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 COVID-19 patients, having previously demonstrated safety in 5,000 hospitalized patients.

Patients and Methods: From April 3 to June 2, 2020, the US FDA 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*=89; <1%), thromboembolic or thrombotic events (*n*=87; <1%), and cardiac events (*n*=680, ~3%). Notably, the vast majority of the thromboembolic or thrombotic events (*n*=55) and cardiac events (*n*=562) were judged to be unrelated to the plasma transfusion *per se*. The seven-day mortality rate was 8.6% (8.2%, 9.0%), and was higher among more critically-ill patients relative to less ill counterparts, including patients admitted to the intensive care unit vs. not admitted (10.5% vs. 6.0%), mechanically ventilated vs. not ventilated (12.1% vs. 6.2%), and with septic shock or multiple organ dysfunction/failure vs. those without dysfunction/failure (14.0% vs. 7.6%).

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.

Introduction

Coronavirus disease 2019 (COVID-19) continues to be a world-wide pandemic, and the number of deaths attributed to COVID-19 in the US at the time of this writing (~110,000) exceed that of any other nation in the world[1]. The overall case fatality rate for diagnosed COVID-19 ranges from about 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 US 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 anti-viral 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 5,000 patients transfused with COVID-19 convalescent plasma demonstrated an incidence of transfusion-related serious adverse events (SAE) 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 seven-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 5,000 transfused patients under the EAP. We hypothesized that both the seven-day mortality rate and the number of serious adverse events 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.

Methods

As described previously[10], the program is a FDA-initiated, national, multicenter, open-label EAP in hospitalized adults that 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 time 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 1st 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 (DSMB) to oversee the safety analyses. Written informed consent was obtained from the participant or a legally-authorized representative prior to 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.

Participants. Eligible patients were aged 18 years or older, hospitalized with a laboratory confirmed diagnosis of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and had (or were judged by a healthcare 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 – 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 (four-hours and seven-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 seven 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 beginning at the onset of the plasma transfusion and including the four-hour time-period following the transfusion were reported on the transfusion form. By definition, the primary SAEs related to transfusion (including transfusion associated circulatory overload [TACO] and transfusion-related acute lung injury [TRALI]) occurred within six hours of the transfusion. All transfusion-related SAEs occurred within four 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 IND Sponsor (MJJ) and trained designee (AMK) 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 cumulative incidence of each of a series of SAEs was summarized using a point estimate and 95% score confidence interval (CI), as outlined in **Table 2**. To assess mortality, time (in days) between transfusion and mortality was examined using the Kaplan Meier product limit estimator. Participants were censored at their last known vital status and all reported mortalities through seven days were used to estimate the survival function. Data were censored at 0.25 days for patients who did not have follow-up beyond the initial report at four hours post transfusion at time of the analysis. For patients who expired within 24 hours, a survival time of 0.5 days was assigned. Precise time of day for key events was not recorded in the data collection system; thus, these imprecise time estimates were used. The point estimate and 95% CI for mortality were estimated at day seven based on the estimated survival function. 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 5,000 transfused patients have been reported previously[10]. This update reports data from 20,000 patients including the initial 5,000 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 is presented for all 20,000 patients.

Patient Characteristics. Key patient characteristics are presented in **Table 1**. The patient enrollment indicates a wide age range of hospitalized patients with COVID-19, consistent with prior CDC 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 time 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 multi-organ failure or septic shock, but these were a small percentage of the total population.

Serious Adverse Events. Key serious adverse events (SAE) 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 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 four hours of completion of the COVID-19 convalescent plasma transfusion, 146 SAEs classified as transfusion reactions were reported (<1% of all

transfusions). Of these SAEs, there were 83 non-mortality events reported, with 37 reports of transfusion-associated circulatory overload (TACO), 20 reports of transfusion-related acute lung injury (TRALI), and 26 reports of severe allergic transfusion reaction. Of the SAEs reported within four hours of plasma transfusion, there were 63 mortalities (0.3% of all transfusions) and 13 of these mortalities were judged as related (possibly, *n*=12; probably, *n*=1; definitely, *n*=0) to the transfusion of COVID-19 convalescent plasma.

Within seven days of completion of the COVID-19 convalescent plasma transfusion, 1,136 other SAEs were reported. Of these SAEs, 87 thromboembolic or thrombotic events were reported, 406 sustained hypotensive events requiring intravenous pressor support were reported, and 643 patients suffered a cardiac event. Notably, the vast majority of the thromboembolic or thrombotic complications (*n*=55) and cardiac events (*n*=569) 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 seven days after the COVID-19 convalescent plasma transfusion, a total of 1,711 deaths were observed. The overall seven-day mortality rate was 8.56% (95% CI: 8.18%, 8.95%), **Figure 2**. The seven-day mortality rate was higher among the sickest of our critically-ill patients, including patients *admitted* to the intensive care unit (ICU) vs. not admitted to the ICU (10.5% vs. 6.0%), mechanically ventilated vs. not mechanically ventilated (12.1% vs. 6.2%), and those with septic shock or multiple organ dysfunction/failure vs. without septic shock or multiple organ dysfunction/failure (14.0% vs. 7.6%).

Discussion

In this safety update of the US Convalescent Plasma Expanded Access Program of 20,000 hospitalized patients in the US 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 seven-day mortality rate in this extremely high risk cohort was 8.6%. 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 demonstrate a low rate (<1%) of these events within the first seven 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 0.18% and 0.10%, respectively is significantly lower than those reported in previous studies, which ranged from 5-8% and 1-4%, 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.

Limitations. Although this study was not designed to evaluate efficacy of convalescent plasma, we note with optimism that after 20,000 transfused patients the seven-day mortality rate (8.6%) is lower than the mortality rate observed in the first 5,000 transfused patients (12.0%), **Table 2**. While the mortality rate has fallen (**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 time 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 Healthcare 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 compared to the initial cohort of 5000 participants. 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 demonstrate 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 demonstrate 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 fallen 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; **DSMB =** Data and Safety Monitoring Board; **EAP** = Expanded Access Program; **FDA =** Food and Drug Administration; **ICU** = intensive care unit; **IND =** Investigational New Drug; **IRB =** Institutional Review Board; **SAE =** serious adverse event; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus-2; **TACO =** transfusion-associated circulatory overload; **TRALI =** transfusion-related acute lung injury; **US =** United States

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Table 1. Patient Characteristics Stratified by Month of COVID-19 Convalescent Plasma Transfusion.

Characteristic	April n (%)	May n (%)	June n (%)	Total n (%)
No.	6,216	13,357	427	20,000
Age				
18 - 39 years	450 (7.2%)	1,044 (7.8%)	35 (8.2%)	1,529 (7.6%)
40 - 59 years	2,060 (33.2%)	4,157 (31.1%)	138 (32.3%)	6,355 (31.8%)
60 - 69 years	1,802 (29.0%)	3,516 (26.3%)	105 (24.6%)	5,423 (27.1%)
70 - 79 years	1,249 (20.1%)	2,776 (20.8%)	89 (20.8%)	4,114 (20.6%)
80 years or older	650 (10.5%)	1,858 (13.9%)	60 (14.1%)	2,568 (12.8%)
Gender				
Women	2,254 (36.3%)	5,360 (40.1%)	163 (38.2%)	7,777 (38.9%)
Men	3,935 (63.3%)	7,953 (59.5%)	264 (61.8%)	12,152 (60.8%)
Intersex or Transgender	21 (0.3%)	33 (0.2%)	0 (0.0%)	54 (0.3%)
Undisclosed	6 (0.1%)	11 (0.1%)	0 (0.0%)	17 (0.1%)
Weight Status[a]				
Underweight	59 (1.3%)	236 (1.8%)	15 (3.5%)	310 (1.7%)
Normal Weight	828 (17.6%)	2,356 (17.8%)	62 (14.6%)	3,246 (17.7%)
Overweight	1,413 (30.1%)	3,695 (28.0%)	120 (28.2%)	5,228 (28.5%)
Obese	2,397 (51.0%)	6,927 (52.4%)	228 (53.6%)	9,552 (52.1%)
Race				
Asian	408 (6.6%)	580 (4.3%)	18 (4.2%)	1,006 (5.0%)
Black	1,127 (18.1%)	2,690 (20.1%)	94 (22.0%)	3,911 (19.6%)
White	2,988 (48.1%)	6,541 (49.0%)	214 (50.1%)	9,743 (48.7%)
Other or Unknown	1,693 (27.2%)	3,546 (26.5%)	101 (23.7%)	5,340 (26.7%)
Ethnicity				
Hispanic or Latino	2,140 (34.4%)	4,602 (34.5%)	162 (37.9%)	6,904 (34.5%)
Not Hispanic or Latino	4,075 (65.6%)	8,755 (65.5%)	265 (62.1%)	13,095 (65.5%)
Clinical Status				
Current severe or life-threatening COVID-19	4,960 (79.8%)	8,990 (67.3%)	270 (63.2%)	14,220 (71.1%)
High risk of severe or life-threatening COVID-19	1,256 (20.2%)	4,367 (32.7%)	157 (36.8%)	5,780 (28.9%)
Intensive Care Unit (ICU) admission	4,027 (64.9%)	7,270 (55.0%)	171 (48.3%)	11,468 (57.9%)
Mechanical Ventilation[b]	2,291 (46.7%)	3,977 (30.1%)	69 (19.5%)	6,337 (34.3%)

Clinical symptoms[c]				
Respiratory failure	3,579 (72.2%)	5,969 (66.4%)	167 (61.9%)	9,715 (68.3%)
Dyspnea	3,131 (63.1%)	6,326 (70.4%)	203 (75.2%)	9,660 (67.9%)
Blood oxygen saturation ≤ 93%	3,083 (62.2%)	6,421 (71.4%)	199 (73.7%)	9,703 (68.2%)
Lung infiltrates > 50% within 24 to 48 hours	2,106 (42.5%)	3,875 (43.1%)	94 (34.8%)	6,075 (42.7%)
Respiratory frequency ≥ 30/min	1,928 (38.9%)	3,838 (42.7%)	118 (43.7%)	5,884 (41.4%)
P_aO_2:FiO_2 ratio[d] < 300	1,649 (33.2%)	2,901 (32.3%)	78 (28.9%)	4,628 (32.5%)
Multiple organ dysfunction or failure	938 (18.9%)	1,143 (12.7%)	36 (13.3%)	2,117 (14.9%)
Septic shock	733 (14.8%)	949 (10.6%)	19 (7.0%)	1,701 (12.0%)

[a] These data include a subset of the sample (*n* = 18,336).
[b] These data include a subset of the sample (*n* = 18,484).
[c] These data include a subset of the sample (*n* = 14,220), only those patients that currently have severe or life-threatening COVID-19.
[d] The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen ratio.

Table 2. SAE Characteristics in Patients Transfused with COVID-19 Convalescent Plasma. (*n* = 20,000)

Serious Adverse Events (SAE): Transfusion Reactions	**Reported**	**Related**	**Estimate[a] (95% CI)**
Mortality within four hours of transfusion	63	13	0.06% (0.04%, 0.11%)
Transfusion-Associated Circulatory Overload (TACO)	37	37	0.18% (0.13%, 0.25%)
Transfusion-Related Acute Lung Injury (TRALI)	20	20	0.10% (0.06%, 0.15%)
Severe allergic transfusion reaction	26	26	0.13% (0.09%, 0.19%)
Seven-day SAE Reports			
Thrombolic or thromboembolic complication	87	32	0.16% (0.11%, 0.23%)
Sustained Hypotension[b]	406	54	0.27% (0.21%, 0.35%)
Cardiac Events[c]	643	74	0.37% (0.29%, 0.46%)
Seven Day Mortality	**Reported**		**Estimate (95% CI)**
Overall (5,000)[d]	602		12.04% (11.17%, 12.97%)
Overall (20,000)	1,711		8.56% (8.18%, 8.95%)
Clinical Status			
No ICU admission (*n* = 8,323)	501		6.02% (5.53%, 6.55%)
ICU admission (*n* = 11,468)	1,202		10.48% (9.93%, 11.06%)
No Mechanical Ventilation (*n* = 12,147)	749		6.17% (5.75%, 6.61%)
Mechanical Ventilation (*n* = 6,337)	767		12.10% (11.32%, 12.93%)
Clinical Symptoms			
No MOF or Septic Shock (*n* = 17,081)	1,302		7.62% (7.23%, 8.03%)
MOF or Septic Shock (*n* = 2,919)	409		14.01% (12.80%, 15.32%)

Abbreviations: ICU, intensive care unit; MOF, multiple organ failure or dysfunction.

[a] Point estimate of *related* serious adverse event incidence relative to 20,000 transfusions.
[b] Sustained hypotension included events requiring intravenous pressor support.
[c] Cardiac events included ventricular or atrial fibrillation or arrhythmia requiring treatment, and cardiac arrest.
[d] These data were previously published[10] and reported for comparison with current data.

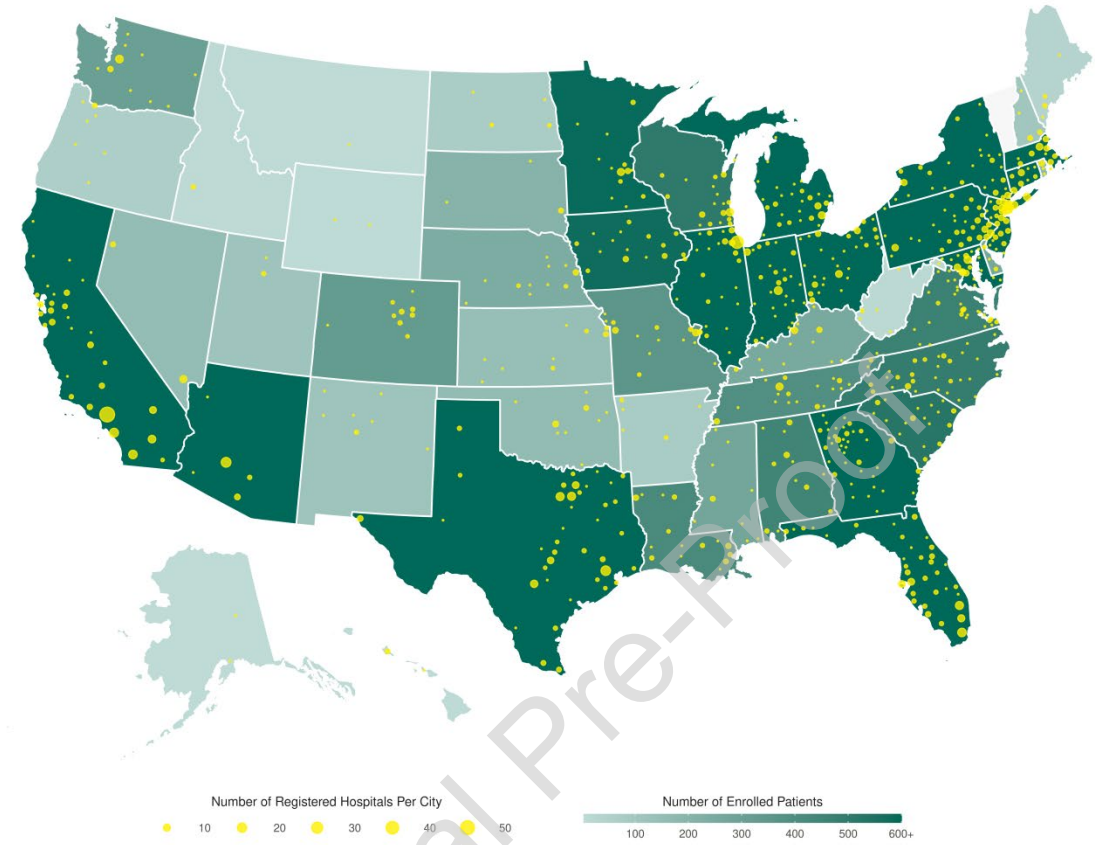

Figure 1. Participation in the US COVID-19 Convalescent Plasma Expanded Access Program (EAP) including data extracted on June 11, 2020. Choropleth map displaying the number of cumulatively enrolled patients in the EAP within each state, with lower enrollment values displayed in a lighter hue of green and higher enrollment values displayed in a darker hue of green. Registered acute care facilities are represented as filled yellow circles, with larger circles indicating greater number of registered facilities within the metropolitan area of a city. The choropleth map does not display data from US territories, including registered facilities in Puerto Rico, Guam and Northern Mariana Islands.

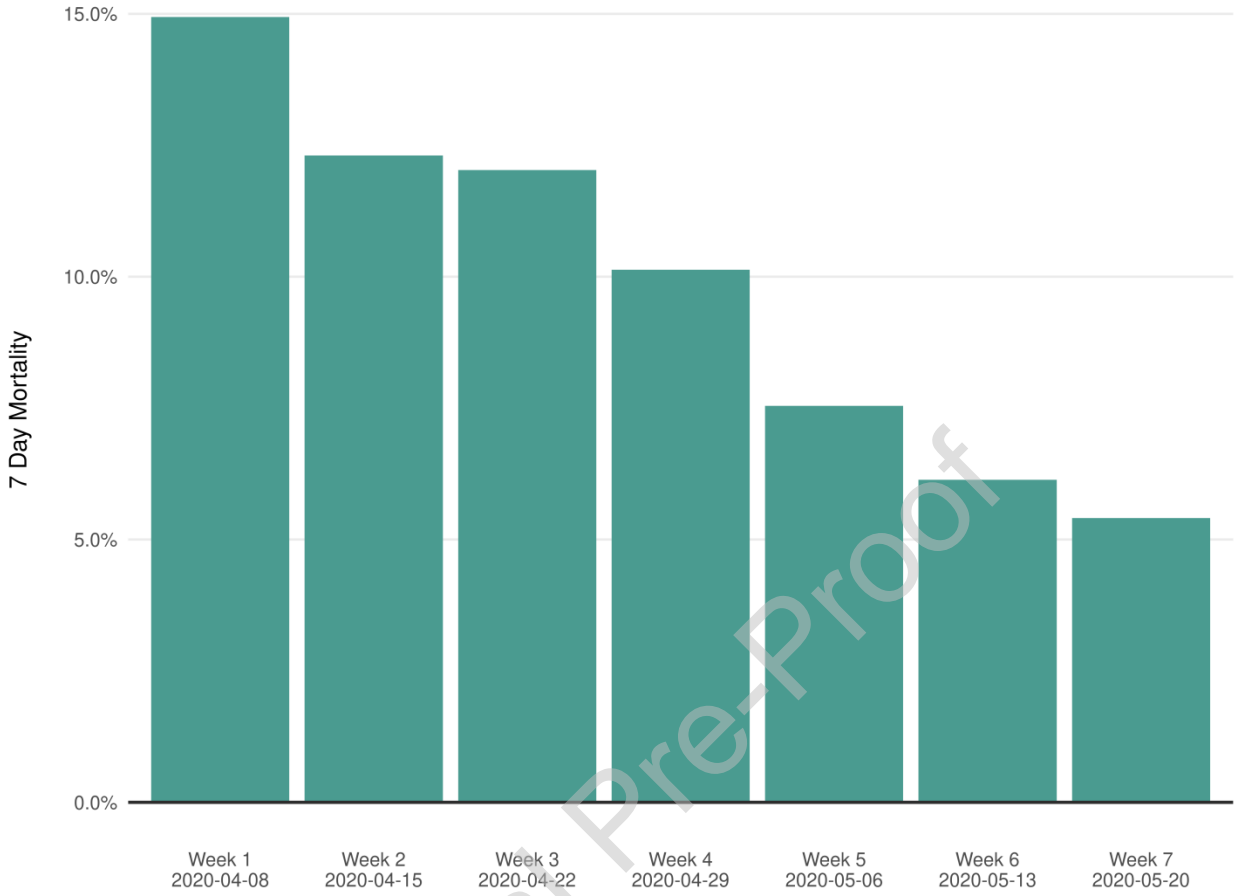

Figure 2. Seven-day Mortality rate in patients transfused with COVID-19 convalescent plasma stratified by week since initiation of the US COVID-19 Convalescent Plasma Expanded Access Program (EAP). Each green bar indicates the seven-day mortality rate stratified by the patients enrolled during a given week since the initiation of the EAP.

