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Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients

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Abstract

Objective: To provide an update on key safety metrics after transfusion of convalescent plasma in hospitalized coronavirus 2019 (COVID-19) patients, having previously demonstrated safety in 5000 hospitalized patients.

Patients and Methods: From April 3 to June 2, 2020, the US Food and Drug Administration Expanded Access Program for COVID-19 convalescent plasma transfused a convenience sample of 20,000 hospitalized patients with COVID-19 convalescent plasma.

Results: The incidence of all serious adverse events was low; these included transfusion reactions (n=78; <1%), thromboembolic or thrombotic events (n=113; <1%), and cardiac events (n=677, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion per se. The 7-day mortality rate was 13.0% (12.5%, 13.4%), and was higher among more critically ill patients relative to less ill counterparts, including patients admitted to the intensive care unit versus those not admitted (15.6 vs 9.3%), mechanically ventilated versus not ventilated (18.3% vs 9.9%), and with septic shock or multiple organ dysfunction/failure versus those without dysfunction/failure (21.7% vs 11.5%).

Conclusion: These updated data provide robust evidence that transfusion of convalescent plasma is safe in hospitalized patients with COVID-19, and support the notion that earlier administration of plasma within the clinical course of COVID-19 is more likely to reduce mortality.

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Coronavirus disease 2019 (COVID-19) continues to be a worldwide pandemic, and the number of deaths attributed to COVID-19 in the United States at the time of this writing (~150,000) exceeds that of any other nation in the world.¹ The overall case fatality rate for

diagnosed COVID-19 ranges from approximately 4% to greater than 50%,²⁻⁶ with higher mortality rates observed in more critically ill patients. In response to the COVID-19 outbreak in the United States and reportedly high case-fatality rates, the US Food and Drug Administration (FDA) in collaboration

with the Mayo Clinic and national blood banking community developed a national Expanded Access Program (EAP) to collect and distribute COVID-19 convalescent plasma. Historical precedent indicates that human convalescent plasma is a viable option for mitigation and treatment of COVID-19.^{7,8} The premise of human convalescent plasma therapy is that plasma of recently infected and currently recovered COVID-19 patients contains antiviral antibodies and other bioactive elements that can be used to treat patients with COVID-19. Convalescent plasma has a strong historical record of some efficacy during acute infectious pandemics.^{7,9} As recently summarized,⁷ convalescent plasma represents a promising treatment strategy with strong historical precedence, biological plausibility, and limited barriers for rapid development and deployment of this investigational therapy.

Recently, our investigation of key safety indicators in 5000 patients transfused with COVID-19 convalescent plasma showed an incidence of transfusion-related serious adverse events (SAEs) of less than 1% and a mortality rate of 14.9%.¹⁰ These early indicators suggest that transfusion of convalescent plasma is safe in hospitalized adults with COVID-19. Because an additional 15,000 hospitalized patients have been transfused with convalescent plasma under the purview of the EAP, a subsequent safety update is warranted. These new data may provide novel insights into the incidence of emerging adverse events associated with COVID-19, including thromboembolic^{11,12} and cardiac events.¹³ Further, these data may provide better understanding of the clinical features contributing to the 7-day mortality rate among transfused patients with COVID-19.

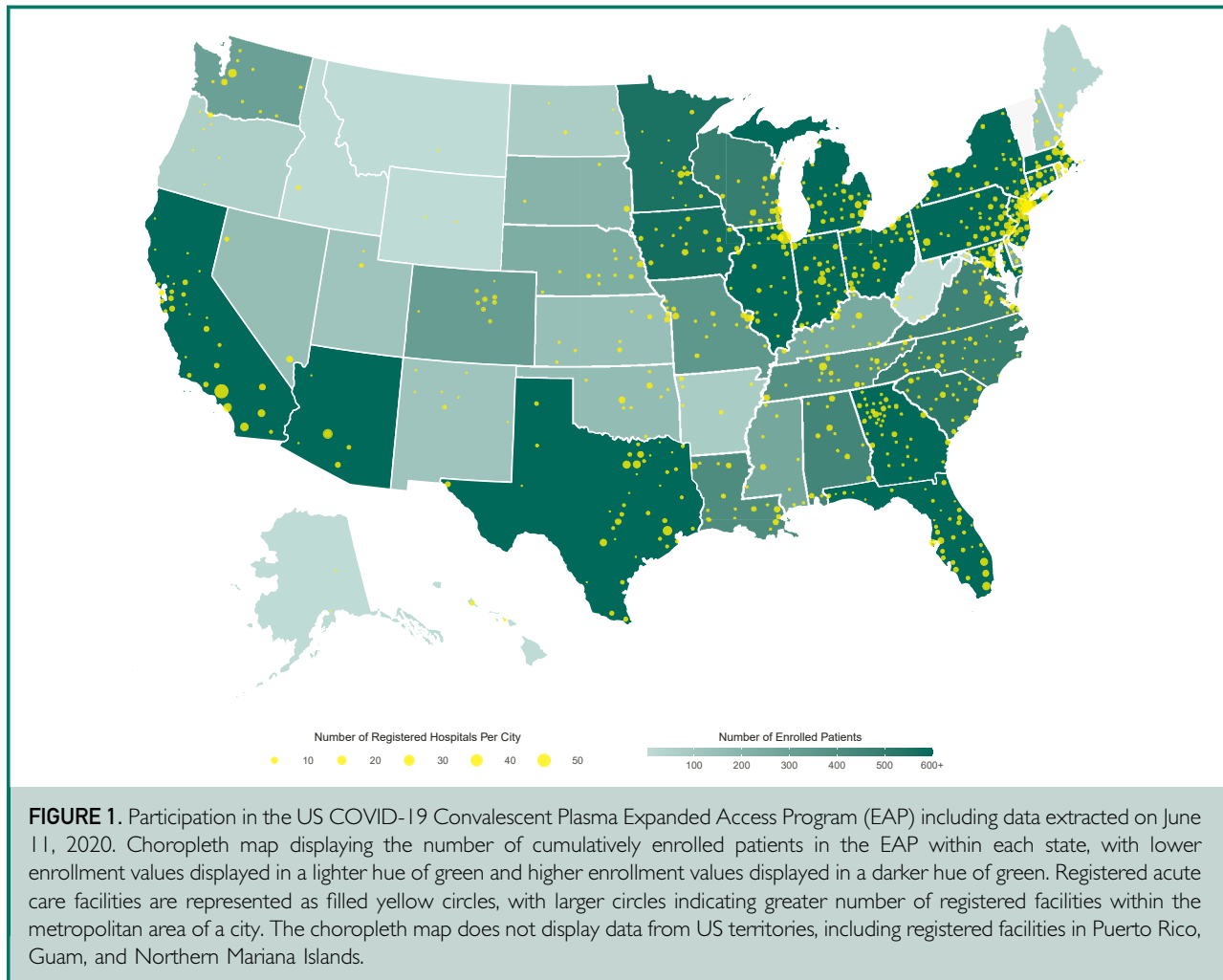
Thus, we analyzed key safety metrics following transfusion of convalescent plasma in 20,000 hospitalized adults with severe or life-threatening COVID-19. These data represent a deeper and larger analysis relative to our initial report of 5000 transfused patients under the EAP. We hypothesized that both the 7-day mortality rate and the

number of SAEs related to the transfusion of convalescent plasma would continue to be low. Additionally, we hypothesized that higher mortality rates would be observed in more critically ill patients.

PATIENTS AND METHODS

As described previously,¹⁰ the program is a FDA-initiated, national, multicenter, open-label EAP in hospitalized adults who had (or were judged to have high risk of progression to) severe or life-threatening COVID-19. The US COVID-19 Convalescent Plasma EAP was conducted as a pragmatic treatment study, empowering local acute care facilities to use the emerging best evidence for care while allowing for administration of convalescent plasma. It was conducted within a modified clinical trial framework: All participants were allowed access to convalescent plasma per the discretion of the treating physician/principal investigator given the nature of the pandemic and the lack of any effective therapies at the time of design. It was the intent a priori to create a control comparator group to determine potential efficacy using patients hospitalized with COVID-19 infections during the same period. This decision was made after collaboration with the US FDA. This report is only on safety of the convalescent plasma for the initial 20,000 subjects. A future publication will discuss potential efficacy.

Between the date of initial Institutional Review Board (IRB) approval of the EAP (April 1, 2020) and June 11, 2020, more than 20,000 patients were transfused with COVID-19 convalescent plasma (Figure 1). The Mayo Clinic IRB served as the central IRB and empaneled an independent Data and Safety Monitoring Board to oversee the safety analyses. Written informed consent was obtained from the participant or a legally authorized representative before enrollment or with use of emergency consent procedures recommended by the US FDA and approved by the Mayo Clinic IRB. The protocol was modified to allow inclusion of incarcerated participants once it became clear that this group was especially vulnerable and at risk.



Eligible patients were aged 18 years or older, hospitalized with a laboratory-confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2, and had (or were judged by a health care provider to be at high risk of progression to) severe or life-threatening COVID-19. The clinical symptoms defining severe or life-threatening COVID-19 are outlined in [Table 1](#).

Procedures

As described previously,¹⁰ ABO-compatible COVID-19 convalescent plasma had no minimum neutralizing-antibody titer level and was donated by recently recovered COVID-19 survivors. Approximately 200 to 500 mL of convalescent plasma was administered

intravenously according to institutional transfusion guidelines. Web-based, standardized data reporting surveys were completed to assess clinical status of patients at regular time intervals (4-hours and 7-days after convalescent plasma transfusion) using the Research Electronic Data Capture system (REDCap, v.9.1.15 Vanderbilt University, Nashville, TN).^{14,15}

Serious Adverse Event Reporting

Separate REDCap data collection forms were used to report each SAE that occurred within 7 days following the convalescent plasma transfusion. Two primary data capture forms were used to report SAEs: a transfusion form and a SAE form. Serious adverse events which occurred during the time window

TABLE 1. Patient Characteristics Stratified by Month of COVID-19 Convalescent Plasma Transfusion^a

	April	May	Total
Characteristic			
N	6214	13,786	20,000
Age, y			
18-39	449 (7.2)	1083 (7.9)	1,532 (7.7)
40-59	2056 (33.1)	4320 (31.3)	6,376 (31.9)
60-69	1798 (28.9)	3611 (26.2)	5,409 (27.0)
70-79	1260 (20.3)	2859 (20.7)	4,119 (20.6)
≥80	651 (10.5)	1913 (13.9)	2,564 (12.8)
Sex			
Female	2262 (36.4)	5499 (39.9)	7761 (38.8)
Male	3924 (63.2)	8241 (59.8)	12,165 (60.8)
Intersex or transgender	22 (0.4)	35 (0.3)	57 (0.3)
Undisclosed	6 (0.1)	11 (0.1)	17 (0.1)
Weight status ^b			
Underweight	61 (1.2)	249 (1.8)	310 (1.7)
Normal weight	868 (17.3)	2454 (18.0)	3322 (17.8)
Overweight	1502 (30.0)	3802 (27.8)	5304 (28.4)
Obese	2587 (51.6)	7166 (52.4)	9753 (52.2)
Race			
Asian	408 (6.6)	591 (4.3)	999 (5.0)
Black	1132 (18.2)	2784 (20.2)	3916 (19.6)
White	2993 (48.2)	6741 (48.9)	9734 (48.7)
Other or unknown	1681 (27.1)	3670 (26.6)	5351 (26.8)
Ethnicity			
Hispanic or Latino	2142 (34.5)	4794 (34.8)	6936 (34.7)
Not Hispanic or Latino	4072 (65.5)	8992 (65.2)	13,064 (65.3)
Clinical status			
Current severe or life-threatening COVID-19	4963 (79.9)	9274 (67.3)	14,237 (71.2)
High risk of severe or life-threatening COVID-19	1251 (20.1)	4512 (32.7)	5763 (28.8)
Intensive care unit admission	4038 (65.0)	7522 (55.0)	11,560 (58.1)
Mechanical ventilation ^c	2709 (48.5)	4155 (30.4)	6864 (35.6)
Clinical symptoms ^d			
Respiratory failure	3574 (72.0)	6155 (66.4)	9729 (68.3)
Dyspnea	3152 (63.5)	6561 (70.7)	9713 (68.2)
Blood oxygen saturation ≤93%	3092 (62.3)	6663 (71.8)	9755 (68.5)
Lung infiltrates >50% within 24 to 48 h	2105 (42.4)	4021 (43.4)	6126 (43.0)
Respiratory frequency ≥30/min	1937 (39.0)	4014 (43.3)	5951 (41.8)
P _a O ₂ :FiO ₂ ^e <300	1642 (33.1)	3014 (32.5)	4656 (32.7)
Multiple organ dysfunction or failure	936 (18.9)	1212 (13.1)	2148 (15.1)
Septic shock	734 (14.8)	987 (10.6)	1721 (12.1)

^aValues shown are n (%).

^bThese data include a subset of the sample (n=18,689).

^cThese data include a subset of the sample (n=19,256).

^dThese data include a subset of the sample (n=14,237), only those patients that currently have severe or life-threatening COVID-19.

^eP_aO₂:FiO₂ the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

beginning at the onset of the plasma transfusion and including the 4-hour period following the transfusion were reported on

the transfusion form. By definition, the primary SAEs related to transfusion (including transfusion associated circulatory overload

TABLE 2. SAE Characteristics in Patients Transfused With COVID-19 Convalescent Plasma (N=20,000)^a

SAE: Transfusion reactions	Reported	Related	% Estimate ^b (95% CI)
Mortality within four hours of transfusion	63	10	0.05 (0.03-0.09)
TACO	36	36	0.18 (0.13-0.25)
TRALI	21	21	0.10 (0.07-0.16)
Severe allergic transfusion reaction	21	21	0.10 (0.07-0.16)
7-day SAE reports			
Thrombotic or thromboembolic complication	113	38	0.19 (0.14-0.26)
Sustained hypotension ^c	457	54	0.27 (0.21-0.35)
Cardiac events ^d	677	80	0.40 (0.32-0.50)
7-day mortality		Reported	
Crude Estimate	2592		12.96 (12.50-13.44)
Clinical status			
No ICU admission (n=8323)	772		9.28 (8.67-9.92)
ICU admission (n=11,560)	1806		15.62 (14.97-16.30)
No mechanical ventilation (n=12,147)	1220		9.85 (9.34-10.38)
Mechanical ventilation (n=6864)	1258		18.33 (17.43-19.26)
Clinical symptoms			
No MOF or septic shock (n=17,081)	1952		11.45 (10.98-11.94)
MOF or septic shock (n=2919)	640		21.72 (20.27-23.24)

^aICU = intensive care unit; MOF = multiple organ failure or dysfunction; SAE = severe adverse event; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury.

^bPoint estimate of related serious adverse event incidence relative to 20,000 transfusions.

^cSustained hypotension included events requiring intravenous pressor support.

^dCardiac events included ventricular or atrial fibrillation or arrhythmia requiring treatment, and cardiac arrest.

[TACO] and transfusion-related acute lung injury [TRALI]) occurred within 6 hours of the transfusion. All transfusion-related SAEs occurred within 4 hours of the transfusion and thus, were all reported on the transfusion form. All other SAEs were reported on the SAE form. The attribution scale used by treating physicians for evaluating SAE relatedness to convalescent plasma transfusion included unrelated, possibility related, probably related, or definitely related. All transfusion-related SAEs were independently adjudicated over the course of the study by the Investigational New Drug sponsor (M.J.J.) and trained designee (A.M.K.) using the National Healthcare Safety Network Biovigilance Component Hemovigilance Module Surveillance Protocol as a conceptual framework.¹⁶

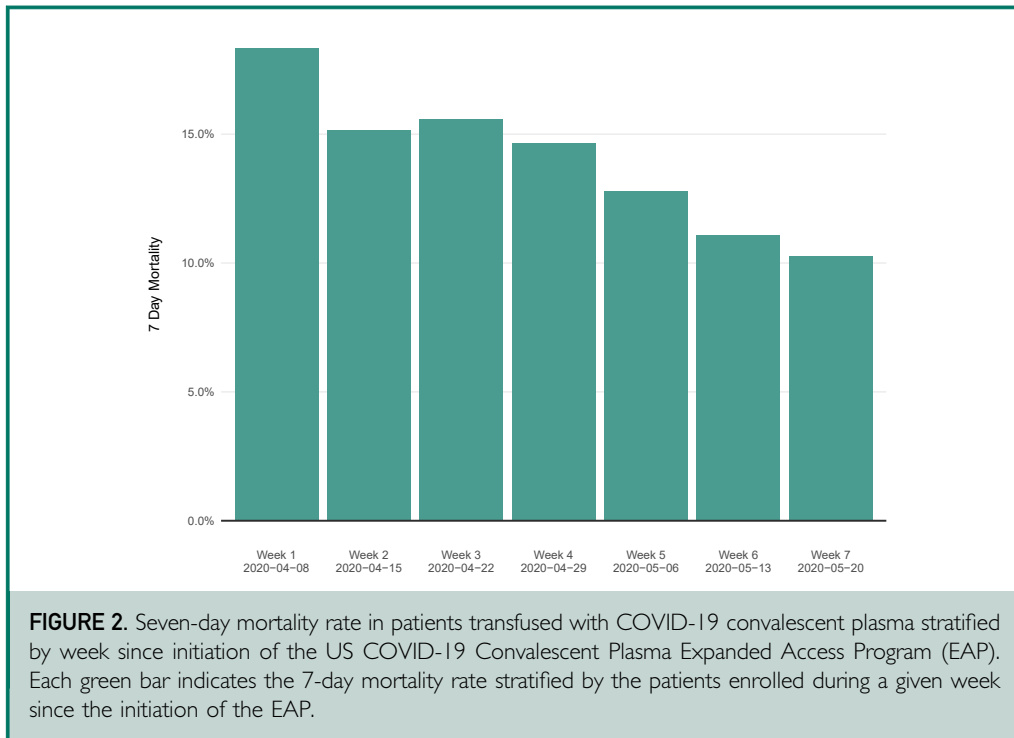
Statistics

Data presented in this safety report may undergo additional data quality control measures as the study continues. The

proportion of each of a series of SAEs was summarized using a point estimate and 95% score CI as outlined in Table 2. The point estimates for mortality were estimated at day 7 based on the crude mortality and Wilson confidence interval calculation for binomial proportions. All analyses and graphics were produced with R version 3.6.2 (Vienna, Austria).

RESULTS

From April 3 to June 11, 2020, a total of 30,117 patients were enrolled in the EAP and a total of 21,987 enrolled patients received a COVID-19 convalescent plasma transfusion (Figure 1). Data from the first 5000 transfused patients have been reported previously.¹⁰ This update reports data from 20,000 patients including the initial 5000 and subsequent 15,000 transfused patients. By June 2, 2020, a total of 20,000 patients had been transfused with COVID-19 convalescent plasma, thus,



7-day mortality data are presented for all 20,000 patients.

Patient Characteristics

Key patient characteristics at the time of enrollment are presented in Table 1. The patient enrollment indicates a wide age range of hospitalized patients with COVID-19, consistent with prior Centers for Disease Control and Prevention published data.¹⁷ The study population was diverse, with 20% of patients being African American, nearly 35% Hispanic, and 5% Asian. The recruitment of a diverse population has improved over the course of the study. Nearly 40% of our subjects were women. Most of the patients enrolled were overweight or obese, consistent with early reports of risk.¹⁸ Nearly all of the patients had severe or life-threatening COVID-19 by design of the investigational protocol. Nearly two-thirds had respiratory failure as well as dyspnea as a primary symptom. Most were hypoxic and nearly half had pulmonary infiltrates. At least one-third had severe

respiratory compromise. Equal numbers appeared to have multiorgan failure or septic shock, but these were a small percentage of the total population.

Serious Adverse Events

Key SAEs related to the transfusion of convalescent plasma are reported in Table 2. Our report is not a comprehensive summary of all risks associated with hospitalization of COVID-19, but it did assume that convalescent plasma potentially could cause life-threatening cardiac events and thrombotic events, so these were collected with an underlying assumption of attribution. Within 4 hours of completion of the COVID-19 convalescent plasma transfusion, 141 SAEs classified as transfusion reactions were reported (<1% of all transfusions). Of these SAEs, there were 78 non-mortality events reported, with 36 reports of TACO, 21 reports of TRALI, and 21 reports of severe allergic transfusion reaction. Of the SAEs reported within 4 hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions)

and 10 of these mortalities were judged as related (possibly, n=10; probably, n=0; definitely, n=0) to the transfusion of COVID-19 convalescent plasma.

Within 7 days of completion of the COVID-19 convalescent plasma transfusion, 1247 other SAEs were reported. Of these SAEs, 113 thromboembolic or thrombotic events were reported, 457 sustained hypotensive events requiring intravenous pressor support were reported, and 677 patients suffered a cardiac event. Notably, the vast majority of the thromboembolic or thrombotic complications (n=75) and cardiac events (n=597) were judged to be unrelated to the plasma transfusion.

Seven-Day Mortality

Seven-day mortality rates stratified by key clinical status indicators are presented in [Table 2](#). Over the first 7 days after the COVID-19 convalescent plasma transfusion, a total of 2592 deaths were observed. The overall 7-day mortality rate was 12.96% (95% CI, 12.50% to 13.44%) ([Figure 2](#)). The 7-day mortality rate was higher among the sickest of our critically ill patients, including patients admitted to the intensive care unit (ICU) versus those not admitted to the ICU (15.6% vs 9.3%), mechanically ventilated versus not mechanically ventilated (18.3% vs 9.9%), and those with septic shock or multiple organ dysfunction/failure versus without septic shock or multiple organ dysfunction/failure (21.7% vs 11.5%).

DISCUSSION

In this safety update of the US Convalescent Plasma Expanded Access Program of 20,000 hospitalized patients in the United States with severe or life-threatening COVID-19, the overall frequency of SAEs classified as attributable or likely secondary to convalescent plasma transfusion continued to be low (<1% of all transfusions) and the 7-day mortality rate in this extremely high-risk cohort was 13.0%. Despite the potential risks associated with plasma transfusion in critically ill

patients,^{16,19} these data provide continued optimism for the safety of COVID-19 convalescent plasma.

Emerging COVID-19 Clinical Complications

Although thrombotic and thromboembolic events are emerging clinical complications of COVID-19,^{11,12,20} our data show a low rate (<1%) of these events within the first 7 days after COVID-19 convalescent plasma transfusion. Cardiac events represent another novel clinical concern of COVID-19,¹³ particularly in the context of open-label use of experimental treatments such as hydroxychloroquine.²¹ In aggregate, adverse cardiac events occurred in ~3% of patients transfused with COVID-19 convalescent plasma. The vast majority of adverse cardiac events of interest were deemed unrelated to the plasma transfusion (88%) by the treating physicians. Collectively, these data suggest that transfusion of COVID-19 convalescent plasma per se does not demonstrably increase the risk of adverse cardiac events. We note that the incidence of TRALI and TACO reported in this study of 0.10% and 0.10%, respectively, is significantly lower than those reported in previous studies, which ranged from 5% to 8% and 1% to 4%, respectively,²² despite the fact that many of the COVID-19 patients receiving plasma were critically ill and likely at risk for clinical conditions which mimic TACO.

Study Limitations

Although this study was not designed to evaluate efficacy of convalescent plasma, we note with optimism that after 20,000 transfused patients, the 7-day mortality rate (13.0%) is low ([Table 2](#)). Although the mortality rate has decreased ([Figure 2](#)), we note that the clinical characteristics of the transfused patients in the EAP have shifted toward less critically ill patients and lower proportions of apparent “rescue therapy.” No therapy has been introduced into clinical use during this period which reduces (to our knowledge) mortality in hospitalized patients with

COVID-19. We postulate that several potential explanations may explain the observed decline in mortality. The ability and success of the US health care community at managing hospitalized COVID-19 patients is likely improving. Second, the blood banking communities have enhanced the availability of convalescent plasma such that more patients received plasma earlier in their hospital course. The more expeditious delivery of plasma to patients reflects improved logistics for the collection, deployment, and use of convalescent plasma, and a larger COVID-19 recovered population that may be potential plasma donors. In this regard it is remarkable that there was no system in place for convalescent plasma use in March 2020 and yet within months the nation is now able to meet most of the demand, despite complex logistics.²³ Given the historical experience that antibody therapies are most effective when given earlier and that convalescent plasma has reduced mortality in prior epidemics,⁷ the lower mortality in more recently treated patients would be consistent with greater efficacy from earlier use. Finally, as recovered COVID-19 patients were more quickly recruited for convalescent plasma donation, the plasma may contain higher levels of neutralizing antibodies or other bioactive elements. However, additional data are required to evaluate these potential explanations for the observed trends.

CONCLUSION

Data from the first 20,000 patients transfused with COVID-19 convalescent plasma show that use of convalescent plasma is safe and carries no excess risk of complications. Indeed, convalescent plasma may be associated with improvement in survival; however, this report does not establish efficacy. Additionally, our data show that the US health care system is improving in its care for those hospitalized for COVID-19 including managing those critically ill patients with multiple comorbidities included in these analyses. Overall, the mortality observed has decreased with our observations and continued use of

convalescent plasma. Given the accelerating deployment of this therapy, these emerging data provide early safety indicators of convalescent plasma for COVID-19 treatment and suggest research should shift focus from safety toward determining the efficacy of convalescent plasma.

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Abbreviations and Acronyms: COVID-19 = coronavirus disease 2019; EAP = Expanded Access Program; FDA = Food and Drug Administration; ICU = intensive care unit; IRB = Institutional Review Board; SAE = serious adverse event; TACO = transfusion-associated circulatory overload; TRALI = transfusion-related acute lung injury

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REFERENCES

- Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19); cases in US. CDC website. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>. Accessed August 4, 2020.
- Rajgor DD, Lee MH, Archuleta S, Bagdasarian N, Quek SC. The many estimates of the COVID-19 case fatality rate. *Lancet Infect Dis*. 2020;20(7):776-777.
- Wang K, Zhang Z, Yu M, Tao Y, Xie M. 15-day mortality and associated risk factors for hospitalized patients with COVID-19 in Wuhan, China: an ambispective observational cohort study. *Intensive Care Med* [Epub ahead of print]. 2020: <https://doi.org/10.1007/s00134-020-06047-w>.
- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
- Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059.
- Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically ill patients in the Seattle region — case series. *N Engl J Med*. 2020;382(21):2012-2022.
- Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest*. 2020;130(4):1545-1548.
- Zhang JS, Chen JT, Liu YX, et al. A serological survey on neutralizing antibody titer of SARS convalescent sera. *J Med Virol*. 2005;77(2):147-150.

9. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med.* 2006;145(8):599-609.
10. Joyner MJ, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. *J Clin Invest.* 2020: <https://doi.org/10.1172/JCI140200>.
11. Wright FL, Vogler TO, Moore EE, et al. Fibrinolysis shutdown correlates to thromboembolic events in severe COVID-19 infection. *J Am Coll Surg.* 2020. <https://doi.org/10.1016/j.jamcollsurg.2020.05.007>.
12. Wichmann D, Sperhake JP, Lutgehetmann M, et al. Autopsy findings and venous thromboembolism in patients with COVID-19. *Ann Intern Med.* 2020. <https://doi.org/10.7326/M20-2003>.
13. Inciardi RM, Lupi L, Zaccone G, et al. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol.* 2020. <https://doi.org/10.1001/jamacardio.2020.1096>.
14. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377-381.
15. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform.* 2019;95:103208.
16. US Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual. *Biovigilance Component* v2.5. Atlanta, GA: Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases; 2018.
17. Garg S. Hospitalization rates and characteristics of patients hospitalized with laboratory-confirmed coronavirus disease 2019—COVID-NET, 14 States, March 1—30, 2020. *MMWR.* 2020;69(15):458-464.
18. Goyal P, Choi JJ, Pinheiro LC, et al. Clinical characteristics of COVID-19 in New York City. *N Engl J Med.* 2020;382(24):2372-2374.
19. Dzik S. COVID-19 Convalescent Plasma: Now Is the Time for Better Science. *Transfus Med Rev.* 2020. <https://doi.org/10.1016/j.tmr.2020.04.002>.
20. Klok FA, Kruip M, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. *Thromb Res.* 2020;191:148-150.
21. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent guidance for navigating and circumventing the QTc-prolonging and torsadogenic potential of possible pharmacotherapies for coronavirus disease 19 (COVID-19). *Mayo Clinic Proc.* 2020;95(6):1213-1221.
22. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):585-594.
23. Bloch EM, Shoham S, Casadevall A, et al. Deployment of convalescent plasma for the prevention and treatment of COVID-19. *J Clin Invest.* 2020;130(6):2757-2765.