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Convalescent plasma for COVID-19: a meta-analysis, trial sequential analysis, and meta-regression

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Abstract

Background: SARS-CoV-2-specific antibodies, particularly those preventing interaction between the viral spike receptor-binding domain and the host angiotensin-converting enzyme 2 receptor, may prevent viral entry into host cells and disease progression.

Objective: We performed a systematic review, meta-analysis, trials sequential analysis (TSA) and meta-regression of randomized control trials (RCTs) to evaluate the benefit of convalescent plasma for COVID-19. The primary outcome was 28-30-day mortality. Secondary outcomes included need for mechanical ventilation and intensive care (ICU) admission.

Data sources: PubMed, Embase, MedRxiv, and the Cochrane library on 2nd July 2021.

Results: Seventeen RCTs were identified recruiting 15,587 patients with 8027 (51.5%) allocated to receive convalescent plasma. Convalescent plasma use was not associated with a mortality benefit (24.7% vs. 25.5%; OR 0.94 (0.85 – 1.04); p = 0.23; I^2 = 4%; TSA adjusted CI 0.84 – 1.05), or reduction in need for mechanical ventilation (15.7% vs. 15.4%; OR 1.01 [0.92 – 1.11]; p = 0.82; I^2 = 0%; TSA adjusted CI 0.91 – 1.13), or ICU admission (22.4% vs. 16.7%; OR 0.80 (0.21 – 3.09); p = 0.75; I^2 = 63%; TSA adjusted CI 0.0 – 196.05). Meta-regression did not reveal any association with titre of convalescent plasma, timing of administration, nor risk of death and treatment effect (p>0.05). Risk of bias was high in most studies.

Conclusions: In patients with COVID-19, there was no clear mortality benefit associated with convalescent plasma. In patients with mild disease, convalescent plasma did not prevent either the need for mechanical ventilation or ICU admission.

PROSPERO registration: CRD42021234201

Key words: Antibodies; COVID-19; Passive immunization; Meta-analysis; convalescent plasma

Editor's key points

- SARS-CoV-2-specific antibodies can neutralize the virus. The benefit of convalescent plasma in the management of patients with COVID-19 requires evaluation.
- In this systematic review the authors reviewed 17 randomised clinical trials including 15,587 subjects. There was no clear mortality benefit associated with the use of convalescent plasma, nor any reduction in the need for mechanical ventilation or ICU admission.
- There appears to be no benefit associated with convalescent plasma in the management of patients with COVID-19. The benefit of high titre convalescent plasma or monoclonal antibodies against SARS-CoV-2 among seronegative patients with COVID-19 requires further evaluation.

Introduction

Illness severity associated with SARS-CoV-2 is unpredictable, ranging from asymptomatic infection to acute respiratory distress syndrome, multiorgan failure, and death (COVID-19).[1, 2] By April 2021, COVID-19 has claimed over 2.8 million deaths worldwide.[3] Most proposed therapeutic strategies for COVID-19 have either targeted viral clearance or mitigating the excessive host inflammatory response associated with multiorgan failure and death.[4]

SARS-CoV-2-specific antibodies, particularly those preventing viral spike receptor-binding domain (RBD) interaction with the host angiotensin-converting enzyme 2 (ACE2) receptor, can neutralize the virus.[5] The theoretical benefits of convalescent plasma in COVID-19 are supported by the association of its use during SARS coronavirus infection and a reduction in mortality, albeit limited to observational data.[6] Any potential benefits conferred by convalescent plasma in COVID-19 disease therefore require evaluation.

We performed a systematic review, meta-analysis, and trial sequential analysis of randomized controlled trials of convalescent plasma in the treatment of COVID-19. As convalescent plasma may be expected to provide most benefit in those at greatest risk of death, we also performed a meta-regression to investigate the relationship between treatment effect and overall risk. We further evaluated whether administration of convalescent plasma earlier in the disease course, or plasma containing higher titre antibodies, was associated with a mortality benefit.

Methods

This review was registered with the international Prospective Register of Systematic Reviews (PROSPERO registration number: CRD42021234201) and is reported adhering to the Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Supplementary Information).

Information sources and search strategy

PubMed, Embase, MedRxiv, and the Cochrane library were systematically searched using a controlled vocabulary (MeSH) and keywords without date or language restrictions. The last search update was on 2nd July 2021. The Boolean search strategy was as follows: ((COVID-19 OR SARS-CoV-2) AND (convalescent plasma OR convalescent serum OR serotherapy OR passive immunization OR convalescence OR immunoglobulin OR IVIG OR antibody* OR monoclonal OR polyclonal OR recombinant) AND (clinical trials OR randomized trials OR randomised trials OR RCTs)). The control group was not defined in our search terms. Research papers and review articles were hand-searched for any further relevant trials.

Eligibility criteria

Inclusion and exclusion criteria were determined *a priori*. All trials comparing convalescent plasma or plasma products with either a placebo or standard care control group were considered. We included patients being treated with other COVID-19 therapies (co-interventions), details of which are provided in Supplementary Information. Non-randomized clinical trials and paediatric populations were excluded.

Trial selection

Titles and abstracts were independently screened by two investigators (NS, TS) to exclude non-relevant trials with any discrepancies resolved by a third (NA). Any relevant full-text articles were retrieved and analysed for eligibility using the pre-defined inclusion criteria. The same authors performed subsequent data collection and analysis independently with discrepancies resolved by the same third author.

Data collection and analysis

Using a standardised data collection form, information was extracted from the selected trials. Data included country of trial, total number of participants, trial design, age of patients, number of patients admitted to intensive care, number of patients requiring mechanical and/or non-invasive ventilation, and number of patients who died. For patients in the treatment arm, details were collected on the timing of convalescent plasma therapy with regard to symptom onset, dose and duration of convalescent plasma, and antibody titre.

Primary and secondary outcomes

The primary outcome was mortality. Where available, 28 or 30-day mortality were analysed. Secondary outcomes included progression to severe disease defined as a requirement for mechanical ventilation or intensive care admission. As convalescent plasma administration may be expected to provide most benefit in those at the greatest risk of death, we also performed a meta-regression to investigate the relationship between treatment effect and overall risk of death, as defined by the control group mortality. Additionally, the effect on mortality of time from symptom onset to administration of convalescent plasma, and the level of neutralising antibody titre within administered convalescent plasma, were also assessed.

Subgroup analyses

To ascertain whether administration of convalescent plasma was associated with any clinical benefit after the onset of critical illness, we performed subgroup analysis on patients admitted to the ICU at time of enrolment, and on those patients receiving respiratory support at the time of trial enrolment.

Risk of bias assessment

The Cochrane Collaboration tool for assessing risk of bias (RoB2)[7] was used to assess the methodological quality of the randomized control trials. This included the following domains: randomisation process, assignment to intervention, missing outcome data, measurement of outcome, selection of the reported result, other bias and overall bias. The risk of bias in each domain was judged as either low, high, or unclear.

Grading the quality of evidence

The Grading of Recommendation Assessment, Development, and evaluation approach (GRADEpro Guideline Development Tool. McMaster University, 2015)[8] was used to assess the quality of each outcome measure. The quality of evidence was downgraded based on the following assessments: risk of bias, inconsistency, indirectness, imprecision, and other considerations. A funnel plot and Harbord's test were used to assess publication bias.[9] The overall quality of evidence was subsequently rated as high, moderate, low or very low.

Statistical analysis

individual trial data were combined for mortality using Mantel-Haenszel models with the reference group taken as the group randomized to standard care or placebo. The meta-analysis was performed using Revman for Windows (version 5.1, Cochrane Collaboration, Oxford, UK). Statistical heterogeneity was assessed using the I^2 methodology. I^2 values >30%, >50% and >75% indicated moderate, substantial, and considerable heterogeneity among trials, respectively. A random-effects model was used to analyse data. All p values were two-tailed and considered statistically significant if <0.05. Data on dichotomous outcomes are presented as odds ratio (OR), 95% confidence intervals, p-values; I^2 values. Meta-regression was performed using Stata version 16.1 (StataCorp, College Station, TX, USA).

Trial Sequential Analysis (TSA) was performed using TSA program version 0·9·5·10 (www.ctu.dk/tsa) as type 1 errors may occur in meta-analyses with sample sizes that are too small. TSA tests the credibility of the meta-analysis results by combining an estimate of the required information size calculated from the cumulative sample size of included trials, with an adjusted threshold for statistical significance. Meta-analysis monitoring boundaries (Trial Sequential Monitoring Boundaries) and the required information size (RIS) were quantified, alongside diversity adjusted information size (D^2) and adjusted 95% confidence intervals. Diversity adjustment was performed according to an overall type I error of 5% and power of 80%. RIS was calculated using a Relative Risk Reduction (RRR) of 31.5%, based on use of convalescent plasma in influenza A[10] and the control event proportion obtained from our actual meta-analysis.

Protocol changes

The final protocol differed from the published PROSPERO protocol in the following ways: a random effects model was used rather than a fixed effects model due to the number of studies identified but included fixed effects as an additional sensitivity analysis. An additional sensitivity analysis was performed on trials in which the control group only received standard care. In addition to pre-defined primary and secondary outcomes, the odds of adverse events associated with the administration of convalescent plasma were also evaluated. Subgroup analysis was not performed on patients on respiratory support at enrolment as this data was not available. The RRR used for TSA analysis was incorrectly stated in the protocol as 26.6%, the correct RRR of 31.5% was therefore used instead.

Results

Search strategy

The search strategy identified 3493 articles. 3093 articles remained following removal of duplicates and a further 3060 were excluded based on title/abstract alone. Of the remaining 33 trials, 14 were excluded at full review; nine were non-randomized,[11-19] three used a non-convalescent plasma product,[20-22] one had an overlapping data set,[23] and one randomized to early or late convalescent plasma.[24] Two trials administered neutralizing monoclonal antibodies.[25, 26] As there were no primary outcome events (mortality) in one of the two trials,[25] we were unable to perform a meta-analysis on

monoclonal antibodies in COVID-19. All analyses were therefore limited to the 17 trials that used convalescent plasma for COVID-19 disease.[27-43] (Figure 1)

Trial Characteristics

Ten trials enrolled patients requiring advanced respiratory support including mechanical ventilation,[29, 31, 32, 36-42] Seven trials enrolled patients on non-invasive ventilation (NIV),[31, 32, 39-43] and 12 trials enrolled patients on high flow nasal oxygen (HFNO).[31-37, 39-43] (Table 1 and Supplemental Table 1) Convalescent plasma was administered either as three doses on days 1, 3 and 5 in one study,[42] two doses ranging from 200-250 ml [30, 33] 12 hours apart in one trial[40] or 24 hours apart in six trials,[28, 30, 33-35, 38, 41] or as a single dose ranging from 100-600 ml in six trials.[27, 29, 31, 32, 36, 37, 39, 43] Additional COVID-19 directed co-interventions used in the identified trials are listed in Supplemental Table 2. The control group were administered either a normal saline placebo in two trials,[31, 35] non-convalescent plasma in two trials,[37, 39] or intravenous immunoglobulin (IVIG) in one trial.[41] The remaining 12 trials were open label. The 17 selected trials included 15,587 patients with 8027 (51.5%) allocated to the convalescent plasma arm and a mean weighted mortality of 25.1%.

Primary Outcome

Mortality was defined at 21[42] or 25 days[31] in two trials and 28-30 days in the remaining trials. There was no evidence of a mortality benefit with convalescent plasma therapy compared to standard care (24.7% vs. 25.5%; OR 0.94 (0.85 – 1.04); p = 0.23; I^2 = 4%; TSA adjusted CI 0.84 – 1.05). The cumulative Z-curve crossed neither the conventional nor the TSA boundary for benefit or harm but did cross the boundary for futility having accrued more than the required information size (RIS) cases. (Table 2 and Figure 2) At the time of reporting of mortality, 30.2% convalescent plasma group patients and 31.3% control group patients were still in hospital.

Subgroup analysis

Six trials[33, 37-40, 42] reported mortality for patients admitted to the ICU at enrolment including 13,291 (51.1%) allocated to the treatment arm with a mean mortality of 24.9%. Convalescent plasma treatment was not associated with a mortality benefit in ICU patients (24.6% vs. 25.3%; OR 0.91 [0.75-1.09] p=0.31; I^2=39%).

Meta-regression

Meta-regression was used to assess the relationship between antibody titre and treatment effect. Six trials measured neutralising antibody titres[27, 30, 37-39, 42] and five trials measured IgG levels.[28, 31, 32, 35, 36] There was no evidence of association between treatment effect (logOR) and log-concentration of neutralising antibodies (p=0.45; I^2=0%) or IgG (p=0.30; I^2=0%). Additionally, there was no evidence of a relationship between treatment effect and time from symptom onset to administration of convalescent plasma and mortality (p=0.27; I^2=16%), or between treatment effect and risk of death and mortality (p=0.27; I^2=7%).

Sensitivity Analyses

A sensitivity analysis performed on the primary outcome of 28–30-day mortality using a fixed effects model revealed no mortality benefit with convalescent plasma therapy compared to standard care (24.7% vs. 25.5%; OR 0.96 [0.89 – 1.03); p = 0.23; I^2 = 4%; TSA adjusted CI 0.88 – 1.04).

An additional sensitivity analysis was performed excluding the three studies which administered either non-convalescent plasma[37, 39] or IVIG as control.[41] Convalescent plasma was not associated with a mortality benefit (24.7% vs. 25.4%; OR 0.96 [0.90 – 1.04); p = 0.35; I^2 = 0%; TSA adjusted CI 0.89 – 1.04).

As the risk of bias was high in most trials, no additional analyses were performed on trials with a low risk of bias. A TSA sensitivity analysis was attempted using the relative risk reduction calculated from our meta-analysis of 3.0%, however this could not be performed as only 8.4% of RIS cases had been accrued.

Secondary outcomes

Two trials reported incidence of ICU admission[31, 35] including 308 patients of whom (62.5%) were allocated to the treatment group with a combined incidence of 14%. Convalescent plasma was not associated with a reduction in ICU admission compared to standard care (22.4% vs. 16.7%; OR 0.80 [0.21 – 3.09]; p = 0.75; I^2 = 63%; TSA adjusted CI 0.0 – 196.05). The Z-curve crossed neither conventional or TSA boundary for benefit or harm, nor the futility boundary as only 5% of RIS cases had been accrued.

Thirteen trials reported the incidence of mechanical ventilation.[27, 29-38, 40, 43] These included 13,876 patients of whom 7105 (51.2%) were allocated to the treatment group. Convalescent plasma was not associated with a reduction in need for mechanical ventilation (15.7% vs. 15.4%; OR 1.01 [0.92 – 1.11]; p = 0.82; I^2 = 0%; TSA adjusted CI 0.91 – 1.13). The Z-curve crossed neither conventional nor TSA boundary for benefit or harm but did cross the boundary for futility having surpassed the required information size (RIS). (Figure 3)

Adverse events

15 trials reported the incidence of total adverse events.[27, 28, 31-43] These included a total population of 15,060 patients with 7782 (51.7%) allocated to the treatment arm and a combined incidence of 56.2%. Convalescent plasma administration was not associated with an increased rate of total adverse events compared to standard care (55.6% vs. 56.8%; OR 1.03 [0.80-1.34] p=0.80; I^2=28%; TSA adjusted CI 0.72 – 1.50). The Z-curve crossed neither conventional or TSA boundary for benefit or harm but did cross the boundary for futility having exceeded the required information size (RIS). (Supplemental Figure 1) Additional adverse event analyses can be found in the Supplementary Information.

Risk of Bias and GRADE analysis

The risk of bias was high due to the open-label approach taken in 13 trials,[27-30, 32-34, 36, 38, 40-43] industry sponsorship in 15 trials,[27, 28, 30-32, 34-43] and the release of results as non-peer-reviewed pre-prints by 11 trials,[27-29, 33, 34, 36-38, 40-42] thus was adjudged to be serious for GRADE analysis. (Supplementary Table 3) Inconsistency was not serious excluding 'Need for ICU admission' which was deemed serious due to substantial heterogeneity. Indirectness was deemed not serious. Imprecision was judged as not serious in all domains excluding 'Need for ICU admission' as only 5% of RIS had been accrued. Some evidence of publication bias/small study effects was seen due to asymmetry of the funnel plot (Harbord's test, p = 0.010). The overall quality of evidence on GRADE assessment for our primary and secondary outcomes was marked as 'very low'. (Table 3 and Supplemental Figure 2).

Discussion

In patients with COVID-19, use of convalescent plasma was not associated with a mortality benefit. In patients with mild disease, convalescent plasma did not prevent either the need for mechanical ventilation nor ICU admission. A trial sequential analysis suggests futility in continuing trial recruitment. Among patients with mild disease, convalescent plasma was not associated with a reduction in intensive care admission or requirement for advanced respiratory support. No association was seen between the titre of anti-SARS-CoV-2 antibody infused, time from symptom onset to convalescent plasma administration, or risk of death and treatment effect of convalescent plasma.

Data on the significance of seroconversion on mortality in COVID-19 are conflicting. Levels of S- and RBD-specific IgG levels are higher in severe/critically ill patients during hospitalization compared to patients with mild or moderate disease.[44, 45] At both early and late timepoints, plasma concentrations of IgA, IgG and IgM antibodies are higher in survivors compared to those who subsequently die. [46] In contrast, other studies suggest that the generation of S-, RBD-, and N-specific IgG occurs one week later in patients with severe/critically ill COVID-19 compared to those with mild/moderate disease, suggesting that early administration of convalescent plasma may benefit patients with more severe disease.[45]

The potential utility of endogenous anti-SARS-CoV-2 antibodies in overcoming acute infection with COVID-19 was supported by observational data. Early after symptom onset, levels of anti-N antibodies correlated strongly with disease severity.[44] This may reflect illness severity, with greater antibody production in response to a greater antigen burden. We therefore hypothesised that administration of high-titre convalescent plasma may offer the greatest benefit and that anti-SARS-CoV-2 antibodies would have a beneficial effect on patients at greatest risk of death. However, meta-regression did not reveal any association between the risk of death and mortality benefit of convalescent plasma, nor any association between titre of convalescent plasma and mortality benefit.

Indeed, the concept of using convalescent plasma as a means of passive immunisation against COVID-19 was supported by early observational data suggesting administration soon after hospitalization using high-titre anti-spike protein RBD IgG significantly reduced mortality.[47] We were however unable to find any association between timing of convalescent plasma administration with respect to symptom onset and effect on mortality.

None of the clinical trials stratified patients based on their levels of circulating anti- SARS-CoV-2 antibody titres before enrolment. A significant proportion of critically ill patients with COVID-19 generate high titres of anti-SARS-CoV-2 antibodies. The benefit of further augmenting this response through administration of convalescent plasma is questionable. It is not known whether early administration of high titre convalescent plasma could play a role in the management of high-risk patients, or in those with a progressively worsening illness trajectory, who lack endogenous anti-SARS-CoV-2 antibodies. Existing data suggest that administration of convalescent plasma is safe with no increase in adverse events; this provides reassurance for ongoing and future clinical trials.

We found significant heterogeneity between trials about convalescent plasma titres, doses, and timing of administration. These factors are likely to influence the efficacy of treatment. Furthermore, there is no standardised assay for measurement of neutralising antibodies, and different studies measured different antibodies against COVID-19, limiting the interpretation of impact of antibody titre on outcome. The data in this meta-analysis are heavily weighted by the RECOVERY trial, [38] and interpretation of data is limited due to the high risk of bias in more than half of the trials. A significant number of patients enrolled in the trials had also received various co-interventions including antiviral medications, steroids, and other immunomodulators including tocilizumab. We were unable to correct for this and cannot exclude any interaction with convalescent plasma treatment. It was not possible to evaluate the effect of different dosing strategies on outcome. Nine trials permitted more than one dose of convalescent plasma therapy,[28, 30, 33-35, 38, 40-42] but only two reported outcomes with respect to dose administration.[40, 41] Similarly, the reported incidence of allergic reactions, infections and other complications varied significantly between trials. This may be due to differences in definitions, screening, reporting of complications, and variable patient follow-up. Whilst TSA suggests futility in ongoing trial recruitment, a smaller clinically relevant effect may still exist which would require further enrolment. Further trial data are required before firm conclusions can be made. This includes longer term outcomes as a proportion of patients remained as inpatients at the data censure cut point.

In summary, there was no clear benefit associated with convalescent plasma in COVID-19, with futility in continuing trial recruitment. No association was seen between the titre of anti-SARS-CoV-2 antibody infused, time from symptom onset to convalescent plasma administration, or risk of death and treatment effect of convalescent plasma. Early administration of high titre convalescent plasma to high-risk patients with a progressively worsening illness trajectory who lack endogenous anti-SARS-CoV-2 antibodies requires further attention, as does the use of monoclonal antibodies directed against SARS-CoV-2.

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Figure Legends

Figure 1: PRISMA flow chart

Flow chart of included and excluded trials.

Figure 2: Effect of convalescent plasma on mortality in included trials

a. Forest plot of mortality in RCTs. Size of squares for odds ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

b. Trial sequential analysis of mortality in RCTs. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm, respectively. Horizontal lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary. The cumulative Z-curve represents the trial data. A diversity-adjusted required information size (RIS) of 1522 was calculated using α=0·05 (two sided), β=0·20 (power 80%). Relative risk reduction of mortality reduction was 31.5%. The cumulative Z-curve crosses neither the conventional nor the TSA boundary for benefit or harm, but did cross the boundary for futility having exceed the required information size (RIS)

Figure 3: Effect of convalescent plasma on need for mechanical ventilation

a. Forest plot of risk of need for mechanical ventilation. Size of squares for odds ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% confidence intervals.

b. Trial sequential analysis of risk of need for mechanical ventilation. Uppermost and lowermost curves represent trial sequential monitoring boundary lines for benefit and harm respectively. Horizontal lines represent the traditional boundaries for statistical significance. Triangular lines represent the futility boundary.

Table 1: Baseline characteristics of included trials

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Author (Group) / Trial registration	Country	Recruitment dates	Dose administered		Numbers recruited		Age		Mechanical ventilation		NIV		HFO	
			Plasma	Control	Plasma	Control	Plasma	Control	Plasma	Control	Plasma	Control	Plasma	Control
Agarwal (PLACID) **CTRI: 2020/04/024775**	India	22nd April – 14th July 2020	Two doses of 200mL, 24 hours apart	Open label	235	229	52 ± 5	51 ± 5	NS	NS	NS	NS	NS	NS
AlQahtani **NCT: 04356534**	Bahrain	April – June 2020.	Two doses of 200mL over 2 successive days	Open label	20	20	53 ± 15	51 ± 13	NS	NS	NS	NS	3/20 (15%)	1/20 (5%)
Avendaño **(ConPlas-19)** **NCT: 04345523**	Spain	4th April – 10th July 2020	Single dose of 250-300mL	Open label	38	43	61 ± 16	60 ± 15	NS	NS	NS	NS	NS	NS
Bajpai **NCT: 04346446**	India	21st April – 30th May 2020	Two doses of 250ml on consecutive days	Open label	15	16	48 ± 9	48 ± 11	NS	NS	NS	NS	14/15 (93%)	15/16 (94%)
Bennett-Guerrero **NCT04344535**	United States	8th April -- 24th August 2020	Single dose of 2units (approx. 480ml)	Single dose of 2 units (approx. 480ml)	59	15	67 ± 16	64 ± 17	11/59 (19%)	3/15 (20%)	3/59 (5%)	2/15 (13%)	Included in NIV	Included in NIV
Estcourt **(REMAP-CAP)** **NCT: 02735707**	Worldwide	9th March – 18th January 2021	Two doses of 1unit (approx. 550ml) 12hours apart	Open label	1078	909	60 ± 13	60 ± 13	356/1078 (33%)	289/909 (32%)	493/1078 (46%)	407/909 (45%)	225/1078 (21%)	211/909 (23%)
Gharbharan **(ConCOVID)** **NCT: 04342182**	Netherland	8th April – 10th June 2020	Single dose of 300ml	Open label	43	43	54 ± 4	56 ± 5	13/43 (30%)	NS	NS	NS	NS	NS

Gonzalez **NCT: 04381858**	Mexico	5th May – 17th October 2020	Two doses of 200ml on consecutive days	Five doses of IVIG (0.3 grams/kg) on consecutive days	130	60	61 ± 8	56 ± 6	Included but NS	Included but NS	Included but NS	Included but NS	Included but NS	Included but NS
Horby (RECOVERY) **NCT: 04381936**	United Kingdom	28th May 2020 – 15th January 2021	Two doses of 275mls on consecutive days	Open label	5795	5763	64 ± 15	63 ± 15	302/5795 (5%)	315/5763 (5%)	NS	NS	NS	NS
Körper (CAPSID) **NCT: 04433910**	Germany	30th August – 24th December 2020	Three doses of 1unit on days 1, 3 & 5.	Open-label	53	52	59 ± 3	61 ± 3	13/53 (26%)	17/52 (32%)	28/53 (53%)	21/52 (40%)	Included in NIV	Included in NIV
Li **ChiCTR: 2000029757**	China	14th February – 1st April 2020	Single dose of 4-13ml/kg	Open label	52	52	71 ± 5	69 ± 4	14/51 (27%)	11/50 (22%)	21/51 (41%)	23/50 (46%)	21/51 (41%)	23/50 (46%)
Libster **NCT: 04479163**	Argentina	4th June – 25th October 2020	Single dose of 250ml	Normal saline	80	80	76 ± 9	78 ± 8	2/80 (2.5%)	4/80 (5%)	1/80 (1.3%)	6/80 (7.5%)	1/80 (1.3%)	6/80 (7.5%)
O'Donnell **NCT: 04359810**	USA and Brazil	21st April – 27th November 2020	Single dose of 200-250ml	Single dose of 200-250ml non-convalescent plasma	150	73	60 ± 7	62 ± 7	17/150 (11%)	11/73 (15%)	NS	NS	125/150 (83%)	57/73 (78%)
Rasheed	Iraq	3rd April – 1st June 2020	Single dose of 400ml	Open label	21	28	56 ± 18	48 ± 15	17/21 (81%)	22/28 (78.6%)	NS	NS	4/21 (19%)	6/28 (21%)
Ray **CTRI: 2020/05/025209**	India	31st May – 12th October 2020	Two doses of 200ml on two consecutive days.	Open label	40	40	61 ± 12	61 ± 12	NS	NS	NS	NS	NS	NS
Pouladzadeh **IRCT: 20200310046736N1**	Iran	March – May 2020	Single dose of 500ml	Open label	30	30	54 ± 10	57 ± 17	0	0	10/30 (33%)	5/30 (17%)	Included in NIV	Included in NIV

Simonovich (PlasmAr) NCT: 04383535	Argentina	28th May – 27th August 2020	Single dose of up to 500ml	Normal saline	228	106	63 ± 6	61 ± 6	NS	NS	0	0	11/228 (4.8%)	7/106 (6.6%)
ChiCTR: Chinese clinical trial registry; CTRI: Clinical trial registry of India; HFO: High flow oxygen; NCT: National clinical trial registry; NIV: Non-invasive ventilation; NS: Not specified														

Table 2: Primary, sub-group, and secondary outcome data for included trials

Table 2: Primary, sub-group, secondary, and sensitivity outcome data for included trials						
Outcome	**References**	**Intervention group**	**Control group**	**Conventional effect estimate [95% CI]**	**Overall effect**	**I^2 (%)**
Overall mortality	[27-43]	1986/8027 (24.7%)	1929/7560 (25.5%)	0.94 [0.85 – 1.04]	Z = 1.19 p = 0.23	4
ICU Patient Mortality	[33, 37-40, 42]	1673/6796 (24.6%)	1641/6495 (25.3%)	0.91 [0.75 – 1.09]	Z = 1.04 P = 0.30	39
Disease Progression						
ICU admission	[31, 35]	69/308 (22.4%)	31/185 (16.7%)	OR 0.80 [0.21 – 3.09]	Z = 0.32 P = 0.75	63
Mechanical ventilation	[27, 29-38, 40, 43]	1115/7105 (15.7%)	1042/6771 (15.4%)	OR 1.01 [0.92 – 1.11]	Z = 0.23 P = 0.82	0
Adverse Events						
Total	[27, 28, 31-43]	4324/7782 (55.6%)	4136/7278 (56.8%)	OR 1.03 [0.80-1.34]	Z = 0.26 P = 0.80	28
Allergic reactions	[28, 30, 32, 33, 35-41]	214/7763 (2.8%)	173/7293 (2.4%)	OR 1.18 [0.96-1.45]	Z = 1.61 P = 0.11	0

	Transfusion related cardiac overload	27, 28, 30, 37, 38	131/6255 (2.1%)	147/6147 (2.3%)	0.88 [0.70 – 1.12]	Z = 1.02 P = 0.31	0

Table 3: GRADE analysis

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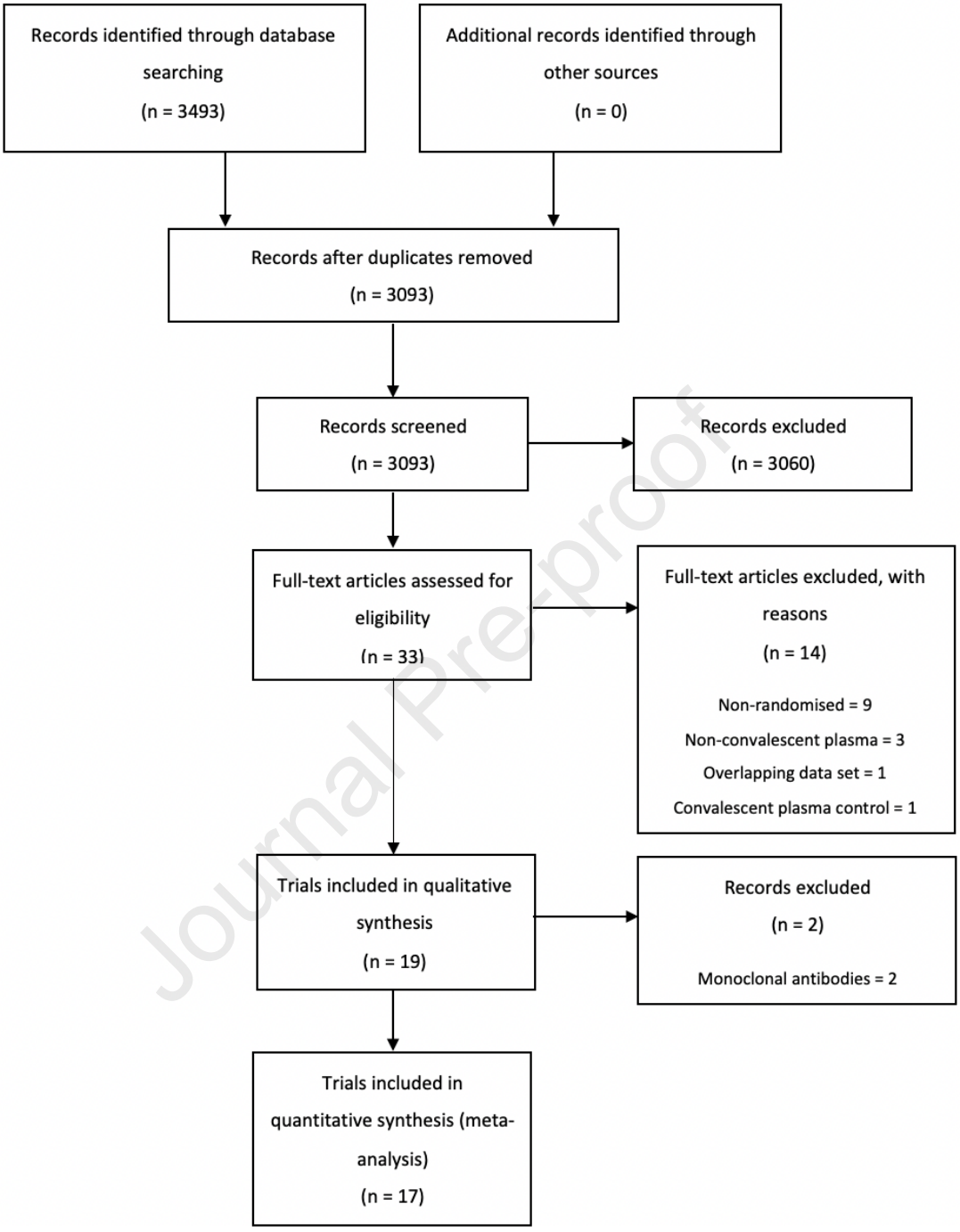
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Convalescent plasma therapy**	**Standard care**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality												
17	randomised trials	very serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected [c,d]	1986/8027 (24.7%)	1929/7560 (25.5%)	**OR 0.94** (0.85 to 1.04)	**12 fewer per 1,000** (from 30 fewer to 8 more)	⨁◯◯◯ VERY LOW	CRITICAL
Need for ICU admission												
2	randomised trials	not serious	serious [e]	not serious	very serious [f]	publication bias strongly suspected [c,d]	69/308 (22.4%)	31/185 (16.8%)	**OR 0.80** (0.21 to 3.09)	**29 fewer per 1,000** (from 127 fewer to 216 more)	⨁◯◯◯ VERY LOW	CRITICAL
Need for Mechanical ventilation												
13	randomised trials	very serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected [c,d]	1151/7105 (16.2%)	1042/6771 (15.4%)	**OR 1.01** (0.92 to 1.11)	**1 more per 1,000** (from 11 fewer to 14 more)	⨁◯◯◯ VERY LOW	CRITICAL
Total Adverse events												
15	randomised trials	very serious [a,b,c]	not serious	not serious	not serious	publication bias strongly suspected [c,d]	4324/7782 (55.6%)	4136/7278 (56.8%)	**OR 1.03** (0.80 to 1.34)	**7 more per 1,000** (from 55 fewer to 70 more)	⨁◯◯◯ VERY LOW	CRITICAL

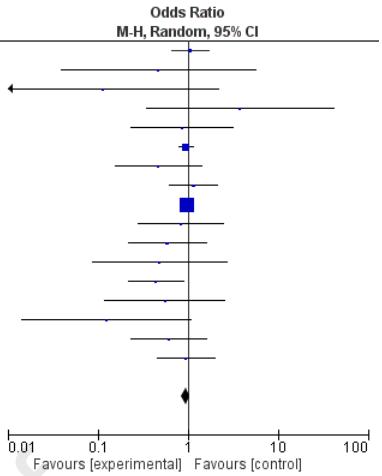
CI: Confidence interval; **OR:** Odds ratio; a. Open label design; b. Pre-print; c. Asymmetrical funnel plot; d. Positive Harbord's test; e. Substantial heterogeneity; f. Only 5% RIS accrued



a.

Study or Subgroup	Plasma Events	Plasma Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Agarwal (PLACID) 2020	44	235	41	229	4.3%	1.06 [0.66, 1.69]
Al-Qahtani 2020	1	20	2	20	0.2%	0.47 [0.04, 5.69]
Avendano-Sola (ConPlas-19) 2020	0	38	4	43	0.1%	0.11 [0.01, 2.19]
Bajpai 2020	3	14	1	15	0.2%	3.82 [0.35, 41.96]
Bennett-Guerrero 2021	14	59	4	15	0.6%	0.86 [0.24, 3.11]
Estcourt (REMAP-CAP) 2021	401	1075	347	904	23.5%	0.96 [0.80, 1.15]
Gharbharan (ConCOVID) 2020	6	43	11	43	0.8%	0.47 [0.16, 1.42]
Gonzalez 2021	44	95	30	70	2.5%	1.15 [0.62, 2.14]
Horby (RECOVERY) 2021	1398	5795	1408	5763	60.2%	0.98 [0.90, 1.07]
Körper (CAPSID) 2021	7	53	8	52	0.8%	0.84 [0.28, 2.50]
Li 2020	8	51	12	50	1.0%	0.59 [0.22, 1.59]
Libster 2021	2	80	4	80	0.3%	0.49 [0.09, 2.74]
O'Donnell 2021	19	150	18	73	1.9%	0.44 [0.22, 0.91]
Pouladzadeh 2021	3	30	5	30	0.4%	0.56 [0.12, 2.57]
Rasheed 2020	1	21	8	28	0.2%	0.13 [0.01, 1.09]
Ray 2020	10	40	14	40	1.1%	0.62 [0.24, 1.63]
Simonovich (PlasmAr) 2020	25	228	12	105	1.8%	0.95 [0.46, 1.98]
Total (95% CI)		**8027**		**7560**	**100.0%**	**0.94 [0.85, 1.04]**
Total events	1986		1929			

Heterogeneity: Tau² = 0.00; Chi² = 16.72, df = 16 (P = 0.40); I² = 4%
Test for overall effect: Z = 1.19 (P = 0.23)



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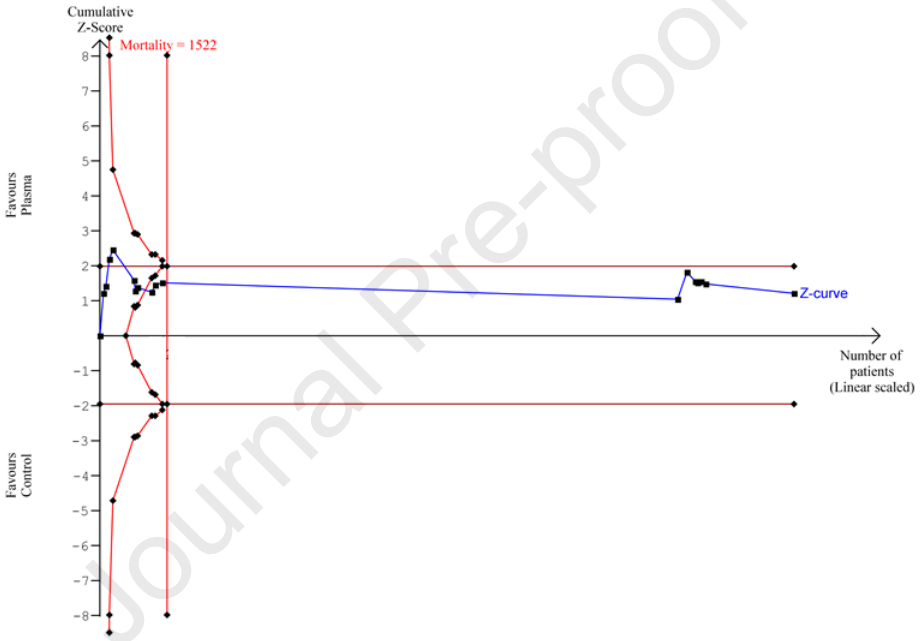

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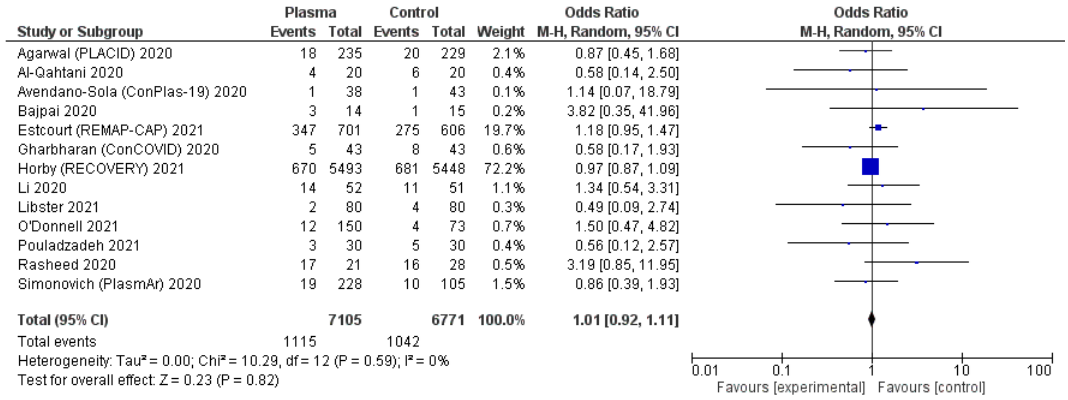

Study or Subgroup	Plasma Events	Plasma Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
Agarwal (PLACID) 2020	18	235	20	229	2.1%	0.87 [0.45, 1.68]
Al-Qahtani 2020	4	20	6	20	0.4%	0.58 [0.14, 2.50]
Avendano-Sola (ConPlas-19) 2020	1	38	1	43	0.1%	1.14 [0.07, 18.79]
Bajpai 2020	3	14	1	15	0.2%	3.82 [0.35, 41.96]
Estcourt (REMAP-CAP) 2021	347	701	275	606	19.7%	1.18 [0.95, 1.47]
Gharbharan (ConCOVID) 2020	5	43	8	43	0.6%	0.58 [0.17, 1.93]
Horby (RECOVERY) 2021	670	5493	681	5448	72.2%	0.97 [0.87, 1.09]
Li 2020	14	52	11	51	1.1%	1.34 [0.54, 3.31]
Libster 2021	2	80	4	80	0.3%	0.49 [0.09, 2.74]
O'Donnell 2021	12	150	4	73	0.7%	1.50 [0.47, 4.82]
Pouladzadeh 2021	3	30	5	30	0.4%	0.56 [0.12, 2.57]
Rasheed 2020	17	21	16	28	0.5%	3.19 [0.85, 11.95]
Simonovich (PlasmAr) 2020	19	228	10	105	1.5%	0.86 [0.39, 1.93]
Total (95% CI)		**7105**		**6771**	**100.0%**	**1.01 [0.92, 1.11]**
Total events	1115		1042			

Heterogeneity: Tau² = 0.00; Chi² = 10.29, df = 12 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)

b.