associated With COVID-19 Infection: A Randomized Trial Comparing the Efficacy and Safety of High-Titer Anti-SARS-CoV-2 Plasma vs. Standard Plasma in Hospitalized Patients With COVID- 19 Infection	United States	Hospitalized with PCR+ COVID-19 infection	Standard Donor Plasma	April 30, 2021
NCT04392414	Randomized, Open Label, Prospective Study of the Safety and Efficacy of Hyperimmune	Russia	COVID-19 pneumonia pattern with 25% damage to lungs, Morning fever ≥ 38.0°C	Non-convalescent fresh frozen plasma	August 1, 2020

	Convalescent Plasma in Moderate and Severe COVID-19 Disease		over the last three days, CRP blood level ≥ 50 mg / ml or ferritin blood level ≥ 600 µg / ml		
NCT04381858	Efficacy and Safety of Convalescent Plasma vs Human Immunoglobulin for the Treatment of COVID-19 Pneumonia: A Randomized Controlled Trial	Mexico	Positive RT-qPCR SARS-CoV-2 test, severe respiratory failure or requiring invasive mechanical ventilation.	Human immunoglobulin	August 30, 2020
NCT04323800	Convalescent Plasma to Stem Coronavirus: A Randomized, Blinded Phase 2 Study Comparing the Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19	United States	Close contact exposure to person with COVID-19	Normal human plasma	December 31, 2022
NCT04358783	Phase II, Randomized, Double-blind, Controlled Clinical Trial Evaluating the Efficacy and Safety of Plasma From Patients Cured of COVID-19 Compared to the Best Available Therapy in Subjects With SARS-CoV-2 Pneumonia	Mexico	Hospital admission for SARS-CoV-2 pneumonia with supplemental oxygen requirements.	Supportive management	February 1, 2021

NCT04333251	Evaluating Convalescent Plasma to Decrease Coronavirus Associated Complications. A Phase I Study Comparing the Efficacy and Safety of High-titer Anti-Sars-CoV-2 Plasma vs Best Supportive Care in Hospitalized Patients With Interstitial Pneumonia Due to COVID-19	United States	Hospitalized with COVID-19 respiratory symptoms and confirmation via COVID-19 SARS-CoV-2 RT-PCR	Oxygen therapy	December 31, 2022
NCT04361253	A Prospective, Randomized, Double-Masked, Placebo-Controlled Trial of High-Titer COVID-19 Convalescent Plasma (HT-CCP) for the Treatment of Hospitalized Patients With COVID-19 of Moderate Severity	United States	Active COVID-19 infection confirmed by positive SARS-CoV-2 PCR, admitted to ICU or non-ICU floor within 5 days of enrollment, PaO2/FiO2 >200 mmHg if intubated.	Standard Plasma (FFP)	June 2021
NCT04345289	Efficacy and Safety of Treatment with Convalescent Plasma for Adults With COVID-19 Pneumonia. A Double-blinded, Randomized, Multicenter Placebo-controlled Trial	Denmark	Confirmed COVID-19 infection, evidence of pneumonia	Saline 0.9% in addition to standard care.	June 15, 2021
NCT04385043	Efficacy and Safety of Hyperimmune Plasma	Italy	Serious Covid-19 infection	Standard therapy	October 15, 2020

	Treatment in Patients With COVID-19 Severe Infection				
NCT04381936	Randomized Evaluation of COVID-19 Therapy	UK	Hospitalized, SARS-CoV-2 infection	Standard Care	December 2021
NCT04366245	Phase I / II Multicentre, Randomized and Controlled Clinical Trial to Evaluate the Efficacy of Treatment With Hyperimmune Plasma Obtained From Convalescent Antibodies of COVID-19ction	Spain	Patients hospitalized for pneumonia COVID-19 without need of mechanical ventilation (invasive or non-invasive), O2 saturation ≤ 94% or PaO2 / FiO2 ≤ 300 mm Hg, Age> 65 years, or comorbidities	Standard of care	December 2021
NCT04452812	Pilot Clinical, Statistical and Epidemiological Study on Efficacy and Safety of Convalescent P lasma for the Management of Patients With COVID-19	Mexico	Patients with COVID-19 defined as severe or critically ill, patients hospitalized in an ICU.	Best available treatment + Placebo (0.9% saline solution)	March 1, 2021
NCT04467151	A Randomized, Double-blind, Placebo-controlled Trial of Anti-SARS-CoV-2 Plasma in Hospitalized Non-ICU Patients With COVID-19.	United States	Hospitalized with COVID-19-related acute respiratory symptoms, COVID-19 severity status on the WHO Ordinal Scale for Clinical Improvement = 3	Placebo (albumin 5%)	October 2021
NCT04476888	Convalescent Plasma Treatm ent in COVID-19 Patients at a Tertiary Care Center in Pakistan	Pakistan	Positive SARS-CoV-2 infection by rRT-PCR, severe or immediately life-threatening COVID-19.	Drugs and supportive care	August 2020

NCT04456413	Phase II Randomized Study of Convalescent Plasma From Recovered CO VID-19 Donors Collected by Plasmapheresis as Treatment for Subjects With Early COVID-19 Infection	United States	COVID-19 infection with onset of first symptoms < 96 hours, one other high-risk feature.	Best Supportive Care	July 2021
NCT04474340	COVID-19 Convalescent Plasma Treatment in SARS-CoV-2 Infected Patients: Multicenter Interventional Study	Kuwait	Patients with moderate or severe COVID-19	Standard COVID-19 treatment.	September 30, 2020
NCT04468009	Treatment of Critically Ill Patients With COVID-19 With Convalescent Plasma	Argentina	Critically ill patients with Covid-19 on mechanical ventilation.	Standard of care	June 2021
NCT04479163	Prevention of Severe COVID -19 in Infected Elderly by Early Administration of Convalescent Plasma With High-titers of Antibody Against SARS-CoV-2	Argentina	Confirmed diagnosis SARS-Cov2 by RT-PCR, Age ≥ 75 or age 65-74 with at least 1 comorbidity	Normal Saline 0.9%	July 30, 2020
NCT04442958	Effectiveness of Convalescent Immune Plasma Therapy in Severe COVID -19 Patients with Acute Respiratory Distress Syndrome	Turkey	Clinical diagnosis of Covid-19	Standard critical care treatment	June 15, 2020
NCT04480632	Therapeutic Plasmapheresis	Colombia	Confirmed	Usual medical care for	August 2021

	in Critically Ill Adult Patients With COVID-19 Confirmed Diagnosis		infection by COVID-19, respiratory failure receiving ventilatory support and high parameters.	critically ill patients at ICU	
NCT04492501	Role of Investigational Therapies Alone or in Combination to Treat Moderate, Severe and Critical COVID -19.	Pakistan	PCR positive confirmed COVID-19 admitted in hospital.	Supportive treatment	July 20, 2020