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TRANSFUSION COMPLICATIONS

TRANSFUSION

Clinical outcomes in hospitalized plasma and platelet transfusion recipients prior to and following widespread blood donor SARS-CoV-2 infection and vaccination

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Abstract

Background: The safety of transfusion of SARS-CoV-2 antibodies in high plasma volume blood components to recipients without COVID-19 is not established. We assessed whether transfusion of plasma or platelet products during periods of increasing prevalence of blood donor SARS-CoV-2 infection and vaccination was associated with changes in outcomes in hospitalized patients without COVID-19.

Methods: We conducted a retrospective cohort study of hospitalized adults who received plasma or platelet transfusions at 21 hospitals during pre-COVID-19 (3/1/2018–2/29/2020), COVID-19 pre-vaccine (3/1/2020–2/28/2021), and COVID-19 post-vaccine (3/1/2021–8/31/2022) study periods. We used multivariable logistic regression with generalized estimating equations to adjust for demographics and comorbidities to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Among 21,750 hospitalizations of 18,584 transfusion recipients without COVID-19, there were 697 post-transfusion thrombotic events, and oxygen requirements were increased in 1751 hospitalizations. Intensive care unit length of stay ($n = 11{,}683$) was 3 days (interquartile range 1–5), hospital mortality occurred in 3223 (14.8%), and 30-day rehospitalization in 4144 (23.7%). Comparing the pre-COVID, pre-vaccine and post-vaccine study periods, there were no trends in thromboses (OR 0.9 [95% CI 0.8, 1.1]; $p = .22$) or oxygen requirements (OR 1.0 [95% CI 0.9, 1.1]; $p = .41$). In parallel, there were no trends across study periods

for ICU length of stay ($p = .83$), adjusted hospital mortality (OR 1.0 [95% CI 0.9–1.0]; $p = .36$), or 30-day rehospitalization ($p = .29$).

Discussion: Transfusion of plasma and platelet blood components collected during the pre-vaccine and post-vaccine periods of the COVID-19 pandemic was not associated with increased adverse outcomes in transfusion recipients without COVID-19.

1 | INTRODUCTION

Multiple randomized clinical trials have examined the safety and efficacy of COVID-19 convalescent plasma (CCP) in preventing severe COVID-19 or death.[1–3] Although uncommon, adverse outcomes were reported in COVID-19 recipients of convalescent plasma and were hypothesized to be related to transfused autoantibodies in CCP units.[4,5] Autoantibodies have been associated with intensive care unit (ICU) admission and death in COVID-19 patients and have been identified in CCP units.[6,7] While there is significant data supporting the overall safety of CCP, there is no safety evidence regarding the transfusion of these products to recipients without COVID-19.[8,9] Adding to these concerns, dramatic boosting of SARS-CoV-2 antibody levels occurs in donors with previous SARS-CoV-2 infections who were vaccinated compared to those who were infected but not vaccinated.[7]

Nationally, a significant rise in the prevalence of SARS-CoV-2 antibodies was recognized in the blood donor population as a byproduct of SARS-CoV-2 infection and vaccination.[10–13] In the United States, infection-induced SARS-CoV-2 seroprevalence in blood donors increased from 11% to 70% from December 2020 to September 2022.[11,13] In parallel, combined infection- and vaccination-induced SARS-CoV-2 donor seroprevalence was estimated to be 96% by September 2022.[12,13] Neutralizing and anti-spike antibodies in blood donors are known to increase by several logs following subsequent exposure to novel SARS-CoV-2 variants or vaccine boosting.[14,15] Elevations of antibodies following SARS-CoV-2 infection or vaccination may include a concomitant rise in autoantibodies associated with adverse events in COVID-19 patients.[16,17] In parallel to patients treated with CCP, passive transfer of donor SARS-CoV-2 antibodies is recognized to occur in transfusion recipients without COVID-19, including recipients of platelet products.[18] Transfusion of SARS-CoV-2 antibodies or autoantibodies in high plasma volume blood components may impact outcomes in recipients without COVID-19, and the receipt of blood from previously infected or vaccinated blood donors has been a concern raised by some patient advocacy groups and even lawmakers.[19,20]

In addition to prolonged hospitalization and death, pulmonary edema and thromboses have separately been associated with severe COVID-19 and blood transfusion.[21–23] In this observational study, we assessed whether transfusion of plasma or plasma-rich platelet products collected during periods of increasing prevalence of blood donor SARS-CoV-2 infection and/or vaccination were associated with changes in rates of thrombotic or pulmonary events, ICU length of stay, hospital mortality, and rehospitalization in transfusion recipients without COVID-19.

2 | METHODS

2.1 | Design overview

We conducted a retrospective cohort study using electronic health record (EHR) data from Kaiser Permanente Northern California (KPNC), which serves a population of 4.6 million members. We included all hospitalized adult, non-obstetric KPNC patients who were transfused plasma or platelet products in 21 hospitals during a 4.5-year period from March 1, 2018 through August 31, 2022. Data were divided into "pre-COVID" (3/1/2018 through 2/29/2020), COVID-19 "pre-vaccine" (3/1/2020 through 2/28/2021), and COVID-19 "post-vaccine" (3/1/2021 through 8/31/2022) study periods based on blood donor SARS-CoV-2 epidemiology and antibody testing results.[10–13] Transfused patients were grouped as recipients of only-plasma blood components, only-platelet components, or both plasma and platelet components given the distinct epidemiology of transfusion indications for these components.[24,25] Patients were allowed to contribute multiple hospital episodes if they were transfused plasma or platelet units during more than one hospitalization. All KPNC patients who were hospitalized during the COVID-19 pandemic were tested for SARS-CoV-2 by nasal swab polymerase chain reaction, and we excluded subjects with a positive result within 90 days prior to hospitalization. Patients with a history of thrombosis or prior anticoagulation, or those who already required increased levels of respiratory support

(i.e., more than the use of a nasal cannula) prior to transfusion were excluded from analysis of thrombosis and respiratory outcomes, respectively. The KPNC Institutional Review Board approved this study.

2.2 | Exposures

Transfusion of plasma and platelet blood components during hospitalization during the pre-COVID-19, COVID-19 pre-vaccine, and COVID-19 post-vaccine study periods.

2.3 | Outcomes

Post-transfusion arterial or venous thrombosis, maximal level of respiratory support, ICU length of stay, hospital mortality, and 30-day rehospitalization.

The incidence of arterial and venous thromboses after plasma or platelet transfusion was defined using the combination of diagnosis codes and timing of new anticoagulant administration following transfusion.[26,27] We categorized the maximal level of respiratory support using mutually exclusive, hierarchical categories (room air, nasal cannula, high flow oxygen, noninvasive ventilation, and invasive ventilation). Maximal level of respiratory support was assessed prior to index transfusion and daily thereafter. We defined increased level of respiratory support as the need for greater oxygen than delivered by nasal cannula 24 to 48 h following index plasma or platelet transfusion.

2.3.1 | Covariates

We considered individual-level factors, including sex, age, body mass index, comorbidities, and SARS-CoV-2 vaccination status. We classified patients as having emergency or elective admission based on whether they were admitted through the emergency department. We classified hospitalizations as surgical admissions based upon the occurrence of surgical procedural codes during hospitalization.[28] We quantified comorbid disease burden using the COPS2 (Comorbidity Points Score, version 2), which is based upon patients' medical diagnoses within the 12 months preceding hospitalization.[28–30] We quantified severity of illness at admission with the LAPS2 (Laboratory Acute Physiology Score, version 2), which is based on laboratory test results, vital signs, and neurologic status within 72 h prior to hospital entry.[29] SARS-CoV-2 vaccination status of transfusion recipients was obtained from the KPNC EHR and California state immunization records. Concomitant transfusion of red blood cell components was analyzed as a covariate in models.

2.4 | Statistical analysis

Descriptive analyses are presented as counts and percentages, medians, and interquartile ranges (IQRs), or proportions. Accordingly, we used chi-square tests for equal proportion or Wilcoxon rank sum tests to test differences. We examined trends in thromboses, oxygen requirements, ICU length of stay, hospital mortality, and 30-day rehospitalization for all patients and for subsets of plasma-only, platelet-only, or both plasma and platelet recipients across the pre-COVID, pre-vaccine, and post-vaccine study periods. In addition, we examined ICU length of stay and rates of 30-day re-hospitalization among patients who survived to hospital discharge. For thrombosis and respiratory outcomes, we examined patient outcomes in subgroups based upon age, sex, emergency or elective surgical or medical status, and SARS-CoV-2 vaccination status.

Using the above covariates, we constructed multivariable regression models with thrombosis, increased respiratory support, and hospital mortality as dependent variables. We used logistic regression via generalized estimating equation (GEE) with exchangeable working correlation structure to account for repeated within-individual observations and included study period as a covariate to test for trends. We reported results for dichotomous outcomes as adjusted odds ratios (OR's) with corresponding 95% confidence intervals (CI).

Statistical significance was indicated by the 95% CI not containing the null or two-sided p-values less than 0.05. Statistical analyses were performed using Stata Version 14.2 and SAS version 9.4.

2.5 | Role of the funding source

The study sponsor collaborated on the study design and had no role in data collection, data analysis, data interpretation, or preparation of the manuscript. The REDS-IV-P publications committee reviewed the manuscript and approved its submission for publication.

3 | RESULTS

3.1 | Patient characteristics and outcomes

From 2018 to 2022, there were 21,750 hospitalizations of 18,584 patients in which patients were transfused plasma or platelet products. The 21,750 hospitalizations were divided into 10,310 pre-COVID, 4580 pre-vaccine, and 6860 post-vaccine study periods based on US blood donor

SARS-CoV-2 antibody testing results (Figure 1), which mirrored the COVID-19 vaccination and mortality rates in the general United States population (Figure A1).[10–13] Among these 21,750 hospitalizations, 10,317 hospitalizations involved transfusion of only platelet components, 7676 involved only plasma components, and 3757 involved both platelet and plasma components (Figure 2).

Baseline recipient characteristics are presented in Table 1. The mean recipient age at the time of hospitalization was 66 years (standard deviation [SD], 16 years), and 42.6% of recipients ($n = 9273$) were female. The median number of hospitalizations per patient was 1 (IQR 1–1), 80.9% ($n = 17,590$) were emergency admissions, and 37.0% ($n = 8057$) of hospitalizations were surgical.

Over the course of the study, a total of 47,285 platelet units and 37,263 plasma units were transfused. Among recipients of each component type, the median number of transfused plasma units was 2 (IQR 1–3) and the median number of transfused platelet units was 2 (IQR 1–3) (Table A1). Eleven thousand six hundred and eighty

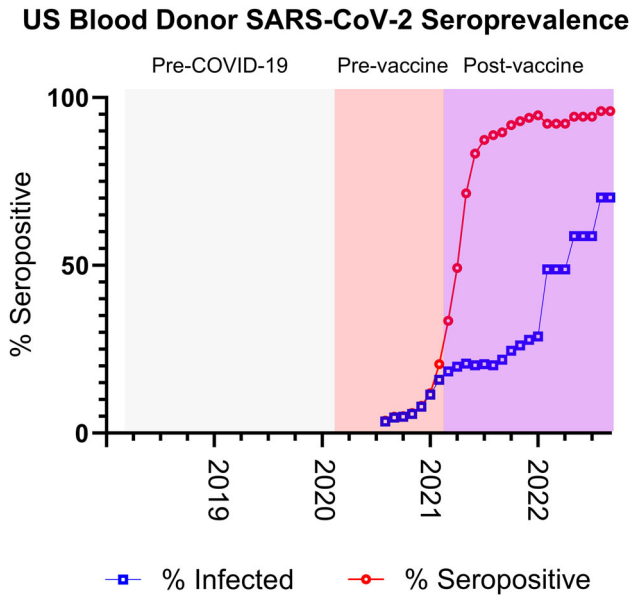

FIGURE 1 Estimate of SARS-CoV-2 seroprevalence and infections among blood donors by study period. Data presented with permission from the National Blood Donor Seroprevalence Study (https://data.cdc.gov/Laboratory-Surveillance/2020-2021-Nationwide-Blood-Donor-Seroprevalence-Su/mtc3-kq6r). The blue line shows the weighted seroprevalence of the blood donor population with both SARS-CoV-2 spike and nucleocapsid antibodies, representing the proportion of the population with antibodies from infection. The red line shows the weighted SARS-CoV-2 spike antibody seroprevalence, representing the proportion of the donor population with antibodies from infection and/or vaccination. [Color figure can be viewed at wileyonlinelibrary.com]

three patients (53.7%) were admitted to the ICU, and the length of stay for these patients was 3 days (IQR 1–6). Death occurred in 3223 (15.6%) hospitalizations, and 30-day rehospitalization occurred in 4144 (23.7%) of hospital survivors.

3.2 | Association of study period on thrombosis and oxygen requirements in transfusion recipients

Among the 21,750 hospitalizations, 5891 (27.1%) had a history of thrombosis or were already on anticoagulation prior to transfusion (Table 1). Excluding these hospitalizations, 697 arterial and venous thromboses occurred in 15,859 hospitalizations (4.4%). Across the study periods, unadjusted trends in thrombosis outcomes (Table 2) were not changed in transfusion recipients of only plasma components ($p = .46$), only platelet components ($p = .15$), and both platelet and plasma components ($p = .09$).

Among the 21,750 hospitalizations, 21.6% ($n = 4701$) of patients had increased oxygen requirements prior to transfusion (Table 1). Excluding these hospitalizations, oxygen requirements were increased in 1751 (10.2%) hospitalizations during the 24-to-48-h period following transfusion. Across the study periods, unadjusted trends in increased oxygen requirements (Table 2) were unchanged in patients transfused only plasma components ($p = .81$), only platelet components ($p = .33$), and both platelet and plasma components ($p = .82$).

In multivariable analysis comparing the pre-COVID, pre-vaccine, and post-vaccine study periods, there were no trends in rates of thromboses (OR 0.9 [95% CI 0.8, 1.1]; $p = .22$) or oxygen requirements (OR 1.0 [95% CI 0.9, 1.1]; $p = .41$). Among recipients of specific blood components, there were no adjusted trends across study periods for thromboses in patients transfused only plasma components (OR 0.9 [95% CI 0.8, 1.1]; $p = .49$), only platelet components (OR 1.0 [95% CI 0.8, 1.1]; $p = .72$), and both platelet and plasma components (OR 0.9 [95% CI 0.7, 1.0]; $p = .09$). In parallel, there were no adjusted trends across study periods for increased oxygen requirements in patients transfused only plasma components (OR 1.0 [95% CI 0.6, 1.3]; $p = .50$), transfused only platelet components (OR 0.9 [95% CI 0.9, 1.0]; $p = .19$), or transfused both platelet and plasma components (OR 1.0 [95% CI 0.9, 1.1]; $p = .78$).

There was no evidence of increased post-transfusion oxygen requirements or thrombotic events across study periods when examined by patient sex and age, admission category, or surgical status (Table A2). In fact, fewer thrombotic events occurred during the post-vaccine study

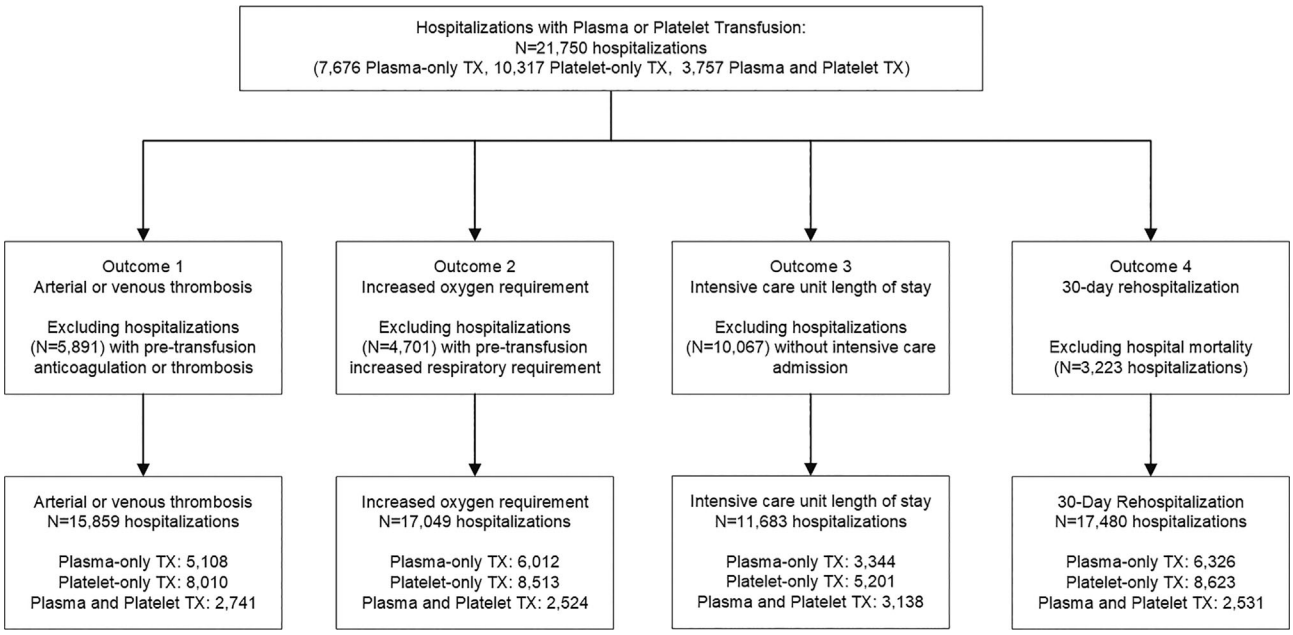

FIGURE 2 Flow Diagram for number of hospitalizations by outcome and transfusion exposure. Number of hospitalizations by outcome (thrombosis, oxygen requirement, intensive care unit length of stay, and 30-day rehospitalization) and transfused component type during hospitalization (plasma-only transfusion, platelet-only transfusion, or transfusion both plasma and platelet components). Tx, transfusion.

period in several age and admission subgroups (Table A3). Across study periods, there were no significant trends in thromboses ($p = .41$) or oxygen requirements ($p = .29$) in unvaccinated patients transfused plasma or platelet components or when examining subgroups of transfusion recipients during the SARS-CoV-2 Omicron variant period from January to August 2022 (Table A4). In addition, we compared vaccinated and unvaccinated recipients during the post-vaccine period and found no differences in thromboses (137/3761 [3.6%] vs. 52/1268 [4.1%]; $p = .46$) or oxygen requirements (448/4096 [10.9%] vs. 129/1287 [10.0%]; $p = .35$).

3.3 | Associations of study period on ICU length of stay and mortality in transfusion recipients

The median ICU length of stay [IQR] was similar in 11,683 transfused ICU patients (Table 3) during the pre-COVID (2.8 days [1.3–5.8]) pre-vaccine (2.8 days [1.3–6.6]) and post-vaccine study periods (2.9 [1.4–6.3]; $p = .83$). This relationship did not differ when examining ICU length of stay excluding patients with a competing risk of death ($p = .57$). In parallel, there were no trends in ICU length of stay across study periods among ICU patients transfused only plasma components ($p = .31$), only platelet components ($p = .79$), or both plasma and platelet components ($p = .31$).

There were no trends across study periods for adjusted hospital mortality (OR 1.0 [95% CI 0.9–1.0]; $p = .36$) including for subsets of recipients of plasma only (OR, 1.0 [CI, 0.9 to 1.1]; $p = .62$), platelet only (OR, 0.9 [CI, 0.9 to 1.0]; $p = .09$), and both platelet and plasma (OR, 1.0 [CI, 0.9 to 1.1]; $p = .79$) components. There were no trends across study periods for adjusted hospital mortality among unvaccinated recipients (OR, 1.0 [CI, 0.9 to 1.0]; $p = .49$). Lastly, among survivors of hospitalization, there were no trends in rates of 30-day rehospitalization across study periods for all transfused recipients ($p = .29$) as well as recipients of plasma-only ($p = .72$), platelet-only ($p = .10$) and both platelet and plasma ($p = .55$) components.

4 | DISCUSSION

In our cohort of transfused patients, we found no trends in unadjusted or adjusted rates of thromboses or increased oxygen requirements in plasma and platelet product recipients during known periods of increasing blood donor SARS-CoV-2 infection and vaccination. We did not identify changes in ICU length of stay, adjusted hospital mortality, or rehospitalization across the study periods. Lastly, there were not worsened outcomes among subgroups of patients, including unvaccinated transfusion recipients. In sum, transfusion of plasma and platelet components collected during the pre-vaccine

TABLE 1 Hospitalization characteristics.

	Pre-COVID	Pre-vaccine	Post-vaccine
	***n* = 10,310**	***n* = 4580**	***n* = 6860**
Age[a]	67 ± 15	66 ± 16	65 ± 16
Male (%)	5880 (57)	2649 (58)	3948 (58)
Body mass index (IQR)	27 (23–32)	27 (23–32)	27 (23–31)
Charlson Comorbidity Index[b]	0 (0–5)	0 (0–5)	0 (0–4)
Comorbidity Point Score 2 (COPS2)[b,c]	64 (30–100)	60 (28–97)	59 (26–97)
Laboratory Acute Physiology Score 2 (LAPS2)[b,d]	77 (44–114)	83 (46–122)	78 (36–122)
Emergency admission (%)	8390 (81)	3736 (82)	5464 (80)
Surgical admission (%)	3852 (37)	1633 (36)	2572 (37)
Intensive care admission (%)	5639 (55)	2558 (56)	3971 (58)
ICU length of stay (days)[b]	2.8 (1.4–5.8)	2.5 (1.2–5.5)	2.8 (1.3–6.0)
Transfused plasma (%)	5690 (55)	2413 (53)	3330 (49)
Transfused platelets (%)	6341 (62)	2941 (64)	4792 (70)
Transfused both platelets and plasma (%)	1721 (17)	774 (17)	1262 (18)
Transfused red blood cells (%)	6040 (59)	2813 (61)	4340 (63)
Pre-transfusion anticoagulation (%)	1427 (14)	657 (14)	1038 (15)
Pre-transfusion thrombosis (%)	1166 (11)	501 (11)	657 (10)
Pre-transfusion oxygen requirement (%)[e]	2214 (22)	1008 (22)	1479 (22)

Abbreviations: ICU, intensive care unit; IQR, interquartile range.
[a]Mean ± standard deviation.
[b]Median (interquartile range).
[c]Longitudinal, diagnosis-based score. Association with hospital mortality rates for scores <50 are less than 2%, while scores above 100 are associated with mortality rates of 5% or more.
[d]Increasing degrees of physiologic derangement are reflected in a higher LAPS2. The univariate association between LAPS2 and mortality is such that mortality rates for scores <50 are less than 1.5% while scores above 125 are associated with mortality rates of 10%–15% or more.
[e]Defined as greater than the use of oxygen delivery by nasal cannula prior to transfusion.

and post-vaccine periods of the COVID-19 pandemic was not associated with worsened outcomes in SARS-CoV-2 negative transfusion recipients.

Prior to the implementation of mitigation strategies, plasma transfusions from female donors were associated with the occurrence of transfusion-related acute lung injury (TRALI), likely through an antibody-mediated mechanism.[31] With few treatments available for severe COVID-19 disease, CCP was investigated as a therapy in a series of randomized controlled clinical trials.[2–5] In some clinical trials, the investigators assessed for cardiopulmonary complications of plasma transfusion, including TRALI as well as transfusion associated circulatory overload (TACO), and transfusion associated dyspnea (TAD).[22] Rare adverse transfusion outcomes were identified in some COVID-19 recipients of CCP.[4,5]

The investigators of the CONCUR clinical trial hypothesized that elevated autoantibody titers in CCP units could be the cause of the adverse reactions. Several studies associated interferon autoantibodies in patients with COVID-19 with adverse events, such as ICU admission and death, and autoantibodies were identified in plasma components manufactured from blood donations from CCP donors.[6,7,32] A subset of patients with severe COVID-19 also have anti-phospholipid antibodies and/or anti–neutrophil extracellular trap autoantibodies that may activate complement and promote thrombosis.[33,34] While titers of pre-existing anti-HLA antibodies are recognized to increase in the setting of vaccination,[17] recent studies have shown that SARS-CoV-2 infection but not vaccination are associated with development of new autoantibodies.[35,36] Autoantibodies associated with adverse outcomes have been identified in severe COVID-19 patients; however, evidence of an effect of these antibodies on COVID-19 pathogenesis remains limited.

Recent findings from animal studies of vaccine-boosted CCP also raised concerns related to the safety of high plasma volume blood components from CCP donors. As noted, SARS-CoV-2 infection followed by vaccination of blood donors is known to result in dramatic boosting of binding and neutralizing antibodies in CCP.[15] Hamsters infected with SARS-CoV-2 who were infused with pooled vaccine-boosted donor CCP (but not pooled normal titer CCP donor plasma or control plasma)

TABLE 2 Thrombosis and oxygen requirements in hospitalizations by study period.

Study period	Pre-COVID		Pre-vaccine		Post-vaccine		
	Unadjusted	Adjusted OR (95% CI)	Unadjusted	Adjusted OR (95% CI)	Unadjusted	Adjusted OR (95% CI)	*p*-value[a]
Arterial or venous thrombosis ($n = 15{,}859$)[b]							
All $N = 15{,}859$	4.8% (360/7468)	**[Ref]**	4.4% (148/3362)	1.0 (0.8–1.2)	3.8% (189/5029)	0.8 (0.6–1.1)	.22
Plasma only $N = 5108$	3.8% (102/2629)	**[Ref]**	3.6% (39/1097)	0.8 (0.6–1.2)	3.1% (43/1382)	0.8 (0.5–1.2)	.49
Platelets only $N = 8010$	4.0% (145/3599)	**[Ref]**	3.9% (66/1690)	0.9 (0.7–1.3)	3.1% (85/2721)	0.8 (0.5–1.0)	.72
Plasma and Platelets $N = 2741$	9.1% (113/1240)	**[Ref]**	7.5% (43/576)	1.1 (0.6–1.8)	6.6% (61/926)	0.7 (0.4–1.2)	.09
Increased oxygen requirement ($n = 17{,}049$)[c]							
All $N = 17{,}049$	11.0% (888/8096)	**[Ref]**	9.8% (350/3572)	0.8 (0.7–0.9)	11.3% (609/5381)	1.0 (0.8–1.1)	.41
Plasma only $N = 6012$	7.6% (239/3156)	**[Ref]**	7.4% (93/1265)	0.9 (0.7–1.1)	8.0% (127/1591)	1.0 (0.8–1.2)	.50
Platelets only $N = 8513$	7.8% (297/3812)	**[Ref]**	6.3% (112/1777)	0.8 (0.7–1.0)	7.2% (209/2824)	0.9 (0.8–1.1)	.19
Plasma and Platelets $N = 2524$	26.7% (301/1128)	**[Ref]**	24.9% (132/530)	0.9 (0.7–1.1)	27.8% (241/866)	1.0 (0.8–1.2)	.78

Note: Adjusted odds ratios (aOR) with 95% confidence interval presented for oxygen requirements and thromboses in pre-vaccine and post-vaccine study periods relative to the Pre-COVID period adjusting for demographics and comorbidities presented in Table 1 and number of plasma, platelet, and RBC units.
Abbreviations: CI, confidence interval; OR, odds ratios.
[b]*p*-value for unadjusted trends in thrombosis for recipients of only plasma ($p = .46$); only platelets ($p = .15$); both platelet and plasma components ($p = .09$).
[c]*p*-value for unadjusted trends in oxygen requirements for only plasma ($p = .81$); only platelets ($p = .33$); both platelet and plasma components ($p = .82$).

developed acute kidney injury and worsened pulmonary outcomes.[37]

Despite these findings in animal models and clinical trials of CCP in patients with COVID-19, we found no association between exposure to plasma-containing blood products and adverse outcomes in SARS-CoV-2 negative patients during the COVID-19 pandemic. We hypothesized that patient outcomes other than mortality might be more sensitive to a potential antibody-mediated effect. We did not identify increased levels of respiratory support or rates of thrombosis following transfusion of plasma or plasma-rich platelet products when comparing study periods prior to and during the COVID-19 pandemic. Complementing hypotheses of worsened thrombotic and respiratory outcomes, we did not identify any changes in ICU length of stay, adjusted hospital mortality, or 30-day rehospitalization across study periods.

Recognizing that there may be risks to specific patient populations, we examined multiple subgroups and found no worsening of outcomes. While speculative, reduced post-transfusion thrombotic events during the post-vaccine period may reflect heightened awareness of the risk of venous thromboembolism during the COVID-19 pandemic. Our study also examined outcomes during the period of SARS-CoV-2 Omicron variant predominance, during which large numbers of vaccinated blood donors were infected with SARS-CoV-2 and may have had substantial boosting of antibody levels. Again, we found no worsening of outcomes in the study-eligible transfused population during this period nor among a subgroup of unvaccinated transfusion recipients; the latter notable because some recipients of blood products have expressed concern about the passive transfer of SARS-CoV-2 antigens or antibodies.[19] Our findings are also consistent with clinical trial and observational data supporting the safety of CCP and laboratory-based studies that did not find evidence of an impact of CCP transfusion on the adaptive immune response of recipients.[38]

We focused on evaluating outcomes among transfusion recipients during study periods with known variation in donor SARS-CoV-2 infection and vaccination.[10–12] However, it is worth recognizing that other factors occurring

TABLE 3 Trends in intensive care length of stay, 30-day rehospitalization, and mortality by study period.

Study period	Pre-COVID	Pre-vaccine	Post-vaccine	*p*-value[a]
Intensive care length of stay in days [interquartile range] (*n* = 11,683)				
All *N* = 11,683	2.8 [1.3–5.8]	2.8 [1.3–6.6]	2.9 [1.4–6.3]	0.83
Plasma only *N* = 3344	2.9 [1.5–5.8]	2.6 [1.3–5.2]	2.9 [1.5–5.9]	0.81
Platelets only *N* = 5201	2.2 [1.2–4.7]	2.1 [1.1–4.1]	2.2 [1.2–4.7]	0.79
Plasma and Platelets *N* = 3138	3.6 [1.8–7.9]	3.6 [1.8–8.0]	3.9 [1.8–8.8]	0.31
30-day rehospitalization (n = 17,480)				
All *N* = 17,480	23.6% (2065/8746)	24.7% (948/3834)	23.1% (1131/4900)	0.19
Plasma only *N* = 6326	21.9% (753/3432)	23.3% (322/1382)	23.2% (351/1512)	0.46
Platelets only *N* = 8623	25.6% (1038/4058)	26.8% (512/1924)	24.0% (633/2641)	0.08
Plasma and Platelets *N* = 2531	21.8% (274/1256)	20.8% (110/528)	19.7% (147/747)	0.52
Hospital mortality, adjusted odds ratio [95% confidence interval] (*n* = 21,750)				
All *N* = 21,750	[Ref]	1.1 [0.9–1.2]	1.0 [0.9–1.1]	0.76
Plasma only *N* = 7676	[Ref]	1.1 [0.9–1.3]	1.1 [0.9–1.3]	0.33
Platelets only N = 10,317	[Ref]	0.9 [0.7–1.3]	0.8 [0.5–1.0]	0.76
Plasma and Platelets *N* = 3757	[Ref]	1.1 [0.6–1.8]	0.7 [0.4–1.2]	0.88

Note: Adjusted odds ratios with 95% confidence interval presented for hospital mortality in pre-vaccine and post-vaccine study periods relative to the pre-COVID study period adjusting for demographics and comorbidities presented in Table 1 and number of plasma, platelet, and RBC units.
[a]*p*-value for trends across study period.

during the COVID-19 pandemic did not appear to impact outcomes in our cohort. Several studies found increased mortality for non-COVID illnesses during the COVID-19 pandemic.[39–41] Widespread disruption of care delivery of healthcare services, including elective surgeries and procedures as well as preventative services, such as cancer screening, was recognized. Periods of national blood shortages also occurred during the COVID-19 pandemic.[42,43] Despite these factors, we found no worsening in outcomes among a group of transfused patients within an integrated healthcare delivery system.

Some limitations should be emphasized. While our patient population reflects the regional community practice of transfused adults at 21 medical centers in Northern California, it may not reflect pediatric age groups, or specific populations (e.g., immunocompromised and obstetric patients). We attempted to control for other factors that might be related to patient survival (e.g., admission severity of illness, comorbidity indices and concomitant RBC transfusions); however, residual confounding may persist.

We chose length of stay as a sensitive but non-specific outcome that might encompass morbidity effects related to a blood donor characteristic. While length of stay provides little insight into biologic mechanisms, a lack of association, in parallel with thrombotic and pulmonary outcomes, is nonetheless reassuring. Lastly, we were unable to examine direct relationships between blood donor antibody titers and outcomes in transfusion recipients and thus may not be able to detect rare adverse effects. Additional analysis will link transfusion of these plasma-containing blood products with donor SARS-CoV-2 spike and nucleocapsid antibody results and survey data on donor infection and vaccination.[44] These planned linked donor-transfusion recipient analyses will also help answer blood safety questions regarding criteria for the timing of blood donation after SARS-CoV-2 infection or vaccination.

In conclusion, we found no associations between periods of differing blood donor SARS-CoV-2 infection and vaccination and multiple clinical outcomes in SARS-CoV-2 negative transfusion recipients of plasma and platelet components. We found no association between pre-COVID, pre-vaccine, and post-vaccine study periods and unadjusted or adjusted rates of thromboses or increased oxygen requirements, ICU length of stay, adjusted hospital mortality, or rehospitalization. Our findings are reassuring for both clinicians and professionals involved in blood banking and do not indicate any changes are necessary to current transfusion practice.

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CONFLICT OF INTEREST STATEMENT

No author reports any relevant conflicts of interest.

ETHICS STATEMENT

All participating sites received IRB approval prior to performing the study.

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APPENDIX

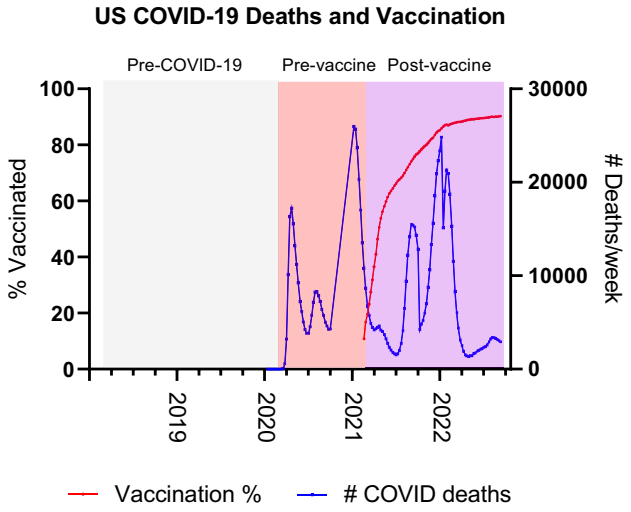

FIGURE A1 Nationwide SARS-CoV-2 mortality and vaccination estimates. Data presented with permission from the Centers for Disease Control https://www.cdc.gov/coronavirus/2019-ncov/vaccines/distributing/about-vaccine-data.html; https://data.cdc.gov/Case-Surveillance/COVID-19-Case-Surveillance-Public-Use-Data-with-Ge/n8mc-b4w4). The blue line shows the total number of reported deaths nationally due to COVID-19 during each study period. The red line shows the proportion of the population who received SARS-CoV-2 vaccination. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE A1 Number and proportion transfused blood components.

Transfused blood component	Pre-COVID (n = 10,310)	Pre-vaccine (n = 4580)	Post-vaccine (n = 6860)
Red blood cell	59%	61%	63%
Number of units per hospitalization	3 (2–5)	3 (2–5)	3 (2–5)
Total number of transfused units	26,468	12,654	20,508
Platelet	62%	64%	70%
Number of units per hospitalization	2 (1–3)	2 (1–3)	2 (1–3)
Total number of transfused units	20,686	9955	16,644
Plasma	55%	53%	49%
Number of units per hospitalization	2 (1–3)	2 (1–3)	2 (1–4)
Total number of transfused units	17,684	8194	11,385

TABLE A2 Trends in increased oxygen requirements in subgroups of plasma or platelet recipients.

Patient characteristics	Component type	Pre-COVID ($n = 8096$)	Pre-vaccine ($n = 3572$)	Post-vaccine ($n = 5381$)	p-value[a]
Male		**510/4523 (11.3)**	**214/2032 (10.5)**	**352/3013 (11.7)**	**.45**
	Plasma	133 (8.0)	49 (7.5)	71 (8.7)	.74
	Platelets	196 (8.8)	79 (7.4)	142 (8.4)	.38
	Plasma and Platelets	181 (27.9)	86 (27.3)	139 (28.1)	.97
Female		**327/3573 (9.2)**	**123/1540 (8.0)**	**225/2368 (9.5)**	**.25**
	Plasma	106 (7.1)	44 (7.2)	56 (7.3)	.98
	Platelets	101 (6.3)	33 (4.7)	67 (5.5)	.25
	Plasma and Platelets	120 (25.1)	46 (21.4)	102 (27.4)	.27
Age 18–59		**240/2147 (11.2)**	**97/1061 (9.1)**	**188/1629 (11.5)**	**.12**
	Plasma	63 (8.9)	27 (8.1)	36 (8.0)	.84
	Platelets	76 (7.3)	24 (4.6)	50 (6.0)	.11
	Plasma and Platelets	101 (25.4)	46 (22.3)	102 (29.5)	.16
Age 60–75		**350/3096 (11.3)**	**140/1327 (10.5)**	**254/2052 (12.4)**	**.24**
	Plasma	89 (8.7)	33 (8.0)	52 (9.9)	.58
	Platelets	131 (8.3)	55 (7.9)	108 (9.1)	.60
	Plasma and Platelets	130 (26.6)	52 (24.0)	94 (27.5)	.65
Age 76+		**247/2853 (8.7)**	**100/1184 (8.5)**	**135/1700 (7.9)**	**.70**
	Plasma	87 (6.1)	33 (6.4)	39 (6.4)	.97
	Platelets	90 (7.6)	33 (5.9)	51 (5.6)	.16
	Plasma and Platelets	70 (29.1)	34 (31.8)	45 (25.3)	.47
Elective admission		**232/1517 (15.3)**	**95/672 (14.1)**	**190/1147 (16.6)**	**.37**
	Plasma	21 (7.5)	7 (5.3)	16 (8.7)	.53
	Platelets	103 (11.8)	45 (11.2)	95 (13.3)	.51
	Plasma and Platelets	108 (29.5)	43 (31.2)	79 (31.6)	.84
Emergency admission		**605/6579 (9.2)**	**242/2900 (8.3)**	**387/4234 (9.1)**	**.38**
	Plasma	218 (7.6)	86 (7.6)	111 (7.9)	.93
	Platelets	194 (6.6)	67 (4.9)	114 (5.2)	.03
	Plasma and Platelets	193 (25.3)	89 (22.7)	162 (26.3)	.43
Surgical admission		**456/2884 (15.8)**	**184/1193 (15.4)**	**337/1925 (17.5)**	**.20**
	Plasma	113 (9.7)	36 (8.4)	64 (10.3)	.58
	Platelets	144 (13.1)	61 (12.0)	125 (14.8)	.32
	Plasma and Platelets	199 (32.3)	87 (34.1)	148 (32.3)	.85
Medical admission		**381/5212 (7.3)**	**153/2379 (6.4)**	**240/3456 (6.9)**	**.37**
	Plasma	126 (6.3)	57 (6.8)	63 (6.5)	.90
	Platelets	153 (5.6)	51 (4.0)	84 (4.0)	.01
	Plasma and Platelets	102 (20.0)	45 (16.4)	93 (22.8)	.12
SARS-CoV-2 unvaccinated		**837/8096 (10.3)**	**335/3568 (9.4)**	**129/1287 (10.0)**	**.29**
	Plasma	239 (7.6)	92 (7.3)	22 (6.0)	.52
	Platelets	297 (7.8)	111 (6.3)	36 (5.3)	.02
	Plasma and Platelets	301 (26.7)	132 (24.9)	71 (30.2)	.31

[a]p-value for trends across study period.

TABLE A3 Trends in thrombosis in subgroups of plasma or platelet recipients.

Patient characteristic	Component type	Pre-COVID ($n = 7468$)	Pre-vaccine ($n = 3362$)	Post-vaccine ($n = 5029$)	p-value[a]
Male		**218/4288 (5.1)**	**95 (4.9)**	**112 (3.9)**	**.05**
	Plasma	61 (4.3)	21 (3.6)	25 (3.3)	.49
	Platelets	84 (3.9)	42 (4.1)	45 (2.8)	.11
	Plasma and Platelets	73 (9.9)	32 (9.3)	42 (7.7)	.38
Female		**142/3180 (4.5)**	**53/1416 (3.7)**	**77/2136 (3.6)**	**.24**
	Plasma	41 (3.4)	18 (3.5)	18 (2.8)	.78
	Platelets	61 (4.2)	24 (3.6)	40 (3.6)	.66
	Plasma and Platelets	40 (8.0)	11 (4.8)	19 (5.0)	.12
Age 18–59		**115/2068 (5.6)**	**54/1063 (5.1)**	**57/1596 (3.6)**	**.02**
	Plasma	26 (4.1)	15 (4.6)	13 (3.1)	.54
	Platelets	44 (4.5)	20 (4.1)	23 (3.0)	.28
	Plasma and Platelets	45 (9.9)	19 (7.6)	21 (5.1)	.03
Age 60–75		**140/2786 (5.0)**	**46/1208 (3.8)**	**89/1847 (4.8)**	**.24**
	Plasma	33 (4.1)	10 (3.0)	18 (4.1)	.63
	Platelets	63 (4.3)	26 (4.0)	41 (3.8)	.83
	Plasma and Platelets	44 (8.6)	10 (4.6)	30 (9.0)	.13
Age 76+		**105/2614 (4.0)**	**48/1091 (4.4)**	**43/1586 (2.7)**	**.04**
	Plasma	43 (3.6)	14 (3.3)	12 (2.3)	.38
	Platelets	38 (3.3)	20 (3.6)	21 (2.4)	.32
	Plasma and Platelets	24 (8.8)	14 (12.7)	10 (5.5)	.09
Elective admission		**89/1498 (5.9)**	**24/664 (3.6)**	**48/1096 (4.4)**	**.04**
	Plasma	12 (5.6)	4 (3.6)	10 (5.8)	.69
	Platelets	41 (4.5)	14 (3.3)	14 (2.0)	.03
	Plasma and Platelets	36 (9.9)	6 (4.5)	24 (10.6)	.12
Emergency admission		**271/5970 (4.5)**	**124/2698 (4.6)**	**141/3933 (3.6)**	**.04**
	Plasma	90 (3.7)	35 (3.6)	33 (2.7)	.29
	Platelets	104 (3.9)	52 (4.1)	71 (3.5)	.66
	Plasma and Platelets	77 (8.8)	37 (8.4)	37 (5.3)	.02
Surgical admission		**194/2758 (7.0)**	**70/1178 (5.9)**	**96/1886 (5.1)**	**.02**
	Plasma	60 (6.3)	17 (4.6)	24 (4.5)	.25
	Platelets	53 (4.8)	5 (4.8)	27 (3.1)	.16
	Plasma and Platelets	81 (11.8)	28 (9.9)	45 (9.2)	.31
Medical admission		**166/4710 (3.5)**	**78/2184 (3.6)**	**93/3143 (3.0)**	**.37**
	Plasma	42 (2.5)	22 (3.0)	19 (2.3)	.61
	Platelets	92 (3.7)	41 (3.5)	58 (3.1)	.57
	Plasma and Platelets	32 (5.8)	15 (5.2)	16 (3.7)	.32
SARS-CoV-2 unvaccinated		**360/7468 (4.8)**	**148/3358 (4.4)**	**52/1268 (4.1)**	**.41**
	Plasma	102 (3.9)	39 (3.6)	13 (3.6)	.89
	Platelets	145 (4.0)	66 (3.9)	24 (3.7)	.94
	Plasma and Platelets	113 (9.1)	43 (7.5)	15 (5.6)	.13

[a]p-value for trends across study period.

TABLE A4 Trends in thrombosis and oxygen requirements in hospitalizations by study period.

			Post-vaccine		
Study period	**Pre-COVID**	**Pre-vaccine**	**Pre-omicron**	**Omicron**	***p*-value[a]**
Increased oxygen requirement ($n = 17{,}049$)					
Plasma only $N = 6012$	7.6% (239/3156)	7.4% (93/1265)	7.7% (74/966)	8.5% (53/625)	.85
Platelets only $N = 8513$	7.8% (297/3812)	6.3% (112/1777)	6.8% (114/1675)	7.6% (95/1249)	.19
Plasma and Platelets $N = 2524$	26.7% (301/1128)	24.9% (132/530)	29.1% (149/512)	26.0% (92/354)	.48
Arterial or venous thrombosis ($n = 15{,}859$)					
Plasma only $N = 5108$	3.8% (102/2629)	3.6% (39/1097)	3.7% (31/837)	2.2% (12/545)	.30
Platelets only $N = 8010$	4.0% (145/3599)	3.9% (66/1690)	3.3% (50/1539)	3.0% (35/1182)	.26
Plasma and Platelets $N = 2741$	9.1% (113/1240)	7.5% (43/576)	7.3% (39/531)	5.6% (22/395)	.12

[a]*p*-value for unadjusted trends across study period including subgroups of pre-Omicron and Omicron periods during the Post-Vaccine period.