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Original Articles

Convalescent Plasma for Patients Hospitalized With Coronavirus Disease 2019: A Meta-Analysis With Trial Sequential Analysis of Randomized Controlled Trials

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Current evidence from randomized controlled trials (RCTs) and systematic reviews on the utility of convalescent plasma (CP) in patients with coronavirus disease 2019 (COVID-19) suggests a lack of benefit. We conducted an updated meta-analysis of RCTs with trial sequential analysis to investigate whether convalescent plasma is futile in reducing mortality in patients hospitalized with COVID-19. We searched 6 databases from December 1, 2019 to August 1, 2021 for RCTs comparing the use of CP with standard care or transfusion of non-CP standard plasma in patients with COVID-19. The risk of bias was assessed using the Cochrane Risk-of-Bias 2 Tool. Random effects (DerSimonian and Laird) meta-analyses were conducted. The primary outcome was the aggregate risk for in-hospital mortality between both arms. We conducted a trial sequential analysis (TSA) based on the pooled relative risks (RRs) for in-hospital mortality. Secondary outcomes included the pooled RR for receipt of mechanical ventilation and mean difference in hospital length of stay. We included 18 RCTs (8702 CP, 7906 control). CP was not associated with a significant mortality benefit (RR: 0.95, 95%-CI: 0.86-1.04, P = .27, high certainty). Subgroup analysis did not find any significant differences (Pinteraction = 0.30) between patients who received CP within 8 days of symptom onset (RR: 0.97, 95%-CI: 0.79-1.19, P = .80), or after 8 days (RR: 0.79, 95%-CI: 0.57-1.10, P = .16). TSA based on a RR reduction of 10% from a baseline mortality of 20% found that CP was not effective, with the pooled effect within the boundary for futility. CP did not significantly reduce the requirement for mechanical ventilation (RR: 1.00, 95%-CI: 0.91-1.10, P = .99, moderate certainty) or hospital length of stay (+1.32, 95%-CI: -1.86 to +4.52, P = .42, low certainty). CP does not improve relevant clinical outcomes in patients with COVID-19, especially in severe disease. The pooled effect of mortality was within the boundary of futility, suggesting the lack of benefit of CP in patients hospitalized with COVID-19.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic continues to progress, and a spike in cases has been noted worldwide since March 2021, with many countries experiencing a second or third wave. Healthcare systems have been burdened globally, and up to 20% of infected patients progress to severe disease and 5% require admission to the intensive care unit (ICU) [1]. It has been reported that mortality rates of patients with severe COVID-19 reach up to 20% [2], and as many as 45% of patients requiring invasive mechanical ventilation do not survive [3]. Several potential therapies have been investigated, but only glucocorticoids, interleukin-6 receptor antagonists, and monoclonal antibodies have shown some survival benefits till date [4-6].

Convalescent plasma (CP) is a potential therapy that has been previously investigated against other respiratory viruses [7,8]. It supposedly engenders a temporary immune response against the viral particles, before the peak production of endogenous IgM and IgG antibodies by the native immune response is established in the
patient [9]. The transient reduction in viral load reduces the stimulus for a hyperinflammatory cytokine storm that mediates further progression. Early administration of convalescent plasma in disease has been proven to be beneficial in some viral illnesses [9,10]. Numerous observational studies, randomized controlled trials (RCTs) and systematic reviews have been published thus far in patients with COVID-19 [11,12], with most recent reviews highlighting a lack of benefit of CP [13].

Multiple RCTs have been terminated early due to the decreasing prevalence of COVID-19, as well as refusal of consent from eligible patients [14–18]. As a result of this, the sample size of these RCTs is insufficient, and they are unable to provide strong evidence for or against CP in COVID-19. As such, we conducted a systematic review and meta-analysis of CP use in patients hospitalized with COVID-19. In addition to this, we performed a trial sequential analysis (TSA) via cumulative meta-analysis similar to interim analyses in RCTs, in order to assess the conclusiveness of the findings from our meta-analysis.

Methodology

Search Strategy and Selection Criteria

This study was registered with PROSPERO (CRD42021253826), and was conducted in adherence with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement [19]. We searched MEDLINE, Embase, Cochrane, Scopus, MedRXiv and COVID-NMA databases from December 1, 2019 to August 1, 2021, using the following keywords and their variations: “COVID-19,” “convalescent plasma,” and “randomised controlled trials” (Supplementary Data 1). We assessed all relevant studies and their citation lists to identify articles for inclusion.

We included all RCTs comparing the use of CP with standard of care or transfusion of non-CP standard plasma in 10 or more adult patients (>18 years) hospitalized with severe COVID-19 reporting on in-hospital mortality, receipt of mechanical ventilation, or hospital length of stay. We excluded any non-human or pediatric studies (<18 years). In the case of overlapping patient data, we included the largest study and excluded any other overlapping studies. Three reviewers (RRL, JLS, FLT) were involved in the screening process and any conflicts were resolved by a fourth reviewer (KR).

Assessment of Risk of Bias and Certainty of Evidence

Study quality was assessed using the Cochrane Risk-of-Bias 2 tool for RCTs [20]. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach to assess the certainty of evidence [21]. The assessment for risk of bias and certainty of evidence was conducted by 3 reviewers (RRL, JLS, FLT) independently, and conflicts were resolved by a fourth reviewer (KR).

Outcomes of Interest and Data Collection

The primary outcome for our meta-analysis is in-hospital mortality, and this is quantified based on the relative risk (RR) between the treatment versus control arms. Secondary outcomes included the receipt of mechanical ventilation, and the hospital length of stay. Other outcomes that were reported descriptively include the ICU length of stay, as well as any other adverse outcomes. Data were collected independently by 4 reviewers (RRL, JLS, FLT, SM) using a prespecified datasheet, and conflicts were resolved by a fifth reviewer (KR). Data collection covered study characteristics, patient demographics, CP characteristics, mortality, and other relevant clinical outcomes (Supplementary Data 2).

Data Synthesis

We estimated the summary RRs for in-hospital mortality between the treatment and control arms for each study, and pooled them using random effects (DerSimonian and Laird) meta-analysis based on the Freeman-Tukey double-arc sine transformation [22–24]. Confidence intervals were computed using the Clopper-Pearson method. We assessed the possibility of publication bias via visual inspection of the funnel plot as well as Egger’s regression test. Small-study effects were corrected using the random-effects trim-and-fill (R₀ estimator) procedure. A previous meta-analysis suggested the exclusion of the study by Agarwal et al. as majority of their patients had received low antibody titers, following which they found significant survival benefits [12]. To test this hypothesis, we conducted a sensitivity analysis excluding the study from the meta-analysis. Another sensitivity analysis was conducted by excluding any studies with high risks of bias.

To further elicit the effect of CP in COVID-19, we performed TSA using TSA v0.9.5.10 (www.ctu.dk/tsa), which combines an information size calculation for a meta-analysis with the threshold of statistical significance whenever an additional trial is included via cumulative meta-analysis. This is similar to group sequential monitoring boundaries in RCTs during interim analyses. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, which recruited patients to detect a RR reduction in mortality of 20%, did not find significant benefits from CP use. As such, in our meta-analysis, we sought to determine if CP had a significant benefit based on a smaller reduction in mortality. Using a type 1 error of 0.05 and a power of 0.80, we estimated the required information size assuming a RR reduction in mortality of 10% (which is closer to the pooled estimate in the meta-analysis) and a baseline in-hospital mortality rate of 20% as reported in the published literature for patients with severe COVID-19, anticipating low-moderate levels of heterogeneity [2].

Subgroup analysis was conducted based on the timing at which CP was given (within 8 days of symptom onset, and later than 8 days). We then pooled the RRs for receipt of mechanical ventilation, and the mean differences in hospital length of stay. Pooling of RRs was conducted with continuity correction by adding a constant of 0.5 to allow inclusion of studies with zero events. For continuous variables, means and standard deviations were derived from the aggregate data as per Wan et al. [25]. Statistical heterogeneity was measured as part of the assessment of certainty of evidence outlined by the GRADE approach. Statistical analysis was conducted on R3.6.1. Nominal P < .05 was considered statistically significant in our analysis.

Post-Hoc Analyses

We conducted several additional post-hoc analyses after extracting the data. Firstly, we conducted a subgroup analysis by regional variation as well as the risk of bias. Secondly, we conducted an additional trim-and-fill analysis for hospital length of stay in view of the significant publication bias (p<.05).

Results

Of 2721 references, we identified 118 potentially relevant studies for full-text evaluation. 20 RCTs were identified and 2 were excluded – one compared the effects of early and deferred CP [26], while another RCT did not report any of the prespecified primary or secondary outcomes [27]. In total, 18 RCTs comprising 16,608 hospitalized patients (CP vs control: 8702 vs 7906 patients) were included (Figure 1) [14–18,28–40]. 15 RCTs reported on 30-day mortality, and one RCT reported on 60-day mortality [36], and in-hospital mortality [37]. The REMAP-CAP trial randomized
2084 patients, but only reported mortality outcomes in 2076 patients. Of note, 3 trials reported on patients with nonsevere and severe COVID-19: Bennett-Guerrero reported on 14 patients with nonsevere COVID-19 [15], while Gharbharan reported on one patient with moderate COVID-19 [16]. 897 patients (8%) in the recovery trial did not receive supplemental oxygen therapy [31]. Various adjuvant therapies including corticosteroids, antiviral medications, and hydroxychloroquine were used in each study; the proportion of patients receiving each adjuvant therapy is summarized in Supplementary Data 3. Study details, patient characteristics and details on CP are summarized in Table 1.

Six RCTs were rated as having low risk of bias, 11 RCTs with some concerns of bias, and 1 RCT with high risks of bias. Most RCTs had some concerns with deviations from the intended intervention. The risk of bias assessment is summarized in Supplementary Data 4. The GRADE assessment for certainty of evidence for primary outcome was high and is summarized in Supplementary Data 5.

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*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Muitrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
Table 1
Demographics and outcomes of included studies

| Study                  | Year | Design                  | Groups | No. of patients | Patient characteristics | Medication regimen | Mortality | Follow-up duration |
|-----------------------|------|-------------------------|--------|----------------|-------------------------|--------------------|-----------|-------------------|
| Agarwal               | 2020 | Multicenter RCT in India | CP     | 235            | 52 (42-60) y males 177 | 2 × 200 mL CP, 24 h apart | 34        | 28 d              |
|                       |      | Control                 | 229    |                | 52 (41-60) y males 177 | HCO, Remdesivir, Lopinavir/Ritonavir, PRED, Dexamethasone, Hydrocortisone, Tocilizumab, Heparin, Azithromycin, Antibiotics | 31        |                   |
| Al Qahtani            | 2020 | Multicenter RCT in Bahrain | CP     | 20             | 52.6 ± 14.9 y males 17 | 2 × 200 mL CP, 24 h apart | 1         | 28 d              |
|                       |      | Control                 | 20     |                | 50.7 ± 12.5 y males 15 | HCO, Lopinavir/Ritonavir, Ribavirin, Azithromycin, Peginterferon, Tocilizumab, PRED, antibiotics, anticoagulation, PPI, ACE-I/ARB, CCB, Bi block, Aspirin, Diuretics, Insulin, Metformin, Thryoxine, Acetylcytoeine | 2         |                   |
| Avendano-Sola         | 2020 | Multicenter RCT in Spain | CP     | 38             | 61.3 ± 16.3 y males 20 | 1 × 250-300 mL CP, VMNT-ID50 assay titer 1:292, Pseudovirus neutralizing ID50 assay titer 1:327 | 0         | 30 d              |
|                       |      | Control                 | 43     |                | 60.3 ± 15.0 y males 5  | HCO, Lopinavir-Ritonavir, Azithromycin, Remdesivir, Glucocorticoid, Tocilizumab, LMWH | 4         |                   |
| Bajpai                | 2020 | Single center RCT in Lok Nayak hospital in India | CP     | 14             | 48.1 ± 9.1 y males 11 | 2 × 250 mL CP, 24 hours apart | 3         | 29 d              |
|                       |      | Control                 | 15     |                | 48.3 ± 10.8 y males 11 | HCO, Azithromycin, Oseltamivir, standard medications for diabetes mellitus and hypertension control | 1         |                   |
| Bennett-Guerrero      | 2021 | Single center RCT in a New York Hospital | CP     | 59             | 67.3 ± 15.8 y males 36 | 2 × 240 mL CP over 1-4 h each | 14 (28 d) | 90 d              |
|                       |      | Control                 | 15     |                | 64.3 ± 17.4 y males 2  | Plaque neutralization assay titer 1:526 | 16 (90 d) |                   |
|                       |      |                        |        |                | 2 immunocompromised BMI 27.8 (23.1-30.2) | Glucocorticoids, Remdesivir, HCQ, Tocilizumab | 4 (28 d) |                   |
| Concor                | 2021 | Multicenter RCT in Canada, the United States, and Brazil | CP     | 614            | 67.8 ± 16.0 y males 183  | 1 × 500 mL CP from 1 - 2 donors | 141 (30 days) | 90 d              |
|                       |      | Control                 | 307    |                | 67.3 ± 14.8 y males 183 | Viral neutralizing antibodies at a titer of >1:160 or antibodies against the receptor binding domain (RBD) of the SARS-CoV-2 Spike protein at a titer of >1:100 | 156 (90 d) |                   |
|                       |      |                        |        |                | BMI 29 (25-33) | Azithromycin, Systemic Corticosteroids, Antiviral Medications, Anticoagulants, Other Covid-19 medications, Other Antibiotics | 63 (30 d) |                   |

(continued on next page)
| Study                | Year   | Design                              | Groups               | No. of patients | Patient characteristics | Medication regimen | Mortality | Follow-up duration |
|---------------------|--------|-------------------------------------|----------------------|-----------------|-------------------------|-------------------|-----------|-------------------|
| Estcourt            | 2021   | **International multicenter RCT**   | Early CP            | 1120            | 60.3 ± 12.8 y 753 males 67 immunocompromised 271 seronegative BMI 30.8 (26.9-35.6) | 2 × 250-310 mL CP within 48 h of randomization Antibody titer ≥ 1:80 | 406/1117 | 28 d              |
|                     |        |                                     | Delayed CP          | 31              | 61.1 ± 17.5 y 18 males BMI 32.4 (28.7-39.7) | Steroids, Remdesivir, immunomodulators, Tocilizumab, Sarilumab | 9         |                   |
|                     |        |                                     | Control             | 933             | 60.2±13.1 y 633 males 60 immunocompromised 149 seronegative BMI 31.1 (26.9-36.5) | 1 × 300 mL CP 2nd unit of CP after 5 days in patients without a clinical response and a persistently positive RT-PCR Antibody titer 1:640 | 354/928 |                   |
| Gharbharan          | 2020   | **Multicenter RCT in Netherlands**  | CP                   | 43              | 61 (56-70) y 29 males 7 seronegative | EMA-approved drugs (chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, anakinra) | 6         | 60 d              |
|                     |        |                                     | Control             | 43              | 63 (55-77) y 33 males 6 seronegative | Antivirals, Steroids, Antibiotics, Vasopressors, Anticoagulants, Platelet aggregation inhibitor | 11        |                   |
| Korper              | 2021   | **Multicenter RCT in Germany**      | CP                   | 53              | 59 (53-65) y 42 males 10 seronegative BMI 29.4 (27.6-33.4) | 3 units of CP on day 1, 3, and 5 with a total median of 846 mL (824-855 mL). PRNT50 neutralisation titer 1:160 | 8         | 35 d              |
|                     |        |                                     | Control             | 52              | 62 (55-66) y 35 males 10 seronegative BMI 29.1 (25.6-31.5) | Antivirals, Steroids, Antibiotics, Vasopressors, Anticoagulants, Platelet aggregation inhibitor | 14        |                   |
| Li                  | 2020   | **Multicenter RCT in China**        | CP                   | 51              | 70 (62-80) y 27 males | 1 × 4-13 mL/kg of CP – 10 mL for the first 15 mins, 100 mL/h subsequently Antibody titer 1:160 | 8         | 28 d              |
|                     |        |                                     | Control             | 50              | 69 (63-76) y 33 males | Antivirals, Interferon, Chinese herbal medicine, Antibacterials, Antifungals, Steroids, Human immunoglobulin Antihypertensives, antidiabetics Antibody titer 1:3200 | 12        |                   |
| Libster             | 2018   | **Multicenter RCT in Argentina**    | CP                   | 80              | 76.4 ± 8.7 y 26 males 77.9 ± 8.4 y 34 males | Antivirals, Interferon, Chinese herbal medicine, Antibacterials, Antifungals, Steroids, Human immunoglobulin Antihypertensives, antidiabetics | 2         | 25 d              |
|                     |        |                                     | Control             | 80              | 76.4 ± 8.7 y 26 males 77.9 ± 8.4 y 34 males | Antivirals, Interferon, Chinese herbal medicine, Antibacterials, Antifungals, Steroids, Human immunoglobulin Antihypertensives, antidiabetics | 4         |                   |
| O'Donnell           | 2021   | **Multicenter RCT in New York and Brazil** | CP                   | 150             | 60 (48-71) y 96 males BMI 30.1 (26.6-34.7) | 1 × 200-250 mL CP over 2h Antibody titer 1:160 | 19        | 28 d              |
|                     |        |                                     | Control             | 73              | 63 (49-72) y 51 males BMI 29.4 (26.2-33.0) | Corticosteroids, Remdesivir, HCQ, Antibacterials | 18        |                   |
| Pouladzadeh        | 2021   | **Single center RCT in Iran Ahvaz Jundishapur University of Medical Sciences** | CP                   | 30              | 53.5±10.3 y 16 males | 1 × 500 mL CP, 2nd unit if no improvement seen after 24 h | 3         | 2 mo              |
|                     |        |                                     | Control             | 30              | 57.2 ± 17.0 y 17 males | Chloroquine phosphate, Lopinavir/Ritonavir | 5         |                   |

(continued on next page)
| Study          | Year | Design                                | Groups | No. of patients | Patient characteristics | Medication regimen                                                                 | Mortality | Follow-up duration |
|---------------|------|---------------------------------------|--------|-----------------|-------------------------|--------------------------------------------------------------------------------------|-----------|--------------------|
| Rasheed       | 2020 | Multicenter RCT in Iraq               | CP     | 21              | 21 ± 55.7 y 18 seronegative 28 ± 47.8 y | 1 × 400 mL CP over 2h H, Azithromycin, PRED 2 × 200 mL CP, 24 h apart                | 1         | 30 d               |
| Ray           | 2020 | Multicenter RCT in India              | Control CP | 28              | 27 males               | Tocilizumab, Remdesivir, HCQ, AZA, Ivermectin, Doxycycline, Corticosteroids, LMWH / unfractionated heparin, Antibiotics, Antidiabetics, Antihypertensives | 8         | 30 d               |
|               |      |                                       | Control | 40              | 30 males               |                                                                                       |           |                    |
| RECOVERY (Horby) | 2021 | Multicenter RCT in UK                 | CP     | 5795            | 63.6 ± 14.7 y 1982 seronegative 3643 males | 1 × 275 mL CP, 2nd unit 75 mL at least 12 hrs later the following day (4675 (81%)) Antibody titers ≥:1:100 Dexamethasone, Lopinavir-Ritonavir, HCQ, azithromycin, colchicine, REGN-COV2 (monoclonal neutralising antibody cocktail), aspirin, tocilizumab | 1398      | 28 d               |
|               |      |                                       | Control | 5763            | 63.4±14.6 y 1629 seronegative 3787 males |                                                                                       |           |                    |
| Sekine        | 2021 | Single center RCT in Brazil           | CP     | 80              | 59.0 (48.0 - 68.5) y 49 seronegative 49 males | 2 × 300 mL, 48 h apart Glucocorticoids and Antibacterials                             | 18        | 28 d               |
|               |      | Hospital de Clinicas de Porto Alegre  | Control | 80              | 62.0 (49.5 - 68.0) y 52 seronegative 44 males | Glucocorticoids and Antibacterials                                                  |           |                    |
| Simonovich    | 2020 | International multicenter RCT         | CP     | 228             | 62.5 (53-72.5) y 65 seronegative 64 males | 5-10 mL/kg/h of CP with an inferior limit 400 mL for patients <70 kg and a superior limit of 600 mL for those >70 kg. Median 500 mL (IQR 415-600 mL) Antibody titer 1:3200 Steroids, Lopinavir/Ritonavir, Tocilizumab, Ivermectin | 25        | 30 d               |
|               |      |                                       | Control | 105             | 62 (49-71) y 34 seronegative 64 males |                                                                                       |           |                    |

ACE-I/ARB, Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; B blocker, beta blocker; CCB, calcium channel blocker; CP, convalescent plasma; HCQ, Hydroxychloroquine; LMWH, Low molecular weight heparin; PRED, Methylprednisolone; PPI, Proton pump inhibitor.
From the 18 RCTs, 2121 (24.4%) of 8699 patients from the CP arm and 1984 (25.1%) of 7901 patients from the control arm did not survive. The pooled RR for in-hospital mortality was 0.95 (95%-CI: 0.86-1.04, P = .27 Figure 2, high certainty). While there was possible evidence of publication bias (P<.05 = .032), the pooled estimate remained relatively similar after correction of small-study effects using the trim-and-fill (R<sub>0</sub>) estimator (RR: 0.98, 95%-CI: 0.86-1.11, P = .71, Figure 3). A futility analysis was conducted based on in-hospital mortality reported by 18 RCTs, the required information size was 17,257. The cumulative Z-curve did not cross the boundaries for benefit or harm, and was within the boundary for futility (Figure 4), suggesting the postulated benefit of CP is unlikely to be achieved with further randomization of patients.
20% baseline mortality is a Two-sided graph

Fig. 4. Trial sequential analysis for a baseline mortality rate of 20%. As the RECOVERY trial had found no significant benefit at a relative risk reduction (RRR) in mortality of 20%, modelled our TSA based on an 10% RRR in mortality to further elicit the effect of convalescent plasma. The required information size is 17257, and this is not achieved. The cumulative Z-curve (red line) does not cross the boundary for conventional (light-blue dotted lines) or TSA-adjusted (upper and lower-most curves) boundaries for benefit or harm. The Z-curve is within the boundary of futility (triangular lines beginning from the middle of the graph).

We then conducted a subgroup analysis based on the timing of CP ($P_{interaction} = .30$). Patients who were treated with CP within 8 days of symptom onset (8 studies, 2204 patients, RR: 0.97, 95%-CI: 0.79-1.19, $P = .80$) did not have a significantly different risk for mortality compared to those who were treated beyond 8 days (7 studies, 12,251 patients, RR: 0.79, 95%-CI: 0.57-1.10, $P = .16$).

Administration of CP did not impact the proportion of patients requiring mechanical ventilation between both groups (8 studies, 6511 CP, 6363 control, RR: 1.00, 95%-CI: 0.91-1.10, $P = .99$, $P_{Egger} = .73$, moderate certainty), nor did it reduce the hospital length of stay (5 studies, 549 CP, 467 control, +1.32 days, 95%-CI: -1.86 to +4.51, $P = .42$, $P_{Egger} = .033$, low certainty). Given the significant Egger’s test, trim-and-fill analysis was conducted for hospital length of stay; after correcting for small-study effects, CP increased the hospital length of stay by 5.08 days (95%-CI: 2.22-7.94, $P=.0005$). Ten studies reported on adverse outcomes related to COVID-19 therapy while 3 studies reported on the ICU length of stay (ranging from 5 to 39 days). The details of the adverse outcomes as well as other clinical outcomes are summarized in Supplementary Data 6.

Post-hoc subgroup analyses by geographical region (Asia, Europe, The Americas, $P_{interaction} = .84$) and by risk of bias (low risk vs some concerns and high risk, $P_{interaction} = .75$, Supplementary Data 7) found no difference in the reduction in mortality across the individual subgroups.

Discussion

Our analysis of the current literature suggests that CP does not appear to have any significant mortality benefits for patients hospitalized with COVID-19 (RR: 0.95, 95%-CI: 0.86-1.04, $P = .27$), majority of whom had severe disease. Sensitivity analyses excluding Agarwal et al. [12,28], and studies with high risks of bias [33], did not significantly change the pooled estimate. Previously published meta-analyses suggested no survival benefits [11]. However, Klassen et al. found significant survival benefits after excluding one study where patients had received “low-levels” of antibodies during transfusion [12,28]. While our meta-analysis had 5 newer RCTs included, our sensitivity analysis after excluding the study did not find any significant survival benefits for patients receiving CP.

Apart from its direct antiviral neutralizing action [9], CP therapy is postulated to provide additional benefit via immunomodulation of the infected host [41]. However, its effectiveness is confounded by the emergence of the newer alpha (B.1.1.7), gamma (P1) and delta (B.1.617.2) variants, some of which may evade immune responses. Secondly, the lowest effective dose and neutralizing antibody titer required for viral clearance remain uncertain. The mortality rates in patients hospitalized due to COVID-19 have been variable globally. While the RECOVERY trial, which enrolled the largest number of patients receiving CP, reported a 24% mortality in the control and intervention arms of predominantly severe COVID-19 patients [31], other observational studies have
shown lower mortality rates in hospitalized patients with COVID-19 [2,42]. Our TSA analysis found that assuming a baseline mortality rate of 20% in this cohort and a RR reduction of 10%, the cumulative Z-curve was within the boundary for futility. This implies that CP in its current state and timing of administration is unlikely to confer survival benefit amongst patients hospitalized with COVID-19, and recruitment of further patients for CP would be futile.

Two interrelated factors could explain the lack of demonstrable efficacy of CP in COVID-19: the serostatus of the recipient and the timing of plasma administration. SARS-CoV-2 viremia peaks at the first week of illness and viral clearance which follows the primary immune response occurs by 10–14 days. Beyond 8 days after symptom onset, nearly all patients with COVID-19 had neutralizing antibody responses [43]. In our analysis, antibody titers across both arms were reported to be similar [28], and as many as 80% of patients receiving CP were seropositive at baseline [14,16,31,40], which could also potentially account for the lack of survival benefit from CP.

Several studies have found that receipt of CP within 72 hours in milder forms of COVID-19 provided significant benefits to survival and disease progression [18,44,45]. Of note, 2 RCTs randomized their patients within 3 days of severe symptoms, and both did not find any survival benefits [30,37]. Patients even in the early stages of severe COVID-19 are likely to have been seroconverted, and as such, CP confers no additional benefit. It is interesting to note that the recent COVID-19 Convalescent Plasma in Outpatients (C3PO) trial, which randomized patients to receive relatively high-titer (1:160) CP within 7 days of symptoms, found no significant mortality benefits of CP, which argues against the possibility of better efficacy of CP in patients who are seronegative. A recent Bayesian re-analysis of the RECOVERY trial data suggested some mortality benefit in seronegative patients receiving CP [46], concordant with a propensity-score matched study investigating CP in patients with immunodeficiency [47]. This may suggest the need to select for recipients who are unable to mount an adequate immune response for transfer of passive immunity and to maximize the effects of CP.

The meta-analysis and TSA are particularly apt as several trials were terminated early, and results were inconclusive [14–18]. The use of trial sequential analysis allowed us to assess the pooled effect in relation to the required information size, as well as assess futility. As such, the added value of our study lies in the finding that further recruitment of patients is futile in eliciting the effect of CP in patients with severe COVID-19, which previous meta-analyses have not investigated. More importantly, the finding of futility holds massive public health implications, particularly when the delta variant becomes increasingly prevalent. Immense amounts of resources are diverted away from other potentially beneficial therapies, as well as vaccine production. More importantly, patients who received CP therapy have been advised to defer vaccination for at least 90 days which puts a dent in the goal to vaccinate everyone as quickly as possible [48].

We recognize several limitations of our study. A large proportion of patients had severe to critical COVID-19, and received CP approximately a week after the onset of symptoms. The results of our meta-analysis are therefore not completely generalizable to patients with mild and moderate COVID-19 where CP is used within a week of symptom onset, or in patients who are immuno-compromised or seronegative at the time of transfusion [47]. This is further compounded by the fact that volumes of CP and antibody neutralizing titers were heterogenous across studies. While some studies have suggested a dose-response relationship in CP for COVID-19 [40], we were unable to account for this as we were limited by study-level data, and the fact that various instruments and scales were used to determine antibody titers across the studies. There is also likely some residual uncertainty for these highly select groups of patients. Most studies included in the analysis had some concerns of bias, with one study being rated as high risk of bias. As such, the results of these trials should be interpreted with caution, and the certainty of the evidence is impacted. This is further compounded by inclusion of data from preprint servers, which can in itself introduce bias. Nevertheless, the concerns of bias mostly lay in deviations from the intended intervention, where studies had patients crossover from the control arm to the CP arm. Such deviations from interventions may be unavoidable in the context of the current pandemic, where withholding a potentially lifesaving treatment may be considered unethical. In addition, the assessment of evidence found high certainty for the primary outcome, and the pooled results did not significantly change based on the trim-and-fill procedure. Most of the patients receiving CP have also been subjected to a range of other therapies, which might confound the findings of the RCTs.

In this meta-analysis of over 16,000 patients hospitalized with COVID-19, CP did not significantly reduce mortality, nor did it provide any significant benefit for any other clinical outcomes. The pooled effect was within the boundary of futility suggesting further recruitment of patients is unlikely to demonstrate mortality benefit of CP as postulated in patients with severe COVID-19. Nonetheless, its therapeutic use in patients unable to mount an adequate immune response remains undetermined. Rather than determining its effectiveness in COVID-19 in general, further research on CP should be directed in highly select patient groups, and determining which subgroup of patients is most likely to benefit.

Data Sharing Statement

All data generated or analyzed during this study are included in the published studies and their supplementary information files.

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Declaration of interest

All authors declare no competing interests.

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Author Contributions Statement

Study design: KR, RRL
Search strategy and screening of articles: RRL, JJLS, FLT, KR
Risk of bias assessment: RRL, JJLS, FLT
Data collection: RRL, JJLS, FLT, SM
Data analysis and interpretation: RRL, JJLS, FLT, BCT, NLS, KR
Tables and figures: RRL, JJLS, FLT
Drafting of manuscript: RRL
Critical revision of manuscript for intellectually important content: KR, SM, RRL, BCT, SSM, BEF
All authors provided critical conceptual input, interpreted the data analysis, read, and approved the final draft.
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