Convalescent Plasma Use in the United States was inversely correlated with COVID-19 Mortality:

Did Convalescent Plasma Hesitancy cost lives?

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

The US Food and Drug Administration (FDA) authorized treatment of hospitalized COVID-19 patients with Convalescent Plasma (CCP) via the Expanded Access Program (EAP) and the Emergency Use Authorization (EUA), leading to the use of CCP in some 500,000 patients during the first year of the pandemic. We tracked the number of CCP units dispensed to hospitals by blood banking organizations and correlated that usage with hospital admission and mortality data over the course of the year. CCP usage per admission peaked after issuance of the EUA, with more than 40% of inpatients estimated to have received CCP between late September and early November 2020. However, following reports of randomized controlled trials that failed to show clear benefit from CCP, usage/admissions declined steadily to a nadir of less than 10% in March 2021. We found a strong inverse correlation (Pearson’s correlation coefficient of -0.5176 with P = 0.00242) between CCP usage/hospital admission and deaths occurring two weeks after admission, and this finding was robust to examination of deaths taking place one, two or three weeks after admission. Changes in the number of hospital admissions, prevalence of variants, and age of patients could not explain these findings. We estimate that the retreat from CCP usage, a phenomenon we termed ‘plasma hesitancy’, might have resulted in 29,000 to 36,000 excess deaths in the period from mid-November 2020 to February 2021. These results highlight the need for additional studies to ascertain the variables associated with efficacy and/or provide other explanations for the robust relationships observed in this study.
Introduction

In the Spring of 2020, the United States embarked on a historic and unprecedented deployment of plasma derived from patients who survived COVID-19 (COVID-19 Convalescent Plasma (CCP)) for treatment of the disease, and one year into this effort more than 500,000 individuals have been treated. The synergism created by the lack of effective alternate therapies, a plentiful supply of plasma from an efficient and high-capacity blood banking network, motivated donors and strong community partners fueled this deployment. Sensible FDA regulatory oversight was provided first by its Expanded Access Program (EAP) in partnership with the Mayo Clinic (April 6, 2020) and then by its Emergency Use Authorization (EUA) of August 23, 2020, both of which restricted CCP use to hospitalized patients (1).

The demonstration by the summer of 2020 that CCP was safe (2, 3), that antibody in plasma correlated with survival in people treated before ventilation (4) along with initial suggestions of efficacy (5-7), fueled interest in and use of this product. However, the use of CCP rose rapidly without the ideal evidence base of efficacy from randomized controlled clinical trials (RCT), since early RCTs though generally trending positively, were unsatisfactory, mostly due to small size or premature termination as the epidemic abated in the early surge regions (8). Later in the pandemic, several larger RCTs reported no mortality benefit (9-11), raising doubts as to CCP efficacy. However, these latter trials were undertaken in hospitalized patients treated late in the course of disease and some used plasma with variable antibody levels (8), and contrasted with a highly successful trial in elderly patients treated within 3 days of illness onset prior to hospitalization (12). Despite potential explanations for the negative studies, the results of these studies were sometimes accompanied by editorials that reinforced message of futility with the British Medical Journal calling it ‘ineffective’ (13) and Nature Biotechnology reporting that CCP fell ‘flat’ (14). In February 2021, JAMA published a meta-analysis of RCT concluding that there was no evidence of benefit from CCP therapy (15).

On March 13, 2021 the New York Times reported that COVID-19 mortality remained high with nearly 1,500 daily deaths despite a drop in the number of new infections since earlier in the year (16). This finding was surprising in light of an apparent reduction in the mortality of hospitalized patients as the epidemic progressed, thought to be from improved management of the disease as clinical experience grew (17). Analyzing weekly reports from the blood banking industry, we noted that plasma use was on the decline, based on the ratio of units dispensed to hospital admissions. The increase in mortality combined with the reduction in CCP use led us to hypothesize first, that the two phenomena were related, and second, that the decline in CCP use reflected reduced use following the disappointing trial findings. The blood banking network maintains careful and complete records for every blood product unit used including time, date and geographic provenance and destination, providing a virtually complete record of trends in CCP use for the US. We therefore examined the use of CCP units as a function of time, assessing the relationship of CCP use to COVID-19 mortality, denominating both plasma units and deaths to hospital admissions. The aim of the study was to determine whether the reduction in plasma use was associated with any change in the pattern of mortality seen in patients hospitalized for COVID-19.

Materials and Methods

Convalescent Plasma Usage. CCP usage was inferred from the distribution of plasma units to hospitals in the USA. For each day, a Comma Separated Values (CSV) file was generated at the Blood Centers of America (West Warwick, RI) with fields that included collections, distributions to hospitals, distributions
to research or other use. This file consolidates all the reports from regional blood bank reports and provides a total of collected units and units distributed to hospitals. The CSV file does not have information on whether a unit is actually transfused but BCA can infer usage from hospital re-ordering information and there is a good correlation between the total number of units shipped to a hospital and the units transfused by that hospital. Hence, the CCP units dispensed to hospitals represent a reasonable proxy value for the total number of units being transfused to patients.

### Admission and mortality data

For population level data on COVID-19 admissions and mortality we relied on publicly available databases. Specifically we used information from the Our World in Data (OWID) [database](https://ourworldindata.org/coronavirus) database. We confirmed these findings using Centers for Disease Control (CDC, Atlanta, GA) data on admissions and deaths [https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions](https://covid.cdc.gov/covid-data-tracker/#new-hospital-admissions) and [https://covid.cdc.gov/covid-data-tracker/#trends_dailyadmissions](https://covid.cdc.gov/covid-data-tracker/#trends_dailyadmissions).

### Statistical analysis

Preliminary descriptive analyses were used to explore the associations of the ratio of number of CCP units dispersed to the number of hospitalizations (CCP utilization ratio) with the ratio of national deaths to national admissions, the latter being a reasonable proxy for the case fatality rate. No individual-level data were available to link the mortality events directly to the individuals hospitalized to permit a calculation of the true case-fatality rate. To address this limitation, the mortality counts reported by the CDC were shifted to better align the deaths with the admitted patients. Since the overwhelming majority of COVID-19 deaths occur in hospitals (18, 19), since CCP is only authorized for use in hospitals, and since death generally occurs a few days to weeks after admission, mortality was adjusted for the time lag between admission and death. The median time between admission and death has been reported as 9 days in the US (20) and 6.7 days in Belgium (21). For the analysis, which was based on weekly aggregated data, a two-week shift was selected to align the mortality with the median and upper quartile estimates in these reports. Spearman correlation coefficient was used to describe the monotonic relationship of the CCP utilization ratio with CFR. To further define this relationship, a linear statistical model was used to regress the utilization ratio onto CFR. This statistical model was weighted by the number of hospitalizations per week. The fit of the model was examined using standard residual-based diagnostic plots and the fit was deemed acceptable using only a linear fit of the CCP utilization ratio.

Three in silico scenarios were created to summarize the effect of alterations to the CCP utilization ratio using the fitted model. In scenario 1, the effect of maintenance of plasma usage was considered. To define maintenance of use, a weighted average of the utilization ratio over the months of August through September 2020 was estimated. This value was then used to estimate the number of deaths that would be expected to occur throughout the study period (admissions starting 8/3/2020 – 2/22/2021). In scenario 2 a constant 50% CCP utilization ratio was set over the entire study period. The utilization rate was the value observed in the early October 2020 period. A final scenario estimated the CFR that may have been observed had CCP not been used at all (i.e., the y-intercept from the model). Model contrasts were used to estimate the change in expected deaths among these scenarios in addition to a fourth condition – the actual number of events reported by the CDC. Values are summarized based on the observed number of hospitalized patients over the study period along with the same values indexed into expected mortality events per 1000 hospitalizations. Pointwise confidence bands for each scenario were obtained by multiplying the model-predicted CFR, and its associated 95% confidence interval, by the number of hospitalizations per week. Cumulative summations were used to
describe the differences in expected deaths over the entire study period. This analysis was repeated independently a third time using a weighted average of utilization ratio of the months October-November on a separate database (OWID) to investigate stability between reporting bodies.

Statistical analyses were conducted using R version 3.6.2. 95% confidence intervals and two-sided p-values were used to summarize association and test for significance at the alpha=0.05 level of significance, respectively.

**Results**

**Convalescent plasma use.** The FDA first allowed compassionate use of CCP on a case-by-case basis in late March 2020, but very quickly initiated the Expanded Access Program in early April 2020. The EAP was, in effect, a registry of all CCP use in the US from April to August 2020 and led to a sharp rise in CCP use. The findings of the EAP, which established that CCP was as relatively safe (2, 3), and that high antibody titer was associated with lower mortality in unventilated plasma recipients (4), were major considerations behind the Emergency Use Authorization of August 23, 2020 (Figure 1), which broadened its use. Distribution of CCP to hospitals rose to 25,000 - 30,000 weekly units by the December 2020 to January 2021 time period, but this rise in plasma distribution largely reflected the great increase in hospital admissions for COVID in those months. (Figure 1). When CCP distributions are analyzed as a function of the number of new hospital admissions per week, peak utilization per capita occurred much earlier, in early October 2020 and declined sharply in the following months (Figure 2).

**Correlation between CCP and mortality.** To explore whether there was a relationship between CCP distribution in the USA and mortality we first compared the doses per patient versus reported COVID-19 deaths per hospital admission from publicly available databases (Figure 2). The comparison of curves showed a trough in deaths per admission coincident with the peak of CCP usage per admission. A plot of mortality versus doses per hospitalized patient using mortality per admission data from the OWID database revealed a strong negative correlation (Pearson's correlation coefficient of -0.5176 with P = 0.00242) (Figure 3). To account for lags in the reporting of death that vary by state, we also investigated whether this correlation was maintained while adding weeks to the time between admission and death (Figure S1). Repeating the analysis using the CDC admission and mortality database yielded a nearly identical result (Table 2) with regression analysis providing a Pearson correlation coefficient of -0.49 with p = .03 and $R^2 = .24$ (excluding weeks 3/20 and 3/27/21 since reliable mortality data is not available at the time of this writing). Additionally, as we show in Supplemental Figure 2, if plasma use is divided into quintiles from lowest using weeks to highest using weeks, a dose-response relationship between use of plasma and mortality is apparent.

**Possible confounders.** Apart from the concerns about delays in death reporting, which were accounted by showing that the results were robust even if additional delays had taken place, we considered three other possible confounders for our analysis.

1. Could the decline in CCP use have resulted from scarcity of the product? This was not the case since the supply of plasma has exceeded the demand in the USA since the late Spring of 2020, before our analysis begins.

2. Could the changes in mortality have reflected differences in the age distribution of admitted patients? Mortality with COVID-19 increases with age (22) and it was possible that the relative increase in mortality associated with reduced CCP usage was simply a consequence of changes
in the age distribution of admissions. Analysis of the CDC database for the age distribution of admitted patients, however, revealed no major differences in the age of patients admitted with COVID-19 (Figure S3). If anything, the trend was towards younger ages among hospitalized patients in the early months of 2021 likely as a result of early vaccination of older age groups, which if anything should have reduced the mortality per admission.

3. Could the surge in admissions in January 2021, which corresponded to a low CCP use period, have had an independent effect on mortality because of crowding in ICU’s and overburdened staff? This explanation, however, is not sustainable, since the correlation between admissions/week and mortality/week in the entire period of observation was virtually null at -.02, explaining about 0.5% of the variance in mortality.

**Estimates of excess deaths.** The linear model using the CCP utilization ratio to predict the CFR fit the data well in that this model explained 25% ($R^2 = 0.254$) of the variance of CFR using only the CCP utilization ratio. The model estimated the CFR decreased by 1.8 percentage points for every 10-percentage point increase in the rate of utilization of CCP ($p = 0.004$). The linear regression analysis yielded a mortality in patients not receiving CCP of 25.2% as the y-intercept. A comparison of this number with that from USA studies shows reasonable agreement between with the average mortality of 23.5% in patients not receiving CCP (Table S1). This percentage also closely matches the 24% mortality for COVID-19 patients for the large RECOVERY trial in the United Kingdom (11) and the 30% mortality of patients receiving late CCP in analysis from the Expanded Access Program (4). An extrapolation of the linear model to the situation where every patient is treated with CCP yields a mortality of 7.6%, which is lower than the average mortality in USA studies, but still within the range reported (Table S1). However, this extrapolation to maximal use is much less reliable given the absence of points in the y axis region above an CCP utilization ratio of 0.6 and uncertainty as to whether the relationship is linear in those ranges. Hence, we caution the reader about making any strong inference from this estimate while noting that it is close to the 6.2% mortality reported for COVID-19 patients treated with high titer CCP very early upon hospitalization (23). Nevertheless, it is possible to use these efficacy numbers to estimate what the effect on deaths would have been had the United States continued to use CCP at the height of its usage in early Fall 2020, when >40% of all patients received plasma therapy.

With this model as a framework for estimating the excess number of deaths, the results of three scenarios were obtained (Figure 4). The total observed deaths over the study period was 356,534. Had the rate of CCP utilization observed during August through October 2020 carried over for the remaining months, the expected number of deaths was 327,516 (95% CI: 293,811 to 361,221), which would result in 29,018 (95% CI: 3535 to 54,501) fewer deaths than observed. This excess death, in comparison, was small relative to the estimate that results from assuming plasma utilization was as high as it was after the EUA was issued. In particular, had 50% utilization of plasma been continued, 62,383 (95% CI: 7599 to 117,166) fewer deaths may have been observed. Under the most extreme scenario comparing no plasma use to the highest observed use, a difference of 158,409 (95% CI: 19,296 to 297,523) deaths is estimated. We repeated this analysis independently for each of the databases used (CDC vs OWID) with concordant results (Figure S4 and Tables S2, S3).

As an alternative method to estimating the excess deaths, which alleviated the need for a model, the data were summarized into two key periods. In each of the seven weeks from September 20th to November 11th, 2020, the estimated proportion of in-patients transfused with convalescent plasma exceeded 40%, averaging 43.8% (Table 2). The two-week lagged mortality ratio for hospitalized patients...
was 18.30%. In the following 18 weeks, transfusion rates declined steadily, averaging 25.2%. In parallel, mortality ratio rose to 20.91% for the 1,388,863 patients admitted in those 18 weeks. Table 2 shows that if the mortality rate in those 18 weeks had been the same as during the high-transfusion period, 36,252 fewer deaths would have taken place.

Discussion

The use of CCP in the USA peaked in the Winter of 2020-2021 when as many as 25,000-30,000 units were distributed each week to hospitals. We note that CCP use rose rapidly in late September 2020 a few weeks after the FDA allowed its widespread use under the EUA of August 23, 2020. It is also noteworthy that the early controversy that followed the EUA with some observers claiming that evidence of efficacy was insufficient for the authorization (24, 25), did not appear to have dented its utilization. However, in the Fall of 2020, RCTs from India (9) and Argentina (10) reporting that CCP use did not reduce mortality in hospitalized patients were followed by a decline in use. This was followed by negative publicity in major newspapers and medical information outlets that further questioned its efficacy. This decline was accelerated after the report in January 2021 that the RECOVERY trial in the UK had stopped enrolling patients after finding no effect on mortality (11). Hence, CCP use increased initially despite the controversy involving the EUA rollout but declined following reports that RCTs were not finding that it reduced mortality. Importantly, this suggests that physicians were more influenced by clinical research data than the controversies that played out in the media. Evidence that reduced usage in the USA reflected concerns about the efficacy of CCP comes from a poll by the American Association of Blood Banks revealing a 50% increase in the number of institutions planning to stop offering CCP between February and March 2021, which cited lack of stronger efficacy data as the major reason for this decision (26).

The results show an inverse temporal correlation between CCP use and mortality in the USA. Although correlation is not causation, and any relationship that implies temporal causation needs to be interpreted very cautiously, analysis of what is known about CCP effects on mortality provides support for a causal relationship. An analysis of several dozen studies for which results were available by mid-January 2021 associated the administration of CCP with reduced mortality, with an effect size of ~35% (27). Convalescent plasma has reportedly proven effective in individuals with defective humoral immunity and B cell defects (28, 29). The finding that the active agent in plasma, antibody titer, is strongly related to mortality in transfused patients (4, 12, 30), is hard to understand if plasma is ineffective.

Additionally, the active agent of CCP, specific antibody to SARS-CoV-2, has powerful antiviral activity and has been shown to reduce the viral load in patients with COVID-19, thus providing a mechanistic explanation for its therapeutic effect (31). Human convalescent plasma is protective in murine models of COVID-19 (32). Patients treated with CCP also manifest reduced inflammatory markers (33-35). Given that the pathogenesis of COVID-19 that leads to demise involves an over-exuberant inflammatory response (36), these findings provide a viable explanation for its efficacy whereby specific antibody reduces viral burden, which in turn reduces the inflammatory response and enhances the likelihood of survival. This also parallels the finding that late use of plasma or its use in people with advanced illness is not likely to be effective, because at that time, the inflammatory response itself is the major pathophysiologic pathway to severe illness and death. Hence, we posit that the inverse association
between CCP use and mortality is causal since it is connected by both clinical evidence and the mechanistic causality of antibody action.

A causal association between the inverse correlation for CCP use per hospitalized patient and increased mortality would provide evidence for the effectiveness of this therapy at a population level. This inference is strengthened by the fact that mortality from COVID-19 among hospitalized patients decreased substantially over most of 2020, consistent with worldwide trends (17), but then began to rise in late November and early December 2020, a period that coincided with precipitous reduction in CCP/admission. Buttressing such a conclusion would require excluding the contribution of other variables that can affect mortality, which is challenging during an ongoing pandemic where information about the pathophysiology and clinical course COVID-19 is accruing rapidly. Nevertheless, consideration of several factors supports the notion that reduced use of CCP contributed to stabilization in previously declining mortality trends. We can exclude shortages in plasma supply leading to reduced use or increased COVID-19 mortality from changes in the age of the population affected by COVID-19 or the increase in hospital admissions as potential confounders. The decline in COVID-19 mortality over 2020 was attributed to general improvements in medical care, which can be expected to have continued through early 2021 since no major therapy was introduced or withdrawn during that time.

The emergence of variants with higher mortality is another variable that must be considered. In the United Kingdom a new lineage of SARS-CoV-2 emerged in the September 2020 known as B.1.1.7, which is associated with higher contagiousness and perhaps, mortality (37). This variant was identified in the United States in early winter 2021 but as of January only 76 cases had been described in 12 states, which was estimated to be <0.5% of the infections at the time (38). Hence this variant constituted a small minority of cases during much of the time involved in our analysis. Even as late as mid-March 2021 the CDC estimated that B.1.1.17 variant comprised only 25% of USA isolates and increased mortality from these infections would not manifest itself until times later than our analysis (39). Limiting our analysis to the time from March 2020 to January 2021 shows maintenance of the trends described here.

The results show that CCP use per hospital admission closely paralleled the severity of the epidemic throughout much of 2020, increasing in parallel with hospital admissions, but then declined late in 2020 and in the early months of 2021, a time following the publication of several negative RCT studies. Of concern, the drop in per capita CCP utilization appeared to be associated with an increase in mortality among hospitalized COVID-19 patients. If there is a causal link between these two trends, we estimate that the decline in per capita CCP use resulted in 29,000-36,000 excess deaths. Given that this analysis was done during the ongoing pandemic and that the variables that affect mortality are not fully understood we urge caution in with our findings. Nevertheless, applying Occam’s razor to the problem, the results do raise the disturbing possibility that reduced CCP use contributed to the death of thousands of patients.

Taking a page from the reluctance of citizens to accept vaccines against SARS-CoV-2, a phenomenon that has been termed ‘vaccine hesitancy’ (40), we call the phenomenon of reduced use of CCP ‘plasma hesitancy’. In this regard, we note that both the vaccines being administered in the USA and CCP are being used under a EUA regulatory framework, since neither has full approval status. Plasma hesitancy may be a result of health care providers overvaluing and over-emphasizing negative results from RCT findings while dismissing other evidence that CCP reduces mortality. We note that on February 17, 2021 the Wall Street Journal reported that Mount Sinai Hospital, which had been a leader in deploying CCP
and reported early encouraging results (7), had stopped using plasma in patients with COVID-19, and the report specifically mentioned the negative results from CCP RCTs in this decision (41). On the other hand, remdesivir has been widely embraced by the health care provider community for treatment of Sars-CoV2, despite a lack published data on reductions in mortality from its use and with conflicting RCT data regarding its clinical usefulness (42, 43). In contrast, CCP has some data demonstrating a reduction in mortality for hospitalized patients with COVID-19 from its early use in non-ventilated patients(27), and yet has met with use hesitancy. Why might this be? One possibility is that there is relatively little recent experience with treating infectious diseases with antibody therapies (44). Hence, we wonder the different receptions for these therapies could reflect some degree of pre-pandemic confirmational professional bias by the health care community in favor of antivirals considering their success against Human immunodeficiency (HIV) and Hepatitis C (HCV) viruses.

We have argued that physicians need to consider all the evidence, from observational studies to RCTs, when evaluating clinical efficacy data (45). We note that the FDA reaffirmed the EUA status of CCP in February 2021 (1) by permitting its continued use in hospitalized patients if used early in COVID-19 and with units that have a sufficient content of specific antibody. In addition, interim guidelines for American Association of Blood Banks (46) and Brazil (47) emphasize that CCP is more likely to be effective when used in early COVID-19 with units having high content of specific antibody. We are hopeful that physicians consider the totality of the available evidence and our findings when making decisions for CCP use in individual patients.

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Table 1. Weeks ordered from lowest to highest percent of admissions transfused in relation to two-week lagged mortality.

| WEEK ENDING | ESTIMATED PERCENT ADMISSIONS TRANSFUSED | TWO-WEEK LAGGED MORTALITY RATIO<sup>1</sup> |
|-------------|----------------------------------------|------------------------------------------|
| 3/27/21     | 6.7%                                   | -                                        |
| 3/20/21     | 8.0%                                   | 18.0 (based on 4/1)                      |
| 3/13/21     | 11.7%                                  | 19.5                                     |
| 3/6/21      | 16.9%                                  | 20.4                                     |
| 2/20/21     | 18.1%                                  | 26.3                                     |
| 2/27/21     | 20.2%                                  | 21.0                                     |
| 2/13/21     | 21.9%                                  | 25.8                                     |
| 1/2/21      | 23.1%                                  | 21.5                                     |
| 12/26/20    | 23.8%                                  | 21.3                                     |
| 1/30/21     | 24.9%                                  | 27.0                                     |
| 12/12/20    | 26.4%                                  | 15.9                                     |
| 1/9/21      | 26.4%                                  | 18.7                                     |
| 1/23/21     | 26.6%                                  | 23.7                                     |
| 1/16/21     | 27.0%                                  | 20.4                                     |
| 2/6/21      | 27.1%                                  | 19.4                                     |
| 12/5/20     | 28.4%                                  | 19.3                                     |
| 12/19/20    | 29.0%                                  | 18.0                                     |
| 8/30/20     | 30.1%                                  | 18.2                                     |
| 8/23/20     | 30.5%                                  | 20.1                                     |
| 8/2/20      | 30.6%                                  | 19.1                                     |
| 8/9/20      | 31.7%                                  | 22.1                                     |
| 9/19/20     | 32.1%                                  | 20.8                                     |
| 9/12/20     | 32.3%                                  | 21.5                                     |
| 11/28/20    | 33.0%                                  | 20.0                                     |
| 8/16/20     | 33.3%                                  | 21.8                                     |
| 11/20/20    | 33.4%                                  | 18.1                                     |
| 9/5/20      | 33.7%                                  | 20.9                                     |
| 7/26/20     | 38.6%                                  | 21.8                                     |
| 11/14/20    | 38.7%                                  | 19.1                                     |
| 11/7/20     | 40.1%                                  | 18.4                                     |
| 10/3/20     | 41.2%                                  | 18.8                                     |
| 10/31/20    | 41.6%                                  | 19.8                                     |
| 10/25/20    | 44.4%                                  | 16.7                                     |
| 10/10/20    | 46.7%                                  | 18.1                                     |
| 10/17/20    | 47.0%                                  | 16.5                                     |
| 9/26/20     | 49.1%                                  | 20.2                                     |
| 7/19/20     | 52.2%                                  | 16.2                                     |

<sup>1</sup> Indicates the ratio of two-week lagged mortality to the estimated percent of admissions transfused.
Linear regression analysis of the data in this table excluding the last two weeks (3/20/21 and 3/27/21) due to likely incomplete data, yielded $R = 0.49$, $p = 0.03$, $R^2 = 0.24$. 
Table 2. Estimated number of excess deaths due to transfusion hesitancy.

| PERIOD       | TRANSFUSION RATE | Number OF ADMISSIONS | DEATHS | MORTALITY RATE | DEATHS IF MORTALITY HAD REMAINED AT 18.3% | EXCESS DEATHS IN LOW TRANSFUSION PERIOD |
|--------------|------------------|----------------------|--------|----------------|------------------------------------------|----------------------------------------|
| HIGH 9/20/20 – 1/7/21 | 43.8%            | 252,518              | 46,214 | 18.30%         | 46,214                                   | 46,214                                 |
| LOW 11/8/20 – 3/13/21 | 25.2%            | 1,388,863            | 290,402| 20.91%         | 254,162                                   | 36,252                                 |
### Table S1. Mortality of COVID-19 in USA CCP efficacy studies.

| Study          | Location            | Type                       | Mortality | Relative risk of death with plasma | Reference |
|----------------|---------------------|----------------------------|-----------|-----------------------------------|-----------|
| Salazar et al. | Houston, TX         | Matched Cohort Design      | 6.2       | 12.5                              | 0.50      | (23) |
| Liu et al.     | New York City       | Matched Cohort Design      | 12.8      | 24.4                              | 0.52      | (7)  |
| Shenoy et al.  | Washington, DC      | Matched Cohort Design      | 25        | 27                                | 0.93      | (48) |
| Donato et al.  | New Jersey          | Matched Cohort Design      | 11.1      | 27.1                              | 0.41      | (49) |
| Yoon et al.    | New York City       | Matched Cohort Design      | 32.8      | 37.5                              | 0.87      | (50) |
| O'Donnell et al.| New York City       | Double Blind Randomized Controlled | 12.6      | 24.6                              | 0.51      | (51) |
| Sostin et al.  | Hartford, CT        | Matched Cohort Design      | 20        | 24.6                              | 0.81      | (52) |
| Sturek et al.  | Charlottesville, VA | Matched Cohort Design      | 6.9       | 10.4                              | 0.66      | (53) |
| **Average**    |                     |                            | 15.9      | 23.5                              | 0.68      |       |
Table S2. Data from and calculations for excess mortality from CCP hesitancy based on the OWID database.

| Week       | Plasma Doses | Deaths | Hospitalized Patients | Admissions | Plasma Doses Per Patient | Mortality (Deaths / Admissions - 2 Week Shift) |
|------------|--------------|--------|-----------------------|------------|--------------------------|-----------------------------------------------|
| 7/18/2020  | 11231        | 5559   | 38045                 | 21481      | 0.52                     | 0.37                                          |
| 7/25/2020  | 12919        | 6513   | 42802                 | 33434      | 0.39                     | 0.22                                          |
| 8/1/2020   | 11724        | 7855   | 49972                 | 38256      | 0.31                     | 0.19                                          |
| 8/8/2020   | 10511        | 7421   | 41313                 | 33153      | 0.32                     | 0.20                                          |
| 8/15/2020  | 10495        | 7126   | 38655                 | 31543      | 0.33                     | 0.20                                          |
| 8/22/2020  | 9218         | 6711   | 34466                 | 30226      | 0.30                     | 0.19                                          |
| 8/29/2020  | 8968         | 6309   | 31031                 | 29776      | 0.30                     | 0.17                                          |
| 9/5/2020   | 8424         | 5855   | 28242                 | 27010      | 0.31                     | 0.20                                          |
| 9/12/2020  | 7894         | 5124   | 26237                 | 28351      | 0.28                     | 0.19                                          |
| 9/19/2020  | 9647         | 5348   | 25382                 | 23924      | 0.40                     | 0.21                                          |
| 9/26/2020  | 11670        | 5439   | 25915                 | 24867      | 0.47                     | 0.21                                          |
| 10/3/2020  | 11101        | 4939   | 27804                 | 27575      | 0.40                     | 0.19                                          |
| 10/10/2020 | 14796        | 5172   | 31370                 | 33658      | 0.44                     | 0.17                                          |
| 10/17/2020 | 16401        | 5222   | 34934                 | 37027      | 0.44                     | 0.16                                          |
| 10/24/2020 | 17827        | 5812   | 39899                 | 40935      | 0.44                     | 0.18                                          |
| 10/31/2020 | 18628        | 6012   | 45983                 | 46467      | 0.40                     | 0.18                                          |
| 11/7/2020  | 19205        | 7303   | 55640                 | 56877      | 0.34                     | 0.20                                          |
| 11/14/2020 | 26176        | 8156   | 69432                 | 70999      | 0.37                     | 0.15                                          |
| 11/21/2020 | 28076        | 11119  | 81702                 | 81834      | 0.34                     | 0.20                                          |
| 11/28/2020 | 28688        | 10814  | 92351                 | 86841      | 0.33                     | 0.21                                          |
| 12/5/2020  | 27350        | 16033  | 98549                 | 94573      | 0.29                     | 0.20                                          |
| 12/12/2020 | 25706        | 17907  | 107227                | 101624     | 0.25                     | 0.16                                          |
| 12/19/2020 | 29842        | 19238  | 112272                | 104959     | 0.28                     | 0.22                                          |
| 12/26/2020 | 24350        | 16363  | 118892                | 106311     | 0.23                     | 0.22                                          |
| 1/9/2021   | 30576        | 23074  | 126420                | 116363     | 0.26                     | 0.19                                          |
| 1/16/2021  | 28946        | 23726  | 120658                | 108721     | 0.27                     | 0.20                                          |
| 1/23/2021  | 25395        | 21843  | 106881                | 93972      | 0.27                     | 0.22                                          |
| 1/30/2021  | 20226        | 22152  | 91286                 | 80589      | 0.25                     | 0.22                                          |
| 2/6/2021   | 18913        | 20667  | 77709                 | 69080      | 0.27                     | 0.19                                          |
| 2/13/2021  | 12303        | 17346  | 63237                 | 55607      | 0.22                     | 0.25                                          |
| 2/20/2021  | 8369         | 13155  | 53512                 | 46421      | 0.18                     | 0.25                                          |
| 2/27/2021  | 8429         | 13706  | 44799                 | 41727      | 0.20                     | NA                                            |
| 3/6/2021   | 6006         | 11791  | NA                    | 32075      | 0.19                     | NA                                            |
Table S3. Replicate excess death calculations based on OWID database.

| Transfused | Scenario 1 | Scenario 2 | Scenario 3 |
|------------|------------|------------|------------|
|            | 38.90%     | 50%        | 0%         |
| Week       | Expected Deaths | Difference | Expected Deaths | Difference | Expected Deaths | Difference |
| 8/1/2020   | 3974.94       | 3880.06    | 3625.35    | 4229.65    | 5332.66      | 1707.31    |
| 8/8/2020   | 6186.78       | 1234.22    | 5642.66    | 1778.34    | 8299.99      | 2657.33    |
| 8/15/2020  | 7079.06       | 46.94      | 6456.47    | 669.53     | 9497.05      | 3040.59    |
| 8/22/2020  | 6134.78       | 576.22     | 5595.23    | 1115.77    | 8230.23      | 2635.00    |
| 8/29/2020  | 5836.86       | 472.14     | 5323.51    | 985.49     | 7830.55      | 2507.04    |
| 9/5/2020   | 5593.16       | 261.84     | 5101.24    | 753.76     | 7503.60      | 2402.36    |
| 9/12/2020  | 5509.89       | -385.89    | 5025.30    | 98.70      | 7391.89      | 2366.60    |
| 9/19/2020  | 4998.05       | 349.95     | 4558.48    | 789.52     | 6705.23      | 2146.75    |
| 9/26/2020  | 5246.20       | 192.80     | 4784.80    | 654.20     | 7038.14      | 2253.34    |
| 10/3/2020  | 4427.00       | 512.00     | 4037.65    | 901.35     | 5939.13      | 1901.48    |
| 10/10/2020 | 4601.50       | 570.50     | 4196.80    | 975.20     | 6173.23      | 1976.43    |
| 10/17/2020 | 5102.60       | 119.40     | 4653.83    | 568.17     | 6845.49      | 2191.66    |
| 10/24/2020 | 6228.23       | -416.23    | 5680.46    | 131.54     | 8355.60      | 2675.14    |
| 10/31/2020 | 6851.64       | -839.64    | 6249.05    | -237.05    | 9191.95      | 2942.91    |
| 11/7/2020  | 7574.80       | -271.80    | 7008.60    | 39.44      | 10162.11     | 3253.51    |
| 11/14/2020 | 8598.46       | -442.46    | 7842.24    | 313.76     | 11535.43     | 3693.20    |
| 11/21/2020 | 10524.78      | 594.22     | 9599.13    | 1519.87    | 14119.72     | 4520.58    |
| 11/28/2020 | 13137.97      | -2323.97   | 11982.50   | -1168.50   | 17625.50     | 5643.00    |
| 12/5/2020  | 15142.93      | 890.07     | 13811.12   | 2221.88    | 20315.29     | 6504.17    |
| 12/12/2020 | 16069.45      | 1837.55    | 14656.16   | 3250.84    | 21558.28     | 6902.12    |
| 12/19/2020 | 17500.21      | 1737.79    | 15961.09   | 3276.91    | 23477.75     | 7516.66    |
| 12/26/2020 | 18804.96      | -2441.96   | 17151.08   | -788.08    | 25228.16     | 8077.08    |
| 1/9/2021   | 19422.09      | 3651.91    | 17713.93   | 5360.07    | 26056.07     | 8342.14    |
| 1/16/2021  | 19672.27      | 4053.73    | 17942.11   | 5783.89    | 26391.71     | 8449.60    |
| 1/23/2021  | 21532.33      | 310.67     | 19638.58   | 2204.42    | 28887.11     | 9248.53    |
| 1/30/2021  | 20118.22      | 2033.78    | 18348.84   | 3803.16    | 26989.99     | 8641.15    |
| 2/6/2021   | 17389.00      | 3278.00    | 15859.65   | 4807.35    | 23328.55     | 7468.89    |
| 2/13/2021  | 14912.55      | 2433.45    | 13601.01   | 3744.99    | 20006.22     | 6405.21    |
| 2/20/2021  | 12782.87      | 372.13     | 11658.63   | 1496.37    | 17149.11     | 5490.48    |
| 2/27/2021  | 10289.77      | 3416.23    | 9384.79    | 4321.21    | 13804.44     | 4419.64    |
| 3/6/2021   | 8589.95       | 3201.05    | 7834.47    | 3956.53    | 11524.01     | 3689.54    |

| Excess Deaths | 28904.69 | 57913.24 | 141669.44 |
Figure 1. Doses of CCP distributed in the United States by the American Red Cross and American Blood Centers (solid) and total COVID-19 cases in the United States reported in OWID (dashed). The vertical black line marks August 23, 2020 when the FDA announced that Emergency Use Authorization for CCP in the USA. The vertical gray line marks April 4, 2020 as the start of the Emergency Access Program.
Figure 2. Doses of CCP per hospital admission (red) and mortality calculated as deaths per hospital admission (green). To account for time between admission to death, deaths from two weeks after admission are used to calculate mortality. The vertical line marks August 23, 2020 when the FDA announced that Emergency Use Authorization for CCP in the USA.
Figure 3. Correlation of mortality (death per admission) and CCP doses per admitted patients. Correlation analysis yields a Pearson’s correlation coefficient of -0.5175537 (p = 0.002416). The black line represents a linear model regression with an adjusted R squared of 0.2435.
Figure 4. Estimated deaths under modeled scenarios of Covid-19 Convalescent Plasma. Panel A presents the longitudinal observed (dashed line) and modeled number of deaths under three scenarios for CCP over the study period (8/3/2020 – 2/22/2021) that included 356,534 deaths in 1,793,502 hospitalized patients. Over the entire study period, the CCP utilization ratio was 29.1%. In the scenario labeled maintenance of plasma, the CCP utilization ratio was set to 39.5%. With the no plasma and 50% plasma usage scenarios, the CCP utilization ratio was set at 0% and 50%, respectively. Panel B provides the pairwise comparisons of these scenarios to estimate the difference in expected number of deaths among the scenarios for the entire hospitalized patients (upper right triangle) and re-indexed to events per 1000 patients (lower left triangle). The rows represent the comparator or reference scenario, columns indicate the altered CCP use scenario. For example, the cell that intersects the observed deaths and the maintenance of plasma column shows that 29,018 fewer deaths would result had plasma use remained at the 39.5% level.
**Supplemental Figure 1.** A series of linear regressions and Pearson's correlation tests comparing weekly reported deaths to new weekly hospital admissions, offset by various numbers of weeks to identify the length of lag between admission and death of patients. Y axes values reflect the parameter of each gray box throughout the shifted weeks. Correlations peak at 2-3 weeks shifted, suggesting the lag time between admission and reported death is roughly two weeks.
Supplemental figure 2. Mortality from COVID-19 by quintile of percent of admissions receiving CCP.
**Supplemental Figure 3.** Investigation of high age group mortality. **A.** The rate of hospitalization of ages 65-84 (solid) compared to the cumulative hospitalization rate (dashed), each measured as hospitalizations per 100,000. **B.** High age fraction (65-84 hospitalization rate / cumulative hospitalization rate; solid) compared to mortality (deaths / hospital admissions; dashed). There is no significant correlation between the rate at which patients aged 65-84 are hospitalized and overall mortality, suggesting changes in mortality are not explainable by an increase in hospitalized high risk patients.
Supplemental Figure 4. Replicated cumulative excess deaths analysis per OWID database for scenario 1 (orange): Maintained plasma transfusion rate from Oct-Nov throughout period, scenario 2 (blue): 50% transfusion rate throughout period, and scenario 3 (red): 0% transfusion rate throughout period. Black dashed line represents observed cumulative deaths per OWID reporting.