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ORIGINAL RESEARCH

TRANSFUSION

Transfusion reactions associated with COVID-19 convalescent plasma therapy for SARS-CoV-2

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Abstract

Background: Convalescent plasma (CP) for treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has shown preliminary signs of effectiveness in moderate to severely ill patients in reducing mortality. While studies have demonstrated a low risk of serious adverse events, the comprehensive incidence and nature of the spectrum of transfusion reactions to CP is unknown. We retrospectively examined 427 adult inpatient CP transfusions to determine incidence and types of reactions, as well as clinical parameters and risk factors associated with transfusion reactions.

Study Design and Methods: Retrospective analysis was performed for 427 transfusions to 215 adult patients with coronavirus 2019 (COVID-19) within the Mount Sinai Health System, through the US Food and Drug Administration emergency investigational new drug and the Mayo Clinic Expanded Access Protocol to Convalescent Plasma approval pathways. Transfusions were blindly evaluated by two reviewers and adjudicated by a third reviewer in discordant cases. Patient demographics and clinical and laboratory parameters were compared and analyzed.

Results: Fifty-five reactions from 427 transfusions were identified (12.9% incidence), and 13 were attributed to transfusion (3.1% incidence). Reactions were classified as underlying COVID-19 (76%), febrile nonhemolytic (10.9%), transfusion-associated circulatory overload (9.1%), and allergic (1.8%) and hypotensive (1.8%) reactions. Statistical analysis identified increased transfusion reaction risk for ABO blood group B or Sequential Organ Failure

Abbreviations: CDC, Centers for Disease Control and Prevention; COVID-19, coronavirus 2019; CP, convalescent plasma; CRP, C-reactive protein; EAP, Expanded Access Protocol to Convalescent Plasma; eIND, emergency investigational new drug; FDA, US Food and Drug Administration; FFP, fresh frozen plasma; FNHTR, febrile nonhemolytic transfusion reaction; ICU, intensive care unit; IL, interleukin; IRB, Institutional Review Board; LDH, lactate dehydrogenase; MSHS, Mount Sinai Health System; NHSN, National Healthcare Safety Network; SARS-CoV-1, severe acute respiratory syndrome coronavirus (2003); SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SOFA, sequential organ failure assessment; TACO, transfusion-associated circulatory overload; TNFα, tumor necrosis factor-α; TRALI, transfusion-related acute lung injury.

Assessment scores of 12 to 13, and decreased risk within the age group of 80 to 89 years.

Conclusion: Our findings support the use of CP as a safe, therapeutic option from a transfusion reaction perspective, in the setting of COVID-19. Further studies are needed to confirm the clinical significance of ABO group B, age, and predisposing disease severity in the incidence of transfusion reaction events.

KEYWORDS

FFP transfusion, immunology (other than RBC serology), transfusion practices (adult)

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel zoonotic coronavirus that was detected in Wuhan, China, in late 2019. By March 2020, with its spread to more than 100 countries, the World Health Organization declared a worldwide pandemic. SARS-CoV-2 causes coronavirus disease 2019 (COVID-19), characterized by a constellation of symptoms including fever, cough, dyspnea/respiratory distress, sore throat, anosmia/ageusia, nausea, diarrhea, and/or new-onset altered mental status and confusion.[1] While studies to date with antiviral drugs such as remdesivir show some benefit in reducing the length of intensive care unit (ICU) stay,[2,3] the absence of a definitive treatment or US Food and Drug Administration (FDA)-approved vaccine at the time of this study has resulted in the proposed use of other modalities including convalescent plasma,[4] which received Emergency Use Authorization from the FDA on 23 August 2020 for the treatment of COVID-19. This, combined with early promising results from China, led to the rapid development and exploration of convalescent plasma (CP) for the treatment of COVID-19.[5,6]

The use of CP for the treatment of viral disease has a well-documented history, dating back as far as the 1800s, when plasma from recovered patients was used to treat infections including diphtheria, poliomyelitis, measles, and other infectious agents.[7] CP transfusion, which is presumed to be based on the presence of neutralizing or opsonizing antibodies to the targeted pathogen, has been used more recently in the setting of H5N1 and H1N1 influenza,[8,9] the 2003 severe acute respiratory syndrome coronavirus (SARS-CoV-1),[10] Middle East respiratory syndrome,[11] and Ebola,[12,13] where it demonstrated variable degrees of effectiveness depending on the pathogen. When effective, it plays an important role in cases where other forms of treatment are not yet available by acting as a rapid source of transferrable passive immunity, helping to support affected patients until they can mount their own immune response.

Because CP is transfused to a patient population with considerable morbidity at baseline, it is first and foremost essential to establish its use as safe. This principle applies as well to posttransfusion sequelae such as longer-term adverse events and to immediate reactions associated with the transfusion itself. Hemovigilance data demonstrate an overall incidence of reactions to plasma or apheresis platelets at 47 and 195 per 100 000 transfusions, respectively,[14] while a recent assessment of safety indicators of COVID-19 CP in 20 000 patients with COVID-19 found incidences of 0.18% and 0.1% for transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI), respectively.[15] Individual case reports have described TRALI in the settings of Middle East respiratory syndrome and Ebola,[16–19] but systematic analyses of CP use do not include a comprehensive examination of all types of transfusion reactions, particularly related to and immediately following the transfusion event.[10,13,20–22] While other studies have focused on serious adverse events overall in CP recipients,[23] we focus here on short-term transfusion-related safety.

2 | METHODS

2.1 | Patients

CP transfusions administered to hospital inpatients between 28 March and 29 April 2020 were reviewed as part of this study. Two hundred fifteen patients with a confirmed polymerase chain reaction–positive diagnosis of COVID-19 were deemed eligible for CP transfusion by use of criteria established by the FDA single patient emergency investigational new drug (eIND) approval pathway, or under the Mayo Clinic Expanded Access Protocol to Convalescent Plasma (EAP).[24,25] Eligible patients were substratified by disease severity, as assessed by oxygen supplementation requirements, respiratory values,

TABLE 1 Demographics and clinical characteristics of all patients who received COVID-19 convalescent plasma

	All patients
Age, y, median (IQR)	63 (53.5-71.5)
Sex, n (%)	
Female	77 (35.8)
Male	138 (64.2)
Race, n (%)	
White	50 (23.3)
African American	35 (16.3)
Other/multiracial	130 (60.4)
Blood type, n (%)	
A	75 (34.9)
B	28 (13.0)
O	104 (48.4)
AB	8 (3.7)
Rh+	205 (95.3)
Rh−	10 (4.7)
Coexisting diseases, n (%)	
Asthma	16 (7.4)
COPD	62 (28.8)
Respiratory – other	22 (10.2)
CAD	59 (27.4)
CHF	37 (17.2)
HTN	72 (33.5)
Cirrhosis	12 (5.6)
HBV	2 (0.9)
HCV	4 (1.9)
CKD	25 (11.6)
ESRD	13 (6.0)
Autoimmune	12 (5.6)
HIV	3 (1.4)
Cancer	21 (9.8)
Solid organ transplant	10 (4.7)
Diabetes	50 (23.3)
Neurologic	21 (9.8)
OB/GYN/pregnancy	7 (3.3)
Obesity	24 (11.2)
Other	81 (37.7)
Ordinal scores, n (%)	
1 - Not hospitalized, resumption of normal activities	0 (0.0)
2 - Not hospitalized, cannot resume normal activities	0 (0.0)
3 - Hospitalized, no supplemental O_2	6 (2.8)
4 - Hospitalized, requires supplemental O_2	126 (58.6)
5 - Hospitalized, requires nasal high-flow O_2 therapy, NIV, or both	57 (26.5)
6 - Hospitalized, requires ECMO, invasive mechanical ventilation, or both	26 (12.1)
7 - Death	0 (0.0)
SOFA scores, n (%)	
0-6 (<10% mortality)	105 (80.2)
7-9 (15-20 mortality)	13 (9.9)
10-12 (40%-50% mortality)	9 (6.9)
13-14 (50%-60% mortality)	3 (2.3)
15 (>80% mortality)	0 (0.0)
15-24 (>90% mortality)	1 (0.8)
Length of days, mean (min-max)	
Ventilation days	1.07 (0.00-19.10)
ICU length of stay	1.62 (0.00-17.79)
Hospitalization length of stay	7.18 (0.00-25.54)
Laboratory values, median, IQR	
Lymphocyte number, K/μL	0.9 (0.9) [N = 150]
White blood cell count, K/μL	7.6 (5.1) [N = 204]
Hemoglobin, g/dL	12.5 (2.775) [N = 205]
Hematocrit, %	37.8 (9.15) [N = 206]
Platelet count, K/μL	254 (156.75) [N = 204]
Fibrinogen, mg/dL	664 (240) [N = 104]
Ferritin, ng/mL	1025 (1861) [N = 195]
Procalcitonin, ng/mL	0.25 (0.51) [N = 160]
Fibrinogen, mg/dL	664 (240) [N = 104]
Ferritin, ng/mL	1025 (1861) [N = 195]
Procalcitonin, ng/mL	0.25 (0.51) [N = 160]
C-reactive protein, mg/L	126.6 (140) [N = 195]
Lactate dehydrogenase, U/L	518 (296) [N = 179]
IL-6, pg/mL	76.1 (158.1) [N = 61]
IL-8, pg/mL	33.3 (46.9) [N = 49]
TNFα, pg/mL	16.55 (17.875) [N = 46]
IL-1β, pg/mL	0.5 (0.6) [N = 25]

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; NIV, noninvasive ventilation; SOFA, sequential organ failure assessment; TNFα, tumor necrosis factor-α.

presence of organ failure, and laboratory parameters with use of previously established scoring systems.[4,26,27] CP was transfused to patients across five medical centers within a single health care system in New York City. Informed consent for transfusion and research was obtained at each participating hospital site, as well as additional separate consent to participate in the eIND or EAP research protocols, as specified by institutional guidelines. For patients transfused via the eIND pathway, FDA authorization was individually requested and obtained by the overseeing physician, Dr N. Bouvier, or her designee. Patients were transfused under the EAP with oversight by Dr Bouvier, who served as the site principal investigator for the health system. COVID-19 CP transfusion was performed with oversight by the Mount Sinai Health System (MSHS) Institutional Review Board (IRB) under MSHS IRB Protocol 20-03574 for the eIND, with Mayo Clinic IRB Protocol 20-003312, and MSHS IRB Protocols 20-03393 and 20-03759, which served as the central IRB for the EAP.[25]

2.2 | Plasma donor screening and transfusion

CP donors who had recovered from previous COVID-19 infection and were no longer symptomatic were screened for elevated SARS-CoV-2 spike antibody titer levels via enzyme-linked immunosorbent assay developed and validated at Mount Sinai Hospital.[28] Individuals with a titer of 320 or greater were considered "high-titer" donors, and referred to a blood collection center for apheresis plasma donation. Recipients were transfused 1 or 2 units, 200 mL each, of ABO-compatible CP, for a total of 427 transfused units. Each unit was infused over a period of 1 to 2 hours as clinically tolerated. Patients were closely monitored for the development of acute or delayed transfusion-related events.

2.3 | Data collection

A chart review of the recipients' electronic medical record was performed. Clinical information consisted of demographic data (age, sex, race, ethnicity), coexisting diseases, and sequential organ failure assessment (SOFA) score. A 7-point ordinal score was calculated based on individual patients' hospitalization status, oxygen requirements, and ventilation status.[29–31] Laboratory data were collected before transfusion and up to 36 hours following transfusion. These data included anti-SARS-CoV-2 antibody titers in the plasma unit; levels of the inflammatory cytokines interleukin (IL)-6, IL-8, tumor necrosis factor-α (TNFα), and IL-1β (Ella COVID-19 Cytokine Analysis Panel, R&D Systems, Minneapolis, Minnesota); complete blood count, and the inflammatory markers ferritin, fibrinogen, procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase (LDH).

2.4 | Retrospective transfusion reaction analysis

As has been done in previous large studies examining the incidence of transfusion reactions, we adopted an "active surveillance" model[32] in which we conducted retrospective chart review for all CP transfusions, irrespective of whether a reaction was reported to the blood bank. A retrospective chart review for transfusion reactions to CP was performed by four independent reviewers (T.V., F.N., V.L., H.L.). Transfusion reactions were determined according to CDC hemovigilance criteria[33] and assessed as either no transfusion reaction, attributed to underlying disease, TACO, transfusion-related acute lung injury (TRALI), allergic reaction, hypotensive reactions, or febrile nonhemolytic transfusion reaction (FNHTR). The

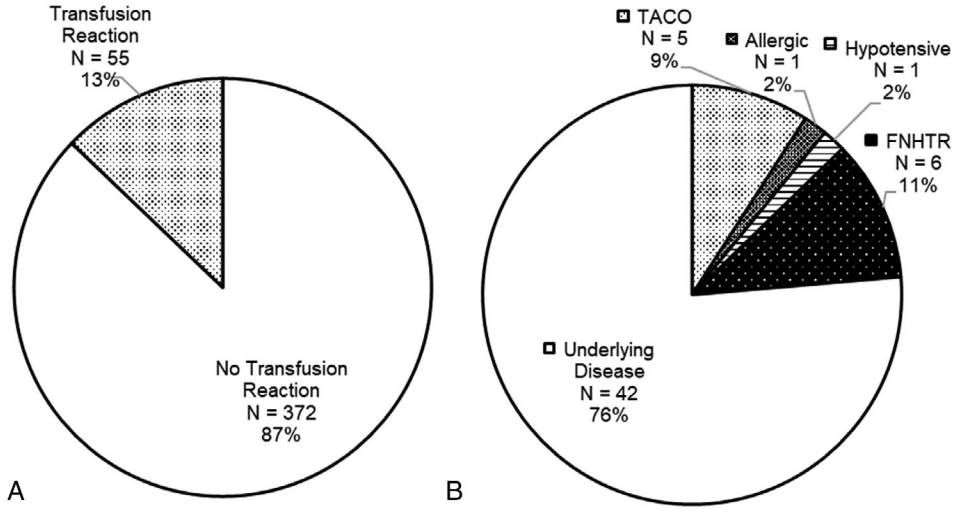

FIGURE 1 A, Distribution of COVID-19 convalescent plasma transfusion events (total of 427) split by outcome of transfusion vs no transfusion reactions. B, Distribution of transfusion reaction events (total of 55) split by type of transfusion reactions include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. FNHTR, febrile nonhemolytic transfusion reaction; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury

TABLE 2 Demographics and clinical characteristics per COVID-19 convalescent plasma transfusion event

	All transfusion events (N = 427) in 215 patients	No transfusion reaction (N = 372) in 199 patients	Transfusion reactions (N = 55) in 41 patients	*P* value
Age, y, median (IQR)	63 (19)	63 (18)	58 (14)	.012
Sex, n (%)				.881
Female	154 (36.07)	135 (36.29)	19 (34.55)	...
Male	273 (63.93)	237 (63.71)	36 (65.4%)	...
Race, n (%)				.431
White	99 (23.19)	89 (23.92)	10 (18.18)	...
African American	68 (15.93)	60 (16.13)	8 (14.55)	...
Other/Multiracial	262 (61.36)	224 (60.22)	38 (69.09)	...
ABO type, n (%)				.115
A	150 (35.13)	136 (36.56)	14 (25.45)	...
B	54 (12.65)	42 (11.29)	12 (21.82)	...
O	207 (48.48)	180 (48.39)	27 (49.09)	...
AB	16 (3.75)	14 (3.76)	2 (3.64)	...
Rh, n (%)				.493
Rh+	407 (95.32%)	353 (94.89)	54 (98.18)	...
Rh−	20 (4.68%)	19 (5.11)	1 (1.82)	...
Co-existing diseases, n (%)				
Asthma	32 (7.49)	27 (7.26)	5 (9.09)	.586
COPD	122 (28.5)	108 (29.03)	14 (25.45)	.635
Respiratory – Other	43 (10.07)	36 (9.68)	7 (12.73)	.473
CAD	116 (27.17)	103 (27.69)	13 (23.64)	.627
CHF	73 (17.10)	65 (17.47)	8 (14.55)	.703
HTN	142 (33.26)	123 (33.06)	19 (34.55)	.878
Cirrhosis	24 (5.62)	19 (5.11)	5 (9.09)	.216
HBV	4 (0.94)	3 (0.81)	1 (1.82)	.425
HCV	8 (1.87)	6 (1.61)	2 (3.64)	.275
CKD	49 (11.48)	40 (10.75)	9 (16.36)	.255
ESRD	26 (6.09)	24 (6.45)	2 (3.64)	.556
Autoimmune	23 (5.39)	17 (4.57)	6 (10.91)	.099
HIV	6 (1.41)	6 (1.61)	0 (0.00)	1.000
Cancer	42 (9.84)	41 (11.02)	1 (1.82)	.028
Solid organ transplant	20 (4.68)	15 (4.03)	5 (9.09)	.159
Diabetes	98 (22.95)	84 (22.58)	14 (25.45)	.610
Neurologic	42 (9.84)	39 (10.48)	3 (5.45)	.333
OB/GYN/pregnancy	14 (3.28)	10 (2.69)	4 (7.27)	.092
Obesity	47 (11.01)	38 (10.22)	9 (16.36)	.171
Other	162 (37.94)	137 (36.83)	25 (45.45)	.235
Ordinal Scores, n (%)				.615
1 - Not hospitalized, resumption of normal activities	0 (0.00)	0 (0.00)	0 (0.00)	...
2 - Not hospitalized, cannot resume normal activities	0 (0.00)	0 (0.00)	0 (0.00)	...

(Continues)

TABLE 2 (Continued)

	All transfusion events (N = 427) in 215 patients	No transfusion reaction (N = 372) in 199 patients	Transfusion reactions (N = 55) in 41 patients	*P* value
3 - Hospitalized, no supplemental O_2	12 (2.81)	11 (2.96)	1 (1.82)	...
4 - Hospitalized, requires supplemental O_2	251 (58.78)	222 (59.68)	29 (52.73)	...
5 - Hospitalized, requires nasal high-flow O_2 therapy, NIV, or both	113 (26.46)	97 (26.08)	16 (29.09)	...
6 - Hospitalized, requires ECMO, invasive mechanical ventilation, or both	51 (11.94)	42 (11.29)	9 (16.36)	...
7 – Death	0 (0.00)	0 (0.00)	0 (0.00)	...
SOFA scores, n (%)				.126
0-6 (<10% mortality)	208 (80.31)	181 (80.80)	27 (77.14)	...
7-9 (15-20 mortality)	25 (9.65)	23 (10.27)	2 (5.71)	...
10-12 (40%-50% mortality)	18 (6.95)	14 (6.25)	4 (11.43)	...
13-14 (50%-60% mortality)	6 (2.32)	4 (1.79)	2 (5.71)	...
15 (>80% mortality)	0 (0.0)	0 (0.0)	0 (0.0)	...
15-24 (>90% mortality)	2 (0.77)	2 (0.89)	0 (0.00)	...
Length of days, median (IQR)				
Ventilation days	10.40 (5.90)	3.70 (5.00)	10.40 (9.40)	.0085
ICU length of stay	5.13 (5.58)	3.63 (5.38)	5.13 (8.33)	.0001
Hospitalization length of stay	7.58 (5.98)	6.13 (5.92)	7.58 (9.94)	.0582
Laboratory values, median (IQR) [N = number of transfusion events]				
Lymphocyte number, K/μL	0.9 (0.9) [N = 382]	0.9 (0.9) [N = 331]	0.9 (0.8) [N = 51]	.812
White blood cell count, K/μL	7.6 (5.1) [N = 409]	7.7 (5.0) [N = 356]	6.8 (4.8) [N = 53]	.1183
Hemoglobin, g/dL	12.5 (2.8) [N = 411]	12.6 (2.8) [N = 358]	12.3 (2.6) [N = 53]	.6461
Hematocrit, %	37.8 (9.2) [N = 413]	38.0 (9.4) [N = 360]	37.3 (8.3) [N = 53]	.9504
Platelet count, K/μL	255.0 (158.0) [N = 409]	258.0 (156.0) [N = 356]	216.0 (178.0) [N = 53]	.078
Fibrinogen, mg/dL	664.0 (242.0) [N = 208]	666.0 (233.0) [N = 179]	562.0 (294.0) [N = 29]	.0595
Ferritin, ng/mL	1025.0 (1870.5) [N = 391]	1025.0 (1859.0) [N = 341]	1277.0 (1831.3) [N = 50]	.6056
Procalcitonin, ng/mL	0.3 (0.5) [N = 319]	0.3 (0.5) [N = 279]	0.3 (0.5) [N = 40]	.5294
C-reactive protein, mg/L	126.4 (140.6) [N = 391]	130.3 (139.9) [N = 342]	111.0 (139.5) [N = 49]	.537
Lactate dehydrogenase, U/L	516.0 (295.0) [N = 357]	518.0 (302.5) [N = 312]	496.0 (271.0) [N = 45]	.730
IL-6, pg/mL	74.1 (147.2) [N = 119]	66.6 (123.9) [N = 101]	91.5 (254.8) [N = 18]	.1622
IL-8, pg/mL	33.3 (49.9) [N = 96]	33.5 (54.4) [N = 78]	31.8 (34.4) [N = 18]	.6464
TNFα, pg/mL	16.4 (19.1) [N = 90]	16.4 (18.3) [N = 73]	14.8 (19.6) [N = 17]	.5844
IL-1β, pg/mL	0.5 (0.6) [N = 50]	0.5 (0.7) [N = 36]	0.4 (0.9) [N = 14]	.6464
Plasma unit titer, n (%)				.634
200	4 (1.65)	3 (1.34)	1 (2.86)	...
400	48 (19.75)	42 (18.75)	6 (17.14)	...

TABLE 2 (Continued)

	All transfusion events (N = 427) in 215 patients	No transfusion reaction (N = 372) in 199 patients	Transfusion reactions (N = 55) in 41 patients	*P* value
800	73 (30.04)	67 (29.91)	6 (17.14)	...
1600	79 (32.51)	70 (31.25)	9 (25.71)	...
3200	24 (9.88)	20 (8.93)	4 (11.43)	...
6400	6 (2.47)	6 (2.68)	0 (0.00)	...
12 800	9 (3.70)	9 (4.02)	0 (0.00)	...

Note: Transfusion reaction events include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. Fisher's exact test was used for categorical variables, and 2-sample *t* test was used for continuous variables.

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; FNHTR, febrile nonhemolytic transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; NIV, noninvasive ventilation; SOFA, sequential organ failure assessment; TACO, transfusion-associated circulatory overload; TNFα, tumor necrosis factor-α; TRALI, transfusion-related acute lung injury.

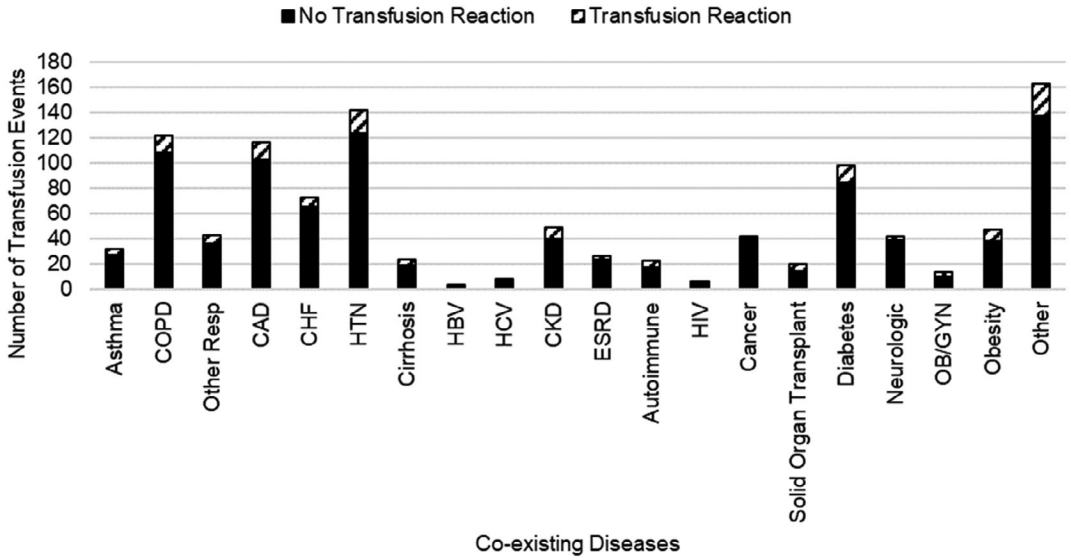

FIGURE 2 Coexisting disease distribution of the recipient patients (215) of COVID-19 convalescent plasma transfusion events (427) split by the outcome of transfusion reaction. Transfusion reactions include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; FNHTR, febrile nonhemolytic transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; OB/GYN, obstetrics and gynecological conditions; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury

events were categorized as having a transfusion reaction if defined as definite or probable, and categorized as "not a transfusion reaction" if the reaction was defined as possible, doubtful, or unrelated.[33] Due to significant overlap in clinical symptoms between FNHTR and COVID-19 pneumonia, a more stringent definition of FNHTR was voluntarily applied in our study, defined as (a) afebrile for 24 hours before CP transfusion with subsequent development of fever >1°C/2 °F within 4 hours of CP transfusion, and with return to baseline temperature without subsequent fevers for the next 12 hours, or (b) patient had been febrile within 24 hours before CP transfusion, and demonstrates fever within 4 hours following transfusion of at least 1.5°C above the highest temperature from the preceding 24 hours, followed by return to baseline fever for at least 12 hours. To determine the incidence and distribution of transfusion reactions to CP, review of clinical data was randomized to the four reviewers for CP recipients in a blinded fashion. Results from blinded reviews were compared, and discordances were adjudicated by a third independent reviewer (K.L. or I.B.).

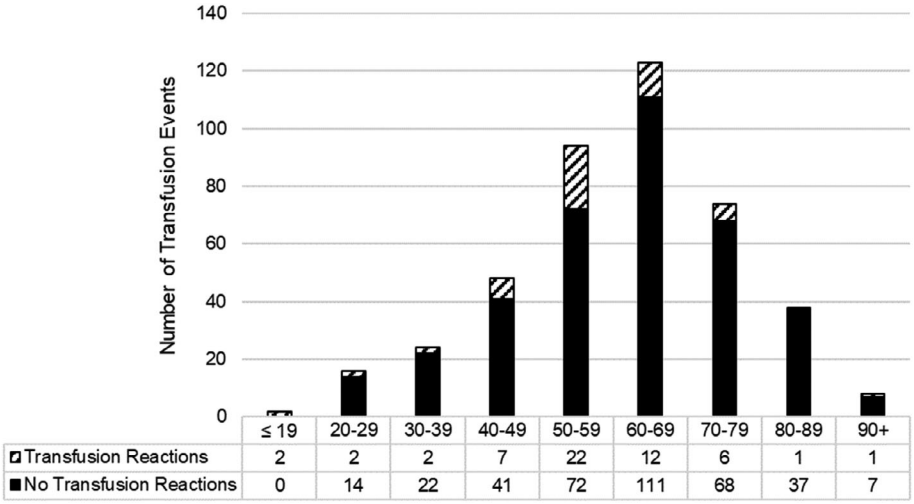

FIGURE 3 Age distribution of the recipient patients (215) of COVID-19 convalescent plasma transfusion events (427) split by the outcome of transfusion reaction. Transfusion reactions include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. FNHTR, febrile non-hemolytic transfusion reaction; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury

2.5 | Statistical analysis

A database was created to centralize and collate the collected information. The outcomes variable was the incidence of a transfusion reaction. Types of transfusion reactions included underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. The initial analysis focused on determining if there was a statistically significant difference in the various patient demographic factors and clinical laboratory tests. Fisher's exact test was applied for independent categorical variables (disease severity, ordinal scores, SOFA scores, sex, race, coexisting diseases, and ABO and Rh blood type groups). A two-sample *t* test was applied for independent continuous variables such as clinical laboratory values such as IL-6, IL-8, TNFα, and IL-1β levels, lymphocyte number, white blood cell count, hemoglobin, hematocrit, platelet count, fibrinogen, ferritin, pro-calcitonin, CRP, LDH, age, and number of days on ventilation support, in the ICU, or hospitalized length of stay. Subsequently, a univariate logistic regression (categorical and continuous) analysis was performed to determine whether an independent variable was a statistically significant risk or protective factor for the incidence of a transfusion reaction event. All statistical analyses were performed with computer software (Stata Release 16.1; StataCorp, College Station, Texas).[34]

3 | RESULTS

To assess the transfusion reaction safety profile of CP in patients with COVID-19, and to identify factors associated with increased likelihood of any transfusion reaction, we reviewed clinical and laboratory information for 427 transfusion events of CP to 215 patients between 28 March and 29 April 2020 under the FDA eIND process for convalescent plasma use[24] and the EAP[25] (Table 1). Four hundred thirteen of 427 (96.7%) transfusions were ABO identical, with the remaining 14 of 427 (3.3%) being ABO compatible. By institutional policy, each patient was transfused 2 units of CP; however, some patients ultimately received only 1 unit due to a potential transfusion reaction. Determination of a transfusion reaction was performed by four independent physicians in a blinded fashion, with expert adjudication as described in Section 2, in a fashion similar to prior large studies examining transfusion reactions.[32] Transfusion reactions were determined as defined in the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) Hemovigilance Module Surveillance Protocol version 2.5.2,[33] with the exception of FNHTRs, for which we used alternative and more stringent criteria as described in Section 2.4, to better distinguish FNHTRs from COVID-19–associated fever.

We identified reactions to 55 CP transfusion events out of 427 total events across our hospital system, comprising 13% of total convalescent plasma transfusions (subset; Figure 1A). Forty-two of these (76.4% of subset, 9.8% overall) were attributed to underlying disease. Unsurprisingly, the majority of these were characterized by fever, hypoxia, or both. Febrile reactions attributed to underlying disease were cases where either fever was present within the preceding 24 hours to the transfusion, where it was intermittently present following the transfusion, or where it did not rise significantly above the patient's baseline fever, that is, scenarios in which the patient did not meet our study's more stringent definition of FNHTR. Cases of hypoxia attributed to underlying disease were scenarios in which the patient was

TABLE 3 Risk factors associated with COVID-19 convalescent plasma transfusion reaction events, which include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR based on univariate logistic regression analysis

	Odds ratio	*P* value
Age	0.978	.013
30-39	0.318	.219
40-49	0.598	.461
50-59	1.069	.913
60-69	0.378	.131
70-79	0.300	.089
80-89	0.095	.042
90+	0.700	.772
Sex		
Male	...	...
Female	1.0793	.801
Race		
White	...	...
African American	1.304	.606
Other/multiracial	1.659	.196
ABO type		
A	...	...
B	2.776	.018
O	1.388	.684
AB	1.457	.28O
Rh+ vs. Rh−	2.907	.303
Coexisting diseases		
Asthma	1.278	.631
COPD	0.835	.584
Respiratory – Other	1.361	.484
CAD	0.808	.529
CHF	0.804	.591
HTN	1.068	.828
Cirrhosis	1.858	.238
HBV	2.278	.479
HCV	2.302	.315
CKD	1.624	.227
ESRD	0.547	.422
Autoimmune	2.557	.060
HIV	...	...
Cancer	0.150	.063
Solid organ transplant	2.380	.107
Diabetes	1.171	.636
Neurologic	0.493	.251
OB/GYN	2.839	.087
Obesity	1.720	.178
Other	1.429	.220
Ordinal scores		
4 - Hospitalized, requires supplemental O_2	1.437	.733
5 - Hospitalized, requires nasal high-flow O_2 therapy, NIV, or both	1.814	.581
6 - Hospitalized, requires ECMO, invasive mechanical ventilation, or both	2.357	.439
SOFA scores		
2	2.708	.079
2	2.321	.174
4	1.970	.327
5	1.083	.925
9	3.611	.163
10	3.611	.163
12	10.833	.028
13	10.833	.028
Laboratory values		
Lymphocyte number, K/μL	1.006	.812
White blood cell count, K/μL	0.936	.099
Hemoglobin, g/dL	1.033	.645
Hematocrit, %	1.002	.950
Platelet count, K/μL	0.998	.079
Fibrinogen, mg/dL	0.998	.061
Ferritin, ng/mL	0.999	.606
Procalcitonin, ng/mL	0.984	.581
C-reactive protein, mg/L	0.999	.536
Lactate dehydrogenase, U/L	0.999	.730
IL-6, pg/mL	1.001	.174
IL-8, pg/mL	0.998	.645
TNFα, pg/mL	1.010	.580
IL-β, pg-mL	1.519	.186
Plasma unit titers		
200	...	...
400	0.429	.492
800	0.269	.286

(Continues)

(Continues)

TABLE 3 (Continued)

	Odds ratio	*P* value
1600	0.386	.430
3200	0.600	.689

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus 2019; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; FNHTR, febrile nonhemolytic transfusion reaction; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; IL, interleukin; IQR, interquartile range; NIV, noninvasive ventilation; SOFA, sequential organ failure assessment; TACO, transfusion-associated circulatory overload; TNFα, tumor necrosis factor-α; TRALI, transfusion-related acute lung injury.

intermittently hypoxic before transfusion, and/or the intermittent hypoxia occurring following transfusion was not significantly worse than that before transfusion. A minority were characterized by nonspecific symptoms such as hypotension following transfusion that was also intermittently present before, or subjective dyspnea without evidence of hypoxia/hypoxemia. These were cases in which it was felt there was significant overlap clinically with the ongoing progression of the patient's underlying COVID-19. Of the remaining 13 attributed to transfusion (23.6% of subset, 3.1% overall), six were attributed to FNHTR (10.9% of subset, 1.4% overall), five to TACO (9.1% of subset, 1.2% overall), and one each to mild allergic and hypotensive reactions (each 1.8% of subset, 0.2% overall) (Figure 1B). No cases of other transfusion reaction types including TRALI or severe allergic (anaphylactic) reactions were identified per the CDC hemovigilance criteria. This compares to our institutional 5-year baseline transfusion reaction incidence of 0.3% for blood products overall and a combined 4-year incidence of 0.3% to plasma and plasma-rich products specifically, including platelets and cryoprecipitate.

We compared reaction and nonreaction CP recipient cohorts using Fisher's exact test and two-sample *t* test to identify demographic, clinical, and laboratory factors associated with transfusion reactions. No significance was found between groups for parameters of sex, ethnicity, underlying respiratory disease including asthma and chronic obstructive pulmonary disease, underlying cardiovascular disease including heart failure and coronary disease, hepatic or renal disease, autoimmune disease, immunocompromised status including HIV, or plasma unit anti–SARS-CoV-2 spike antibody titer, as well as numerous other coexisting diseases (Table 2, Figure 2). A significant association was found between patients with cancer and the incidence of a transfusion reaction ($P = .028$). Forty-seven of 55 reactions (85.4%) occurred in CP recipients between the ages 40 and 79, a patient age group representing 339 of 427 (79.4%) transfusion events (Figure 3). Univariate logistic regression analysis was performed to identify potential risk or protective factors that might contribute to the incidence of transfusion reactions. Significant associations with reactions were identified for patients aged between 80 and 89 (odds ratio [OR] = 0.095; $P = .042$), demonstrating a decreased likelihood of reaction, but not above or below this range (Table 3). Transfusion reactions were also associated significantly with increased median duration of ICU stay (5.13 vs 3.63 days, $P = .0001$), increased median number of days on mechanical ventilation (10.40 vs 3.70, $P = .0085$), a SOFA score of 12 or 13 (OR = 10.883; $P = .028$) (Table 2, Figure 4), and group B blood type (OR = 2.776; $P = .018$) (Table 3, Figure 5). Unfortunately, our study was not powered to distinguish between factors associated with reactions judged to be due to underlying disease vs reactions due to all other causes.

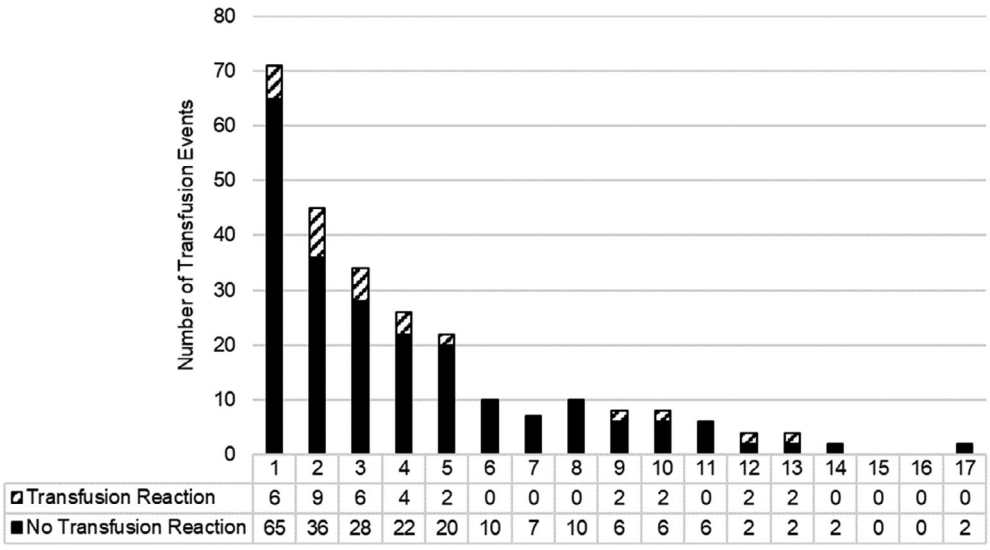

FIGURE 4 Sequential organ failure assessment (SOFA) score distribution of the recipient patients (215) of COVID-19 convalescent plasma transfusion events (427) split by the outcome of transfusion reaction. Transfusion reactions include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. FNHTR, febrile nonhemolytic transfusion reaction; TACO, transfusion-associated circulatory overload, TRALI, transfusion-related acute lung injury

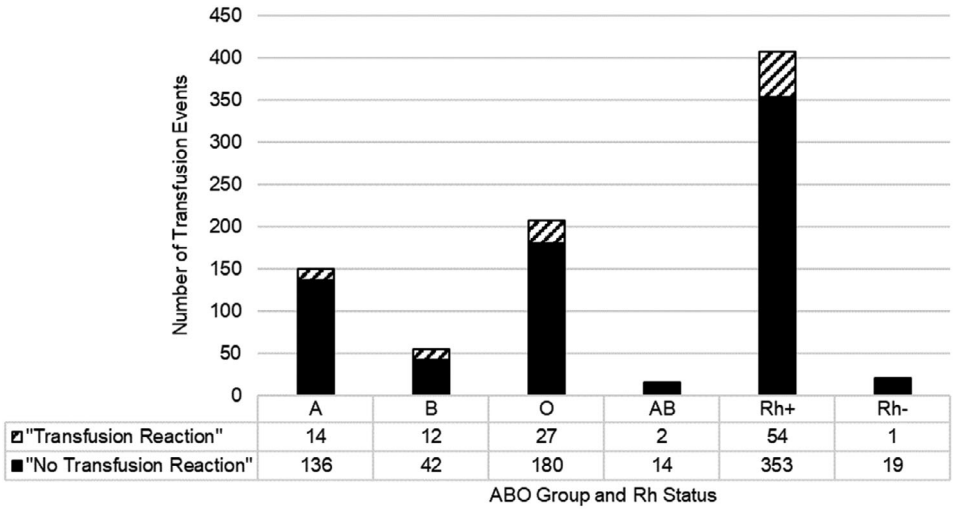

FIGURE 5 ABO group and Rh status distribution of the recipient patients (215) of COVID-19 convalescent plasma transfusion events (427) split by the outcome of transfusion reaction. Transfusion reactions include underlying disease, TACO, TRALI, allergic, hypotensive, and FNHTR. FNHTR, febrile nonhemolytic transfusion reaction; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury

We next applied similar analysis to the same patient cohorts to identify laboratory parameters associated with transfusion reactions. We examined pretransfusion complete blood count parameters; absolute lymphocyte number; fibrinogen; the inflammatory markers ferritin, CRP, LDH, and procalcitonin; and inflammatory cytokine levels including TNFα, IL-1β, IL-6, and IL-8. None of these parameters was significantly associated with transfusion reactions. The apparent association between fibrinogen levels and increased likelihood of transfusion reaction approached but did not reach statistical significance ($P = .061$), and is not of clinical significance (OR = 0.998).

4 | DISCUSSION

In this study, we sought to evaluate the safety profile of CP use in patients with COVID-19 from the perspective of transfusion reactions. We found that, overall, the use of CP was safe in this patient population, as no severe or life-threatening transfusion reactions were identified. However, we did find that specific patient factors such as age, a SOFA score of 12 or 13, and ABO blood group B were associated with transfusion reactions.

We identified 55 reactions out of a total of 427 transfusion events, 13 of which were determined to be definitively attributed to the transfusion itself rather than underlying disease, for an incidence of 12.9% overall, and 3.1% for transfusion-related reactions. When examined on a per-patient basis, a total of 23 patients had a reaction event to one of two transfused units, while 16 patients had a reaction event to both transfused units. The incidence rates reported in our study are higher than our historical institutional baseline reaction rate of just 0.3%, a rate that is reflected similarly in a recent study of overall safety indicators in 5000 convalescent plasma recipients.[23] There are several factors that might account for this discrepancy.

First, while our finding of 10.9% incidence of FNHTR in our population is considerably higher than what one previous study has cited for plasma,[35] it should be noted that there is considerable variability across studies for this incidence that ranges almost 25-fold.[36,37] Furthermore, these studies focus on plasma transfusion in a variety of clinical contexts, including trauma and surgical bleeding, whereas our study focuses on the COVID-19 population specifically, where the incidence of FNHTR is not well characterized. This may contribute to the higher rate seen in our study.

Second, the majority of transfusion reactions identified (42/55; 76%) were attributed to underlying disease, with an additional 6 classified as FNHTR, to comprise a total of 48 of 55 (87%) transfusion reactions. It is probable that the high proportion of reactions classified as underlying disease was in large part due to our self-imposed stringent definition of FNHTR for this study, which required criteria beyond what are established in the CDC NHSN Hemovigilance Module. The goal of this was to acknowledge and account for the confounding effects of COVID-19–associated pneumonia, which includes symptoms of recurrent fevers and rigors, among others. Our definition of "attributed to underlying disease" in this study includes reactions in which the patient may have had recurrent fevers within the 24 hours following transfusion but not before; these would be determined as transfusion-related FNHTRs if standard CDC criteria were used. Therefore, our stringent definition likely causes us to underestimate the true incidence of FNHTR in this population. Given the large overlap in symptoms, distinguishing FNHTR from COVID-associated fever will likely remain a challenge with the use of CP going

forward. In a similar vein, evidence has shown that there can be longer-term adverse events to blood product transfusion that occur beyond the time frames established by the CDC NHSN criteria.[38–40] Thus, it is possible that other complications of CP transfusion may not have been identified by our study. Identification of such associations require far larger studies than conducted here to account for the myriad confounding variables that would be present in the COVID-19 patient population. Conversely, given the febrile and hypoxic status of our transfused patient population, actual transfusion-related events not meeting our more stringent criteria may be masked, and may be attributed to underlying disease. Ultimately, large trials comparing CP to fresh frozen plasma (FFP) transfusion in patients with COVID-19 would be required to elucidate these differences.

Third, patients with moderate to severe COVID-19 exist in a state of generalized immune activation,[41] with increased levels of proinflammatory cytokines. While our study did not find differences in inflammatory cytokine levels between positive and negative transfusion reaction groups, numerous other mechanisms for innate immune activation in COVID-19 exist, such as evidence of inflammasome activation and pyroptosis,[42] increased levels of activated $CD14^{+}16^{+}$ monocytes,[43] and activation and deployment of neutrophils and neutrophil extracellular traps.[44,45] It is possible that patients with COVID-19 represent a population who are primed for pulmonary neutrophil activation, similar to the mechanism proposed for Type II TRALI.[46] There is evidence from studies involving patients with sickle cell disease and autoimmune disease showing that a higher baseline rate of inflammation in these patients was associated with a higher likelihood of alloantibody formation.[47–50] Similarly, the higher rate of transfusion reactions seen in CP recipients may be due to a preprimed state in the recipients, a hypothesis that warrants further study.

Fourth, while our active surveillance approach is a strength of our study in that it is proven to more frequently and accurately detect transfusion reaction incidence,[36,51–53] it does introduce the very real possibility of observer bias. While analogous posttransfusion monitoring and reporting for reactions is a required component of the EAP protocol, this was conducted via passive surveillance, in which the protocol organizers relied on reports sent by transfusing institutions, an approach known to lead to significant underreporting of transfusion reactions. Furthermore, the EAP reporting requirements focused only on "serious adverse events," which was interpreted in the context of transfusion reactions to mean TACO and TRALI, while our study focused on all reaction types. Therefore, this may also serve to explain the increased incidence seen in the CP recipient population as compared to our institutional baseline or that seen in other studies, which are reliant on reporting from clinicians who may not be as familiar with CDC reaction criteria. It is likely that these factors contributed to our higher rate of detection for reactions overall and transfusion-related reactions specifically.

Our univariate logistic regression analysis revealed several factors associated with increased likelihood of transfusion reactions. We found that an increased SOFA score of 12 or 13 was associated with a greater likelihood of transfusion reactions. The SOFA score, originally developed to measure organ failure and later validated to predict mortality in critically ill patients, has also been shown recently to predict mortality in a retrospective cohort study of 191 hospitalized patients with COVID-19 in Wuhan, China.[3,54,55] While it is not surprising to speculate that patients with more severe disease are more likely to develop transfusion reactions due to their higher baseline inflammatory state, our findings showing no association with cytokine levels such as IL-6, IL-1β, or TNFα raises questions. One possibility might be that patients with more severe disease are more susceptible to potential transfusion-related immunomodulatory effects, a phenomenon traditionally associated with red blood cells, but with evidence for its existence in plasma transfusion as well.[40,56] Studies demonstrate decreased levels of IL-1β, IL-8, and TNFα secretion by monocytes in vitro when exposed to FFP as compared to spray-dried detergent-treated plasma, raising the possibility of immunomodulatory effects of plasma itself,[56] while another study reported decreased inflammatory markers, poorer overall survival, and increased metastatic disease in a study of patients with colorectal cancer receiving FFP during their hospital stay.[40] It is possible that plasma transfusion causes a blunted innate immune response, thereby increasing clinical manifestations of underlying COVID-19 in patients with a higher SOFA score. The overall characterization of CP, including concentration of these potentially immunomodulatory factors, is currently unknown and is an area warranting further study. We do note, however, that the number of transfused patients with SOFA scores of 12 or 13 was relatively small ($N = 4$ for each group). Therefore, while our analysis did find statistical significance, we recommend caution in interpreting this data further until larger studies support it.

Similarly, we identified an association between age and likelihood of reaction, with significantly decreased likelihood of reaction for patients between the ages of 80 and 89. This may reflect an age-related lower baseline rate of immune reaction to plasma transfusion, which would correlate inversely with the overall increased general severity of COVID-19 in patients with increasing age.[3] Consistent with this theory, when focusing on the

subset of patients within the 50-to-59 age bracket, we note that despite representing the second-largest age bracket of transfused patients, it accounted for the largest proportion of transfusion reactions, due to both underlying disease and other causes. This possibly reflects a more robust response to viral infection and reactions to plasma transfusion compared to older age groups. However, it is important to mention that the patient sample for this age bracket limits our study power, preventing us from analyzing each age bracket subset to a larger degree. Therefore, additional studies are required before conclusions can be firmly drawn here.

Perhaps the most unexpected association found in our study was that between transfusion reactions and group B blood type based on transfusion event analysis. Two studies, one of which is a preliminary study of over 750 000 individuals, appear to support an association between a non-O blood type and increased risk for SARS-CoV-2 infection, indicating that group O blood type may exert a protective effect,[57,58] though another study of over 7600 patients did not reproduce this effect, instead finding increased odds of polymerase chain reaction positivity for COVID-19 for blood group types B and AB.[59] However, the distribution of ABO types in our analyzed population (48.6% Group O, 35.0% Group A, 13.1% Group B, 3.3% Group AB) largely reflects the general distribution nationwide in the United States. Also, 413 of 427 (96.7%) transfusions were ABO identical, with the remaining 14 of 427 (3.3%) ABO compatible. Therefore, potential involvement of anti-ABO isohemagglutinins in reaction likelihood could not be assessed here. One potential explanation from established literature may come from studies in SARS-CoV-1, which has identified the presence of N-linked glycans in the SARS-CoV-1 spike protein that resembles ABO antigens, raising the possibility of cross-reactivity with ABO isohemagglutinins.[60] Additionally, it has been shown that high-titer anti-A antibody levels confers relative resistance to SARS-CoV-1 infection[61] through inhibition of the SARS-CoV-1 spike protein and its receptor, but low-titer anti-A levels do not. It is known that the SARS-CoV-2 spike protein targets the same angiotensin-converting enzyme 2 receptor as SARS-CoV-1.[62,63] It is also known that group B patients often possess lower titers of anti-A than group O patients, and lack the anti-A,B antibody as well. We can speculate that it is possible that this subset of patients, who in our study received exclusively group B plasma, represents a lower-titer group that is more susceptible to worsening disease symptoms following transfusion, though these data were not available for examination. However, we do note that we did not see any association with group A recipients, which have associated in other studies with increased disease severity. Furthermore, the low number of group AB transfusions in our study limits our ability to identify associations with this blood type. Therefore, it may be possible that association with transfusion reactions operates via an alternative unknown mechanism. Clearly, future work examining the levels of anti-A or -B titers in both plasma units and recipients would be of value. Furthermore, given the conflicting findings of several large studies on this point, additional large studies need to continue to examine this potential association before any reliable associations can be made.

Institutional guidelines for collection of plasma from convalescent donors under both the FDA eIND and EAP protocols followed FDA guidance suggesting antibody titers of 320 or greater.[64] Recent small studies have demonstrated that convalescent patients produce antibodies that demonstrate neutralizing activity[65] and is supported by analysis of 285 cases from the Korean Centers for Disease Control in which patients tested "repositive" following recovery from initial COVID-19.[66] They found that in all cases, neutralizing antibody was present, viral cell culture results were negative, and that these repositive individuals were not infectious. Furthermore, previous studies show a strong correlation between spike antibody levels and neutralization activity.[28] Therefore, there may be a role for higher antibody levels, which might induce exacerbation of underlying disease, possibly through antibody-dependent enhancement. This is a concentration-dependent phenomenon seen in the context of coronavirus and other viral infections[67,68] by which antibodies bound to pathogen can enhance viral entry into cells and manifest as acute worsening of clinical status. It is currently unknown if such a phenomenon may be occurring following CP transfusion. Therefore, it is reassuring to note that we did not observe a correlation between antibody titer levels in plasma units and increased likelihood of transfusion reactions, indicating that CP transfusion is likely safe in this aspect.

In this study, we set out to investigate the incidence and spectrum of transfusion reactions associated with the use of CP in patients with COVID-19. While we did identify a significantly increased incidence of transfusion reactions overall, the overwhelming majority of these represented underlying disease or FNHTR, and none were severe enough to require urgent intervention. It will remain an ongoing but important challenge to distinguish true transfusion reactions, including FNHTR and TRALI, from underlying COVID-19 given the overlap in symptoms. Even when excluding underlying disease as a cause, there appears to remain an increase in the incidence of FNHTR reactions in patients with COVID-19, highlighting the importance of increased vigilance and active posttransfusion surveillance, especially in patients with more severe disease. Nonetheless, the absence of severe or life-threatening reactions demonstrates the

short-term safety of CP transfusion in patients with COVID-19 from a transfusion reaction perspective. While further corroborating studies are clearly warranted, our initial identification of several previously uncharacterized risk factors for transfusion reactions may raise preliminary considerations to transfusion teams as to the potential risk of reactions when transfusing certain patients. Our findings raise interesting questions into the characterization of and mechanisms underlying CP when transfused in different recipient populations and serve as a basis for future studies.

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CONFLICT OF INTEREST

Mount Sinai has licensed serologic assays for anti–SARS-CoV-2 antibodies to commercial entities and has filed for patent protection for serologic assays. F.K. is listed as one of the inventors. The remaining authors declare no conflicts of interest.

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