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Letter to the Editor

Convalescent plasma in the management of COVID-19 pneumonia

Few therapeutic agents have been proven to be effective in the management of COVID-19 pneumonia in randomized trials, thus the treatment options for this condition remain limited [1,2]. Convalescent plasma is a strategy of infusing specific antibody from the plasma of convalescent patients, and has been previously used to treat other viral diseases. Recent randomized trials have evaluated the efficacy of convalescent plasma with mixed findings [3,4]. In this context, we aimed to conduct a comprehensive meta-analysis of randomized trials to study the efficacy and safety of convalescent plasma in the management of COVID-19 pneumonia on a wide scale of outcomes.

A search of MEDLINE, SCOPUS and Cochrane databases was performed without language restrictions through January 2021, using the terms "convalescent plasma", "COVID-19 pneumonia" separately and in combination to identify relevant randomized clinical trials that evaluated the outcomes of patients with COVID-19 related acute pneumonia and received convalescent plasma versus standard of care irrespective of the severity of the illness. Screening of bibliographies of the retrieved studies, prior meta-analyses, preprint domains and **ClinicalTrials.gov** was also performed, to identify any relevant studies not retrieved through the initial search. This meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [5]. A protocol for this meta-analysis was prospectively registered at PROSPERO (CRD42021231762).

Two independent investigators (A.E and M.S) extracted the study design, baseline characteristics, intervention strategies and clinical outcomes of eligible trials. Discrepancies among investigators were resolved by consensus. The primary outcome was all-cause mortality. The secondary outcomes included the composite of progression to severe respiratory illness or all-cause mortality, progression to severe respiratory illness, clinical improvement, and requirement of invasive ventilation. The safety outcomes included the reported infusion-related adverse events in each clinical trial. Outcomes were reported at the longest follow-up.

The quality of the included trials was assessed using the Cochrane risk assessment tool of bias. We pooled data using random-effects models by using inverse variance methods as the primary analysis and using fixed effects as a secondary model. We assessed for statistical heterogeneity across trials by I^2 statistics, with I^2 statistic values <25%, 25% to 50%, and >50% considered as low, moderate, and high degree of heterogeneity, respectively. Subgroup analyses were performed for the primary outcome in studies according to the severity of COVID-19 pneumonia as well as the time from symptom onset to intervention (i.e., symptom-to-intervention time). Since the number of included studies was <10, we did not assess for publication bias [6]. P-values were 2-tailed and considered statistically significant if ≤ 0.05 for all analyses, and <0.1 when evaluating subgroup interactions. All analyses were conducted using the Rstudio software using "meta" packages (RStudio, Inc, Boston, MA).

The final analysis included 6 randomized studies with a total of 1226 patients [3,4,7–10]. The weighted follow-up period was 33 days. Four out of the 6 included trials were terminated prematurely before achieving the target enrollment numbers. Ling et al. enrolled only 52% of the target population due to local control of the pandemic [7]. The ConCOVID study stopped enrollment early at 20% of the target population due to detectable baseline neutralizing antibody among many enrolled patients and concern for study futility [8]. The Con-Plas-19 was prematurely terminated after enrolling only 29% of the target population due to poor recruitment [9]. The INFANT trial also enrolled only 76% of the target population due to local control of the pandemic [10]. All studies were open label except the INFANT-COVID-19 and PlasmAr studies [4,10]. For other risk of bias criteria, all studies were deemed to be of low-risk of bias, except 2 studies [3,9].

There was no significant difference in mortality between the convalescent plasma and control groups (11.1% vs. 13.5% odds ratio [OR] 0.83; 95% confidence interval [CI] 0.48 to 1.18) with no evidence of statistical heterogeneity (I^2=0%) (Fig.). Subgroup analysis according to the severity of COVID-19 at randomization showed no significant difference in all-cause mortality between studies enrolling mild/moderate COVID-19 versus severe COVID-19 ($P_{interaction}$= 0.86). Subgroup analysis showed no difference in all-cause mortality according to symptom-to-intervention time between studies with early intervention (<3 days) versus studies with delayed intervention (>3 days) ($P_{interaction}$= 0.43).

There was no difference in the incidence of the composite of progression to severe respiratory illness or all-cause mortality (14.4% vs. 17.0%, OR 0.65; 95% CI 0.26 to 1.64). Similarly, no difference was observed between both groups in the progression to severe respiratory illness (8.5% vs. 12.8%, OR 0.61; 95% CI 0.29 to 1.27), or requirement of mechanical ventilation (7.5% vs. 8.0%, OR 0.88; 95% CI 0.54 to 1.42). There was no difference between the convalescent plasma and control groups in the rates of clinical improvement (65.4% vs. 60.6%, OR 1.31; 95% CI 0.78 to 2.22) **(Fig.).** The findings of the primary and secondary outcomes were consistent in the secondary analysis using a fixed-effect model**.** There was no significant difference in the incidence of adverse events in the convalescent plasma and control groups (3.5% vs. 2.0%, OR 1.83; 95% CI 0.51 to 6.54; $P = 0.35$).

In this meta-analysis of 6 randomized clinical trials including 1226 patients with COVID-19, there was no significant difference between convalescent plasma and the standard of care treatment in all-cause mortality among patients with COVID-19. Exploratory subgroup analyses suggested no differences in the mortality according to the severity of COVID-19 at presentation or timing of administration of convalescent plasma with respect to symptom onset. There were no differences between the convalescent plasma and control groups in the composite of

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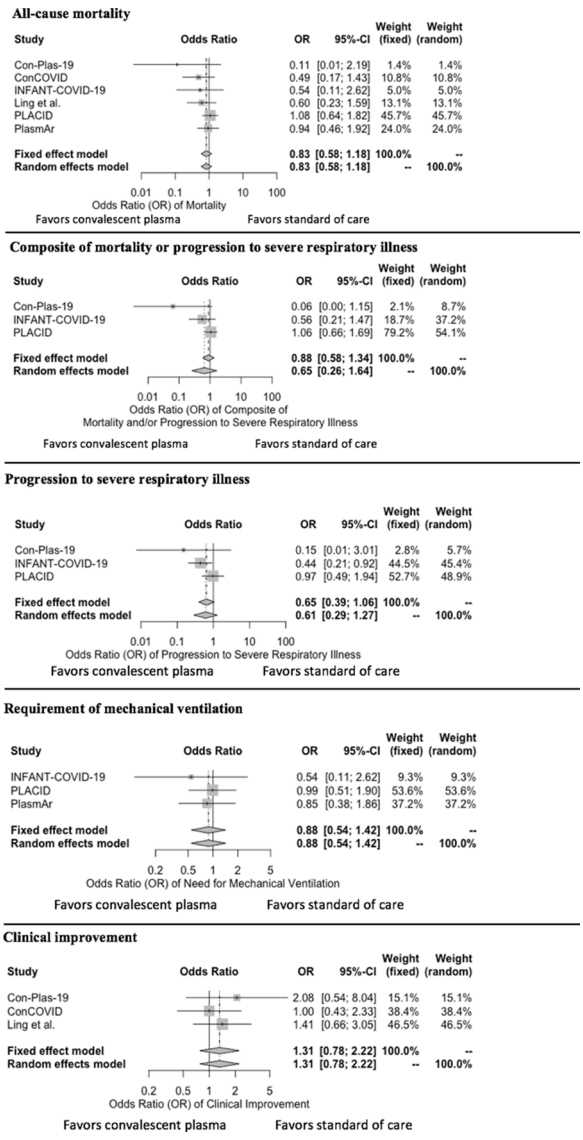

Fig. 1. Forest plot for the outcomes.
The relative size of the data markers indicates the weight of the sample size from each study.
CI = confidence interval; OR = odds ratio.

progression to severe respiratory illness or mortality, progression to severe respiratory illness, requirement of mechanical ventilation or rates of clinical improvement. The majority of the included trials were prematurely terminated and used a different level of plasma donor antibody titers. The overall results of this study-level meta-analysis complement the results of the individual trials and provide insight into the overall effectiveness of convalescent plasma in patients with COVID-19 pneumonia.

Few limitations should be kept in consideration when interpreting the study findings. First, the trials included heterogenous group of patients with COVID-19 ranging from outpatients with mild illness to exclusively enrolling patients with severe COVID-19. Second, 4 of the included trials were prematurely terminated, hence, are considered underpowered to detect true differences in their primary endpoints. Third, the lack of patient-level data prevented exploring the outcomes according to antibody titers in the donated plasma. Finally, the inclusion criteria and definition of primary endpoints varied across the included studies. However, we did not observe significant statistical heterogeneity for the outcomes.

In this meta-analysis of randomized clinical trials, there was no significant difference between convalescent plasma and standard of care treatment in all-cause mortality among hospitalized patients with COVID-19. Similarly, there was no difference between convalescent plasma and the standard of care treatment in halting progression to severe respiratory illness or mechanical ventilation among patients with COVID-19. In light of the heterogenous population, differences in the donor antibody titers, and premature termination of many of the included trials, future high-quality trials are warranted with emphasis on potential recipients who may derive the highest benefit from convalescent plasma therapy.

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Disclosures

All the authors have no conflicts of interest to disclose.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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