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Reply to: Concerns about estimating relative risk of death associated with convalescent plasma for COVID-19

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Reply to: Concerns about estimating relative risk of death associated with convalescent plasma for COVID-19

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REPLYING TO M. J. Joyner et al. Nature Medicine https://doi.org/10.1038/s41591-021-01638-6 (2021).

We thank Joyner and colleagues for their commentary on the findings of the CONCOR-1 trial.

CONCOR-1 was a randomized trial of COVID-19 convalescent plasma compared with the standard of care conducted in 940 patients from 3 countries and involving 4 blood suppliers[1]. Convalescent plasma did not reduce the risk of intubation or death in patients who were admitted to the ward with COVID-19 respiratory illness. Broad enrollment criteria and recruitment from multiple sites enhanced the generalizability of the findings. Variation between study sites and blood suppliers was accommodated by randomizing within centers and conducting stratified analyses; treatment by supplier interaction terms was used to assess the homogeneity of effects. By convention, the prespecified primary analysis was according to the intent-to-treat principle. Results from per-protocol analyses, which are subject to confounding due to selection bias[2], were reported as Supplementary information.

The results of the CONCOR-1 trial were similar to the C3PO trial[3] in ambulatory patients presenting within 7 d of symptom onset ($n=511$), the RECOVERY trial[4] for ward patients ($n=11{,}558$) and the REMAP-CAP trial[5] for patients in intensive care ($n=2{,}011$). Each of these randomized controlled trials reported no difference in clinical outcomes with convalescent plasma containing high titer-neutralizing antibodies (≥1:100). Although all convalescent plasma units in the CONCOR-1 trial met minimum criteria for antibody levels (ranging from ≥1:100 anti-receptor-binding domain (RBD) of the SARS-CoV-2 spike protein to neutralizing titer of ≥1:160), the range of antibody profiles of convalescent plasma units from the four different blood suppliers provided a unique opportunity to evaluate the effect-modifying role of quantitative and functional antibody measurements. The results suggested that the transfusion of convalescent plasma-containing antibodies with low capacity to neutralize virus or eliminate virus-infected cells was associated with a higher risk of intubation or death, compared with convalescent plasma-containing antibodies that were high titer for neutralization or antibody-dependent cellular cytotoxicity (ADCC).

High anti-spike immunoglobulin (Ig)G was associated with a harmful effect of convalescent plasma in the multivariate, but not in the univariate, analysis. This suggests that the harm does not come only from having high levels of anti-spike IgG, but rather from having anti-spike IgG with poor function. Indeed, we found that high levels of anti-spike IgG were not always associated with high Fc function[1]. One can consider ADCC function per anti-spike IgG as a measure of antibody potency. This potency varied across units used in CONCOR-1 and correlated with the clinical effect of convalescent plasma more than overall neutralization or ADCC capacity (Fig. 4D). We speculate that the potency of transfused antibody, relative to the potency of the recipients' own antibodies, could determine the treatment effect. Ongoing analyses of pre- and post-treatment patient samples will help clarify this complex immunological process.

In a retrospective analysis of patients who received convalescent plasma through the Food and Drug Administration's expanded access program (EAP)[6], nonintubated patients receiving high-titer plasma had a lower risk of death (115/515, 22.3%) than nonintubated patients receiving low-titer plasma (166/561, 29.6%) (relative risk (RR) = 0.66). In the absence of a control group, one cannot tell whether this difference can be explained by a protective effect of high-titer convalescent plasma or a harmful effect of low-titer convalescent plasma. CONCOR-1 and other randomized trials have helped elucidate that high-titer convalescent plasma does not improve outcomes and suggest that low-titer convalescent plasma may worsen outcomes.

In the EAP cohort, there was no difference in mortality between high- and low-titer convalescent plasma in intubated patients (RR = 1.02). The authors' explanation for this was that mechanically ventilated patients had entered an advanced phase of the disease when antibodies would not be expected to affect the risk of

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death[6]. Likewise, disrupting the patient's antibody response with poor-quality convalescent plasma would not be expected to worsen the disease course, which may be why a negative effect of convalescent plasma has not been observed in intubated patients. Patients in the CONCOR-1 trial received convalescent plasma at a median of 8 d (95% confidence interval 5–10 d) after symptom onset. Although earlier treatment was originally hypothesized to be important for the potential protective effect of convalescent plasma, a recent trial of prehospital convalescent plasma that contained very high-titer antibodies (neutralization > 1:160; median titer 1:641) showed no difference in disease progression compared with placebo[3].

The findings from CONCOR-1 are aligned with other randomized controlled trials showing no improvement in clinical outcomes with convalescent plasma in patients with COVID-19 respiratory illness. Our investigations of the antibody profiles underscore the complexity of using passive immunity as a therapeutic strategy.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41591-021-01639-5.

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Competing interests

The authors declare no competing interests.

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