High-titer convalescent plasma therapy for coronavirus disease 2019 and mortality

One of the limited number of choices for the treatment of coronavirus disease 2019 (COVID-19) is to administer plasma, containing neutralizing anti-viral antibodies, from donors who have recovered from the disease. This so-called convalescent plasma (CP) is a form of passive immunotherapy that has been used for the treatment and prevention of various infectious diseases for more than a century.

Recently published reports indicate that CP provides a clinical benefit when it is given early in the course of COVID-19 and has a high titer of neutralizing antibodies. Despite the only recent use of CP in the treatment of COVID-19, several systematic reviews and meta-analyses have already been published. These publications have reached conflicting conclusions, probably because of the heterogeneity of the design of the studies included (e.g., peer-reviewed publications, preprints, randomized controlled trials [RCTs], and non-randomized studies), the patients' baseline characteristics (e.g., severity of COVID-19, time since symptom onset), number of doses transfused, and plasma titers. Taking this heterogeneity into consideration and incorporating data from a newly published systematic review,[1] we reappraised the mortality outcome according to the amount of antibody in the therapeutic CP units. We were not able to undertake further subgroup analyses because the data reported from primary studies were limited and not stratified uniformly or clearly for other variable of interest (e.g., baseline characteristics of patients). For the mortality subgroup analysis, we selected three RCTs reporting the use of high-titer CP.[2-4] The study by Simonovich et al.[5] was not included because not reporting outcomes stratified by antibody titer.

The study weight was calculated using the Mantel–Haenszel method and statistical heterogeneity was assessed using the I^2 statistic. Measures of treatment effect were risk difference (RD) together with 95% confidence interval (CI). All calculations were conducted using Review Manager, version 5.4 software. The results of the analysis are shown in Figure 1. Treatment with high-titer CP decreased all-cause mortality significantly (RD, -0.06; 95 % CI, -0.12/0.00; p=0.05); the assumed risk of mortality in the control group was 11.5%, and the corresponding risk in the CP group was 5.8%. These data are in contrast to the results of the more recent systematic review,[1] in which the analysis was performed not considering the CP titer in the primary studies, and included also data from six studies in which variable CP titers (low, unclear, or with no minimum titer cutoff) were given. In the overall analysis of the 10 RCTs included in the systematic review, CP transfusion was not associated with a decrease in all-cause mortality (RR, 1.02; 95% CI, 0.92/1.12; $p = 0.68$).[1]

We used the principles of the Grading of Recommendations Assessment, Development and Evaluation system to assess the quality of the body of evidence on the outcome analyzed (all-cause mortality), and constructed a 'Summary of findings' table (Table 1) using the Review Manager software. The certainty of a body of evidence involves consideration of within-trial risk of bias, directness of evidence, heterogeneity, precision

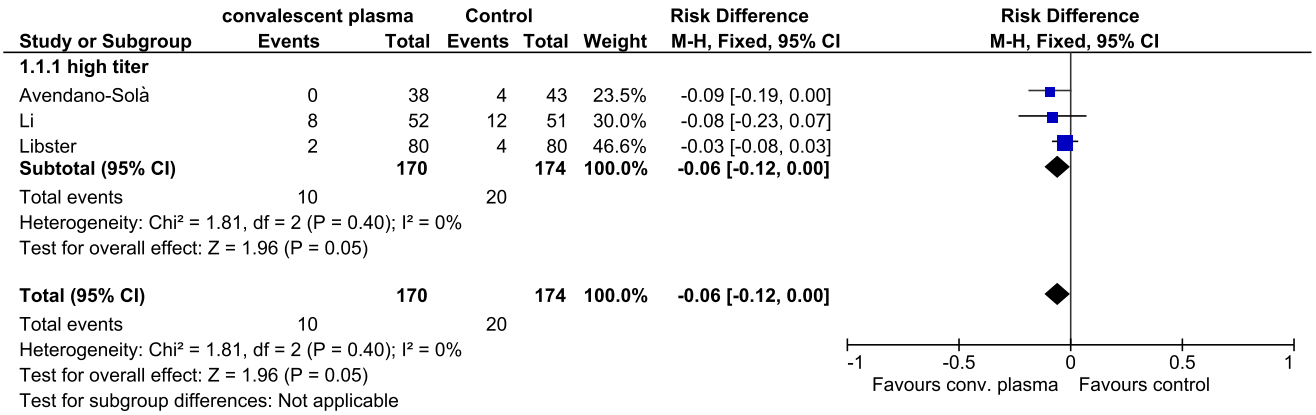

FIGURE 1 Forest plot of a comparison of the outcome, all-cause mortality. Data are from three randomized controlled trials using high-titer convalescent plasma [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Summary-of-findings table

Use of high-titer convalescent plasma (CP)						
Patients: subjects with COVID-19						
Settings: hospitalized pts (two studies) and outpatients (one study)						
Intervention: High-titer CP						
Comparison: Placebo and/or standard of care						
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Comparison	CP				
All-cause mortality	The mean mortality was 11.5% (20/174)	The mean mortality was 5.8% (10/170)	RD:-0.06 (-0.12, 0.00)	344 patients (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	Treatment with high-titer CP reduces significantly mortality compared to controls

Note: GRADE Working Group grades of evidence—High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

Abbreviations: CI, confidence interval; RD, risk difference.

[a]The basis for the assumed risk is the control-group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[b]Although on average the studies analyzed had few methodological limitations, we downgraded once the quality of the evidence because two trials were stopped early due to the fall in recruitment related to control of the pandemic and were judged at high risk of attrition bias,[2-4] and two studies were judged at unclear risk of selection bias;[2-4]; we judged the masking of outcome assessor to treatment allocation at "low risk" of bias for three studies in which the assessment was performed by someone not involved in the study, and at unclear risk of bias for one study in which it was unclear whether adequate measures were taken to ensure that the assessors were unaware of treatment allocation; two of the included studies[2-4] were open-label, and we judged them in this domain as being at "high risk" of bias; however, masking has limited importance for the outcome of mortality compared to other subjective outcomes. None of the included studies showed serious inconsistency (lack of heterogeneity), indirectness, or lack of imprecision in effect size.

of effect estimates, and risk of publication bias. Publication bias was not assessed because of the relatively low number of studies (<10). Bias assessment using Cochrane methodology showed that two of the studies analyzed were at high risk of attrition bias due to early interruption (see Figures S1 and S2, and Table 1), and for this reason, we downgraded the certainty of the evidence one level. On the other hand, no serious inconsistency (lack of heterogeneity), indirectness, or lack of imprecision in effect size was detected. Hence, we graded the available evidence as moderate-certainty evidence, which means that we are moderately confident in the effect estimate, and that the true effect is likely to be close to the estimate of the effect, but there is a moderate possibility that it is substantially different. Based on the available evidence, we conclude that high-titer CP will confer the greatest benefit, and that this conclusion needs to be taken into consideration, along with early CP treatment, in future studies.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

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