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

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We read with great interest the CONCOR-1 study[1], which reported no significant difference in 30-day mortality between patients with COVID-19 treated with convalescent plasma and those treated with standard of care in a randomized controlled trial. Bégin and colleagues[1] provide a substantive addition to the literature by also presenting the immunologic profiles associated with convalescent plasma use and by showing that receipt of convalescent plasma with high levels of viral neutralization was associated with reduced mortality.

Despite the overall null findings associated with mortality, Bégin and colleagues suggest that transfusion of convalescent plasma with unfavorable antibody profiles may actually be harmful. To support this suggestion, Bégin and colleagues[1] refer to our study[2]. We found that transfusion of plasma with high anti-SARS-CoV-2 antibody levels was associated with a lower risk of mortality than transfusion of plasma with low antibody levels—a finding supported by separate analyses performed by the US Food and Drug Administration[3]. Bégin and colleagues[1] claim that the observed reduction in relative risk of mortality could be explained by increased risk of death among the low-antibody-plasma group rather than improved risk of death among the high-antibody-plasma group. We believe this to be a misinterpretation of our results[2]. While we agree that without a control group, in principle, any apparent mortality benefit in a dose–response study could be the result of increased mortality at the lower dose, in the case of our study we feel that this interpretation is not viable. If low-antibody-titer convalescent plasma was harmful in our study, it appears to have spared patients treated late or on mechanical ventilators. The mortality benefit of high-titer anti-SARS-CoV-2 IgG was found only in categories of patients prehypothesized to benefit from plasma—patients treated early in the COVID-19 disease course and those not receiving mechanical ventilation. Moreover, we believe that our findings[2] and those of the US Food and Drug Administration[3] are consistent with the CONCOR-1 findings, that high levels of viral neutralization are associated with lower mortality.

The authors also suggest that the convalescent plasma issued under the purview of CONCOR-1 by blood supplier 3, which was associated with worse clinical outcomes (odds ratio (OR) = 1.89, 95% confidence interval (CI) 1.05–3.43), is the same as that used in clinical practice as part of the emergency use authorization. Bégin and colleagues are here referring to a blood supplier that provided just 174 of the 1,192 units of convalescent plasma used in CONCOR-1, and the suggestion is implausible that these 174 units are identical to the convalescent plasma units collected over the entire United States and provided to some 500,000 patients who received convalescent plasma under the emergency use authorization.

We believe that several other aspects of the analyses associated with the CONCOR-1 study warrant further discussion.

First, the harmful effect of anti-S IgG appears only in the multivariable analysis (OR = 1.53, 95% CI 1.14–2.05) but not in the univariate analysis (OR = 1.01, 95% CI 0.82–1.23). When a finding emerges only after statistical adjustments have been made, extreme caution in interpretation is required. Two key adjustment variables were plasma supplier and antibodies other than anti-S IgG. Bégin and colleagues provide evidence that convalescent plasma from supplier 1 showed the most benefit (relative risk = 0.95) and also had the highest levels of all antibodies, including the putatively dangerous anti-S IgG. By controlling for both supplier 1 and all other antibodies, Bégin and colleagues have shown that anti-S IgG might possibly be harmful, but only if provided separately from all other antibodies that ordinarily accompany it and provide benefit. However, this circumstance did not occur in the CONCOR-1 study. This adjustment is thus primarily theoretical and introduces the likelihood of hidden interpolation.

Second, while CONCOR-1 excluded ventilated patients, patients were not treated early in their disease course. Approximately 90% of participants had abnormal chest X-rays, most participants were on steroids and many were treated after several days of symptoms. The authors' comparison of the CONCOR-1 study to the randomized clinical trial of Libster and colleagues[4], which found a mortality benefit associated with convalescent plasma, is perhaps inappropriate, because the early subset in CONCOR-1 were inpatients randomized within 3 days of diagnosis while in the study of Libster and colleagues all participants were outpatients and were treated within 3 days of onset of symptoms[4].

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Third, the authors analyze their findings by the intention-to-treat population and according to the per-protocol population, in whom the treatment arm received two units of convalescent plasma within 24 h of randomization. These two analyses showed differences in 30-day mortality (23.0% for the intention-to-treat population, 20.8% for the per-protocol population). Given that the control group experienced a 30-day mortality of 20.5%, removal of late-treated plasma recipients virtually eliminates the modest mortality excess in the convalescent plasma arm. The 66 participants who were not included in the per-protocol analysis had a remarkably high mortality rate of 40.9%, a surprising finding that may deserve further exploration.

Bégin and colleagues[1] should be commended for their rigorous and informative study, and we agree that future studies should examine use of high-quality plasma early in the disease course[2]. We believe that the null findings of the CONCOR-1 study may reflect the use of low antibody potency for some patients, as well as treatment of a proportion of patients with late-stage disease.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-021-01638-6.

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Data availability

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

Author contributions

All authors designed the paper by discussing the key concerns for inclusion. M.J.J., N.S.P., J.W.S. and A.C. wrote the initial draft. D.F., K.A.B., R.S.W. and R.E.C. revised the initial draft. All authors approved the final draft.

Competing interests

The authors declare no competing interests.

Additional information

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