Received: 12 November 2020 | Revised: 3 February 2021 | Accepted: 4 February 2021

DOI: 10.1002/jca.21888

RESEARCH ARTICLE

Journal of Clinical Apheresis ASFA WILEY

A matched cohort study of convalescent plasma therapy for COVID-19

Oleg V. Sostin[1] | **Pramuditha Rajapakse**[2] | **Brigid Cruser**[3] | **Dorothy Wakefield**[1] | **Daniel Cruser**[4] | **Joann Petrini**[1]

[1]Department of Research and Innovation, Danbury Hospital, Nuvance Health, Danbury, Connecticut

[2]Department of Medicine, Danbury Hospital, Nuvance Health, Danbury, Connecticut

[3]Texas Tech Univesity Health Sciences Center, School of Medicine, Lubbock, Texas

[4]Department of Pathology, Vassar Brothers Medical Center, Nuvance Health, Poughkeepsie, New York

Correspondence
Dr. Oleg V. Sostin, Department of Research and Innovation, Danbury Hospital, Nuvance Health, 5 West, 24 Hospital Avenue, Danbury CT, 06810.
Email: oleg.sostin@nuvancehealth.org

Abstract

Introduction: COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a public health crisis. Prior studies demonstrated successful use of convalescent plasma therapy for treatment of other viral illnesses. Our primary objective was to evaluate treatment efficacy of convalescent plasma in patients with COVID-19.

Materials and Methods: In this retrospective matched cohort study, we enrolled recipients of convalescent plasma collected from donors recovered from laboratory-confirmed SARS-CoV-2 infection under the single patient eIND process. We individually matched 35 cases with 61 controls based on age, gender, supplemental oxygen requirements, and C-reactive protein level at the time of hospital admission. We compared the outcomes of in-hospital mortality and hospital length of stay between the groups.

Results: In-hospital mortality was 20% among the cases and 24.6% among the controls ($P = .61$). A multivariable logistic regression model that included age, gender, duration of symptoms, need for mechanical ventilation, and pharmacologic interventions revealed no significant difference in mortality by study group ($P = .71$). The median length of stay was significantly greater among convalescent plasma recipients compared with controls, 10 (IQR, 6-17) vs 7 (IQR, 4-11) days, $P < .01$. The difference was not significant after controlling for covariates ($P > .1$).

Conclusions: We did not find convalescent plasma reduced in-hospital mortality in our sample, nor did it reduce length of stay. Further investigation is warranted to determine the efficacy of this treatment in patients with COVID-19, particularly early in the disease process.

KEYWORDS

convalescent plasma therapy, COVID-19, fresh frozen plasma

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the greatest global public health crisis since the influenza outbreak in 1918. It likely ranks as the third leading cause of death in the United States in 2020.[1] While public health measures are in place to prevent the transmission of the disease, clinicians and investigators are working diligently to find an effective treatment. Current evidence suggests dexamethasone, remdesivir, tocilizumab, and therapeutic anticoagulation

are associated with improved clinical outcomes.[2-5] Hydroxychloroquine and lopinavir/ritonavir have been shown to have no benefit in patients hospitalized with COVID-19.[6,7] Additionally, trials are underway to evaluate convalescent plasma for treatment of COVID-19.[8]

Convalescent plasma is collected via apheresis from individuals who have recovered from COVID- 19.[9] The anticipated mechanism of action relies on the antibodies that might suppress viremia by viral neutralization (neutralizing antibodies).[10,11] In COVID-19, inflammatory reactions may perpetuate organ damage due to hyper-immune response leading to systemic hyper-inflammation or "cytokine storm".[12,13] In addition to neutralizing antibodies, convalescent plasma contains anti-inflammatory cytokines, host defense peptides (defensins), natural antibodies, and a class of pattern recognition receptors named pentraxins, which are postulated to have an immunomodulatory effect by making the severe inflammatory response more tolerable.[14,15] At the same time, administering pathogen-specific antibodies and pro-inflammatory cytokines contained in convalescent plasma carries a risk of aggravating the hyper-immune response.[16]

The use of this inexpensive and widely available treatment dates back almost 100 years, with some evidence of benefit against rabies, hepatitis B, polio, measles, influenza, Ebola, and other pathogens.[16] Data from the prior outbreaks of infections caused by a coronavirus, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS), documented safety and faster viral clearance with use of convalescent plasma, particularly when given early in the disease course.[17-19]

In the spring of 2020, the U.S. Food and Drug Administration (FDA) established the single patient emergency investigational new drug (eIND) process and worked with multiple federal partners and academia to open an expanded access protocol to facilitate access to convalescent plasma treatment for patients with COVID-19 disease.[20] In August of 2020, the FDA issued an emergency use authorization for convalescent plasma as a potentially promising COVID-19 treatment, acknowledging the need for further investigation to establish its safety and efficacy.[9,21]

The primary objective of this study was to explore the efficacy of convalescent plasma as a treatment for COVID-19 among hospitalized patients. We hypothesized that treatment with convalescent plasma may reduce in-hospital mortality and hospital length of stay in patients who were diagnosed with COVID-19.

2 | MATERIALS AND METHODS

We conducted a matched retrospective cohort study at five Nuvance Health Hospitals. The protocol was reviewed by the Biomedical Research Alliance of New York (BRANY) and the Vassar Brothers Medical Center Institutional Review Board. Patients received convalescent plasma therapy for laboratory-confirmed COVID-19 under the criteria established by the Food and Drug Administration (FDA) for the single patient eIND process.[9] Patients or their representatives provided written consent for the treatment.

2.1 | Convalescent plasma collection

Convalescent plasma was collected at New York Blood Center and American Red Cross (Albany, NY) via apheresis, utilizing the Trima Accel automated blood collection system (Terumo Blood and Cell Technologies, Lakewood, Colorado). Plasma (250-750 mL) was collected from each donor and split into separate units, approximately 200-250 mL each. Donors had a documented history of laboratory-confirmed SARS-CoV-2 infection. They had been asymptomatic for at least 14 days and tested negative for SARS-CoV-2 by the RT-PCR test prior to the donation. All donors were negative for human immunodeficiency virus, hepatitis B virus, hepatitis C virus, Zika virus, West Nile virus, human T-lymphotropic virus I/II, Chagas disease, syphilis, and anti-human leukocyte antigen antibodies, as per the FDA regulations for blood and blood components.[22] We could not determine donor anti-SARS-CoV-2 antibody levels as samples from each convalescent plasma unit were not saved.

2.2 | Case selection

We enrolled patients in the study if they were at least 18 years of age and received convalescent plasma therapy under the eIND criteria.[23] Patients were eligible to receive a COVID-19 convalescent plasma if they had laboratory confirmed, severe or immediately life-threatening COVID-19, within 21 days after symptom onset. Severe disease was defined as dyspnea, respiratory frequency $\geq$ 30/min, blood oxygen saturation $\leq$ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio $<$ 300, and/or lung infiltrates $>$50% within 24 to 48 hours. Life threatening disease was defined as respiratory failure, septic shock, and/or multiple organ dysfunction or failure. Patients enrolled in drug trials that precluded use of other investigational treatment, recipients of pooled immunoglobulin in past 30 days, female subjects who were pregnant or breastfeeding, and patients with contraindications to transfusion or history of transfusion reactions were excluded from consideration for convalescent plasma therapy under the eIND.

The same eligibility criteria were applied at all study sites. We excluded those convalescent plasma recipients who presented to the hospital on the date before the convalescent plasma therapy was introduced at our network, with the treatment becoming available later in the hospital course. The cases presented to the hospital between April 10, 2020 and May 5, 2020. Laboratory testing for SARS-CoV-2 infection is described in Appendix 1.

2.3 | Convalescent plasma transfusion

The patients received 1 to 2 units (based on the body mass index) of ABO-matched convalescent plasma. The second unit was administered either on the same day or the day following transfusion of the first unit. Each unit, measured approximately 200 to 250 mL in volume, was infused over one to two hours. During the infusion, the patients were closely observed. Vital signs were obtained in 15 minutes after initiation of transfusion and then hourly for the duration of procedure, followed by close monitoring for transfusion reactions for 24 hours.

2.4 | Matching

We selected controls from the Nuvance Health registry of patients hospitalized for treatment of laboratory-confirmed COVID-19. We performed propensity score matching using SAS software. Estimated propensity scores were based on age (< 65 years or ≥ 65 years), gender, admission C-reactive protein (CRP) value, and oxygen requirement at admission. Random 1:2 matching was then performed using the estimated propensity scores. Due to a limited number of potential controls, nine cases were matched to one control; the rest (26 cases) were matched to two controls. Age and gender were chosen as matching criteria as older age and male sex have been linked to higher odds of in-hospital death.[24,25] We defined disease severity by supplemental oxygen requirements and CRP value at the time of hospital admission, as admission CRP has been shown to have a good prognostic value in patients with COVID-19.[26] Five categories of oxygen requirement status were used for matching: Room air, low-flow oxygen supplementation (1-5 L/min), high-flow oxygen supplementation (6-15 L/min), Optiflow high flow oxygen supplementation (>15 L/min), and mechanical ventilation. We also categorized CRP value according to the following groups: 0-9.99, 10-49.99, 50-199.99, and > 200 mg/L. The selected controls presented to the hospital between March 12, 2020 and April 25, 2020.

2.5 | Measures

The primary outcome was in-hospital mortality defined as death prior to discharge from the hospital. The secondary outcome of hospital length of stay (LOS) defined as the total number of inpatient days in the hospital. We included numerous patient and treatment level variables as potential confounders. We included age as a dichotomous variable (<65 years or ≥ 65 years), as well as gender and intubation. We also included the use of any systemic steroids, including dexamethasone, hydrocortisone, and methylprednisolone. We included use of an IL-6 inhibitor (tocilizumab) and therapeutic dose anticoagulation. Therapeutic dose anticoagulation was defined as continuous intravenous infusion of heparin or subcutaneous administration of enoxaparin in the dose of greater than 40 mg/24 hours. We included patient-reported duration of symptoms as a continuous variable. Lastly, we characterized subjects according to comorbidities and laboratory parameters that have been linked to prognosis in patients with COVID-19.[24,27-30] In addition, we determined time between symptom onset and convalescent plasma transfusion, characterized laboratory parameters at the time of transfusion, as compared to the admission parameters, and evaluated supplemental oxygen requirements for 7 days.

2.6 | Statistical analysis

We computed descriptive statistics and compared all variables across study groups with chi-square analyses for categorical variables and t-tests/Wilcoxon rank-sum tests, as appropriate, for continuous variables. Similar analyses were performed to compare potential covariates by outcomes. Multivariable logistic analysis assessed the risk differences in mortality between groups while adjusting for covariates. Potential covariates were age, gender, racial/ethnic group, hospital of admission, duration of symptoms, comorbidities, intubation, and pharmacologic interventions. Final covariates included age group, racial/ethnic group and gender, as well as those that showed a significant or near significant ($P \leq .2$) relationship in the univariate analyses. In post hoc analysis, we used a similar logistic regression model to examine the subgroup of patients never intubated during their hospitalization. We used Poisson regression models to examine the relationship between study group and LOS (secondary outcome). All covariates, as well as mortality, were included in this model.

We performed 2-tailed hypothesis testing and defined statistical significance a priori at $P < .05$. All analyses

were performed using SAS statistical software (SAS Institute, Cary, NC), version 9.4.

3 | RESULTS

3.1 | Convalescent plasma recipients

Thirty-five patients met the inclusion/exclusion criteria and were included in the study. The median age of the convalescent plasma recipients was 59.8 years (Table 1). The sex ratio was approximately 1:1. Most patients were Caucasian, followed by the Hispanic/Latino racial/ethnic group. Almost one half of the patients were obese. The most common co-morbidities were hypertension and diabetes. The median (IQR) time between symptom onset and convalescent plasma transfusion was 10 (7–13) days. The patients received transfusion approximately 3 (IQR 2-5) days after admission to the hospital. At the time of the procedure, the median (IQR) CRP level was 23.9 (17.4-114.1) mg/L and troponin T was 0.03 (0-0.03) ng/mL; neutrophil-lymphocyte ratio was 7.3 (4.7-11.9). These values were not statistically different compared to the hospital admission values. Forty-four percent of patients had D-dimer >2000 ng/mL, a significant increase from the 26.5% at admission ($P < .01$). None of the patients experienced a transfusion reaction. Only 31% of patients experienced a decrease in supplemental

TABLE 1 Patient characteristics

Characteristic	Cases (n = 35)	Controls (n = 61)	*P*
Age – years, median (IQR)	59.8 (55.5-68.3)	59.7 (48.0-78.7)	.68
Age Group - n (%)			
< 65 years old	23 (65.7)	38 (62.3)	.74
≥ 65 years old	12 (34.3)	23 (37.7)	
Gender - n (%)			
Female	17 (49)	30 (49)	.95
Male	18 (51)	31 (51)	
Racial/ethnic group - n (%)			
African-American	6 (17)	11 (18)	.67
Asian	1 (3)	1 (2)	
Caucasian	16 (46)	25 (41)	
Hispanic/Latino	11 (31)	17 (28)	
other	0	0	
unknown	1 (3)	7 (11)	
Body-mass index >30 kg/m^2 - n (%)			
Comorbidities – n (%)	17 (48.6)	24 (40.0)	.42
Chronic obstructive pulmonary disease	1 (3)	8 (13)	.15
Coronary artery disease	3 (9)	5 (8)	.68
Congestive heart failure	0	9 (15)	.02
Current smoker	1 (2.9)	2 (3.3)	.91
Diabetes mellitus	13 (37)	17 (28)	.35
End-stage renal disease	0	2 (3)	.53
Hypertension	16 (46)	32 (52)	.52
Duration of symptoms prior to admission – days, median (IQR)			
Laboratory parameters	7 (5–10)	5 (2-7)	.02
C-reactive protein - mg/L, median (IQR)	28.6 (13.7-100.1)	50.2 (21.6-114.9)	.16
D-dimer >2000 ng/mL, n (%)	9 (26.5)[a]	6 (20)[a]	.54
Neutrophil-lymphocyte ratio, median (IQR)	7.2 (4.1-11.4)	6.5 (3.6-8.4)	.12
Troponin T - ng/mL, median (IQR)	0.03 (0-1.1)	0 (0-0.07)	.23
Oxygen requirement on admission - n (%)			
Room air	6 (17)	13 (21)	.78
Low flow (1–5 L/min)	17 (49)	32 (53)	
High flow (6-15 L/min)	8 (23)	9 (15)	
Optiflow high flow (over 15 L/min)	0	0	
Mechanical ventilation	4 (11)	7 (11)	

[a]D-dimer level at admission was available for 34 cases and 30 controls.

TABLE 2 Comparison of in-hospital mortality and LOS (in days) among convalescent plasma recipients and controls

	Expired,	n (%)	*p*	LOS, median (IQR)	*P*
Study Group					
Convalescent Plasma	7 (20.0)		0.61	10 (6–17)	<.01
Control	15 (24.6)			7 (4–11)	
Age Group					
< 65 years old	5 (8.2)		<0.01	8 (4–11)	.47
≥ 65 years old	17 (48.6)			8 (5-15)	
Gender					
Female	11 (23.4)		0.91	8 (4–11)	.72
Male	11 (22.5			8 (4-13)	
Racial/ethnic group					
African-American	2 (11.8)		0.14	8 (4-16)	.89
Caucasian	14 (34.2)			7 (4–13)	
Hispanic/Latino	5 (17.9)			8.5 (5-11)	
Other/Unknown	1 (10.0)			7.5 (6–10	
Hospital					
Danbury Hospital	8 (22.9)		0.95	7 (3-10)	.11
Norwalk Hospital	8 (24.2)			9 (6–11)	
Vassar Brothers Medical Center	5 (20.0)			10 (6–19)	
Putnam and Sharon Hospitals	1 (33.3)			16 (5-17)	
Intubation					
Yes	8 (42.1)		<0.01	14 (11-20)	<.01
No	14 (18.2)			6 (4-10)	
Systemic steroids					
Yes	12 (48.0)		0.03	13 (7-20)	.02
No	10 (14.1)			8 (4–11)	
Therapeutic anticoagulation					
Yes	9 (25.7)		0.62	12 (7-20)	<.01
No	13 (21.3)			6 (4–10)	
IL-6 Inhibitor					
Yes	2 (15.4)		0.49	9 (8–12)	.28
No	20 (12.1)			8 (4–11)	
Diabetes mellitus					
Yes	11 (36.7)		0.03	9.5 (6-20)	.03
No	11 (16.7)			7.5 (4–10)	
Hypertension					
Yes	10 (20.8)		0.63	8.5 (6-14.5)	.05
No	12 (25.0)			6.5 (4-10.5)	
Congestive heart failure					
Yes	2 (22.2)		0.96	7 (3-15)	.72
No	20 (23.0)			8 (1-12)	

oxygen requirement by at least one category (as defined in the *Matching* section) within seven days after transfusion.

3.2 | Comparison of the cases and controls

Descriptive analyses demonstrated balanced groups across variables with a few exceptions (Table 1). There was a higher proportion of patients in the control group with congestive heart failure, and a small but statistically significant difference in the duration of symptoms prior to hospitalization.

3.3 | Hospital course

There was no significant difference in the rate of intubation or in the peak CRP levels during hospitalization. Among the patients who were not intubated at admission, 19% in the case group and 15% in the control group required intubation during hospitalization ($P = .59$). Median (IQR) peak CRP level during hospitalization was 33.2 (21.3-160.3) mg/L among plasma recipients and 112.7 (36.5-218.2) mg/L among the controls ($P = .1$). Additionally, a higher proportion of plasma recipients (17%) compared to the controls (3%) developed a thromboembolic event ($P = .05$).

Lastly, there was a significantly greater proportion of convalescent plasma recipients exposed to therapeutic anticoagulation (18 vs 69%, $P < .01$), systemic steroids (13 vs 31%, $P = .03$), and IL-6 inhibitor (tocilizumab, 8 vs 23%, $P = .04$).

3.4 | Mortality

In-hospital mortality was 20% among the cases and 24.6% among the controls ($P = .61$). Table 2 shows the relationships between potential confounders and mortality. Age 65 and older, diabetes mellitus, intubation, and systemic steroid therapy were significantly associated with mortality. The results of the multivariable logistic regression model are displayed in Table 3. After adjusting for covariates, there was no significant difference in mortality by study group ($P = .71$).

In our patient population, age ≥ 65, intubation, and male gender were significant predictors of mortality in the multivariate regression analysis (Table 3). Duration of symptoms prior to admission was not significant ($P = .60$) and was dropped from the model. Patients 65 or older were more than 78 times as likely to die as younger patients. Patients who were intubated at any time during hospitalization were 14.5 times more likely to die than patients who were not intubated. Males were 5 times more likely to die than females. African American patients were less likely to die when compared to Caucasian patients. The differences between Caucasian and Hispanic/Latino, and Other racial/ethnic groups were not significant.

Due to the strong relationship between mortality and intubation, a post hoc logistic regression analysis was run for the subgroup of patients who were never intubated (n = 71). There were no deaths among patients younger than 65 in this subgroup, so age was included as a continuous covariate. No statistically significant association between study group, gender, or any of the therapies and in-hospital mortality was noted, while age remained a significant predictor of mortality (OR (95% CI): 1.21 (1.04, 1.40), $P = .01$). A *post-hoc* power analysis showed that we had 7% power to detect the difference in mortality this small (20% vs 24.6%) with 35 cases and 61 controls.

3.5 | Hospital Length of Stay

The median (IQR) LOS was significantly greater among the convalescent plasma recipients compared to the

TABLE 3 Results of multivariate regression analysis predicting in-hospital mortality

Parameter	Comparison	Estimate (SE)	Odds Ratio (95% CI)	*P*
Study Group	Case vs Control	−0.22 (0.37)	0.65 (0.15, 2.77)	.56
Age Group	≥ 65 vs <65 years	2.18 (0.59)	78.18 (7.72, 791.38)	<.01
Gender	Male vs Female	0.84 (0.44)	5.34 (0.95, 30.03)	.06
Race				.08
	Black vs White	−2.27 (1.06)	0.03 (0, 0.44)	.03
	Hispanic vs White	0.25 (0.69)	0.4 (0.07, 2.42)	.72
	Other vs White	0.87 (1.06)	0.75 (0.05, 10.47)	.41
Intubation	Yes vs No	1.34 (0.44)	14.5 (2.61, 80.47)	<.01
Systemic steroids	Yes vs No	0.82 (0.47)	5.12 (0.81, 32.22)	.08
Diabetes mellitus	Yes vs No	0.69 (0.4)	3.95 (0.83, 18.85)	.08

controls, 10 (6-17) vs 7 (4-11) days, $P < .01$. After controlling for age, gender, comorbidities (diabetes mellitus and hypertension), hospital, intubation, and pharmacologic interventions (systemic steroids and therapeutic anticoagulation), we found there was not a significant difference in LOS among patients who received convalescent plasma therapy when compared to those who did not ($P > .1$). In contrast, intubation, systemic steroid therapy, and co-morbidities (diabetes mellitus or hypertension) were associated with significantly longer LOS ($P < .01$).

In post hoc analysis, a similar model that excluded patients who expired in the hospital and those who were intubated, found that patients who received plasma had LOS approximately 3 days longer than the controls ($P = .02$); the patients aged 65 and up stayed 4 days longer than those younger than 65 ($P < .01$).

4 | DISCUSSION

In this matched cohort study of patients hospitalized with COVID-19, we aimed to explore the efficacy of convalescent plasma treatment. We found no statistically significant difference in overall in-hospital mortality and LOS between subjects who received convalescent plasma therapy and the controls, after matching on demographic characteristics and disease severity at the time of hospital admission and controlling for covariates. We observed a 4.6% difference in in-hospital mortality between the groups; however, our study was not powered to detect such a small difference.

In viral infections, initial innate immune response, which involves production of interferon and other cytokines, is followed by adaptive cellular and antibody responses after 6 to 8 days.[31] During the second week of disease, certain patients with COVID-19 develop hyperimmune response and pneumonia, which may progress to acute respiratory distress syndrome.[12,13,31] Therefore, timing of convalescent plasma therapy, based on the idea that administered antibodies may suppress viremia, and disease severity at the time of transfusion are major factors to consider when evaluating study results.

In the first randomized clinical trial of convalescent plasma therapy for COVID-19 from Wuhan (China), Li et al. reported no effect on time to clinical improvement or mortality among 103 patients with severe and life-threatening disease, despite a higher negative conversion rate of viral PCR at 72 hours among the plasma recipients. [32] The median (IQR) interval between the onset of symptoms and randomization was 30 (20–39) days. In contrast, patients in our study received convalescent plasma therapy at the median (IQR) time of 10 (7–13) days after symptom onset. In addition, a smaller percentage of subjects in our study required artificial ventilation (11% vs 25%) at the time of enrollment. However, despite earlier timing and lesser disease severity, no effect on clinical outcomes was observed in our population. A plausible explanation for the lack of efficacy could be the presence of autologous antibodies to SARS-CoV-2 at the time of convalescent plasma administration. In the Con-COVID trial from the Netherlands, the median (IQR) time between symptom onset and enrollment was similar to our cohort, at 10 (6–15) days after symptom onset.[33] However, the trial was discontinued early due to concerns for potential lack of benefit of convalescent plasma as most patients (about 80%) already had high titers of anti-SARS-CoV-2 total Ig G/Ig M and neutralizing antibodies at the time of hospital admission.

Liu and colleagues reported results of a propensity score-matched control study of convalescent plasma therapy in 39 patients with severe and life threatening COVID-19 and found the therapy to be potentially effective.[34] Subgroup analyses suggested significant survival benefits of convalescent plasma in patients who were not intubated and those who had a shorter duration of symptoms (≤7 days before admission). In our study, duration of symptoms prior to admission and percentage of subjects requiring intubation were similar to the study by Liu *et al*. However, while intubation was a significant predictor of mortality among our patient population, there was no benefit of convalescent therapy noted regardless of intubation status. Our results among non-intubated patients are consistent with findings of Rogers *et al*., who found no significant difference in the risk of in-hospital mortality in 64 non-intubated convalescent plasma recipients with severe COVID-19 and matched controls.[35] The median (IQR) time between symptom onset and convalescent plasma transfusion was shorter (7 (5–9) days) compared to our patient population. Two other studies evaluated the effectiveness of convalescent plasma when administered relatively early, at the median of 8 days after symptom onset, and found no effect on clinical status or mortality.[36,37] However, they targeted a different patient population compared to our study, patients with COVID-19 severe pneumonia and moderate COVID-19.

A potential benefit of early convalescent plasma treatment was suggested by data from the expanded access program that was a result of collaboration between the FDA and Mayo Clinic and included over 35 000 patients.[38] The seven-day and 30-day mortality was significantly lower in patients transfused within 3 days of COVID-19 diagnosis compared to transfused 4 or more days after the diagnosis, with a gradient of mortality seen in relation to IgG antibody levels in the transfused plasma. Unfortunately, the study did not include a

control group, and no data on the time from symptom onset to the transfusion was available. In a randomized, placebo-controlled trial by Libster *et al*, high-titer convalescent plasma administered within 72 hours after the onset of mild COVID-19 symptoms in older adults reduced the disease progression.[39] The data on convalescent plasma use in patients with SARS also suggests that it is more effective in earlier stage of disease.[18,40] Further research is needed to establish the optimal time frame for convalescent plasma therapy in COVID-19.

In our study, a significantly greater proportion of convalescent plasma recipients were exposed to IL-6 inhibitor, systemic steroids, and therapeutic anticoagulation. However, we found no signal of difference in disease severity between the groups. As there was a trend towards later admission dates among the cases compared to the controls, the differences in pharmacologic interventions are likely related to changes in provider practices guided by evolving evidence on management of COVID-19. In addition, a period prevalence of thromboembolic events, requiring anticoagulation, was higher among the cases. However, despite the potential additive effect of these pharmacologic interventions, in addition to the convalescent plasma therapy, the overall in-hospital mortality among the plasma recipients was not significantly lower compared to the controls, with plasma recipients staying in the hospital longer than controls, which argue against a potential therapeutic benefit of convalescent plasma therapy. Moreover, in the multivariable regression analysis that accounted for the potential effects of the pharmacologic interventions, there was no signal of a potential benefit of convalescent plasma treatment.

This study was not designed/powered to evaluate predictive role of baseline patient characteristics on the prognosis. However, we were able to validate previously established correlation between increasing age, male gender, diabetes mellitus, and increased risk of dying in patients hospitalized with COVID-19.

In addition to the limitations discussed above, this study has other limitations. Although we employed matching and the patient characteristics were well balanced between the study groups, the conclusions drawn from the data are less robust compared to a randomized study design. The modest sample size limited our ability to perform subgroup analysis. Our study evaluated mortality only during hospitalization associated with the initial diagnosis of COVID-19. No data on titers of anti-viral antibodies in the donors was available to evaluate dose-response relationship. Finally, results of this study should be interpreted considering the fact that cases presented to the hospital at a later time period compared to controls. However, no survival benefit among convalescent plasma recipients was observed despite the potential advantage of an evolved understanding of the disease and therapeutic approaches.

While we observed no transfusion reaction in our study, there are potential risks associated with convalescent plasma therapy. Immune-mediated reactions include allergy/anaphylaxis, transfusion-related acute lung injury (TRALI), and hemolysis, which are uncommon (<1% of transfusions) but potentially life-threatening.[41-44] While there is evidence that convalescent plasma therapy may have immunomodulatory effect by blunting the cytokine response, it also has a potential to aggravate the disease through antibody-mediated enhancement of proinflammatory effects, which is a concern given that "cytokine storm" is the main pathophysiological mechanism responsible for severe and life-threatening COVID-19.[12,16,45] The risk of transfusion-related circulatory overload (TACO) with fresh frozen plasma infusion for management of coagulopathies is typically higher than the risk of immune-mediated reactions and could be underreported.[44] However, the risk of TACO with convalescent plasma treatment is likely lower given that a smaller volume (1-2 units) of product is infused. With the rigorous standards for blood products in developed countries, risk of microbial transmission is extremely low.[41]

5 | CONCLUSIONS

In this case-control study, we detected no signal of improved in-hospital mortality or shortened hospital length of stay associated with convalescent plasma therapy in patients hospitalized for COVID-19. The role of convalescent plasma therapy administered early in the disease process should be a major focus of future exploration.

ACKNOWLEDGMENTS

We thank all the healthcare providers who worked tirelessly to care for the patients enrolled in this study. We applaud the altruism of patients who donated convalescent plasma and acknowledge the hard work of blood bank staff at New York Blood Center, American Red Cross (Farmington, CT), and Nuvance Health Hospitals. We thank medical and surgical residents at Danbury Hospital and Vassar Brothers Medical Center who assisted with collecting data for the COVID-19 registry. We are grateful for the assistance of Laura Morales, James Nitzkorski, Helene Rached, Stephanie Stroever, and Danbury Hospital internal medicine residency program with logistical issues related to this project. This study has not been registered with ClinicalTrials.gov due to the retrospective nature of study design. This study has

been approved by the Biomedical Research Alliance of New York (BRANY). No patient consent was obtained given that it is a retrospective study.

CONFLICT OF INTEREST

The authors have no disclaimer or conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Oleg V. Sostin https://orcid.org/0000-0002-5681-5263

REFERENCES

1. Ellis, Ralph. COVID likely third leading cause of death in U.S. WebMD [Internet]. 2021 Retrieved from https://www.webmd.com/lung/news/20210107/covid-likely-third-leading-cause-of-death-in-u-s
2. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19—preliminary report. *N Engl J Med*. 2020. http://doi.org/10.1056/nejmoa2021436.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - preliminary report. *N Engl J Med*. 2020;383:1813-1826.
4. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, White A, Anderson AS, Chilton R. The role of anticoagulation in COVID-19-induced hypercoagulability. *Curr Cardiol Rep*. 2020;22(7):53.
5. De Rossi N, Scarpazza C, Filippini C, et al. Early use of low dose tocilizumab in patients with COVID-19: a retrospective cohort study with a complete follow-up. *EClinicalMedicine*. 2020;100459:17.
6. Horby P, Mafham M, Linsell L, et al. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N Engl J Med*. 2020;383(21):2030-2040.
7. Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020;382(19):1787-1799.
8. NIH. U.S. national library of medicine. COVID-19 studies from the world health organization database [Internet]. 2020. Available from: https://clinicaltrials.gov/ct2/who_table
9. Food and Drug Administration. Recommendations for Investigational COVID-19 Convalescent Plasma [Internet]. U.S. Food & Drug Administration. 2020. Available from: www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma
10. Wu F, Wang A, Liu M, Wang Q, Chen J, Xia S, et al. Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.30.20047365.
11. Coughlin MM, Prabhakar BS. Neutralizing human monoclonal antibodies to severe acute respiratory syndrome coronavirus: target, mechanism of action, and therapeutic potential. *Rev Med Virol*. 2012;22(1):2-17.
12. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: the current evidence and treatment strategies. *Front Immunol*. 2020;11:1708.
13. McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. *Autoimmun Rev*. 2020;19(6):102537.
14. Lünemann JD, Nimmerjahn F, Dalakas MC. Intravenous immunoglobulin in neurology—mode of action and clinical efficacy. *Nat Rev Neurol*. 2015;11(2):80-89.
15. Garraud O, Heshmati F, Pozzetto B, et al. Plasma therapy against infectious pathogens, as of yesterday, today and tomorrow. *Transfus Clin Biol*. 2016;23(1):39-44.
16. Marano G, Vaglio S, Pupella S, et al. Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus*. 2016;14(2):152-157.
17. Who Mers-Cov Research Group. State of knowledge and data gaps of middle East respiratory syndrome coronavirus (MERS-CoV) in humans. *PLoS Curr*. 2013;12:5.
18. Cheng Y, Wong R, Soo YOY, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis*. 2005;24(1):44-46.
19. Wong VWS, Dai D, Wu AKL, Sung JJY. Treatment of severe acute respiratory syndrome with convalescent plasma. *Hong Kong Med J*. 2003 Jun;9(3):199-201.
20. Tanne JH. Covid-19: FDA approves use of convalescent plasma to treat critically ill patients. *BMJ*. 2020;26:368, m1256.
21. Food and Drug Administration. FDA issues emergency use authorization for convalescent plasma as potential promising COVID–19 treatment, another achievement in administration's fight against pandemic [Internet]. U.S. Food & Drug Administration. 2020. Available from: www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment
22. Food and Drug Administration. HHS. Requirements for blood and blood components intended for transfusion or for further manufacturing use. Final rule. *Fed Regist*. 2015;80(99):29841-29906.
23. FDA. Investigational COVID-19 Convalescent Plasma-Emergency INDs. [Internet]. 2020. Available from: https://natap.org/2020/COVID/032320_39.htm
24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
25. Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. *Metab Clin Exp*. 2020;108:154262.
26. Luo X, Zhou W, Yan X, Guo T, Wang B, Xia H, et al. Prognostic value of C-reactive protein in patients with coronavirus 2019. *Clinical Infectious Diseases*. 2020;71(16):2174-2179.

27. Centers for Disease Control and Prevention. Your health: People with certain medical conditions [Internet]. Coronavirus Disease 2019 (COVID-19). 2020. Available from: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fneed-extra-precautions%2Fgroups-at-higher-risk.html
28. Vardavas CI, Nikitara K. COVID-19 and smoking: a systematic review of the evidence. *Tob Induc Dis*. 2020;18:20.
29. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810.
30. Ciccullo A, Borghetti A, Zileri Dal Verme L, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line. *Int J Antimicrob Agents*. 2020;56(2):106017.
31. National Institute of Allergy and Infectious Disease. Immune response to COVID-19. Comprehensive analyses of innate and adaptive immune responses during acute COVID-19 infection and convalescence. [Internet]. 2020. Available from: https://www.niaid.nih.gov/research/immune-response-covid-19
32. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *Jama*. 2020;324(5):460-470.
33. Gharbharan A, Jordans CCE, GeurtsvanKessel C, et al. Convalescent plasma for COVID-19. A randomized clinical trial. *medRxiv*. 2020;1. https://doi.org/10.1101/2020.07.01.20139857.
34. Liu STH, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: a propensity score-matched control study. *Nat Med*. 2020;26(11):1708-1713.
35. Rogers R, Shehadeh F, Mylona EK, et al. Convalescent plasma for patients with severe COVID-19: a matched cohort study. *Clinical Infectious Diseases*. 2020. https://doi.org/10.1093/cid/ciaa1548.
36. Simonovich VA, Burgos Pratx LD, Scibona P, et al. A randomized trial of convalescent plasma in Covid-19 severe pneumonia. *N Engl J Med*. 2020. http://doi.org/10.1056/nejmoa2031304.
37. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate covid-19 in adults in India: open label phase II multicentre randomised controlled trial (PLACID trial). *BMJ*. 2020;m3939:371.
38. Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv*. 2020. https://doi.org/10.1101/2020.08.12.20169359.
39. Libster R, Pérez Marc G, Wappner D, et al. Early high-titer plasma therapy to prevent severe Covid-19 in older adults. *N Engl J Med*. 2021. http://doi.org/10.1056/nejmoa2033700.
40. Soo YOY, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect*. 2004;10(7):676-678.
41. MacLennan S, Barbara JAJ. Risks and side effects of therapy with plasma and plasma fractions. *Best Pract Res Clin Haematol*. 2006;19(1):169-189.
42. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med*. 2006;145(8):599-609.
43. NIH. Convalescent Plasma [Internet]. COVID-19 treatment guidelines. 2020. Available from: www.covid19treatmentguidelines.nih.gov/immune-based-therapy/blood-derived-products/convalescent-plasma/
44. Pandey S, Vyas GN. Adverse effects of plasma transfusion. *Transfusion*. 2012;52(Suppl 1):65S-79S.
45. Hung IF, To KK, Lee C-K, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza a (H1N1) 2009 virus infection. *Clin Infect Dis*. 2011;52(4):447-456.

How to cite this article: Sostin OV, Rajapakse P, Cruser B, Wakefield D, Cruser D, Petrini J. A matched cohort study of convalescent plasma therapy for COVID-19. *J Clin Apher*. 2021;36:523–532. https://doi.org/10.1002/jca.21888

APPENDIX 1

Testing for SARS-CoV-2 infection

The Abbott RealTime SARS-CoV-2 and several SARS-CoV-2 RNA tests were used for laboratory diagnosis of SARS-CoV-2 infection in the subjects. The Abbott RealTime SARS-CoV-2 assay is a Nucleic-acid Amplification test (NAAT), which allowed qualitative detection of the viral nucleic acids in nasal swabs; the testing was performed by Nuvance Health laboratories. The various SARS-CoV-2 RNA tests are real time reverse transcriptase (RT PCR) assays utilizing qualitative multitarget detection of the viral RNA in nasopharyngeal swabs. They were performed by the New York State Wadsworth Center, Sunrise Medical Laboratories, and Quest Diagnostics, using Roche, Panther Hologic, and both Quest and Wadsworth lab developed tests, all of which received FDA emergency use authorization. The swabs were obtained in outpatient, emergency department, or inpatient settings and transported to the laboratories in universal transport media (for the RT-PCR tests) or paper swab packages (Abbott RealTime).