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Potential predictors of outcomes among hospitalized COVID-19 patients treated with convalescent plasma: a single-center study

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ABSTRACT

Background: The coronavirus disease 2019 pandemic is a major international public health crisis, which has led to over 3 million deaths as of April 2021. Several therapeutics have been tried for this deadly illness including antivirals, immunosuppressive agents and convalescent plasma (CP). In this study, we present our inner-city safety net hospital experience with CP therapy.

Methods: This was a retrospective chart review of hospitalized patients with confirmed COVID-19 who were treated with CP.

Results: A total of 60 patients received CP during the study period. The mean age for patients in this study was 58.95 years. The most common presenting symptoms were shortness of breath (85%) and cough (73%). Hypertension (65%) and diabetes mellitus (55%) were the most common comorbidities in our patients. In our multivariate regression analysis, male sex, nausea and loss of appetite at presentation were associated with improvement in oxygenation after CP. Total survival time, history of obstructive airway disease, home use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers were associated with decreased survival, whereas Hispanic ethnicity showed a trend towards lower survival after CP therapy.

Conclusions: Our study highlights several important characteristics of inner-city safety net hospital patient population who might benefit from CP therapy.

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Convalescent plasma; COVID-19; ethnicity

1. Introduction

The coronavirus disease 2019 pandemic is a major international public health crisis since the 1918 pandemic influenza. The disease is caused by SARS-CoV2, which is a single-stranded RNA virus [1]. Clinical presentation ranges widely with more than half of patients developing asymptomatic infection. In patients whose infection becomes severe, it can lead to acute respiratory failure, multi-organ damage and death. In an effort to contain this pandemic, several therapies have emerged over the last few months. Convalescent plasma (CP) therapy is thought to be helpful against SARS-CoV2 due to its prior success against RNA viruses [2,3]. CP therapy works by direct neutralization of the virus, as well as controlling an exaggerated inflammatory cascade [4]. In August 2020, the US Food and Drug Administration (FDA) issued an emergency use authorization (EUA) for CP use in patients with coronavirus disease 2019 (COVID-19) [5]. Despite its widespread use, available clinical data has not demonstrated a consistent benefit of this therapy [6]. Based on the evidence available, CP has been shown to be more efficacious when high-titer plasma is used early in the course of COVID-19 illness [7–9]. There were also concerns regarding the safety of CP therapy. In a large safety study of 20,000 patients, 146 serious adverse events (transfusion reactions) were reported within 4 hours of completion of therapy [10].

BronxCare Health System is located in the South Bronx of New York City, and it serves a predominantly ethnic minority patient population. During the course of the pandemic, we have encountered a significant reluctance among our COVID-19 patients in their willingness to accept various available therapeutic modalities, including CP. In this study, we aim to analyze the characteristics of all adult COVID-19 patients admitted to our hospital and who received CP from 1 March 2020 to 10 December 2020.

2. Materials and methods

We conducted this study at BronxCare Health System, which is the largest not-for-profit health system in the Bronx borough of New York City. A retrospective chart review of all adults admitted with COVID-19 illness and received CP between the

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period of 1 March 2020 to 10 December 2020 was performed. COVID-19 was diagnosed based on positive reverse transcriptase polymerase chain reaction (RT-PCR) analysis via a nasopharyngeal swab at any point during their hospitalization. We performed a subgroup analysis based on ethnicity to assess if there was a difference in subgroups. The need for consent was waived due to the retrospective nature of this study.

During the study period, an inpatient guide for the management of COVID-19 was developed by the Department of Medicine at BronxCare Health System. Our patients received supportive and therapeutic modalities based on the individual physician's clinical discretion and the best available evidence at that time.

Data extraction for this study was done from our electronic medical records. The data obtained included demographics, comorbidities, self-reported symptoms at the time of presentation, therapeutic modalities received during the hospitalization, baseline laboratory findings and final disposition. The study outcomes were defined as an improvement in oxygenation status after CP therapy (which was assessed using a 5-point scale as described below) and overall mortality.

We categorized patients based on the following 5-point scale, which depicts the severity of their illness before and after receiving CP.

0 = Patients on room air

1 = Patients requiring low-flow supplemental oxygen

2 = Patients requiring high-flow supplemental oxygen

3 = Patients requiring non-invasive positive pressure ventilation

4 = Patients requiring invasive mechanical ventilation

Any improvement or worsening in clinical status after CP therapy was assessed using this point-based scale.

During the study period, our patients received CP from two different blood banks. Blood Bank #1 was used predominantly during the first wave of COVID-19 surge and accounted for all 30 (100%) of the transfusions before 5 May 2020. Blood Bank #2 was first used after 5 May and accounted for 24 out of 30 (80%) of the CP transfusions after that date. It is noteworthy that the care of COVID-19 patients and therapeutics have significantly evolved over the period of time; therefore, any interpretation of our study results should take into consideration the unmeasured confounders that could affect the outcomes of patients receiving CP treatment during a specific time interval.

2.1. Statistical analysis

Continuous normally distributed variables were reported using means and standard deviation. Continuous variables were compared using the Student's *t*-test. If the normality was not met, the rank Kruskal–Wallis test was applied instead. Equality of variances was tested using Levene's test. Continuous non-normally distributed variables were reported using median and first and third quartiles (Q1 and Q3). Normality was assessed using the Shapiro–Wilk test. Categorical variables were compared using the chi-squared test. We studied the total survival time and the difference between pre- and post-plasma oxygenation scores. Then, multivariate models were built, Cox for the hazard of death and the regression model for the post-plasma oxygenation score difference. Due to numerical reasons, the final models were obtained using a block-wise backward procedure with the *p*-value for removal set at <0.1. Blocks of variables were created based on theoretical baseline information, baseline comorbidities, symptoms, laboratory parameters and interventions. Only the results significant at 0.05 levels were interpreted. The proportional hazard assumption in the final Cox model was tested using Schoenfeld residuals.

3. Results

A total of 60 patients were included in our study. Of these, 45 were Hispanics and 15 were non-Hispanics. Among non-Hispanics, 11 were African Americans/Blacks, 2 were Whites and 2 patients belonged to Asian and other races. Acceptance to CP therapy was noted to be lower among the African American/Black patients. The mean age for patients in this study was 58.95 years (Table 1). Most common presenting symptoms were shortness of breath (85%) and cough (73%), followed by fever (58%), diarrhea (23%) and abdominal pain (15%). Hypertension (65%) and diabetes mellitus (55%) were the most common comorbidities, followed by obstructive airway disease (27%), coronary artery disease (15%), chronic kidney disease (13%) and congestive heart failure (10%). 18% of our patients were on angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-receptor blockers (ARB) at home prior to presentation. At the time of admission, median hemoglobin levels were 14.5 g/dl (interquartile range [IQR] 7.25–24.75), absolute lymphocyte counts were 0.75 k/μl (IQR 0.5–1.1), serum creatinine levels were 1.1 mg/dl (IQR 0.9–1.6), D-dimers were 572 ng/ml (IQR 380.5–1110.5), serum lactate dehydrogenase (LDH) levels were 450 units/L (IQR 320–681), serum

ferritin levels were 610.5 ng/ml (250.5–1175.5), C-reactive protein levels were 116.4 (IQR 51–205.3) and lactic acid levels were 1.7 mmoles/L (IQR 1.3–2.2). In-hospital treatment included systemic steroids (93%), antibiotics (97%), anticoagulation (80%), remdesivir (45%), tocilizumab (58%) and oseltamivir (58%). Prior to receiving CP therapy, 3 (5%) patients were on room air, 13 (21.7%) patients were on low-flow nasal cannula, 5 (8.3%) patients were on high-flow nasal cannula, 17 (28.3%) patients were requiring non-invasive positive pressure ventilation and 22 (36.7%) were on invasive mechanical ventilation. When comparing Hispanics to non-Hispanics, non-Hispanics had a higher rate of obesity (median body mass index [BMI] 35 (IQR 28.3–38.44) vs median BMI 29 (IQR 26.6–33.6), $p = 0.035$), had higher serum lactate dehydrogenase (LDH) levels (552 units/L [IQR 466–705] vs 437 [IQR 278.5–540.5], $p = 0.046$) and were more likely to have received inpatient antiretroviral therapies (Table 2). Improvement from baseline oxygenation status was evaluated on a 5-point scale oxygenation scale before and after CP therapy. In our univariate regression analysis, there were no significant differences in pre- and post-plasma oxygenation scores between Hispanics and Non-Hispanics ($p = 0.897$) and between the two blood banks ($p = 0.153$). In our multivariate regression analysis, male gender, the presence of nausea and loss of appetite at presentation, and those who received CP from Blood Bank #2 were associated with an improvement in oxygenation scores. On the other hand, patients who presented with generalized weakness and abdominal discomfort were more likely to have worsening in oxygenation scores after CP therapy (Table 3). In our multivariate analysis for total survival time, history of obstructive airway disease and home ACEI/ARB use were associated with decreased survival, whereas Hispanic ethnicity showed a trend towards lower survival after CP therapy ($p = 0.07$) (Table 4). Interestingly, time on mechanical ventilation was associated with an increased survival time.

4. Discussion

In this study, we evaluated patients who were admitted with COVID-19 and treated with CP at our inner-city hospital, with approximately 97% of our study patients belonging to an ethnic minority. Our study has identified several patient characteristics that could help identify patients who may benefit from CP therapy. Male gender and presenting symptoms of nausea and loss of appetite were associated with an improvement in oxygenation scores, whereas history of obstructive airway disease and home ACEI/ARB use were associated with decreased survival time after CP therapy. Patients who are of Hispanic origin also showed a trend towards decreased survival after CP therapy; however, this outcome did not reach a statistical significance. Interestingly, time on mechanical ventilation was associated with increased survival time after CP.

The role of CP therapy in ethnic minorities has not been studied extensively. Social and health inequities are known to increase the risk of poor outcomes in COVID-19, and this is especially prevalent in the racial and ethnic minority groups [11,12]. Racial and ethnic minority groups are less likely to be insured and experience an increased barrier to the access of healthcare, compounded by factors such as the lack of child care, transportation, crowded living facilities, along with language and cultural barriers [13,14]. They are also disproportionately represented in the essential workforce and industries, leading to an increased exposure to COVID-19 [15]. Furthermore, disparities in access to higher education may lead to lower-paying and less stable jobs, thereby making it harder for them to miss a workday, even when they are sick [16]. Therefore, our study will provide a valuable perspective on the existing literature on CP therapy in COVID-19. Specifically, our study has shown that Hispanic patients showed a trend towards a lower survival time after CP therapy.

Many studies have investigated the role of different pharmacological therapies for COVID-19 patients. Current evidence suggests that males are more likely to have severe symptoms and a higher mortality compared to females [17–19]. It is not fully understood if immune responses, hormonal mechanisms or underlying genetics plays a role in determining the severity of illness in male COVID-19 patients. Furthermore, most studies investigating therapeutic interventions in COVID-19 lacked either a gender-based design or a post-hoc gender-specific analysis [20]. In our study, males were more likely to have an improvement in oxygenation status after receiving CP therapy when compared to females. This finding differs from the majority of published literature, where males are more likely to have a poorer outcome with COVID-19, and has not been reported in CP therapy literature thus far. The most significant association between male sex and CP is shown in studies, which assessed the titers of neutralizing antibody in CP donors. It was shown that males had higher convalescent antibody titers, after adjusting for hospitalization and severity of illness [21,22]. While the reason for the association seen in our study is unclear, we postulate that further boosting with preformed antibodies in CP of an already enhanced immune response in males could confer the benefits seen in our study.

Additionally, patients with underlying obstructive airway diseases and those who were using ACEI/ARB at home prior to developing COVID-19 had lower

Table 1. Baseline demographics and clinical characteristics.

Variable	Patients (N = 60)
Age (mean years (SD))	58.95 (13.51)
Sex (females), *n* (%)	25 (42%)
BMI, kg/m^2, median (IQR)	29.4 (26.6–35.6)
Race	
African American/Black	11 (18.3%)
Hispanics/Latino	45 (75%)
Whites	2 (3.3%)
Asian/others	2 (3.3%)
Symptoms, *N* (%)	
Fever	35 (58%)
Cough	44 (73%)
Shortness of breath	51 (85%)
Abdominal pain	9 (15%)
Diarrhea	14 (23%)
Baseline comorbidities/risk factors, *N* (%)	
Hypertension	39 (65%)
Diabetes mellitus	33 (55%)
Obstructive airway disease	16 (27%)
Chronic liver disease	1 (2%)
Congestive heart failure	6 (10%)
Coronary artery disease	9 (15%)
Chronic kidney disease	8 (13%)
HIV	2 (3%)
Malignancy	2 (3%)
Tobacco use	
No	48 (80%)
Yes	2 (3%)
Home medications, *N* (%)	
Angiotensin-converting ezyme inhibitor/angiotensin-receptor blocker (ACEI/ARB)	11 (18%)
Systemic steroids	2 (3%)
Anticoagulation	2 (3%)
Baseline labs, median (IQR)	
Hemoglobin (g/dl)	14.5 (7.25–24.75)
Serum sodium (mEq/L)	136 (134–138.5)
Serum potassium (mEq/L)	4.4 (3.9–4.7)
Serum creatinine (mg/dl)	1.1 (0.9–1.6)
White blood cell count (k/μl)	7.6 (5.55–10.5)
Absolute neutrophil count (ANC) (k/μl)	5.8 (4.07–8.5)
Absolute lymphocyte count (ALC) (k/μl)	0.75 (0.5–1.1)
ANC/ALC ratio	8.6 (6.21–15.81)
D-Dimer (ng/ml)	572 (308.5–1110.5)
Serum LDH (unit/L)	450 (320–681)
C-reactive protein	116.4 (51–205.3)
Serum ferritin (ng/ml)	610.5 (250.5–1175.5)
Lactic acid (mmoles/L)	1.7 (1.3–2.2)
Aspartate aminotransferase (unit/L)	43.5 (28–71.5)
Alanine aminotransferase (unit/L)	29 (20.5–49.25)
In-hospital therapies, *N* (%)	
Hydroxychloroquine	26 (43%)
Anti-retrovirals	4 (7%)
Antibiotics	58 (97%)
Oseltamivir	35 (58%)
Remdesivir	27 (45%)
Systemic steroids	56 (93%)
Anticoagulation	48 (80%)
Barcitinib	1 (2%)
Tocilizumab	35 (58%)
Pre-plasma oxygenation status	
Room air	3 (5%)
Low-flow oxygen	13 (21.7%)
High-flow oxygen	5 (8.3%)
Non-invasive positive pressure ventilation	17 (28.3%)
Invasive mechanical ventilation	22 (36.7%)

IQR: interquartile range; SD: standard deviation.

Table 2. Baseline demographics and interventions by ethnicity.

	Non-Hispanic (n = 15)	Hispanic (n = 45)	*p*-Value
Age in years (mean (SD))	61.47 (12.90)	58.11 (13.74)	0.409
Sex (females), *n* (%)	8 (53%)	17 (38%)	0.290
BMI, kg/m^2, median (IQR)	35 (28.2–38.44)	29 (26.6–33.6)	0.035
Symptoms, *N* (%)			
Fever	9 (60%)	26 (58%)	0.880
Cough	12 (80%)	32 (71%)	0.500
Shortness of breath	15(100%)	36 (80%)	0.060
Abdominal pain	1 (7%)	8 (18%)	0.297
Diarrhea	3 (20%)	11 (24%)	0.724
Baseline comorbidities/risk factors, *N* (%)			
Hypertension	11 (73%)	28 (62%)	0.435
Diabetes mellitus	7 (47%)	26 (58%)	0.454
Obstructive airway disease	3 (20%)	13 (29%)	0.500
Chronic liver disease	0	1 (2%)	0.560
Congestive heart failure	2 (13%)	4 (9%)	0.619
Coronary artery disease	2 (13%)	7 (16%)	0.835
Chronic kidney disease	3 (20%)	5 (11%)	0.380
HIV	1 (7%)	1 (2%)	0.406
Malignancy	1 (7%)	1 (2%)	0.406
Tobacco use			
No	12 (80%)	36 (80%)	0.027
Yes	2 (3%)	0	
Home medications			
ACEI/ARB	4 (27%)	7 (16%)	0.335
Systemic steroids	2 (13%)	0	0.013
Anticoagulation	1 (7%)	1 (2%)	0.406
Baseline labs, median (IQR)			
Hemoglobin (g/dl)	16 (12–21)	14 (7–25)	0.675
Serum sodium (mEq/L)	138 (135–140)	136 (134–138)	0.234
Serum potassium (mEq/L)	4.2 (3.9–4.5)	4.4 (3.9–4.7)	0.321
Serum creatinine (mg/dl)	1.1 (0.9–1.4)	1.1 (0.85–1.65)	0.817
White blood cell count (k/μl)	8.3 (7.3–8.8)	7.1 (4.9–10.65)	0.407
Absolute neutrophil count (ANC) (k/μl)	6.3 (5.4–7.7)	5.6 (3.75–8.7)	0.601
Absolute lymphocyte count (ALC) (k/μl)	0.7 (0.6–1.4)	0.8 (0.5–1.05)	0.244
ANC/ALC ratio	6.4 (3.7–16.12)	10.5 (6.7–16.15)	0.135
D-Dimer (ng/ml)	668 (383–2824)	568 (297.5–1068)	0.246
Serum LDH (unit/L)	552 (466–705)	437 (278.5–540.5)	0.046
C-reactive protein	105.1 (53.4–218.7)	127.7 (48.3–198.8)	0.889
Serum ferritin (ng/ml)	745 (354–1485)	591 (244–1175.5)	0.6312
Lactic acid (mmoles/L)	1.7 (1.3–2.2)	1.7 (1.3–2.35)	0.972
Aspartate aminotransferase (unit/L)	29 (22–76)	53 (29.5–71)	0.206
Alanine aminotransferase (unit/L)	23 (16–52)	31 (22.5–47.5)	0.249

(*Continued*)

Table 2. (Continued).

	Non-Hispanic (n = 15)	Hispanic (n = 45)	p-Value
In-hospital therapies, N (%)			
Hydroxychloroquine	7 (47%)	19 (42%)	0.764
Antiretrovirals	3 (20%)	1 (2%)	0.017
Antibiotics	15 (100%)	43 (96%)	0.406
Oseltamivir	7 (47%)	28 (62%)	0.290
Remdesivir	5 (33%)	22 (49%)	0.294
Systemic steroids	15 (100%)	41 (91%)	0.232
Anticoagulation	13 (87%)	35 (78%)	0.456
Barcitinib	1 (7%)	0	0.081
Tocilizumab	9 (60%)	26 (58%)	0.880

HIV: human immunodeficiency virus; IQR: interquartile range; LDH: lactate dehydrogenase; SD: standard deviation.

survival after receiving CP in our study. The use of ACEI/ARB inhibitors in COVID-19 illness has been the focus of multiple research studies since the start of the pandemic due to a theoretical concern that it may increase the expression of the ACE2 receptor, which is needed by the SARS CoV-2 virus for cell entry [23,24]. However, this has not been validated in subsequent studies [25,26]. In our study, the use of ACEI/ARB was associated with lower survival after

Table 3. Multivariate regression for improvement in oxygenation score.

Variable	Estimate	SE	p-Value	95% CI
Male sex	−0.79	0.26	0.003	−1.31 to −0.28
Abdominal discomfort	0.73	0.35	0.041	0.03 to 1.43
Nausea	−1.06	0.37	0.007	−1.81 to −0.31
Loss of appetite	−3.71	1.36	0.009	−6.44 to −0.97
Generalized weakness	0.99	0.3	0.002	0.39 to 1.61
Blood Bank #1 vs #2	0.96	0 .28	0.001	−1.53 to −0.40
Constant	0.99	0.3	0.002	0.39 to 1.61

Table 4. Multivariate analysis for total survival time.

Variable	Estimate	SE	p-Value	95% CI
Hispanic ethnicity	7.79	8.82	0.07	0.85 to 71.62
Obstructive airway disease	6.25	4.48	0.011	1.53 to 25.44
Home angiotensin-converting ezyme inhibitor/angiotensin-receptor blocker (ACEI/ARB)	23.70	26.03	0.004	2.75 to 203.97
Mechanical ventilation	0.77	0.06	<0.001	1.53 to 25.44

CP therapy. The reason for this association is unclear, and it has not been addressed in existing COVID-19 CP literature. On the other hand, chronic obstructive pulmonary disease (COPD) has been shown to be an independent risk factor for all-cause mortality in COVID-19 patients [27], whereas asthma has not been shown to be an independent risk factor for poor outcome in these patients [28,29].

Our study has several limitations. This is a small single-center study with unique patient demographics, and our findings may not be applicable to the general population. Our study is not designed to assess the efficacy of CP therapy in treating patients with COVID-19. Finally, the antibody titers in the CP used in our study were not available; therefore, we will not be able to assess why patients in our study who had received CP from different blood banks have had different responses in terms of improvement in oxygenation.

5. Conclusions

Our study highlights several characteristics of a predominantly ethnic minority safety net hospital patient population that could determine the outcome of CP therapy for COVID-19. Most notably, male gender and time on mechanical ventilation were associated with improved outcomes, whereas a history of chronic obstructive disease and home use of ACEI/ARB were associated with adverse outcomes. Hispanic patients who had received CP therapy also showed a trend towards an adverse outcome.

Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of Bronx Care Health System, NY (IRB # 01 14 21 14 and 14 January 2021).

Informed consent statement

Patient consent was waived due to the retrospective nature of the study. No identifiable patient information is presented in this study.

Data availability statement

Data is available for review on a reasonable request and after institutional approval. Check www.bronxcare.org for more information on the institutional policies regarding data sharing.

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Author contributions

All authors participated in conceptualization, methodology, validation, data curation, resources and writing of the manuscript. All authors have read and agreed to the published version of the manuscript. Magdalena Murawska performed statistical analysis of the study.

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