

Limitations of Safety
Update on
Convalescent Plasma
Transfusion in
COVID-19 Patients



To the Editor: Joyner et al¹ have reported a safety update on the use of convalescent plasma transfusion in a convenience sample of 20,000 hospitalized patients with coronavirus disease 2019 (COVID-19). The authors should be applauded for undertaking this monumental effort in providing the medical community with this valuable data in a timely manner amid the pandemic. Upon reflecting on the methods and results, I would like to express reservation on some of the methods used and how the findings were interpreted.

First, Table 1 offers important insights on the significant variability in the temporal trends of key variables. For example, a proportion of patients who had “current severe or life-threatening COVID-19” decreased by ~22% from April to June 2020. The proportion of patients who had “high risk of severe or life-threatening COVID-19” increased by ~85% in the same time interval. This may lead us to conclude that pooling the mortality proportion without stratifying by calendar month may not have been appropriate. This is also evident from Figure 2 which shows that the mortality decreased by nearly 70% from weeks 1 to 7.

Second, it seems that the reported cumulative incidence proportion of mortality is crude and was not adjusted for potential confounders. This is probably the most serious flaw in the analysis and

interpretation of these data. Some of these confounders include age groups, sex, comorbidities (cardiovascular disease, hypertension, diabetes, chronic kidney disease, and lung disease), laboratory data (hematology and liver and renal function), clinical status, clinical symptoms, time since hospitalization, and calendar month (as described earlier). Furthermore, these data were collected from all over the United States where lockdown measures and stay-at-home orders varied significantly during that time interval. Such variables should have been considered as potential confounders. In addition, numerous empirical medical practices were, and many are, practiced; for example, the use of hydroxychloroquine, or experimental drugs such as remdesivir. Such data were not collected/reported in this study which makes it impossible for the authors to decisively attribute, or not, whatever they observe regarding convalescent plasma.

Third, given the purely descriptive nature of this study, this is a large case series with no comparison group; it is not appropriate to make any inferential statements. This includes the authors’ strong statements on no increased risk of adverse cardiac or thrombotic/thromboembolic events or low mortality. With a group of hospitalized COVID-19 patients who were not exposed to convalescent plasma transfusion, the authors may have been able to test a safety profile benefit or lack thereof.

Fourth, the explanation to the declining mortality rate over the study period can also be confounded, positively or negatively, by other variables, including the decreasing mean

age of COVID-19 patients² who have been shown to have a substantially lower risk of mortality.³ Although it is true from their data that there were more critically ill patients later in the study than earlier, there was also a higher proportion of patients who were at higher risk of severe or life-threatening COVID-19, as we described earlier. Attributing the decline in mortality to the “expedient” availability of convalescent plasma is invalid and may not be relevant to the study findings, once again, given the absence of a comparison group.

Fifth, time since first symptom, hospitalization, intensive care unit admission, and mechanical ventilation to convalescent plasma transfusion should have been reported to take into account their potential impact on the timing of transfusion on mortality.^{4,5}

Sixth, the authors state that “[this study] ...support[s] the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.” No data are provided to directly or indirectly support this. No comparison group, no temporal data on the natural progression of the disease in relation to convalescent plasma transfusion, no statistical adjustment for potential confounders, and no adjusted subgroup or sensitivity analyses.

Finally, comparing these 20,000 patients to a group of patients who did not receive convalescent plasma transfusion would significantly contribute to the body of evidence in this area, not only in terms of safety but also effectiveness to reduce mortality, or even better, a randomized controlled trial to assess efficacy to reduce mortality.

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1. Joyner MJ, Bruno KA, Klassen SA, et al. Safety update: COVID-19 convalescent plasma in 20,000 hospitalized patients [published ahead of proof July 19, 2020]. *Mayo Clin Proc.* 2020;95(9):1888-1897.
2. Transcript for the CDC Telebriefing Update on COVID-19 Press Briefing Transcript Thursday, June 25, 2020. <https://www.cdc.gov/media/releases/2020/t0625-COVID-19-update.html>. Accessed July 26, 2020.
3. Bonanad C, García-Blas S, Tarazona-Santabalbina F, et al. The effect of age on mortality in patients with COVID-19: a meta-analysis with 611,583 subjects. *J Am Med Dir Assoc.* 2020;21(7):915-918.
4. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020;395(10223):497-506.
5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020;395(10229):1054-1062.

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of Safety Update on
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To The Editor: The authors thank Dr Farag for his letter in response to our manuscript “Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients.”¹ The letter raises important questions about the presentation of our updated safety report from the Convalescent Plasma Expanded

Access Program (EAP). The fundamental element of our response to all of the questions raised by Dr Farag is the need to frame the context of the paper. Establishing clinical efficacy for a potential therapeutic agent deployed during a public health crisis involves a climb through an epistemic ladder, and the comments from Dr Farag primarily highlight future rungs of that ladder. Our response can be summarized in three key points:

1) SAFETY FIRST

The primary purpose of our paper was to describe the key safety metrics following transfusion of convalescent plasma in 20,000 hospitalized adults with severe or life-threatening coronavirus disease 2019 (COVID-19). As such, the data reported in our paper are descriptive. Although no comparator group was used in our safety report, there is substantial data about the range of expected incidence of key transfusion-related complications.²⁻⁴ In this context, the incidence of complications in this patient cohort was (objectively) low relative to historical perspective and is especially noteworthy given the critically ill cohort of transfused patients.

2) EXPLORATORY ANALYSES OF EFFICACY ARE FORTHCOMING

This analysis, focused on safety signals, should not be construed as evidence of efficacy. Adjusted analyses of mortality were beyond the scope of the paper. The many putative confounding factors that are raised by Dr Farag are justified and are being considered as part of adjusted analysis that is ongoing.

3) PRAGMATIC STUDY DESIGN VERSUS RANDOMIZED CONTROLLED TRIAL

The issue of a randomized controlled trial is of great interest; however, the EAP was a pragmatic study design, organized to allow routine clinical care to dictate the timing and administration of plasma with the collection of real world data. Changes in patient characteristics at the time of enrollment over the first ~8 weeks of the pandemic should not come as a surprise as the world rapidly shared information on the treatment of COVID-19. Additionally, as more plasma became available during April and May, there was a shift toward earlier treatment in less severely or critically ill patients.

How the EAP evolved into a much bigger program to administer a product that — when the EAP started — scarcely existed across the country while obtaining rudimentary outcomes data will be addressed comprehensively in the coming months. This discussion will include the logistical issues associated with conducting a randomized controlled trial on convalescent plasma during the COVID-19 pandemic.

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