Convalescent plasma for COVID-19: Evidence review of the clinical benefits and harm

South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: CONVALESCENT PLASMA FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 9 April 2021 *(update of initial review of 11 June 2020)*

Note: Although additional studies have been published, their generalizability is limited by the variability in convalescent plasma utilized in different settings. In the absence of a standardized and well-characterised product, with proven neutralizing ability against emergent variants of concern, further reviews of the literature are not considered to be useful at this time. There is also very limited access to convalescent plasma, outside of clinical trials.

Key findings

- We conducted a rapid review of available clinical evidence regarding the efficacy and safety of convalescent plasma therapy in patients with severe COVID-19.
- Following a search update on 10 June 2020, we identified 11 published reports (one RCT, six case series, two retrospective observational studies, and two single arm trials), as well as 106 ongoing studies and seven expanded access protocols.
- Based on 10 observational studies and one underpowered RCT, it is not known whether including convalescent plasma in the treatment of COVID-19 has any effect on outcomes critical for decision-making (e.g. mortality, time to hospital discharge or decreased need for respiratory support).
- It is unclear whether clinical improvement can be directly related to convalescent plasma, other interventions, or the natural course of disease (8/11 included studies had no control group, and most patients received other experimental treatments).
- The evidence is very uncertain regarding the risk of adverse reactions; with anaphylactic shock, non-severe allergic and non-hemolytic reactions, and severe dyspnea reported.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: Based on this rapid evidence review, the NEMLC Subcommittee suggests not to use convalescent plasma for severe COVID-19 outside of a clinical trial setting.
Rationale: There is currently insufficient evidence to recommend routine use of convalescent plasma in children or adult patients with severe COVID-19. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
Level of Evidence: III Case series

(Refer to appendix 2 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Patients with severe COVID-19 urgently require safe, effective treatment options. Convalescent plasma has been used to treat other viral infections and is being studied as a potential treatment.

Convalescent plasma is collected by apheresis from people who have recovered from COVID-19 (caused by SARS-CoV-2)[1]. Convalescent plasma contains neutralising antibodies,[2] which bind to SARS-CoV-2 spike glycoproteins with consequent inhibition of viral binding and entry into host cells[3]. Other possible antiviral effects include antibody-dependent phagocytosis, virolysis, and apoptosis of infected cells[4,5]. In addition to neutralising antibodies, convalescent plasma may have immunomodulatory effects, potentially reducing inflammation and limiting tissue damage[3].

Evidence regarding the efficacy of convalescent plasma in other viral respiratory infections is limited and conflicting. A meta-analysis of eight observational studies in patients with either severe **SARS coronavirus** (not SARS-CoV-2) **or influenza** found that convalescent plasma was associated with lower mortality compared to placebo or no treatment: pooled odds ratio 0.25 (95% confidence interval 0.14 to 0.45)[6]. However, a recent meta-analysis of four randomised controlled trials only evaluating patients with **influenza** showed no significant effect on mortality: relative risk 0.94 (95% confidence interval 0.49 to 1.81, very low quality of evidence)[4].

Convalescent plasma is relatively safe, with few reported serious adverse effects[4,6]. Potential adverse effects include fever, allergic reactions, transfusion-related lung injury, and transfusion-associated circulatory overload[7].

This review aims to summarise the current evidence regarding the efficacy and safety of convalescent plasma in patients with severe SARS-CoV-2 infection.

RESEARCH QUESTION: Should convalescent plasma be used to treat confirmed severe COVID-19, with or without other medicines?

METHODS

We conducted a rapid review of the evidence relating to convalescent plasma through the systematic searching of three electronic databases (Epistemonikos, the Cochrane COVID Register and www.covid-nma.com) on 26 May 2020, as well as an updated search on 10 June 2020. The search strategy is shown in Appendix 1. Screening of records was done independently and in duplicate (AB and MM) using Covidence systematic review software. Systematic review quality was appraised in duplicate using the AMSTAR 2 tool[8]. The quality of randomised controlled trials was assessed, in consensus discussion (AB and MM) using the Risk of Bias 2.0 tool[9], and visualised with the *robvis* application[10]. Evidence profiles were generated, in consensus discussion (MM and AB), using GRADEPro software[11]. A single reviewer conducted data extraction (MM/AB), with results reviewed and checked by the second reviewer (AB/MM). Relevant study data were extracted in a narrative table of results. TY, RdW and GR reviewed the overall report.

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age. Disease severity such that hospitalisation required.
Sub-population 1: patients with confirmed COVID-19, no restriction to age. Disease severity such that oxygen required.
Sub-population 2: patients with confirmed COVID-19, no restriction to age. Disease severity such that ventilation required.

Intervention: Convalescent plasma either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality, duration of hospitalisation, progression to ICU admission, progression to mechanical ventilation, duration of ventilator support, duration of ICU stay, duration of mechanical ventilation, adverse reactions and adverse events, proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis, time to negative SARS-CoV-2 PCR on nasopharyngeal swab.

Study designs: Case series, non-randomised cohorts as well as randomised controlled trials, and systematic reviews of studies in humans. Single case reports excluded.

RESULTS

***Results of the search*:**

After the removal of 211 duplicates, two reviewers screened 751 records and identified five potentially eligible systematic reviews, as well as 10 additional potentially eligible primary studies (six of which were already incorporated in one or more included systematic review(s)[12-17] - see Appendix 3 for the PRISMA flow diagram). One of these primary studies was a parallel arm randomised controlled trial (RCT), assigning convalescent plasma or standard treatment according to Chinese national COVID-19 treatment guidelines[18]. Of the systematic reviews, the review by Valk et al 2020[7] was considered high quality and included six eligible studies - five case-series[12-16], and one prospectively planned, single-arm intervention study[17] - with 30 participants. The remaining reviews by Rajendran et al 2020[19], Tobaiqy et al 2020[20], Martinez-Vizcaino et al 2020[21] and Pimenoff et al[22] were classified as moderate, low, critically low and critically low quality respectively. Rajendran included five completed eligible studies[12,14-17], all included in Valk et al 2020. Tobaiqy et al 2020 included one study[23] (out of 41 looking at various therapies) including convalescent plasma, with six participants, which was not included in Valk et al 2020[7]. Pimenoff included seven eligible studies, five of which[12,14-17] were included in Valk et al 2020 and the remaining two identified in the initial search[24,26]. Martinez-Vizcaino et al 2020 looked at ongoing studies[21]. Included in this rapid review are seven primary studies already included in reviews[12-17,23] and four other studies[18,24-26] identified in the search.

A total of 106 ongoing studies and seven expanded access protocols (EAPs) were identified among the 128 eligible full-text records (Appendix 3). Table 1 shows the main characteristics and outcomes of the included primary studies. Table 2 describes the excluded studies and Table 3 summarises the planned and ongoing studies as well as EAPs.

Included studies:

One RCT[18], six case-series[12-16,26], two retrospective observational studies[23,25], one prospectively planned, single-arm intervention study[17] and one non-randomised single arm trial[24]. The RCT planned a sample size of 200 (80% power to detect a difference in clinical improvement within 28 days), but was terminated after enrolling 103 patients, due to a lack of further cases in the area. The quality appraisal of the included RCT can be found in Appendix 4. The evidence profiles for the results from this study are found in Appendices 5.1 to 5.3.

The currently available evidence on the safety and effectiveness of convalescent plasma and hyper-immune immunoglobulin for treatment of people with COVID-19 allows for overall recommendations of very low certainty. The vast majority of the included patients received other concomitant therapy, including antivirals, antibiotics, and corticosteroids. In the studies with no control arm, any clinical improvements seen might have been due to convalescent plasma, concomitant treatment, or the natural history of the disease.

All-cause mortality at hospital discharge

It is not known whether convalescent plasma has any effect on all-cause mortality.

The only published RCT, which failed to complete enrolment, found no significant difference in 28-day mortality overall (low certainty evidence, OR (95% CI)=0.65 (0.29 to 1.46)[18], for those requiring oxygen (low certainty evidence, absolute difference (95% CI)= -9.1% (-25.6% to 7.4%)[18] or ventilation (low certainty evidence, OR (95% CI)=0.80 (0.37 to 1.72)[18].

From non-RCT publications: One patient died in a non-randomised single arm trial[24], while in the retrospective observational study[25] 5/6 (83%) patients died compared to 14/15 (93%) in the control group. All other participants who received convalescent plasma reportedly survived, except for participants from one retrospective observational study[23] with unclear mortality outcomes.

Time to discharge from hospital

From the same RCT, no significant differences were found in time to hospital discharge overall (low certainty evidence, HR (95%)=1.68 (0.92 to 3.08)[18], in patients requiring oxygen (low certainty evidence, HR (95% CI)=1.74 (0.89 to 3.41)[18], or those requiring ventilation (low certainty evidence, HR (95%)=1.90 (0.45 to 8.04)[18].

From non-RCT publications: It is not known whether convalescent plasma has any effect on time to hospital discharge (very low certainty evidence, n= 5 studies[12-16]). The time to discharge after convalescent plasma therapy ranged from four to 35 days.

Progression to intensive care unit admission

Ten observational studies[12-17,23-26] included participants who were critically ill. Six patients from one case series were not in ICU at baseline[15]. None of these patients were admitted to ICU during follow up, and five were discharged from hospital. Ten patients from three studies[13,17,26] were probably not in ICU, with seven probably not being admitted and the remaining three having unclear outcomes.

Progression to mechanical ventilation

None of the included studies reported on this outcome.

Duration of ventilator support

It is not known whether convalescent plasma decreases the need for respiratory support (n= 6 observational studies[12-17]), or whether improvements were due to other interventions, or the natural course of disease. Ten patients from four studies[12,14,16,17] were ventilated at baseline, with seven weaned from the ventilator between 15 and 37 days following convalescent plasma therapy.

Length of ICU stay

We could not evaluate the length of stay in the ICU as none of the included studies consistently reported this outcome. Eight observational studies[12-17,23,25] reported on discharge from ICU following convalescent plasma therapy. The majority of critically ill patients were no longer in the ICU or no longer required mechanical ventilation at final follow-up.

Duration of mechanical ventilation

None of the included studies reported on this outcome.

Adverse events and reactions

We are very uncertain whether convalescent plasma therapy substantially affects the risk of moderate to severe adverse events (very low certainty evidence). All included studies reported on adverse events. The RCT[18] reported no adverse events in the control arm and two in the convalescent plasma arm: one case with definite non-severe allergic and probable non-severe febrile nonhemolytic transfusion reactions in the subpopulation requiring oxygen; one case with possible severe transfusion-associated dyspnea in the subpopulation requiring ventilation. One case study reported anaphylaxis[13]. The non-randomised single-arm trial reported deep vein thrombosis and pulmonary embolism likely unrelated to convalescent plasma[24]. One retrospective observational study reported no adverse transfusion reactions[23]. Seven studies reported no moderate or severe adverse events or reactions[12,14-17,25,26].

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab

Convalescent plasma may result in a large increase in viral nucleic acid negative rate in hospitalised COVID-19 patients, at 24 and 48h (low certainty evidence; 1 RCT[18]), but the evidence is very uncertain about the effect of convalescent

plasma on viral nucleic acid negative rate at 72h. In hospitalised COVID-19 patients requiring oxygen, convalescent plasma may increase viral nucleic acid negative rate at 48h (low certainty evidence; 1 RCT[18]), but the evidence is very uncertain about its effect on negative rates at 24 and 72h. In hospitalised patients with COVID-19 who require ventilation, the evidence is very uncertain about the effect of convalescent plasma on viral nucleic acid negative rate at 24, 48 and 72h.

Time to negative SARS-CoV-2 PCR on nasopharyngeal swab

As summarized in table 1, patients receiving convalescent plasma had a significantly shorter time to negative RT-PCR. This likely has little direct clinical relevance, but may reflect reduced infectivity – additional evidence is required to clarify this potential benefit.

Two of the three patients with recurrence, defined as a positive swab following a negative swab, in one case series[26] achieved two consecutive negative swabs by RT-PCR within two to 24 days from receiving convalescent plasma. The remaining patient still had a positive swab at the end of follow-up (45 days post-infusion). All three patients were treated with antivirals and systemic corticosteroids while receiving convalescent plasma[26]. Two patients in a second case series[15] had positive throat swabs by RT-PCR before receiving convalescent plasma: one case with a positive swab at baseline; the second with a negative swab at baseline, but positive swab before infusion. Throat swabs in these patients turned negative by RT-PCR between one and eight days; following multiple infusions. These patients also received concomitant treatment: one received levofloxacin; both received arbidol.

Ongoing studies

There are currently a large number of trials on convalescent plasma being planned or conducted worldwide (see Appendix 6); with at least 106 registered trials comprising 57 RCTs, 9 non-randomised studies with control arms, 36 trials with single group assignment, and 4 observational studies (Table 3).

The South African National Blood Service (SANBS) and the Western Cape Blood Service (WCBS) are currently commencing a large convalescent plasma trial, 'A PROspective cohort study of the collection of convalescenT plasma from patients who have rECovered from COVID-19 to be used as a Treatment of passive antibodies against SARS-CoV-2' (PROTECT) in South Africa. This study aims to recruit generally healthy plasma donors, aged 18 to 65 years, are nulligravid (for females), weigh at least 55 kg, and are fully recovered (defined as 28 days since last symptoms, or 14 days since second negative COVID-19 test).

CONCLUSION

The current evidence is insufficient to support the inclusion of convalescent plasma in treatment guidelines for severe COVID-19 in South Africa. More high-quality evidence is required. This review will be updated as further evidence becomes available.

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Declaration of interests: AB, MM and TY (Centre for Evidence-based Health Care, Stellenbosch University, and SA Grade Network), GR (Department of Paediatrics & Child Health, University of the Witwatersrand) and RdW (School of Public Health and Family Medicine, University of Cape Town) have no relevant conflicts of interest to declare.

REFERENCES

1. Accorsi P, Berti P, de Angelis V, et al. Position paper on the preparation of immune plasma to be used in the treatment of patients with COVID-19. *Blood Transfus* 2020; 18(3): 163-6.
2. Wu F, Wang A, Liu M, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications (posted 6 April 2020). *medRxiv* 2020.
3. Rojas M, Rodriguez Y, Monsalve DM, et al. Convalescent plasma in Covid-19: Possible mechanisms of action. *Autoimmun Rev* 2020: 102554.
4. Devasenapathy N, Ye Z, Loeb M, et al. Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis. *CMAJ* 2020.
5. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020; 130(4): 1545-8.

6. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015; 211(1): 80-90.
7. Valk SJ, Piechotta V, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a rapid review. *Cochrane Database Syst Rev* 2020; 5: CD013600.
8. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017 Sep 21;358:j4008.
9. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366:l4898.
10. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods* 2020:1-7.
11. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University 2015. Developed by Evidence Prime, Inc.). Available from gradepro.org.
12. Ahn JY, Sohn Y, Lee SH, et al. Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. *Journal of Korean Medical Science* 2020; 35(14):e149
13. Pei S, Yuan X, Zhimin ZZ, et al. Convalescent plasma to treat COVID-19: Chinese strategy and experiences. *medRxiv* 2020. [DOI: 10.1101/2020.04.07.20056440]
14. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020. [DOI: 10.1001/jama.2020.4783]
15. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *Journal of Medical Virology* 2020. [DOI: 10.1002/jmv.25882]
16. Zhang B, Liu S, Tan T, et al. Treatment with convalescent plasma for critically ill patients with SARSCoV-2 infection. *Chest* 2020 Mar 31 [Epub ahead of print]. [DOI: 10.1016/j.chest.2020.03.039]
17. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. In: National Academy of Sciences of the United States of America. Vol. 202004168. 2020. [DOI: 10.1073/pnas.2004168117]
18. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clincal trial. *JAMA* 2020; 3 June 2020.
19. Rajendran K, Krishnasamy N, Rangarajan J, et al. Convalescent plasma transfusion for the treatment of COVID-19: Systematic review. *Journal of Medical Virology* 2020:1-9.
20. Tobaiqy M, Qashqary M, Al-Dahery S, et al. Therapeutic Management of COVID-19 Patients: A systematic review. *medRxiv* 2020.
21. Martinez-Vizcaino V, Mesas AE, Cavero-Redondo I, et al. The race to find a SARS-CoV-2 drug can only be won by a few chosen drugs: a systematic review of registers of clinical trials of drugs aimed at preventing or treating COVID-19. *medRxiv* 2020.
22. Pimenoff VN, Elfström M, Dillner J. A systematic review of convalescent plasma treatment for COVID19. *medRxiv* 2020.
23. Xu Y, Xu Z, Liu X, et al. Clinical findings in critical ill patients infected with SARS-Cov-2 in Guangdong Province, China: a multi-center, retrospective, observational study. *medRxiv* 2020.
24. Salazar E, Perez KK, Ashraf M, et al. Treatment of COVID-19 Patients with Convalescent Plasma in Houston, Texas. *The American Journal of Pathology* 2020: pre-proof.
25. Zeng QL, Yu ZJ, Gou JJ, et al. Effect of Convalescent Plasma Therapy on Viral Shedding and Survival in COVID-19 Patients. *Journal of Infectious Diseases* 2020:1-6.
26. Jin C, Gu J, Yuan Y, et al. Treatment of 6 COVID-19 patients with convalescent plasma. *medRxiv* 2020.

Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings
Li, L. et al. JAMA 2020[18] Journal publication See ROB II for relevant outcomes in Appendix 4	Open label, Parallel group RCT Multicenter (n=7) Date and setting: 14 February to 28 April 2020 Trial was terminated early due to lack of COVID cases in late March.	China N=103 (52 intervention; 51 control) Age, median (IQR): 70 (62-80) intervention; 69 (63-76) control Gender Male, n (%) 27 (51.9) Interventions, 33 (64.7) control SARS-CoV-2 positive PCR Pneumonia confirmed by chest imaging All hospitalised, disease stratified as **severe** (respiratory distress; ≥30 breaths/min, O_2 saturation ≤93% or PaO_2/FIO_2 ≤300) or **life-threatening** (respiratory failure requiring ventilation, shock or organ failure other than lungs) Co-morbidities: hypertension, cardiovascular disease, cerebrovascular disease, diabetes, liver disease, cancer, kidney disease Excluded: pregnant or lactating, Ig allergy, IgA deficiency, pre-existing condition presenting risk of thrombosis, life expectancy <24h, disseminated intravascular coagulation, severe septic shock, PaO_2/FIO_2 <100, severe congestive heart failure, high titer of S protein-RBD-specific IgG (≥1:640), contraindications, patients in other COVID-19 clinical trials	Patients in both trial arms received standard treatment according to the Chinese national COVID-19 guidelines and hospital practice (possible treatment with antivirals, antibacterials, steroids, human immunoglobulin, Chinese herbal medicines and other medication). Patients in the **convalescent plasma** trial arm received an infusion of approximately 4 to 13 mL/kg body weight ABO-compatible, RBC cross-matched, fresh-frozen convalescent plasma. Rate of administration was 10 mL in 15 minutes initially, then increased gradually increased to 100 mL/h with monitoring. Convalescent plasma was obtained from donors who been discharged for more than 2 weeks following two negative PCR results from nasopharyngeals swabs (at least 24h apart). To ensure therapeutic potency only plasma units with an S-RBD-specific IgG titer of ≥1:640 were used.	**28-day mortality** Total group: 8/51 in intervention and 12/50 in control arm; OR (95% CI)=0.65 (0.29-1.46), p=0.30 Severe disease group: 0/23 in intervention and 2/22 in control arm; absolute difference (95% CI) = -9.1% (-25.6%-7.4%), p=0.49 Life-threatening disease group: 8/28 in intervention and 10/28 in control arm; OR (95% CI)=0.80 (0.37-1.72), p=0.57 **Duration from hospitalisation to discharge** Total group: median (IQR) of 41 (31-indeterminate) days in intervention and 53 (35-indeterminate) days in control arm; HR (95% CI)=1.68 (0.92-3.08), p=0.09 Severe disease group: median (IQR) of 32 (26-40) days in intervention and 41 (30-53) days in control arm; HR (95% CI)=1.74 (0.89-3.41), p=0.11 Life-threatening disease group: median (IQR) of indeterminate (46-indeterminate) days in intervention and indeterminate days in control arm; HR (95% CI)=1.90 (0.45-8.04), p=0.38 *indeterminate: too few patients had reached improvement or discharge by the end of the study **Viral nucleic acid negative rate** Total group: at **24h** 21/47 in intervention and 6/40 in control arm; OR (95% CI)=4.58 (1.62-12.96), p=0.003. At **48h** 32/47 in intervention and 13/40 in control arm; OR (95% CI)=4.43 (1.80-10.92), p=0.001. At **72h** 41/47 in intervention and 15/40 in control arm; OR (95% CI)=11.39 (3.91-33.18), p<0.001 Severe disease group: at **24h** 7/21 in intervention 2/17 in control arm; OR (95% CI)=3.75 (0.66-21.20), p=0.15). At **48h** 13/21 in intervention and 6/17 in control arm; OR (95% CI)=2.98 (0.79-11.25), p=0.10. At **72h** 19/21 in intervention and 7/17 in control arm; OR (95% CI)=13.57 (2.36-77.95), p<0.001

Citation	Study design	Population (n)	Treatment	Main findings
				Life-threatening disease group: at **24h** 14/26 in intervention and 4/23 in control arm; OR (95% CI)=5.54 (1.47-20.86), p=0.01. At **48h** 19/26 in intervention and 7/23 in control arm; OR (95% CI)=6.20 (1.79-21.46), p=0.003. At **72h** 22/26 in intervention and 8/23 in control arm; OR (95% CI)=10.31 (2.63-40.50), p<0.001 **Adverse events** Total group: Two participants reported transfusion-related adverse events following convalescent plasma therapy. Both resolved with treatment. Severe disease group: one patient developed chills and rash within 2h. Determined as definite nonsevere allergic transfusion reaction and probable nonsevere febrile nonhemolytic transfusion reaction. Life-threatening disease group: one patient presented with shortness of breath, cyanosis, and severe dyspnea within 6h. Determined as possible severe transfusion-related dyspnea.
Ahn, JY. et al. Journal of Korean Medical Science 2020[12] Journal publication	Case series Setting and dates: ICU, 22 February to 29 March 2020 Single center	South Korea N=2 Age: 67 and 71 Gender: 1 male, 1 female Disease severity: critical, both requiring intubation and mechanical ventilation Additional diagnoses: case 2; hypertension Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empiric antibiotics, 4 L/min oxygen flow via nasal cannula, high-flow oxygen therapy	Received convalescent plasma 500mL total, 2 doses Duration of follow up: 26 days Concomitant therapy: 400 mg of hydroxychloroquine once daily and lopinavir/ritonavir 400 mg/100 mg twice daily, empiric antibiotics, intubation and mechanical ventilator care, IV methylprednisolone (0.5/1 mg/kg/day daily). Unclear whether these treatments were stopped before plasma infusion or continued	**Mortality at follow-up** No deaths reported **Need for respiratory support** One patient weaned from ventilator by day 18 following convalescent plasma therapy. Date of cessation of respiratory support in other patient not reported, but tracheotomy and weaning were reported during study period **Hospital discharge** One patient discharged on day 18 following convalescent plasma, one appears to have remained in ICU **ICU stay after convalescent plasma** One patient discharged, one likely remained **Adverse events** No Grade 3 or 4 adverse events or SAEs reported,

Citation	Study design	Population (n)	Treatment	Main findings
Duan, K. et al. National Academy of Sciences of the United States of America 2020[17] Journal publication	Prospective single-arm pilot study Setting and dates: inpatient, 23 January 2020-19 February 2020 Multi-center (n=3)	China N=10 Median age: 52.5 (IQR 45-59) Gender: 6 male, 4 female Disease severity: critical Additional diagnoses: cardiovascular and/or cerebrovascular diseases and essential hypertension Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen support (9/10 before CP therapy, 8/10 after CP therapy): mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation antiviral treatments (10/10): arbidol 0.2 g every 8 h) orally, monotherapy or combination therapy with remdesivir 0.2 g per day IV or ribavirin 0.5 g per day IV or peramivir 0.3 g per day IV, or ribavirin 0.5 g per day IV monotherapy, IFN-α 500 MIU per day inhalation, oseltamivir 75 mg every 12 h orally, peramivir 0.3 g per day IV, antibacterial or antifungal treatment (8/10): when participants had coinfection, corticosteroids (6/10): IV methylprednisolone (20 mg every 24h)	Received convalescent plasma 200mL total, administered between 10 and 20 days after admission (median: 16.5 days). Duration of follow up not reported Concomitant therapy: mechanical ventilation, high-flow nasal cannula oxygenation, conventional low-flow nasal cannula oxygenation, arbidol 0.2 g every 8 h orally, monotherapy or combination therapy with remdesivir 0.2 g per day IV or ribavirin 0.5 g per day IV or peramivir 0.3 g per day IV, or ribavirin 0.5 g per day IV monotherapy, IFN- α 500 MIU per day inhalation, oseltamivir 75 mg every 12h by mouth, peramivir 0.3 g per day IV, antibacterial or antifungal treatment when participants had coinfection, IV methylprednisolone (20 mg every 24 h)	**Mortality at follow-up** No deaths reported **Need for respiratory support** Need for respiratory support was decreased in four out of 10 participants within three days of receiving convalescent plasma. One participant required only intermittent oxygen after previously receiving continuous low-flow oxygen via nasal cannula. Two participants did not require respiratory support prior to convalescent plasma infusion. **Hospital discharge** Unclear whether patients were discharged **ICU stay after convalescent plasma** 3 patients appear to have been in ICU at baseline, 1 appears to remain in ICU at end of follow up **Adverse events** No Grade 3 or 4 adverse events or SAEs reported.
Pei, S. et al. medRxiv 2020[13] Pre-print	Case series Setting and dates: NR	China N=3	Received convalescent plasma 200-500mL total, administered between 12 and 27 days after admission.	**Mortality at follow-up** No deaths reported **Hospital discharge**

Citation	Study design	Population (n)	Treatment	Main findings
	Single center	Age not reported, inclusion criterion for patients aged between 18 and 55 years Disease severity: moderate to critical Patient characteristics in supplementary material; not accessible Inclusion criteria: severely and critically ill COVID-19 patients, and patients suffering advanced stages of the disease. Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): NR	Duration of follow up 36 days. No concomitant therapy reported.	3/3 patients discharged on Day 6, 14 and 23 following convalescent plasma. **ICU stay after convalescent plasma** 2/3 patients appear to have been in ICU at baseline, all were discharged by the end of follow-up **Adverse events** 1/3 SAE (anaphylactic shock) following receipt of convalescent plasma
Shen, C. et al. JAMA 2020[14] Preliminary communication	Case series Setting and dates: 20 January to 25 March 2020 Single center	China N=5 Hospitalised Age: 36-65 years Gender: 3 male, 2 female Disease severity: critical Comorbidities: hypertension, mitral insufficiency (1 participant), none in 4 participants Inclusion/exclusion criteria: severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; P_aO_2/F_iO_2 <300; and mechanical ventilation Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): antiviral therapy (including	Received convalescent plasma 400mL total, 2 doses (each dose 200-250 mL) on the same day. Administered between 10 and 22 days after admission. Duration of follow up: up to 63 days from hospital admission.	**Mortality at follow-up** No deaths reported **Need for respiratory support** One patient was on ECMO and four on mechanical ventilation at baseline, no patients on ECMO by day 7 following convalescent plasma and two on mechanical ventilation by day 15 to 37 following convalescent plasma **Hospital discharge** 3/5 patients discharged on day 32, 33 and 35 after convalescent plasma **ICU stay after convalescent plasma** 5/5 patients appear to have been in ICU at baseline, 2 or 3 were probably discharged **Adverse events** No Grade 3 or 4 adverse events or SAEs reported,

Citation	Study design	Population (n)	Treatment	Main findings
		lopinavir/ritonavir; interferon alfa-1b; favipiravir, arbidol; darunavir), corticosteroids (methylprednisolone), mechanical ventilation		
Ye, M. et al. Journal of Medical Virology 2020[15] Journal article	Case series Setting and dates: inpatient, 31 January to 22 March 2020 Single center	China N=6 Age: 28-75 years Disease severity: critical, except patient 5 Comorbidities: bronchitis and Sjögren syndrome in participants 3 and 4, none in other participants Additional diagnoses: none Previous treatments (e.g. experimental drug therapies, oxygen therapy, ventilation): oxygen therapy (nasal) in 4 participants, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in 1 participant	Received convalescent plasma 200mL, doses ranged from 1-3 Follow up until discharge Concomitant therapy: oxygen therapy, antiviral therapy (arbidol in all participants), antibiotics (levofloxacin in two participants)	**Mortality at follow-up** No deaths reported **Need for respiratory support** Four of six patients were on oxygen support (1 via nasal cannula, others unspecified). No patients were on respiratory support at 7 days post-treatment until the end of follow-up **Hospital discharge** 5/6 patients discharged on day 4, 6, 6, 10 and 1 patient unclear **ICU stay after convalescent plasma** 0/6 patients in ICU at baseline, none progressed to ICU **Adverse events** No Grade 3 or 4 adverse events or SAEs reported **Viral clearance** One case had positive RT-PCR throat swab at baseline, which turned negative 18 days post-infusion. A second case did not have a positive RT-PCR throat swab at baseline, but she had a positive throat swab prior to, and a negative throat swab one day after, receiving convalescent plasma **Note:** Although the stated inclusion criteria included critical illness, it appears that patients were probably not critically ill at the time of enrolment
Zhang, B. et al. Chest 2020a[16] Epub ahead of print	Case series Setting and dates: hospitals in China, 30 January to 17 March 2020	China N=4 Age: 31-73 years 2 male, 2 female Disease severity: critical Comorbidities: hypertension (participants 1 and 3), COPD	Received convalescent plasma ranging from 200-2400mL, from 1-8 doses from 11-41 days since admission. Duration of follow-up: up to 51 days Concomitant therapy:	**Mortality at follow-up** No deaths reported **Need for respiratory support** Two patients were on ECMO, one on mechanical ventilation and intubated, and one on NIV and high-flow at baseline. One patient on ECMO was discharged on day 7 following convalescent plasma and received home oxygen therapy by day 15 post-treatment. By day 30 post-

Citation	Study design	Population (n)	Treatment	Main findings
	Multi-center (n=4)	(participant 2), chronic kidney impairment (participant 3), pregnancy (participant 4) Additional diagnoses include critical conditions such as ARDS (participants 2, 3 & 4), bacterial pneumonia (pt 1). Extensive previous treatment including antiviral therapy (patients 1-4), antibacterial therapy (patient 1), non-invasive mechanical ventilation (patient 2) and mechanical ventilation and ECMO (patients 3 & 4).	* participant 1: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha), antibacterial therapy, antifungal therapy, supportive care, IVIG, albumin, zadaxin, mechanical ventilation * participant 2: antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2a), noninvasive mechanical ventilation/high-flow nasal cannula, corticosteroids (methylprednisolone) * participant 3:antiviral therapy (arbidol, lopinavir-ritonavir, interferon alpha 2b, oseltamivir, ribavirin), mechanical ventilation, renal replacement therapy, antifungal therapy (caspofungin, voriconazole), venovenous ECMO *participant 4: antiviral therapy (lopinavir-ritonavir, ribavirin), mechanical ventilation, renal replacement therapy, antibacterial therapy (imipenem, vancomycin), caesarean section, venovenous ECMO	treatment one patient remained on ECMO, one receiving home oxygen and two were no longer ventilated. **Hospital discharge** 3/4 discharged on Day 7, 25 and 27 **ICU stay after convalescent plasma** 4/4 in ICU at baseline, three patients discharged by end of follow-up **Adverse events** No Grade 3 or 4 adverse events or SAEs reported,

Citation	Study design	Population (n)	Treatment	Main findings
Salazar, E. et al. The American Journal of Pathology 2020[24] Pre-proof	Non-randomised single arm trial Setting and dates: March 28 to April 14, 2020 Single center	N=25 patients with severe and/or life-threatening RT-PCR confirmed COVID-19 disease, **all on oxygen support** Median age 51 (IQR 42.5 to 60), 14 (56%) were female, median BMI 30.4 (IQR 26.5 to 37), 88% were smokers, and 64% had underlying conditions. Five patients had bacterial or other viral co-infections. Median time from symptom onset to treatment was 10 days (IQR 7.5 to 12.5), hospitalisation to treatment was median (IQR) 2 (2 to 4).	**All patients received one 300-mL dose of convalescent-phase plasma** from a laboratory-confirmed SARS-CoV-2 infected healthy donor who had been asymptomatic for 14 days, and one patient received a second dose six days later. The majority of patients received concomitant anti-inflammatory treatments within five days of the plasma infusion, including tocilizumab and steroids. Most received other investigational treatments, including courses of HCQ and AZM, ribavirin, and/or lopinavir/ritonavir, and two patients received remdesivir.	**Adverse events** No adverse events attributed to convalescent plasma infusion occurred within 24 hours. Two patients developed deep-vein thrombosis (DVT) four and eight days after treatment, and one patient developed a DVT and a pulmonary embolism four days post-infusion. These thrombotic events are consistent with findings reported for untreated COVID-19 patients. **Mortality and improvement of symptoms (assessed by modified 6-point WHO ordinal scale)** By day 14 post-infusion, 19 (76%) patients improved from baseline: an additional four patients were discharged, eight patients improved from baseline, three patients remained unchanged, three had deteriorated, and one patient died from a condition not caused by convalescent plasma **Length of stay** The average overall length of hospital stay was 14.3 days (range 2 to 25 days). The average post-treatment length of hospital stay was 11 days (range 1 to 21 days)
Zeng, Q. et al. Journal of Infectious Diseases 2020[25]	Retrospective observational study Setting and dates: clinical outcomes were followed up until 1 April 2020 Multi-center (n=2)	China N=21 ICU patients Comorbidities: DM, HPT, chronic liver disease, respiratory system diseases. Median age 61.5 years in treatment and 73 years in control group. Five out of six (83%) were male in treatment group, 11 out of 15 (73%) were male in control group. Demographic characteristics, clinical parameters and management strategies were balanced in the two arms.	n=6 patients received a median of 300mL (IQR 200 to 600) convalescent plasma from young donors who had been recovered for one to two weeks, n=15 patients received usual care.	**Mortality** 5/6 deaths in convalescent plasma group vs 14/15 deaths in control group (p=0.18). Each group had 1 recovered patient. The survival period was longer in the treatment group than in the control group (p=0.03). **Discharge from hospital** One patient in each group was discharged from hospital, none from either group remained in hospital. **Adverse events** No immediate adverse events where observed with convalescent plasma infusions. **Viral clearance** Viral clearance was achieved after convalescent plasma in all 6 patients in the treatment group. Among patients who died, all 5 (100%) in the treatment group and 3 of 14

Citation	Study design	Population (n)	Treatment	Main findings
				(21.4%) in the control group had undetectable SARS-CoV-2 before death (p=0.005).
Xu, Y. et al. medRxiv 2020[23] Pre-print	Retrospective observational study Setting and dates: January to February 2020 Multi-center (n=7 ICUs)	China N=45, **of which 6 critically ill received convalescent plasma. All 6 were intubated at baseline.** Mean age in the total group 56 (SD 15) 29 (64%) male in the total group Unclear comorbidity characteristics of convalescent plasma patients	6 patients received **convalescent plasma** All patients received antiviral and antibacterial agents, and others received antifungals, glucocorticoids, immunoglobulins and albumin	**Mortality** Mortality in convalescent plasma group unknown **Respiratory support** 20 (44.4%) patients required intubation and nine (20%) patients required extracorporeal membrane oxygenation **Duration of stay in ICU** All patients in ICU at baseline, only half in the total group had been discharged by study submission. Duration or discharge of patients in convalescent plasma group unknown **Adverse events or reactions** In the total group, 37 (82.2%) patients developed ARDS, 13 (28.9%) patients developed septic shock. No transfusion reactions occurred in those receiving convalescent plasma.
Jin, C. et al. medRxiv 2020[26] Pre-print	Case series Single center Setting and dates: Guizhou Jiangjunshan Hospital in Feb to April 2020	China N=6 Median age 64 n=4 patients were critically ill, n= 2 classified general Inclusion criteria: (1) patients with positive throat swab; (2) COVID-19 infections which are difficult to cure	**Received convalescent plasma**, unknown dose Concomitant treatment included antivirals and systemic corticosteroids.	**Mortality** No deaths reported **Adverse events or reactions** No adverse events or SAEs **Time to negative throat swab** In patients (n=3) with recurrence, the minimum time for viral clearance (n=2) with throat swab for two consecutive tests after the treatment of convalescent plasma ranged from 2 to 24 days. The final patient still had a positive swab at reporting (45 days after receiving convalescent plasma).

Citation	Study design	Population (n)	Treatment	Main findings
		(defined as negative RT-PCR) and severe disease which developed rapidly; (3) recurrent patients, defined as those who had a positive throat swab after a negative throat swab		

Table 2. Characteristics of excluded studies

Citation	Type of record	Reason for exclusion
Adeli SH, Asghari A, Tabarraii R, Shajari R, Afshari S, Kalhor N, Vafaeimanesh J. *Using therapeutic plasma exchange as a rescue therapy in CoVID-19 patients: a case series*. Polish Archives of Internal Medicine 2020: no pagination.	Journal article	Wrong intervention
Bajestani, N.S. IRCT20200418047116N1, first registered 4 May 2020. *Effect of Intravenous immunoglobulin (IVIG) versus Kaletra (lopinavir and ritonavir) tablets in patients with acute respiratory infection (COVID-19): A clinical trial studies.*	Trial registry	Wrong intervention
Cao W, Liu X, Bai T, Fan H, Hong K, Song H, Han Y, Lin L, Ruan L, Li T. *High-dose intravenous immunoglobulin as a therapeutic option for deteriorating patients with coronavirus disease 2019*. Open Forum Infectious Diseases 2020;7(3):1-6.	Journal article	Wrong intervention
CH Versailles. EUCTR2020-001768-27, first registered 27 April 2020. *Study of the efficiency of normal human immunoglobulins (IVIG) in patients aged 75 years and over COVID-19 with severe acute respiratory failure (GERONIMO 19).*	Trial registry	Wrong intervention
Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, Couban R, Bégin P, Guyatt G. *Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: a systematic review and meta-analysis*. Canadian Medical Association Journal 22 May 2020.	Journal article	Wrong patient population
DRK-Bluspendedienst Baden-Württemberg-Hessen gGmbH. EUCTR2020-001310-38-DE, first registered 6 April 2020. *Clinical Study to assess positive value of blood plasma from donors having built immunity against the new corona virus (SARS-CoV-2) transfused to patients suffering from SARS-CoV-2 infection.*	Trial registry	Duplicate
Eastern Theater General Hospital. ChiCTR2000031501, first registered 2 April 2020. *The efficacy of convalescent plasma in patients with critical novel coronavirus pneumonia (COVID-19): a pragmatic, prospective cohort study.*	Trial registry	Duplicate
Fundació Clínic per a la recerca Biomèdica. EUCTR2020-001722-66, first registered 23 April 2020. *Plasma turnover in patients with COVID-19 disease and invasive mechanical ventilation.*	Trial registry	Duplicate
Fundació Clínic per a la recerca Biomèdica. EUCTR2020-001722-66, first registered 23 April 2020. *Plasma turnover in patients with COVID-19 disease and invasive mechanical ventilation: a randomized study.*	Trial registry	Wrong intervention
Fundacion Clinic per a la Recerca Biomédica. NCT04374539, first registered 5 May 2020. *Plasma Exchange in Patients With COVID-19 Disease and Invasive Mechanical Ventilation: a Randomized Controlled Trial.*	Trial registry	Wrong intervention
Gharebaghi, N. IRCT20200501047259N1, first registered 17 May 2020. *Intravenous immunoglubolin (IVIG) effect on improvement of severe pulmonary damage in COVID 19 disease.*	Trial registry	Wrong intervention
GHU Paris Psychiatrie et Neurosciences. EUCTR2020-001570-30-FR, first registered 6 April 2020. *ICAR (IgIV in Covid-related ARds).*	Trial registry	Wrong intervention
Instituto Nacional de Ciencas Medicas y Nutricion Salvador Zubiran. NCT04388410, first registered 14 May 2020. *Safety and Efficacy of Convalescent Plasma Transfusion for Patients With COVID-19.*	Trial registry	Duplicate
Khodashahi, R. IRCT20200325046859N1, first registered 2 April 2020. *Evaluation of the efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 (Before intubation phase) who have not responded to treatment with the standard three-drug protocol (hydroxychloroquine / chloroquine + lupinavir / ritonavir.*	Trial registry	Wrong intervention
King Saud Medical City. ISRCTN21363594, first registered 15 May 2020. *Therapeutic plasma exchange (removal of the non-cell portion of blood) in critically ill adult patients with serious SARS CoV-2 disease (COVID-19).*	Trial registry	Wrong intervention
Luo S, Yang L, Wang C, Liu C, Li D. *Clinical observation of 6 severe COVID-19 patients treated with plasma exchange of tocilizumab.* Journal of Zhejiang University Medical Sciences 2020;49(2):227-31.	Journal article	Wrong intervention
Mahmoodpoor, A. IRCT20091012002582N21, first registered 18 May 2020. *Effect of intratracheal injection of processed autologous serum derived from patients with Covid-19 in oxygenation parameters and pulmonary complications.*	Trial registry	Wrong intervention

Citation	Type of record	Reason for exclusion
Mashhad University of Medical Sciences. ICTRP inaccessible. *The efficacy of intravenous immunoglobulin (IVIg) in patients with severe COVID-19 who have not responded to standard three-drug protocol.*	Trial registry	Wrong intervention
Mayo Clinic. NCT04325672, first registered 27 March 2020. *Convalescent plasma to limit coronavirus associated complications.*	Trial registry	Cancelled by investigator
Pawar AY, Hiray AP, Sonawane DD, Bhambar RS, Derle DV, Ahire YS. *Convalescent plasma: A possible treatment protocol for COVID- 19 patients suffering from diabetes or underlying liver diseases.* Diabetes & Metabolic Syndrome 2020;14(4):665-9.	Journal article	Wrong study design
Peking Union Medical College Hospital. NCT04261426, first registered 7 February 2020. *The Efficacy of Intravenous Immunoglobulin Therapy for Severe 2019-nCoV Infected Pneumonia.*	Trial registry	Wrong intervention
Piero Luigi Ruggenenti. NCT04346589, first registered 15 April 2020. *Convalescent Antibodies Infusion in COVID 19 Patients.*	Trial registry	Duplicate
Prisma Health-Upstate. NCT04374149, first registered 5 May 2020. *Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS.*	Trial registry	Wrong intervention
Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, Eubank T, Bernard DW, Eagar TN, Long SW, Subedi S, Olsen RJ, Leveque C, Schwartz MR, Dey M, Chavez-East C, Rogers J, Shehabeldin A, Joseph D, Williams G, Thomas K, Masud F, Talley C, Dlouhy KG, Lopez BV, Hampton C, Lavinder J, Gollihar JD, Maranhao AC, Ippolito GC, Saavedra MO, Cantu CC, Yerramilli P, Pruitt L, Musser JM. *Treatment of COVID-19 Patients with Convalescent Plasma.* The American Journal of Pathology 2020.	Journal article (pre-proof)	Duplicate
Semnan University of Medical Sciences. IRCT20151228025732N53, first registered 10 April 2020. *Therapeutic effects of plasma of recovered people from COVID-19 on hospitalized patients with this disease.*	Trial registry	Duplicate
Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins. NCT04323800, first registered April 2020. *Efficacy and Safety Human Coronavirus Immune Plasma (HCIP) vs. Control (SARS-CoV-2 Non-immune Plasma) Among Adults Exposed to COVID-19.*	Trial registry	Wrong patient population
Sinopharm Wuhan Blood Products Co., Ltd. ChiCTR2000030381, first registration 29 February 2020. *A randomized, open-label, controlled and single-center trial to evaluate the efficacy and safety of anti-SARS-CoV-2 inactivated convalescent plasma in the treatment of novel coronavirus pneumonia (COVID-19) patient.*	Trial registry	Cancelled by investigator
Tabriz University of Medical Sciences. IRCT20200317046797N3, first registered 11 April 2020. *Intravenous immunoglobulin (IVIG) in the treatment of COVID-19-induced cytokine storm.*	Trial registry	Wrong intervention
Tahvildari A, Arbabi M, Farsi Y, Jamshidi P, Hasanzadeh S, Moore Calcagno T, Nasiri MJ, Mirsaeidi M. *Clinical features, Diagnosis, and Treatment of COVID-19: A systematic review of case reports and case series.*medRxiv 2020.	Pre-print	Wrong intervention
The First Affiliated Hospital of Nanchang University. ChiCTR2000030179, first registered 24 February 2020. *Experimental study of novel coronavirus pneumonia rehabilitation plasma therapy severe novel coronavirus pneumonia (COVID-19).*	Trial registry	Wrong intervention
Thomas Jefferson University. NCT04344015, first registered 14 April 2020. *COVID-19 Plasma Collection.*	Trial registry	Wrong study design
Weill Medical College of Cornell University. NCT04348656, first registered 16 April 2020. *A Trial of CONvalescent Plasma for Hospitalized Adults With Acute COVID-19 Respiratory Illness.*	Trial registry	Duplicate
Yale University. NCT04325672, first registration unknown. *Convalescent plasma to limit coronavirus associated complications.*	Trial registry	Cancelled by investigator
Yeh KM, Chiueh TS, Siu LK, Lin JC, Chan PK, Peng MY, Wan HL, Chen JH, Hu BS, Perng CL, Lu JJ, Chang FY. *Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital*. The Journal of Antimicrobial Chemotherapy 2005;56(5):919-22.	Journal article	Wrong time (before COVID-19)
Zhang L, Pang R, Xue X, Bao J, Ye S, Dai Y, Zheng Y, Fu Q, Hu Z, Yi Y. *Anti-SARS-CoV-2 virus antibody levels in convalescent plasma of six donors who have recovered from COVID-19.* Aging 2020;12(8):6536-42.	Journal article	Wrong study design
Zhang J, Yang Y, Yang N, Ma Y, Zhou Q, Li W, Wang X, Huang L, Luo X, Fukuoka T, Ahn HS, Lee MS, Luo Z, Chen Y, Lui E, Yang K, Fu Z. *Effectiveness of Intravenous Immunoglobulin for Children with Severe COVID-19: A Rapid Review*. medRxiv 2020.	Pre-print	Wrong intervention

Table 3. Characteristics of planned and ongoing studies identified in the current search

Citation	Study design	Population (n)	Treatment
Trial registries			
A.O. Osperdale Papa Giovanni XXIII. NCT04346589, first registered 15 April 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive anti-coronavirus antibodies (immunoglobulins) from convalescent patients
Abolghasemi, H. IRCT20200325046860N1, first registered 30 March 2020	Clinical trial with single group assignment	An estimated 200 patients will be recruited	Patients will receive 500 mL convalescent plasma in 4h in addition to their current treatment
Affiliated Hospital of Xuzhou Medical University. ChiCTR2000030039, first registered 21 February 2020	Non-randomised trial with parallel assignment	An estimated 90 patients will be recruited	Patients will receive conventional thera**py or conventional therapy plus two 200-500 mL infusions of convalescent plasma**
Ahvaz University of Medical Sciences. IRCT20200310046736N1, first registered 1 April 2020	Randomised controlled trial with parallel assignment	An estimated 45 patients will be recruited	Patients will be randomised to routine care with no new therapeutic interventions, or plasma-derived immunoglobulin-enriched solution given intravenously at 0.2-0.4 g/kg/d, or **200 cc/d convalescent plasma given intravenously over 1-4 hours for 1-4 days (only critical patients not responding to routine treatment)**
Ain Shams University. NCT04348877, first registered 16 April 2020	Clinical trial with single group assignment	An estimated 20 participants will be recruited	Participants will receive 400 mL of antibody-rich plasma from COVID-19 recovered patients
Ain Shams University. NCT04376788, first registered 6 May 2020	Randomised controlled trial with parallel assignment	An estimated 15 participants will be recruited	Participants will be randomised to exchange transfusion of 500 cc blood with replacement of one unit washed RBCs, e**xchange transfusion of 500 cc blood with replacement of one unit washed RBCs and IV methylene blue 1mg/kg over 30 minutes with 200 cc plasma from convalescent donor match, intravenous transfusion of IV methylene blue 1 mg/kg over 30 minutes with 200 cc plasma from convalescent donor match**
Andalusian Network for Design and Translation of Advanced Therapies. NCT04366245, first registered 28 April 2020	Randomised controlled trial with parallel assignment	An estimated 72 participants will be recruited	Participants will be randomised to hydroxychloroquine plus azitromycin plus lopinavir/ritonavir plus interferon β-1b, **or the plasma of convalescent COVID-19 patients**
Ardabil University of Medicine Sciences. IRCT20150808023559N21, first registered 9 May 2020	Randomised controlled trial with parallel assignment	An estimated 60 patients will be recruited	Participants will be randomised to routine treatment, **or routine treatment plus 500 mL convalescent plasma administered over 4 hours**
Artesh University of Medical Sciences. IRCT20200404046948N1, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 60 patients will be recruited	Patients will be randomised to conventional therapy or **conventional therapy plus two infusions of 200-500 mL convalescent plasma over two consecutive days**
Ascension South East Michigan. NCT04411602, first registered 2 June 2020	Clinical trial with single group assignment	An estimated 90 participants will be recruited	Participants will receive a single (in the case of weighing < 90 kg) or double (in the case of weighing > 90 kg) unit of anti-SARS-CoV-2 convalescent plasma on days 0, 2, 4, 6, and 8
Asghari, R. IRCT20200501047258N1, first registered 4 May 2020	Randomised controlled trial with parallel assignment	An estimated 120 patients will be recruited	Patients will be randomised to standard treatment (according to the standard national guideline), **transfusion of 2-5 cc/kg convalescent plasma on day 1, 3 and 5 following standard treatment, or transfusion of 8-10 cc/kg on day 1 following standard treatment**

Citation	Study design	Population (n)	Treatment
Assitance Publique - Hôpitaux de Paris. NCT04345991, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 120 participants will be recruited	Participants will be randomised to standard of care or **two units of 200-220 mL each of convalescent plasma transfused intravenously as early as possible and no later than 10 days after onset of clinical symptoms**
Assiut University. NCT04383548, first registered 12 May 2020	Clinical trial with single group assignment	An estimated 100 participants will be enrolled	Participants will receive hyper immunoglobulins containing anti-corona VS2 immunoglobulin
Azienda Ospedaliero, Universitaria Pisana. NCT04393727, first registered 19 May 2020	Randomised controlled trial with parallel assignment	An estimated 126 participants will be recruited	Participants will be randomised to standard therapy or **200 cc convalescent plasma**
Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. NCT04403477, first registered 27 May 2020	Randomised controlled trial with parallel assignment	An estimated 20 participants will be recruited	Participants will be randomised to standard treatment (oxygen, enoxaparine, antibiotic, fluid, immune modulator and/or antiviral), **standard treatment plus 200 mL apheretic convalescent plasma administered in a single transfusion, or standard treatment plus 400 mL apheretic convalescent plasma administered in a single transfusion**
Baylor Research Institute. NCT04333251, first registered 3 April 2020	Randomised controlled trial with parallel assignment	An estimated 115 participants will be recruited	Participants will be randomised to best supportive care (oxygen therapy) or **2 units of ABO matched high-titer SARS-CoV-2 plasma (>1:64)**
Benfield, T. NCT04345289, first registered 14 April 2020	Randomised controlled trial with parallel assignment	An estimated 1500 participants will be recruited	Participants will be randomised to glucose monohydrate capsules (oral placebo), baricitinib 4 mg, hydroxychloroquine 600 mg, 600 mL 0.9% saline (injected placebo), sarilumab 200 mg, **or 600 mL convalescent anti-SARS-CoV-2 plasma as a single dose intravenous infusion plus 600 mL 0.9% saline**. All arms will receive standard care
Bernasconi, E. NCT04365439, first registered 28 April 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive convalescent plasma from patients recovered from COVID-19
Biofarma. NCT04407208, first registered 29 May 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive 100 mL of convalescent plasma (minimum titer of 1/80) three times on day 0, 3, and 6
Birjand University of Medical Sciences. IRCT20200413047056N1, first registered 17 April 2020	Randomised controlled trial with parallel assignment	An estimated 15 patients will be recruited	Patients will be randomised to treatment according to common national protocol, common national protocol plus 400 mg/kg/d intravenous immunoglobulin, **or common national protocol plus 200 cc of convalescent plasma given twice (total volume 400 cc)**
Brigham and Women's Hospital. NCT04361253, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 220 participants will be recruited	Participants will be randomised to standard fresh frozen plasma or **high-titer COVID-19 convalescent plasma**
Centenario Hospital Miguel Hidalgo. NCT04381858, first registered 11 May 2020	Randomised controlled trial with parallel assignment	An estimated 500 participants will be recruited	Participants will be randomised to 5 doses of human immunoglobulin at 0.3 g/kg/d or **2 units (400 mL) convalescent plasma**
Centro de Hematología y Medicina Interna. NCT04357106, first registered 22 April 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive 200 mL of convalescent plasma in a single dose
Choghakabodi, P.M. IRCT20200310046736N1, first registered 1 April 2020	Randomised controlled trial with parallel assignment	An estimated 45 patients will be recruited	Patients will be randomised to routine care without any therapeutic interventions, 0.2-0.4 g/kg/d intravenous plasma-derived immunoglobulin-enriched solution, or **200 cc per day of convalescent plasma for 1-4 days, administered intravenously for 1 to 4 hours**

Citation	Study design	Population (n)	Treatment
Darmanara Co. IRCT20200325046860N1, first registered 30 March 2020	Randomised controlled trial with parallel assignment	An estimated 200 patients will be recruited	Patients will be randomised to routine treatment or **an infusion of 500 mL convalescent plasma in 4 hours**
Department of Epidemiology & Biostatistics, Hamadan University of Medical Sciences. IRCT20120215009014N353, first registered 27 April 2020	Randomised controlled trial with parallel assignment	An estimated 100 patients will be recruited (inpatients and outpatients)	Patients will be randomised to routine care (inpatients receive 200 mg lupinavir and 50 mg ritonavir every 12h for 14 days) or **routine care plus 500 U plasma from convalesced COVID-19 patients every week for at least three weeks**
Department of Infectious Diseases, Hvidovre Hospital. EUCTR2020-001367-88-DK, first registered 1 April 2020	Randomised controlled trial with parallel assignment	An estimated 1 500 subjects will be enrolled	Subjects will be randomised to **convalescent plasma** and/or Plaquenil, Olumiant (various concentrations), or Kevzara
Dillner, J. NCT04384497, first registered 12 May 2020	Clinical trial with single group assignment	An estimated 50 participants will be recruited	Participants will receive treatment with 200 mL convalescent plasma daily, up to a maximum of 7 slow infusions over 1h
Dillner, J. NCT04390178, first registered 15 May 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive treatment with 180-200 mL convalescent plasma from individuals who have recovered from SARS-CoV-2 infection
Direction Centrale du Service de Santé des Armées. NCT04372979, first registered 4 May 2020	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be randomised to an intravenous injection of 2 units of 200-230 mL each standard plasma inactivated by amotosalen, **or an intravenous injection of 2 units of 200-230 mL each SARS-CoV-2 convalescent plasma inactivated by amotosalen**
DRK-Bluspendedienst Baden-Württemberg-Hessen gGmbH. EUCTR2020-001310-38, first registered 6 April 2020	Randomised controlled trial with parallel assignment	The estimated number of participants to be recruited is not reported	Participants will be randomised to best supportive care **or convalescent plasma**
Eastern Theater General Hospital. ChiCTR2000031501, first registered 2 April 2020	Prospective cohort	An estimated 20 patients will be recruited	Patients will receive routine treatment alone, **or routine treatment plus an infusion of convalescent plasma**
Erasmus Medical Center. NCT04342182, first registered 10 April 2020	Randomised controlled trial with parallel assignment	An estimated 426 participants will be recruited	Participants will be randomised to receive standard of care (supportive care, oxygen and antibiotics) or **standard of care plus 300 mL convalescent plasma from COVID-19 recovered donors**
Federal Research Clinical Center of Federal Medical & Biological Agency, Russia. NCT04392414, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 60 participants will be recruited	Participants will be randomised to two units (300 mL each) non-convalescent standard plasma within 24 hours of each other, **or two units (300 mL each) convalescent hyperimmune plasma within 24 hours of each other**
Fondazione Policlinico Universitario Agostini Gemelli IRCCS. NCT04374526, first registered 5 May 2020	Randomised controlled trial with parallel assignment	An estimated 182 participants will be recruited	Participants will be randomised to standard therapy or **standard therapy plus ABO matched, pathogen-inactivated COVID-19 convalescent plasma at a dose of 200 mL/d for 3 consecutive days (day 1, 2 and 3)**
Foundation IRCCS San Matteo Hospital. NCT04321421, first registered 25 March 2020	Clinical trial with single group assignment	An estimated 49 participants will be recruited	Participants will receive hyperimmune plasma on day 1 and, based on clinical response, on day 3 and 5
Fundacion Arturo Lopez Perez. NCT04384588, first registered 12 May 2020	Non-randomised trial with parallel assignment	An estimated 100 participants will be recruited	Participants in all four groups (cancer patients with COVID-19 infection and severity criteria, cancer patients with COVID-19 infection and risk factors, non-Cancer patients

Citation	Study design	Population (n)	Treatment
			COVID 19 infection and severity criteria, and non-Cancer patients COVID 19 infection and risk factors) will receive 1 or more units of convalescent plasma
Gailen D. Marshall Jr. NCT04412486, first registered 2 June 2020	Clinical trial with single group assignment	An estimated 100 participants will be recruited	Participants will receive one unit of COVID convalescent plasma administered as transfusion on day 0
Grupo Mexicano para el Estudio de la Medicina Intensiva. NCT04405310, first registered 28 May 2020	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be stratified as having pneumonia phase 2 and 3. They will be randomised in these strata to conventional therapy (azithromycin and hydroxychloroquine) plus 20% albumin in 250 cc Hartman solution, **or conventional therapy plus hyperimmune plasma from convalesced patients**
Hackensack Meridian Health. NCT04343755, first registered 13 April 2020	Clinical trial with single group assignment	An estimated 55 participants will be recruited	Participants will receive a single infusion of fresh convalescent plasma
Hajifathali, A. IRCT20200416047099N1, first registered 21 April 2020	Clinical trial with single group assignment	An estimated 10 patients will be recruited	Patients will receive 2 or 3 injections of 250-300 mL plasma from a patient who recovered from COVID-19 every other day
Hamilton Health Sciences Corporation. NCT04348656, first registered 16 April 2020	Randomised controlled trial with parallel assignment	An estimated 1200 participants will be recruited	Participants will be randomised to institutional standard of care or **500 mL of convalescent plasma in 2 units of 250 mL administered within 12 hours of each other**
Henry Ford Health System. NCT04385199, first registered 12 May 2020	Randomised controlled trial with parallel assignment	An estimated 30 participants will be recruited	Participants will be randomised to standard therapy (as defined by institutional protocols) or **a transfusion of 200 mL ABO compatible convalescent plasma over 3 hours**
Heydari, F. IRCT20181104041551N1, first registered 24 March 2020	Clinical trial with single group assignment	An estimated 30 patients will be recruited	Patients will receive approximately 450 mL of plasma from recently recovered COVID-19 patients according to blood type
Hilton Pharma Pvt. Ltd. IRCT20200414047072N1, first registered 28 April 2020	Clinical trial with single group assignment	An estimated 357 patients will be recruited	Patients will receive ABO compatible convalescent plasma intravenously at a rate not exceeding 1 mL/kg/min
Hilton Pharma. NCT04352751, first registered 20 April 2020	Clinical trial with single group assignment	An estimated 2000 participants will be recruited	Participants will receive convalescent plasma from COVID-19 recovered patients at a dose of 15 mL/kg over 4-6 hours in pediatric patients under 35 kg, and 450-500 mL over 4-6 hours in adults
Hospital Italiano de Buenos Aires. NCT04383535, first registered 12 May 2020	Randomised controlled trial with parallel assignment	An estimated 333 participants will be recruited	Participants will be randomised to a single infusion of saline solution at 10-15 mL/kg at a rate of 5-10 mL/kg/h in addition to standard care, or **standard care plus convalescent SARS COVID-19 plasma at 10-15 mL/kg at a rate of 5-10 mL/kg/h**
Hospital San Jose Tec de Monterrey. NCT04333355, first registered 3 April 2020	Clinical trial with single group assignment	An estimated 20 participants will be recruited	Participants will receive convalescent plasma plus continued supportive standard care
Hospital San Vicente Fundación. NCT04391101, first registered 18 May 2020	Randomised controlled trial with parallel assignment	An estimated 231 participants will be recruited	Participants will be randomised to support treatment (based on institutional management guidelines; including antiviral, antimalarial or anti-inflammatory drugs) or **support treatment plus two units (between 400-500 mL) of convalescent plasma**
Hospital Universitario Dr. Jose E. Gonzalez. NCT04358783, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 30 participants will be recruited	Participants will be randomised to supportive management (best available therapy) or **supportive management plus a single 200 mL dose of convalescent plasma from cured COVID-19 patients**

Citation	Study design	Population (n)	Treatment
Hosseini, N. IRCT20200404046948N1, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 60 patients will be recruited	Patients will be randomised to conventional therapy alone, **or conventional therapy plus two intravenous infusions of 200-500 mL convalescent plasma over two consecutive days**
Indonesia University. NCT04380935, first registered 8 May 2020	Randomised controlled trial with parallel assignment	An estimated 60 participants will be recruited	Participants will be randomised to standard of care or **standard of care plus convalescent plasma from recovered COVID-19 donors**
Institute for Transfusion Medicine of RNM. NCT04397523, first registered 21 May 2020	Clinical trial with single group assignment	An estimated 20 participants will be recruited	Participants will receive anti-SARS-CoV-2 convalescent plasma
Institute of Liver and Biliary Sciences, India. NCT04346446, first registered 15 April 2020	Randomised controlled trial with parallel assignment	An estimated 40 participants will be recruited	Participants will be randomised to 200-600 mL random donor plasma plus supportive care or **to convalescent plasma from recently recovered COVID-19 patients plus supportive care**
Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado. NCT04356482, first registered 22 April 2020	Clinical trial with single group assignment	An estimated 90 participants will be recruited	Participants will receive convalescent plasma in a dose which will be determined by severity of disease (intubated or not intubated)
Instituto Estadual de Hematologia Arthur Siqueira Cavalcanti, Rio de Janeiro. RBR-4vm3yy, first registered 15 May 2020	Clinical trial with single group assignment (with historical control group)	An estimated 20 patients will be recruited	Patients will receive hyperimmune plasma anti-SARS-CoV-2
Instituto Nacional de Ciencas Medicas y Nutrion Salvador Zubiran. NCT04388410, first registered 14 May 2020	Randomised controlled trial with parallel assignment	An estimated 250 participants will be recruited	Participants will be randomised to 200 mL normal saline solution or **two 200 mL infusions of convalescent plasma administered with 24-72 hours in between**
Instiute of Blood Transfusion, Chinese Academy of Medical Sciences. ChiCTR2000030702, first registered 10 March 2020	Randomised controlled trial with parallel assignment	An estimated 50 patients will be recruited	Patients will be randomised to conventional treatment alone, or **conventional treatment plus convalescent plasma therapy**
Johns Hopkins University. NCT04373460, first registered 4 May 2020	Randomised controlled trial with parallel assignment	An estimated 1344 participants will be recruited	Participants will be randomised to SARS-CoV-2 non-immune control plasma or **200-250 mL SARS-CoV-2 convalescent plasma with antibody titers of ≥ 1:320 or current FDA standard titer for COVID-19**
Johns Hopkins University. NCT04377672, first registered 8 May 2020	Clinical trial with single group assignment	An estimated 30 participants will be enrolled	Participants will receive 1-2 units (200-250 mL per unit) of plasma with anti-SARS-CoV-19 titers of ≥1:320; total volume infused based on weight (5 mL/kg) with a maximum volume of 500 mL
King Fahad Specialist Hospital Dammam. NCT04347681, first registered 15 April 2020	Non-randomised trial with parallel assignment	An estimated 40 participants will be recruited	Participants will share their clinical and laboratory data, if consenting to do so, in the no intervention group, **or will receive 10-15 mL/kg body weight convalescent plasma at least once and up to 5 sessions daily**
Lifefactors Zona Franca, SAS. NCT04395170, first registered 20 May 2020	Randomised controlled trial with parallel assignment	An estimated 75 participants will be recruited	Participants will be randomised to standard therapy (pharmacological recommendations of the Colombian Association of Infectious Diseases), **anti-COVID-19 human immunoglobulin 10% IgG solution at 50 mL for a patient of 50 kg or more on days 1 and 3 of treatment or 1 mL/kg for a patient of less than 50 kg on days 1 and 3**

Citation	Study design	Population (n)	Treatment
			of treatment, or pathogen-reduced plasma from convalesced COVID-19 patients at doses of 200-250 mL on days 1 and 3 of treatment
Mashhad University of Medical Sciences. IRCT20200409047007N1, first registered 12 April 2020	Randomised controlled trial with parallel assignment	An estimated 32 patients will be recruited	Patients will be randomised to care according to existing standards (all available supportive and specific therapies) or **care according to standard treatments as well as 500 cc of survivors plasma up to three times a day**
Max Healthcare Institute Limited. NCT04374487, first registered 5 May 2020	Randomised controlled trial with parallel assignment	An estimated 100 participants will be recruited	Participants will be randomised to standard care treatment according to institutional protocols or **200 mL of ABO compatible convalescent plasma**
Mazandaran University of Medical Sciences. NCT04327349, first registered 31 March 2020	Clinical trial with single group assignment	An estimated 30 participants will be recruited	Participants will receive convalescent plasma
Medical College of Wisconsin. NCT04354831, first registered 21 April 2020	Clinical trial with single group assignment in two cohorts	An estimated 131 participants will be recruited in 2 cohorts	Participants in the ICU cohort and the non-ICU cohort will receive 1-2 units (200-400 mL, maximum dose as 7 mL/kg) of convalescent plasma as a single intravenous infusion.
Merin, N. NCT04353206, first registered 20 April 2020	Clinical trial with single group assignment	An estimated 60 participants will be recruited	Participants will receive single or double units of convalescent plasma infused on day 0 and potentially days 3 and 6
Mikaeili, H. IRCT20200406046968N2, first registered 22 April 2020	Clinical trial with single group assignment	An estimated 30 patients will be recruited	Patients will receive 200-400 cc of convalescent plasma in addition to current antivirals and supportive care therapies
National and Kapodistrian University of Athens. NCT04408209, first registered 29 May 2020	Clinical trial with single group assignment (with historical matched control group)	An estimated 60 participants will be recruited	Participants will receive multiple doses of convalescent plasma
National Blood Center Foundation, Hemolife. NCT04385186, first registered 12 May 2020	Randomised controlled trial with parallel assignment	An estimated 60 participants will be recruited	Participants will be randomised to best support treatment (according to institutional protocol) or **best support treatment plus two doses of 200 mL ABO-Rh compatible inactivated convalescent plasma administered via transfusion with a 24h interval**
Northside Hospital, Inc. NCT04408040, first registered 29 May 2020	Non-randomised trial with parallel assignment	An estimated 700 participants will be recruited	Critical, severe and high risk patients, as well as healthcare workers, will receive 200-425 mL convalescent plasma
NYU Langone Health. NCT04364737, first registered 28 April 2020	Randomised controlled trial with parallel assignment	An estimated 300 participants will be recruited	Participants will be randomised to lactated Ringer's solution/sterile saline solution or **1-2 units (250-500 mL each) of SARS-CoV-2 convalescent plasma with antibodies as per 2020 directive by the FDA**
O'Donnell, M.R. NCT04359810, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 105 participants will be recruited	Participants will be randomised to 1 unit (200-250 mL) of non-convalescent, standard plasma or **1 unit (200-250 mL) of convalescent plasma containing antibody titers against SARS-CoV-2**
Orthosera Kft. NCT04345679, first registered 14 April 2020	Clinical trial with single group assignment	An estimated 20 participants will be recruited	Participants will receive an infusion of one unit, approximately 200 mL, of anti-SARS-CoV-2 convalescent plasma over 4 hours
Pontificia Universidad Catolica de Chile. NCT04375098, 5 May 2020	Randomised controlled trial with parallel assignment	An estimated 30 participants will be recruited	Participants will be randomised to **200 mL convalescent plasma on day 1 and 2 following confirmation of eligibility**, or to **200 mL of convalescent plasma on day 1 and 2 only if respiratory function is worsening or COVID-19 symptoms are persisting for more than 7 days following enrollment**

Citation	Study design	Population (n)	Treatment
Priscilla Hsue. NCT04421404, first registered 9 June 2020	Randomised controlled trial with parallel assignment	An estimated 30 participants will be recruited	Participants will be randomised to a single infusion of 250 mL ABO-compatible standard fresh frozen plasma, **or a single infusion of 250 mL ABO-compatible fresh frozen convalescent plasma**
Royal College of Surgeons in Ireland - Medical University of Bahrain. NCT04356534, first registered 22 April 2020	Randomised controlled trial with parallel assignment	An estimated 40 participants will be recruited	Participants will be randomised to local standard of care or **local standard of care plus 400 mL of convalescent plasma given as 200 mL over 2 hours in 2 consecutive days**
Saint Francis Care. NCT04343261, first registered 13 April 2020	Clinical trial with single group assignment	An estimated 45 participants will be recruited	Participants will receive treatment with 2 units of convalescent plasma
Seddigh-Shamsi, M. IRCT20200409047007N1, first registered 12 April 2020	Randomised controlled trial with parallel assignment	An estimated 32 patients will be recruited	Patients will be randomised to existing standard treatment (all available supportive and specific therapies), **or existing standard treatment plus 500 cc of survivors plasma up to 3 times a day**
Semnan University of Medical Sciences. IRCT20151228025732N53, first registered 10 April 2020	Non-randomised trial with parallel assignment	An estimated 12 patients will be recruited	Patients will receive conventional treatment or **two units of intravenous convalescent plasma obtained from convalescent COVID-19 cases through plasmapheresis**. Units, from two different donors, will be given over 2h with a 1h interval between administration
Shanghai Public Health Clinical Center. NCT04292340, first registered 3 March 2020	Prospective observation of cases	An estimated 15 participants will be recruited	Investigators collected clinical information and clinical outcomes of COVID-19 patients using anti-2019-nCoV inactivated convalescent plasma
Sinopharm Wuhan Blood Products Co., Ltd. ChiCTR2000030929, first registered 17 March 2020	Randomised controlled trial with parallel assignment	An estimated 60 patients will be recruited	Patients will be randomised to receive ordinary plasma or **anti-SARS-CoV-2 virus inactivated plasma**
Solá, C.A. NCT04345523, first registered 14 April 2020	Randomised controlled trial with parallel assignment	An estimated 278 participants will be recruited	Participants will be randomised to standard of care or **pathogen-reduced convalescent plasma from recovered COVID-19 patients**
Stony Brook University. NCT04344535, first registered 14 April 2020	Randomised controlled trial with parallel assignment	An estimated 500 participants will be recruited	Participants will be randomised to 450-550 mL of standard donor plasma with low titer anti-SARS-CoV-2 antibodies or **450-550 mL plasma containing anti-SARS-CoV-2 antibody titer ideally >1:320, but meeting minimum titer per FDA guidelines**
The Christ Hospital. NCT04355897, first registered 21 April 2020	Clinical trial with single group assignment	An estimated 100 participants will be recruited	Participants will receive an intravenous infusion of 500 mL convalescent COVID-19 plasma
The First Affiliated Hospital of Zhejiang University. ChiCTR2000029850, first registered 15 February 2020	Non-randomised trial with parallel assignment	An estimated 20 patients will be recruited	Patients will receive standardised comprehensive treatment alone, **or standardised comprehensive treatment plus convalescent plasma treatment**
The First Affiliated Hospital of Zhengzhou University. ChiCTR2000030627, first registered 8 March 2020	Randomised controlled trial with parallel assignment	An estimated 30 patients will be recruited	Patients will be randomised to routine treatment alone, **or routine treatment plus convalescent plasma therapy**
The Hospital for Sick Children. NCT04377568, first registered 6 May 2020	Randomised controlled trial with parallel assignment	An estimated 100 participants will be recruited	Participants will be randomised to standard of care or **standard of care plus 10 mL/kg, up to a maximum of 500 mL, COVID-19 convalescent plasma**
TriHealth, Inc. NCT04392232, first registered 18 May 2020	Clinical trial with single group assignment	An estimated 100 participants will be recruited	Participants will receive convalescent plasma obtained from an FDA-registered blood establishment

Citation	Study design	Population (n)	Treatment
Union Hospital of Tongji Medical College, Huazhong University of Science and Technology. ChiCTR2000030841, first registered 15 March 2020	Non-randomised trial with parallel assignment	An estimated 10 participants will be recruited	Patients will receive gamma-globulin or **immunoglobulin of cured patients**
Universidad del Rosario. NCT04332380, first registered 2 April 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive 500 mL of convalescent plasma: 250 mL on the first day of the protocol and a second 250 mL on the second day
Universidad del Rosario. NCT04332835,	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be randomised to 400 mg hydroxychloroquine every 12h for 10 days, **or 400 mg hydroxychloroquine every 12h for 10 days plus 500 mL of convalescent plasma distributed as 250 mL each of the first and second day of the protocol**
University Hospital, Basel, Switzerland. NCT04389944, first registered 15 May 2020	Clinical trial with single group assignment	An estimated 15 participants will be recruited	Participants will receive 200 mL of convalescent plasma at enrollment and a second 200 mL at 12-24 hours follow-up
University of Catanzaro. NCT04385043, first registered 12 May 2020	Randomised controlled trial with parallel assignment	An estimated 400 patients will be recruited	Participants will be randomised to standard therapy or **standard therapy plus hyperimmune plasma**
University of Chicago. NCT04340050, first registered 9 April 2020	Clinical trial with single group assignment	An estimated 10 participants will be recruited	Participants will receive an infusion of approxiamtely 300 mL convalescent plasma over 4 hours
University of Pennsylvania. NCT04388527, first registered 14 May 2020	Clinical trial with single group assignment	An estimated 50 participants will be enrolled	Participants will receive 2 units of convalescent plasma collected from ABO-compatible donors who have recovered from COVID-19
University of Pennsylvania. NCT04397757, first registered 21 May 2020	Randomised controlled trial with parallel assignment	An estimated 80 participants will be recruited	Participants will be randomised to standard care alone, **or standard care plus 2 units of COVID-19 convalescent plasma compatible with their blood type**
University of Sao Paulo General Hospital. NCT04415086, first registered 4 June 2020	Randomised controlled trial with parallel assignment	An estimated 120 participants will be recruited	Participants will be randomised to standard of care, **or standard of care plus 200 mL (ranging from 150-300 mL) convalescent plasma**
University of Sulaimani, Sulaimani, Iraq. ChiCTR2000033323, first registered 28 May 2020	Case series	An estimated 24 patients will be recruited	Patients will receive convalescent plasma of COVID
University of Virginia. NCT04374565, first registered 5 May 2020	Clinical trial with single group assignment (with retrospective chart review historical control)	An estimated 29 participants will be recruited	Participants will receive 2 units (approximately 200 mL each for a total of 400 mL) pathogen-reduced SARS-CoV-2 convalescent plasma, preferably given in one day
Vanderbilt University Medical Center. NCT04362176, first registered 24 April 2020	Randomised controlled trial with parallel assignment	An estimated 500 participants will be recruited	Participants will be randomised to receive 250 mL of Ringer's lactate containing multivitamins intravenously, **or a transfusion of convalescent plasma at a rate of 500 mL/h**
West Virginia University. NCT04376034, first registered 6 May 2020	Non-randomised trial with parallel assignment	An estimated 240 participants will be recruited	Participants with mild severity of disease and no progression will receive standard of care, **those with moderate severity of disease will receive 1 unit (200-250 mL) of convalescent plasma (for adults) and 10 mg/kg up to 1 unit of convalescent plasma (for children), those with severe of critical severity will receive up to 2 units of**

Citation	Study design	Population (n)	Treatment
			convalescent plasma (for adults) and 10 mg/kg up to 2 units of convalescent plasma (for children)
Wuhan Institute of Biological Products Co., Ltd. ChiCTR2000030046, first registered 21 February 2020	Single-arm case series	An estimated 10 patients will be recruited	Patients will receive anti-2019-nCoV virus inactivated plasma
Wuhan Jinyintan Hospital (Wuhan Infectious Diseases Hospital). ChiCTR2000030010, first registered 19 February 2020	Randomised controlled trial with parallel assignment	An estimated 100 patients will be recruited	Patients will be randomised to receive ordinary plasma or **anti-SARS-CoV-2 virus inactivated plasma**
Wuhan Union Hospital. NCT04264858, first registered 11 February 2020	Non-randomised trial with parallel assignment	An estimated 10 participants will be recruited	Participants will receive 0.2 g/kg intravenous gamma-globulin for 3 days, **or 0.2 g/kg intravenous immunoglobulin from cured patients for 3 days**
Zangoue, M. IRCT20200413047056N1, first registered 17 April 2020	Randomised controlled trial with parallel assignment	An estimated 15 patients will be recruited	Patients will be randomised to standard treatment (according to common national protocol), standard treatment plus 400 mg/kg/d intravenous immunoglobulin, or **standard treatment plus two infusions of 200 cc each of convalescent plasma from recovered individuals**
Expanded access protocols			
AdventHealth. NCT04374370, first registered 5 May 2020	Expanded access protocol	Patients with severe or life-threatening illness owing to COVID-19; intermediate-sized population	Treatment with SARS-CoV-2 convalescent plasma collected from matched donors
Mayo Clinic. NCT04338360, first registered 8 April 2020	Expanded access protocol	Patients in acute care facilities infected with SARS-CoV-2, intermediate-sized population	Access to investigational convalescent plasma
Rutgers, The State University of New Jersey. NCT04420988, first registered 9 June 2020	Expanded access protocol	Hospitalised patients severely or life-threateningly ill with COVID-19; intermediate-sized population	Treatment with investigational COVID-19 convalescent plasma
Saba, N. NCT04358211, first registered 24 April 2020	Expanded access protocol	Intubated, mechanically ventilated patients with confirmed COVID-19 pneumonia by chest X-ray or chest CT; hospitalized patients with acute respiratory symptoms between 3 and 7 days after the onset of symptoms, with COVID-19; intermediate-sized population	Treatment with SARS-CoV-2 convalescent plasma (1-2 units; approximately 200-400 mL at neutralization antibody titer >1:160
University of Arkansas. NCT04363034, first registered 27 April 2020	Expanded access protocol	Up to 100 subjects with severe or life-threatening, laboratory	Treatment with 1-2 units (200-400 mL per unit, not to exceed 550 mL total) of ABO compatible, low isohemagglutinin titer, COVID-19 convalescent plasma

Citation	Study design	Population (n)	Treatment
		confirmed COVID-19, intermediate-sized population	
University of Colorado, Denver. NCT04372368, first registered 4 May 2020	Expanded access protocol	150 or more individuals with moderate to severe or life-threatening manifestations of COVID-19	Access to COVID-19 convalescent plasma
US Army Medical Research and Development Command. NCT04360486, first registered 24 April 2020	Expanded access protocol	Patients diagnosed with severe or life-threatening COVID-19 or as judged by the subinvestigator (treating physician)	To provide convalescent plasma as a treatment

Appendix 1: Search strategy

Epistemonikos

(title:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*) OR abstract:("covid-19" OR covid19 OR "covid 19" OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*)) AND (title:(plasma OR hyperimmune OR "hyper-immune" OR IVIG OR immunoglobulin OR globulin OR "gamma-globulin" OR γ-Globulin OR "hyper-Ig" OR serum OR sera OR donor OR donation OR "convalescent plasma") OR abstract:(plasma OR hyperimmune OR "hyper-immune" OR IVIG OR immunoglobulin OR globulin OR "gamma-globulin" OR γ-Globulin OR "hyper-Ig" OR serum OR sera OR donor OR donation OR "convalescent plasma"))

Records retrieved: 489 (11 relevant to PICO question)

Cochrane COVID Register

plasma OR hyperimmune OR “hyper-immune” OR IVIG OR immunoglobulin OR globulin OR “gamma-globulin” OR γ-Globulin OR “hyper-Ig” OR serum OR sera OR donor OR donation OR "convalescent plasma" AND “covid-19” OR covid19 OR “covid 19” OR coronavirus* OR coronovirus* OR corona-virus OR corono-virus* OR nCoV*

Records retrieved: 471 (4 relevant to PICO question)

www.covid-nma.com

Searched the website for the terms “convalescent plasma”

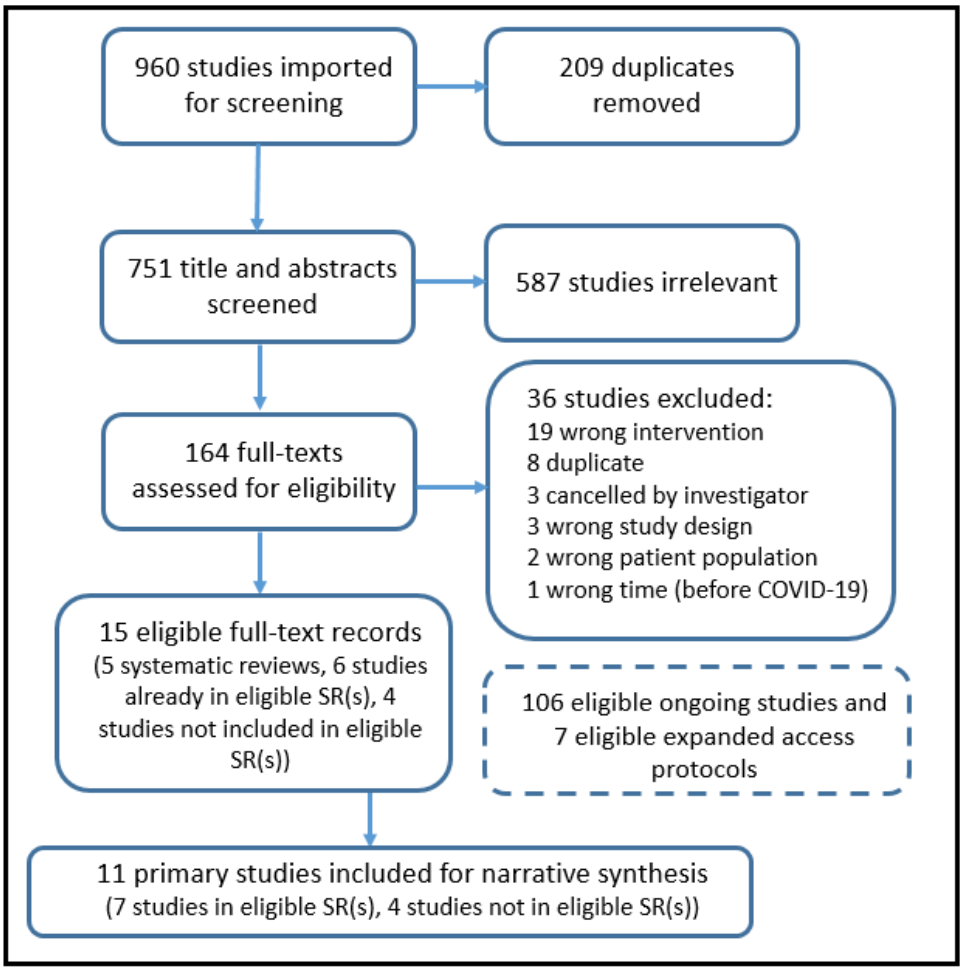
Records retrieved: 0

Appendix 2: Evidence to decision framework

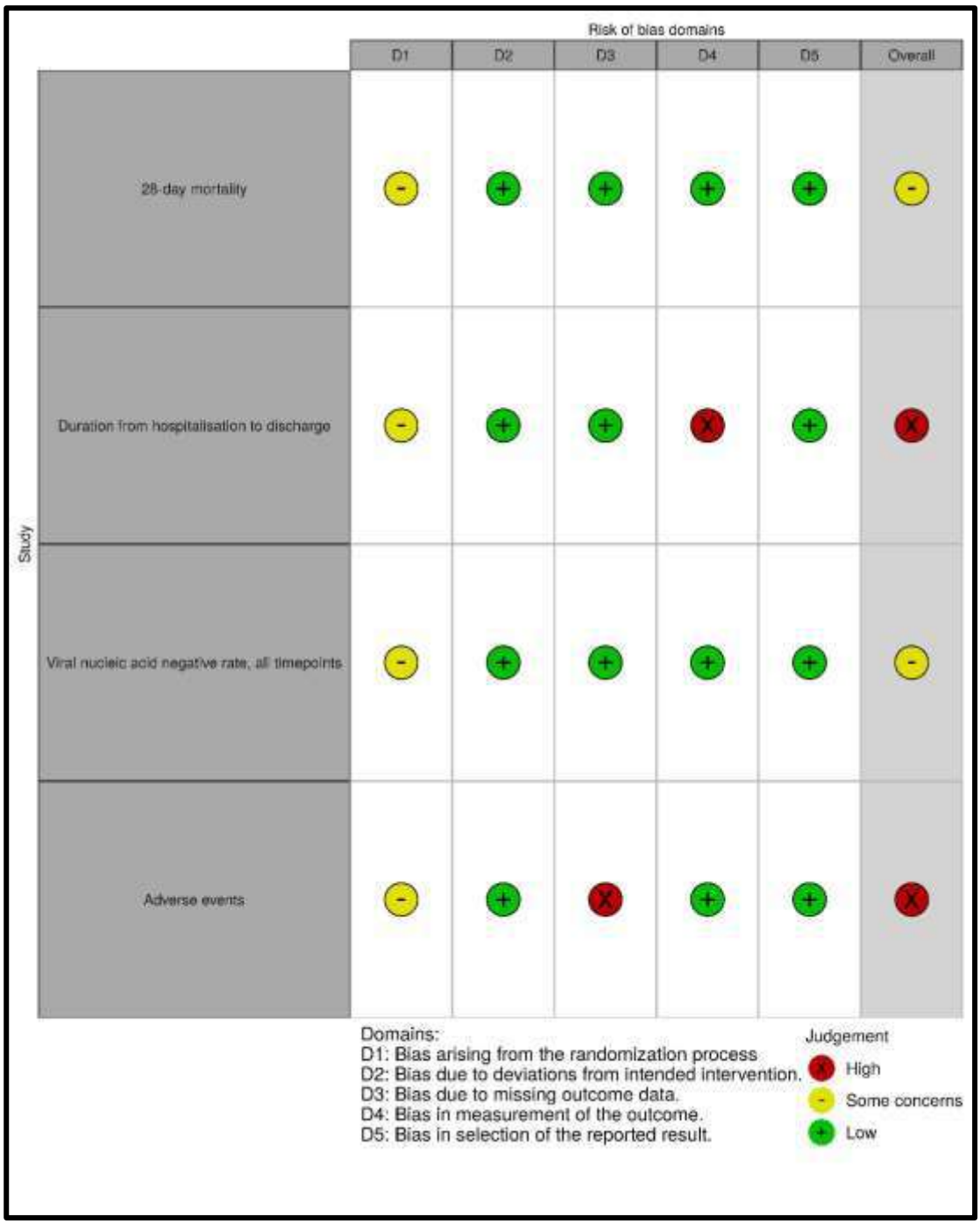
	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain X	The currently available evidence does not allow for this to be determined. Once additional RCT data emerge this will require re-evaluation
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small X None ☐	The currently available evidence does not allow for this to be accurately determined; however, substantial harm appears unlikely considering previous experience with plasma infusions. Once additional RCT data emerge this will require re-evaluation
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain X	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low X *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☐ Uncertain X	Product may possibly be accessed through the South African National Blood Service, on request by the National Department of Health/National Institute for Communicable Diseases.
RESOURCE USE	**How large are the resource requirements?** More intensive X Less intensive ☐ Uncertain ☐	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** Convalescent plasma | n/a **Additional resources:** If convalescent plasma becomes available, it would presumably cost more than standard of care. The cost is currently unknown.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor X Major ☐ Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes X No ☐ Uncertain ☐	Patients: No specific research surveying patients' value of this therapeutic agent is currently available, and NEMLC Subcommittee judged this as "minor". Healthcare providers possibly consider this option to be acceptable.
EQUITY	**Would there be an impact on health inequity?** Yes ☐ No ☐ Uncertain X	Dependent on access to convalescent plasma.

Version	Date	Reviewer(s)	Recommendation and Rationale
1.0	11/06/2020	AB, MM, RdW, GR	Suggest not using convalescent plasma for severe COVID-19; as currently there is insufficient evidence for routine use - consider in context of clinical trial setting.

Appendix 3: PRISMA Flow diagram



Appendix 4: Risk of Bias 2.0 judgments for included RCT (Li et al. 2020[18])



Appendix 5.1: GRADE evidence profiles for all hospitalised patients with COVID-19 (Li et al. 2020[18])

Convalescent plasma compared to standard treatment for COVID-19

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard treatment	With convalescent plasma	Relative effect (95% CI)	Risk with standard treatment	Risk difference with convalescent plasma
Mortality at 28 d (follow up: mean 28 days)											
101 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	12/50 (24.0%)	8/51 (15.7%)	**OR 0.65** (0.29 to 1.46)	240 per 1,000	**70 fewer per 1,000** (from 156 fewer to 76 more)
Time from hospitalization to discharge (follow up: mean 28 days)											
103 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	Median (IQR) of 41 (31-indeterminate) days in intervention and 53 (35-indeterminate) days in control arm; HR (95% CI)=1.68 (0.92-3.08)				
Viral nucleic acid negative rate (24h)											
87 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	6/40 (15.0%)	21/47 (44.7%)	**OR 4.58** (1.62 to 12.96)	150 per 1,000	**297 more per 1,000** (from 72 more to 546 more)
Viral nucleic acid negative rate (48h)											
87 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	13/40 (32.5%)	32/47 (68.1%)	**OR 4.43** (1.80 to 10.92)	325 per 1,000	**356 more per 1,000** (from 139 more to 515 more)
Viral nucleic acid negative rate (72hr)											
87 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	15/40 (37.5%)	41/47 (87.2%)	**OR 11.39** (2.36 to 77.95)	375 per 1,000	**497 more per 1,000** (from 211 more to 604 more)
Adverse events											
101 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	0/50 (0.0%)	2/51 (3.9%)	**OR 19.61** (0.03 to 11 371.96); approximate*	0 per 1,000	**36 more per 1,000** (from 2 fewer to 956 more); approximate*

***Approximate OR (95% CI)/anticipated effects:** approximated using 0.1 events in control group; **CI:** Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Downgraded by 1 for serious imprecision; b. Downgraded by 1 for risk of bias (High); c. Downgraded by 2 for very serious imprecision

Appendix 5.2: GRADE evidence profiles for hospitalised patients with COVID-19 requiring oxygen (Li et al. 2020[18])

Convalescent plasma compared to standard treatment for COVID-19 requiring oxygen

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard treatment	With convalescent plasma	Relative effect (95% CI)	Risk with standard treatment	Risk difference with convalescent plasma
Mortality at 28 d (follow up: mean 28 days)											
45 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/22 (9.1%)	0.1/23 (0.4%)	**Absolute Difference (%) -9.1** (-25.6 to 7.4)	91 per 1,000	**-- per 1,000** (from -- to --)
Time from hospitalization to discharge (follow up: mean 28 days)											
103 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	median (IQR) of 32 (26-40) days in intervention and 41 (30-53) days in control arm; HR (95% CI)=1.74 (0.89-3.41)				
Viral nucleic acid negative rate (24h)											
38 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	2/17 (11.8%)	7/21 (33.3%)	**OR 3.75** (0.66 to 21.20)	118 per 1,000	**216 more per 1,000** (from 37 fewer to 621 more)
Viral nucleic acid negative rate (48h)											
38 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	6/17 (35.3%)	13/21 (61.9%)	**OR 2.98** (0.79 to 11.25)	353 per 1,000	**266 more per 1,000** (from 52 fewer to 507 more)
Viral nucleic acid negative rate (72hr)											
38 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	7/17 (41.2%)	19/21 (90.5%)	**OR 13.57** (2.36 to 77.95)	412 per 1,000	**493 more per 1,000** (from 211 more to 570 more)
Adverse events											
45 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	0/22 (0.0%)	1/23 (4.3%)	**OR 9.57** (0.01 to 6 534.32); approximate*	0 per 1,000	**37 more per 1,000** (from 4 fewer to 963 more); approximate*

***Approximate OR (95% CI)/anticipated effects:** approximated using 0.1 events in control group; **CI:** Confidence interval; **HR:** Hazard Ratio; **OR:** Odds ratio

Explanations

a. Downgraded by 1 for serious imprecision; b. Downgraded by 1 for risk of bias (High); c. Downgraded by 2 for very serious imprecision

Appendix 5.3: GRADE evidence profiles for hospitalised patients with COVID-19 requiring ventilation (Li et al. 202018)

Convalescent plasma compared to standard treatment for COVID-19 requiring ventilation

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard treatment	With convalescent plasma	Relative effect (95% CI)	Risk with standard treatment	Risk difference with convalescent plasma
Mortality at 28 d (follow up: mean 28 days)											
56 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	10/28 (35.7%)	8/28 (28.6%)	**OR 0.80** (0.37 to 1.72)	357 per 1,000	**0 fewer per 1,000** (from 0 fewer to 0 fewer)
Time from hospitalization to discharge (follow up: mean 28 days)											
103 (1 RCT)	serious [b]	not serious	not serious	serious [a]	none	⨁⨁◯◯ LOW	median (IQR) of indeterminate (46-indeterminate) days in intervention and indeterminate days in control arm; HR (95% CI)=1.90 (0.45-8.04)				
Viral nucleic acid negative rate (24h)											
49 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	4/23 (17.4%)	14/26 (53.8%)	**OR 5.54** (1.47 to 20.86)	174 per 1,000	**364 more per 1,000** (from 62 more to 641 more)
Viral nucleic acid negative rate (48h)											
49 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	7/23 (30.4%)	19/26 (73.1%)	**OR 6.20** (1.79 to 21.46)	304 per 1,000	**426 more per 1,000** (from 135 more to 599 more)
Viral nucleic acid negative rate (72hr)											
49 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	8/23 (34.8%)	22/26 (84.6%)	**OR 10.31** (2.63 to 40.50)	348 per 1,000	**498 more per 1,000** (from 236 more to 608 more)
Adverse events											
56 (1 RCT)	serious [b]	not serious	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	0/28 (0.0%)	1/28 (3.6%)	**OR 10.00** (0.01 to 6 796.22); approximate*	0 per 1,000	**31 more per 1,000** (from 4 fewer to 957 more); approximate*

***Approximate OR (95% CI)/anticipated effects:** approximated using 0.1 events in control group; **CI:** Confidence interval; **OR:** Odds ratio; **HR:** Hazard Ratio

Explanations

a. Downgraded by 1 for serious imprecision; b. Downgraded by 1 for risk of bias (High); Downgraded by 2 for very serious imprecision