Title

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Journal

mBio, 14(5)

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et al.

Publication Date

2023-09-19

DOI

10.1128/mbio.00618-23

Peer reviewed

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio

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Early antibody treatment, inflammation, and risk of post-COVID conditions

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ABSTRACT Post-COVID conditions (PCCs) are common and have significant morbidity. Risk factors for PCC include advancing age, female sex, obesity, and diabetes mellitus. Little is known about treatment, inflammation, and PCC. Among 882 individuals with confirmed SARS-CoV-2 infection participating in a randomized trial of COVID-19 convalescent plasma (CCP) vs control plasma with available biospecimens and symptom data, the association between early CCP treatment, cytokine levels, and PCC was evaluated. Cytokine and chemokine levels were assessed at baseline, day 14, and day 90 using a multiplexed sandwich immunoassay (Meso Scale Discovery). Presence of any self-reported PCC symptoms was assessed at day 90. Associations between CCP treatment, cytokine levels, and PCC were examined using multivariate logistic regression models. One third of the 882 participants had day 90 PCC symptoms, with fatigue (14.5%) and anosmia (14.5%) being most common. Cytokine levels decreased from baseline to day 90. In a multivariable analysis, female sex (adjusted odds ratio [AOR] = 2.69 [1.93–3.81]), older age (AOR = 1.32 [1.17–1.50]), and elevated baseline levels of IL-6 (AOR = 1.59 [1.02–2.47]) were independently associated with development of PCC. Those who received early CCP treatment (≤5 days after symptom onset) compared to late CCP treatment had statistically significant lower odds of PCC.

IMPORTANCE Approximately 20% of individuals infected with SARS-CoV-2 experienced long-term health effects, as defined PCC. However, it is unknown if there are any early biomarkers associated with PCC or whether early intervention treatments may decrease the risk of PCC. In a secondary analysis of a randomized clinical trial, this study demonstrates that among outpatients with SARS-CoV-2, increased IL-6 at time of infection is associated with increased odds of PCC. In addition, among individuals treated early, within 5 days of symptom onset, with COVID-19 convalescent plasma, there was a trend for decreased odds of PCC after adjusting for other demographic and clinical characteristics. Future treatment studies should be considered to evaluate the effect of early treatment and anti-IL-6 therapies on PCC development.

KEYWORDS COVID-19, COVID-19 serotherapy, post-COVID condition (PCC), post-acute sequelae of COVID (PASC), interleukin-6, cytokines, chemokines

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 600 million people worldwide and more than 97 million people in the United States (1). Many survivors of coronavirus disease 2019 (COVID-19) report long-term health

Editor Suresh Mahalingam, Griffith University-Gold Coast Campus, Gold Coast, Australia

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Aaron A. R. Tobian and David J. Sullivan are shared senior authors.

See Acknowledgments for conflicts of interest.

See the funding table on p. 13.

Received 13 March 2023
Accepted 2 June 2023
Published 19 September 2023

effects, including persistent symptoms, the development of new comorbidities, and exacerbation of underlying pre-existing conditions. The medical community has formally recognized the long-term health effects of COVID-19 by establishing a diagnosis of post-COVID conditions (PCCs). The World Health Organization (WHO) (2) and U.S. Centers for Disease Control and Prevention (CDC) (3) differ in the definition of the timeline of this diagnosis, but both require that patients have sustained health conditions after resolution of acute COVID-19. According to the WHO, the diagnosis is a history of COVID-19 at least 3 months prior who have had symptoms for at least 2 months that an alternative diagnosis cannot explain (2). The CDC defines PCC as symptoms persisting beyond 4 weeks after acute infection (4).

Although the true incidence of PCC is unknown due to differences in study populations and methodologies, its clinical impact is substantial. Recent data suggest that the prevalence is approximately 20%, with the most commonly reported symptoms being fatigue, shortness of breath, and cognitive dysfunction (5) with higher rates among those >65 years of age (6). Previous studies have demonstrated several host factors that are associated with the development of PCC, including the severity of acute COVID-19, female sex (7–9), advanced age (6, 10, 11), being unvaccinated (11, 12), and presence of pre-COVID comorbidities.

Early treatment for COVID-19 is recommended to prevent hospitalization and death. While a recent observational study has suggested decreased PCC with early treatment with nirmatrelvir (13), the relationship between early effective COVID therapy and the development of PCC has been unclear. In addition to demographic factors and comorbidities, inflammation appears to play a critical role in COVID-19 prognosis. Individuals with elevated levels of IL-6 and C-reactive protein are more likely to have more severe disease and an increased risk of hospitalization during the acute phase (14–18), particularly among males (19). Few studies have evaluated whether cytokines are associated with PCC (20–26), and the limited data demonstrate inconsistent results. Some studies have shown an association between PCC and IL-6 (20, 22), while others have not (24, 25). This is likely due to study limitations, including small sample sizes, lack of prospective monitoring of symptoms and sample collection, and inconsistent timing in the disease course in relation to cytokine evaluation.

To investigate these relationships, we analyzed prospectively collected data from participants enrolled in a randomized outpatient treatment trial of COVID-19 convalescent plasma (CCP) to identify factors associated with the development of PCC, including early treatment and biomarkers measured early in the course of disease.

MATERIALS AND METHODS

Participants

The Convalescent Plasma to Limit SARS-CoV-2 Associated Complications (CSSC-004) trial was a double-blind, multicenter, randomized, controlled trial investigating the use of CCP for the prevention of hospitalization among outpatients when compared to control plasma, as previously described (27). The trial recruited 1,225 symptomatic adult outpatients with acute SARS-CoV-2 infection from 3 June 2020 to 1 October 2021 at 23 sites. Of these, 1,181 participants received either CCP or control plasma transfusion. Trial participants were transfused within 9 days of symptom onset. Follow-up clinic visits were conducted at days 14, 28, and 90 post-transfusion. For this analysis, we restricted the study sample to those with blood drawn at screening, day 14, and day 90, and complete symptom data on day 90. Subsequently, we excluded 21 screening samples, 23 day 14 samples, and 26 day 90 samples, due to inadequate sample volume, laboratory error in cytokine measurement, or missing results leading to exclusion of the sample. These lost samples were from different individuals at each time point, so these individuals were included in the analyses at other time points, when data were available.

Outcomes

The primary outcome was PCC, which was defined as the presence of any self-reported symptom (cough, fatigue, shortness of breath, headache, neurologic changes, loss of taste, loss of smell, nausea, vomiting, diarrhea, runny/stuffy nose, myalgias, sore throat, chills, fever, or skin manifestations) at the 90-day visit. All CSSC-004 trial participants were asked about the presence and severity of symptoms at days 0, 1, 3, 5, 7, 10, 14, 28, and 90 through a structured, self-report form administered via phone (days 1, 3, 5, 7, and 10) and at in-person visits (days 0, 14, 28, and 90).

Variable definition

Age was modeled as a continuous variable in regressions. Sex was defined as biologic sex assigned at birth (male/female). Race (Black, American Indian/Alaskan Native [AI/AN], white, multiple, or other race] and ethnicity (Hispanic, non-Hispanic) were self-reported at enrollment. Body mass index (BMI) was calculated using height and weight at the screening visit. Calendar time was used as a surrogate for SARS-CoV-2 variant (transfusions prior to 15 June 2021 were classified as occurring during the pre-Alpha/Alpha wave, and those from 15 June 2021 to 1 October 2021 were classified as occurring during the Delta wave). Baseline comorbidities were collected through self-report and abstracted from medical records at enrollment. Treatment was categorized into receipt of early control plasma (≤5 days post-symptom onset), late receipt of control plasma (>5 days post-symptom onset), early receipt of CCP (≤5 days post-symptom onset), and late receipt of CCP (>5 days post-symptom onset)—a timing threshold consistent with the original trial analysis (27). Vaccination status was defined as fully vaccinated (i.e., more than 2 weeks from the second mRNA vaccine or 2 weeks from the first vector vaccine), partially vaccinated (i.e., receipt of one mRNA vaccine or less than 2 weeks from a vector vaccine), or unvaccinated.

Cytokine measurement

Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes, and plasma was separated and isolated within 2–8 hours after collection by centrifugation and stored at –80°C until cytokines were measured.

Custom multiplexed sandwich immunoassays using MULTI-ARRAY electrochemiluminescence detection technology (Meso Scale Discovery, Gaithersburg, MD, USA) were used for the quantitative evaluation of 21 different human cytokine and chemokine analytes in plasma samples following the manufacturer's instructions. The cytokines and chemokines were selected based on previous SARS-CoV-2 studies (28–30). Analytes were considered "detectable" if both runs of each sample had a signal greater than the analyte- and plate-specific lower limit of detection (i.e., 2.5 standard deviations of the plate-specific blank). Analyte concentrations (pg/mL) from both runs of each analyte were averaged for analysis. Cytokine values below the lower limit of detection or above the upper limit of detection were estimated by the multiplex assay using extrapolation from the standard curve. Values above or below the fit curve range were reported missing by the assay.

Statistical analysis

Values that were not reported because they were above or below the fit curve were imputed using a single stochastic draw from the tail of a truncated $\log_{10}$-normal distribution fit to the detectable values of each cytokine. For those below fit curve range, values were randomly drawn from the extrapolated lower tails (from 0 to the minimum available value) of the distribution for each analyte. For those above fit curve range, values were randomly drawn from the extrapolated upper tails (from the maximum available value to 10 times the available maximum) of the distribution for each analyte. Cytokine values were $\log_{10}$ transformed, and the outliers (Q3 + 1.5 × interquartule range

or Q1 − 1.5 × interquartule range) from each visit were excluded to avoid potential lab error.

Two-tailed χ^2 tests were performed to compare the baseline characteristics between treatment arms and PCC groups. Fisher's exact test was used to compare across race categories due to a small number of participants in some racial groups. Spaghetti plots were produced to evaluate the trajectory of each analyte from screening to day 14 to day 90. Wilcoxon rank sum tests were used to compare the cytokine levels at screening between non-PCC and PCC groups. Similar to our previous treatment analyses and consistent with previously established risk factors for PCC, logistic regressions adjusted for the baseline covariates including age (continuous), sex (male vs female), race (white vs non-white), BMI (<30 vs ≥30), vaccine status (partially or fully vs unvaccinated), and diabetes (no vs yes) were used to evaluate the association between each cytokine ($\log_{10}$ transformed values) and PCC. Benjamini-Hochberg correction with a false discovery rate of 0.05 was conducted to control for multiple comparisons across all the cytokines. Univariate and multivariate logistic regressions were modeled to estimate the potential association of baseline characteristics, IL-6, and CCP on the impact of PCC. We conducted *post hoc* separate analyses for IL-6 to evaluate its association with SARS-CoV-2 viral load and major symptoms. Missing data on covariates were handled using available case method to include all cases where the variable(s) of interested were observed for each model. All analyses were performed in R 4.2.1 (R Core Team, Vienna, Austria).

RESULTS

Study population

Of 1,181 transfused trial participants, 589 were randomized to receive control plasma and 592 were randomized to receive CCP, with 257 (43.4%) receiving CCP within 5 days of symptom onset (Fig. 1). A total of 1,061 participants returned for day 90 visits, of whom 882 had biorepository plasma samples and symptom data at baseline, day 14 and day 90. There were no significant differences in baseline characteristics, comorbidities, or COVID-19 vaccine status among those included in this study sampling compared to the entire clinical trial population (Table S1).

The median age of the 882 subjects was 43 years, with 299 (33.9%) ≥50 years. Five hundred six (57.4%) female and 116 Black (13.2%) participants were included. There were no differences by trial treatment group (Table 1) or between those with and without PCC symptom data (Tables S2 and S3). The geometric mean of SARS-CoV-2 viral load was similar comparing control to CCP, while different comparing early to late transfusion of plasma. Demographic factors were also similar among those included in this analysis compared to the entire trial population (Table S1).

There were 590 (66.9%) individuals without PCC and 292 (33.1%) individuals with PCC at day 90 (Table 2). The most common reported symptoms were fatigue (14.5%), anosmia (14.5%), and ageusia (10.0%) (Table S4). Forty-eight participants (5.4%) had both fatigue and anosmia; 80 participants had one or the other, but not both.

Soluble markers of inflammation

Levels of most cytokines decreased over time from baseline screening to day 90 (Fig. 2; Fig. S1). Of the 21 cytokines evaluated, IL-1RA, IL-6, IL-8, IL-15, and MCP-1 were elevated at baseline among those with PCC compared to participants who did not develop PCC (Fig. 3; Fig. S2). Elevated levels of IL-6 were significantly associated with PCC after correcting for multiple comparisons. In a multivariable model adjusting for age, sex, race, BMI, diabetes, vaccine status, and plasma transfused, an elevated level of IL-6 at baseline was associated with the presence of PCC (adjusted odds ratio [AOR] = 1.59, 95% CI = 1.02–2.47) (Table S5).

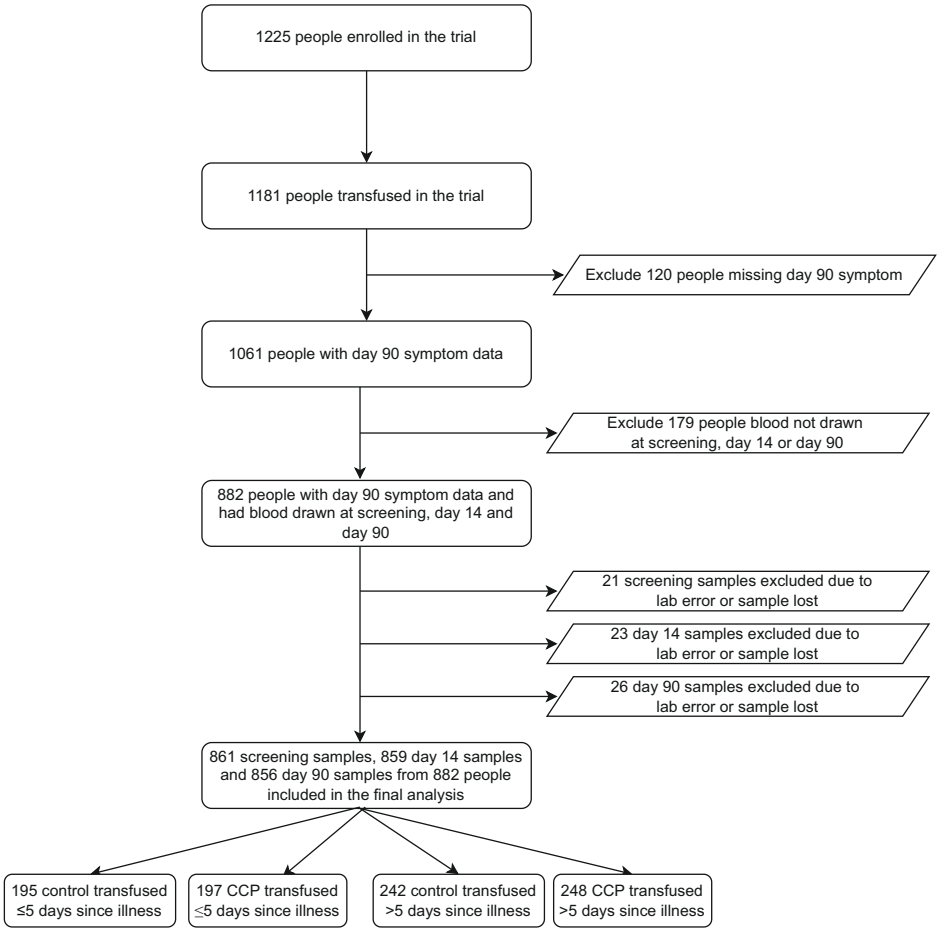

FIG 1 Study population.

Baseline factors associated with PCC

In multivariable analysis, (N = 882) older age, female sex, and baseline elevated IL-6 were associated with PCC (Table 3). There was no difference in the effect of early vs late control plasma or late CCP on the odds of PCC; however, there was a trend for early treatment with CCP to have the lowest odds of PCC (AOR = 0.75 [0.46, 1.23]) compared to early administration of control plasma. (Table 3). Similarly, when evaluating only those who received CCP, there was a statistically significant decreased odds of PCC in those who were treated within 5 days of symptom onset (AOR = 0.60 [0.38, 0.95]) compared to those who received late CCP treatment (Table 4). There was no statistically significant interaction between CCP treatment and IL-6. Similar trends, although not significant, were seen among the full trial population seen at day 90 (N = 1,061) (Tables S6A and S6B).

DISCUSSION

This study is among the first to show elevation of IL-6 at infection was associated with PCC and that early treatment with CCP for COVID-19 trended toward a lower odds of PCC. Notably, greater levels of IL-6 at baseline were associated with the presence of persistent symptoms at day 90, while early treatment with CCP was associated with lower odds of PCC. Finally, consistent with other studies, advanced age (10), diabetes mellitus, and higher BMI were associated with PCC (6, 11, 31).

Approximately one third of participants with outpatient SARS-CoV-2 infection diagnosed early in the pandemic continued to have symptoms 90 days after infection.

TABLE 1 Characteristics of the study population by treatment group[a]

Characteristic	Overall, *N* = 882	Control ≤5 days, *n* = 195	CCP ≤5 days, *n* = 197	Control >5 days, *n* = 242	CCP >5 days, *n* = 248
Age (%)					
18–29	162 (18.4)	38 (19.5)	37 (18.8)	37 (15.3)	50 (20.2)
30–49	421 (47.7)	91 (46.7)	102 (51.8)	117 (48.3)	111 (44.8)
50–64	247 (28.0)	55 (28.2)	49 (24.9)	75 (31.0)	68 (27.4)
≥65	52 (5.9)	11 (5.6)	9 (4.6)	13 (5.4)	19 (7.7)
Sex (%)					
Female	506 (57.4)	108 (55.4)	107 (54.3)	156 (64.5)	135 (54.4)
Male	376 (42.6)	87 (44.6)	90 (45.7)	86 (35.5)	113 (45.6)
Race (%)					
Asian	28 (3.2)	11 (5.6)	4 (2.0)	2 (0.8)	11 (4.4)
Black	116 (13.2)	19 (9.7)	26 (13.2)	29 (12.0)	42 (16.9)
American Indian/Alaska Native	15 (1.7)	4 (2.1)	3 (1.5)	3 (1.2)	5 (2.0)
White	706 (80.0)	154 (79.0)	159 (80.7)	207 (85.5)	186 (75.0)
Mixed/other	17 (1.9)	7 (3.6)	5 (2.5)	1 (0.4)	4 (1.6)
Ethnicity (%)					
Hispanic/Latino	109 (12.4)	29 (14.9)	25 (12.7)	24 (9.9)	31 (12.5)
Non-Hispanic/Latino	773 (87.6)	166 (85.1)	172 (87.3)	218 (90.1)	217 (87.5)
BMI (%)					
<30	522 (59.2)	109 (55.9)	115 (58.4)	141 (58.3)	157 (63.3)
30–34.9	179 (20.3)	45 (23.1)	41 (20.8)	47 (19.4)	46 (18.5)
≥35	141 (16.0)	32 (16.4)	35 (17.8)	40 (16.5)	34 (13.7)
Missing	40 (4.5)	9 (4.6)	6 (3.0)	14 (5.8)	11 (4.4)
Hypertension (%)					
No	675 (76.5)	145 (74.4)	148 (75.1)	195 (80.6)	187 (75.4)
Yes	207 (23.5)	50 (25.6)	49 (24.9)	47 (19.4)	61 (24.6)
Diabetes (%)					
No	810 (91.8)	182 (93.3)	182 (92.4)	224 (92.6)	222 (89.5)
Yes	72 (8.2)	13 (6.7)	15 (7.6)	18 (7.4)	26 (10.5)
Anxiety (%)					
No	822 (93.2)	179 (91.8)	182 (92.4)	231 (95.5)	230 (92.7)
Yes	60 (6.8)	16 (8.2)	15 (7.6)	11 (4.5)	18 (7.3)
Vaccine status (%)					
Unvaccinated	688 (78.0)	148 (75.9)	154 (78.2)	154 (78.2)	192 (77.4)
Partially	55 (6.2)	12 (6.2)	11 (5.6)	11 (5.6)	16 (6.5)
Fully	139 (15.8)	35 (17.9)	32 (16.2)	32 (16.2)	40 (16.1)
Baseline C-reactive protein (%)					
Normal (≤1.0 mg/dL)	662 (75.1)	146 (74.9)	144 (73.1)	180 (74.4)	192 (77.4)
Abnormal (>1.0 mg/dL)	216 (24.5)	49 (25.1)	53 (26.9)	61 (25.2)	53 (21.4)
Missing	4 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.2)
COVID-19 wave (%)					
Pre-Alpha/Alpha	704 (79.8)	152 (77.9)	161 (81.7)	195 (80.6)	196 (79.0)
Delta	178 (20.2)	43 (22.1)	36 (18.3)	47 (19.4)	52 (21.0)
SARS-CoV-2 viral load, geometric mean copies (95% CI)	7,248 (5,909, 8,889)	3,041 (2,197, 4,208)	29,121 (18,489, 45,866)	13,774 (8,665, 21,896)	3,387 (2,404, 4,770)

[a]CCP, COVID-19 convalescent plasma. PCC, post COVID-19 conditions at day 90.

The most common symptoms at day 90 were less likely to be respiratory, and more consistent with neurologic injury including fatigue, loss of smell, and loss of taste (12). A recent study of EHR data from the VA showed that treatment with nirmatrelvir decreased the risk of PCC (13); while another study of online participants demonstrated no benefit

TABLE 2 Baseline characteristics of the study population by PCC[a]

Characteristic	Overall, *N* = 882	Non-PCC, *n* = 590	PCC, *n* = 292	*P*[b] value
Age (%)				
18–29	162 (18.4)	134 (22.7)	28 (9.6)	**<0.001**
30–49	421 (47.7)	274 (46.4)	147 (50.3)	
50–64	247 (28.0)	156 (26.4)	91 (31.2)	
≥65	52 (5.9)	26 (4.4)	26 (8.9)	
Sex (%)				
Female	506 (57.4)	301 (51.0)	205 (70.2)	**<0.001**
Male	376 (42.6)	289 (49.0)	87 (29.8)	
Race (%)				
Asian	28 (3.2)	24 (4.1)	4 (1.4)	0.061
Black	116 (13.2)	74 (12.5)	42 (14.4)	
American Indian/Alaska Native	15 (1.7)	11 (1.9)	4 (1.4)	
White	706 (80.0)	466 (79.0)	240 (82.2)	
Mixed/other	17 (1.9)	15 (2.5)	2 (0.7)	
Ethnicity (%)				
Hispanic/Latino	109 (12.4)	66 (11.2)	43 (14.7)	0.163
Non-Hispanic/Latino	773 (87.6)	524 (88.8)	249 (85.3)	
BMI (%)				
<30	522 (59.2)	365 (61.9)	157 (53.8)	**0.042**
30–34.9	179 (20.3)	119 (20.2)	60 (20.5)	
≥35	141 (16.0)	81 (13.7)	60 (20.5)	
Missing	40 (4.5)	25 (4.2)	15 (5.1)	
Hypertension (%)				
No	675 (76.5)	461 (78.1)	214 (73.3)	0.130
Yes	207 (23.5)	129 (21.9)	78 (26.7)	
Diabetes (%)				
No	810 (91.8)	550 (93.2)	260 (89.0)	**0.045**
Yes	72 (8.2)	40 (6.8)	32 (11.0)	
Anxiety (%)				
No	822 (93.2)	557 (94.4)	265 (90.8)	0.059
Yes	60 (6.8)	33 (5.6)	27 (9.2)	
Vaccine status (%)				
Unvaccinated	688 (78.0)	454 (76.9)	234 (80.1)	0.488
Partially	55 (6.2)	37 (6.3)	18 (6.2)	
Fully	139 (15.8)	99 (16.8)	40 (13.7)	
Baseline C-reactive protein (%)				
Normal (≤1.0 mg/dL)	662 (75.1)	452 (76.6)	210 (71.9)	0.086
Abnormal (>1.0 mg/dL)	216 (24.5)	137 (23.2)	79 (27.1)	
Missing	4 (0.5)	1 (0.2)	3 (1.0)	
Treatment group (%)				
Control ≤5 days since symptom onset	195 (22.1)	131 (22.2)	64 (21.9)	0.244
CCP ≤5 days since symptom onset	197 (22.3)	143 (24.2)	54 (18.5)	
Control >5 days since symptom onset	242 (27.4)	156 (26.4)	86 (29.5)	
CCP >5 days since symptom onset	248 (28.1)	160 (27.1)	88 (30.1)	
COVID-19 wave (%)				
Pre-Alpha/Alpha	704 (79.8)	462 (78.3)	242 (82.9)	0.133
Delta	178 (20.2)	128 (21.7)	50 (17.1)	
SARS-CoV-2 viral load, geometric mean copies (95% CI)	7,248 (5,909, 8,889)	7,208 (5,613, 9,256)	7,329 (5,136, 10,457)	0.943

[a]PCC, post-COVID-19 condition.
[b]*P* values for all variables except race and SARS-CoV-2 viral load were calculated using two-tail χ^2 test. Two-tail Fisher's exact test was used for race due to small cell numbers, and Wilcoxon rank sum test was used for the continuous variable SARS-CoV-2 viral load. *P* values <0.05 are in bold.

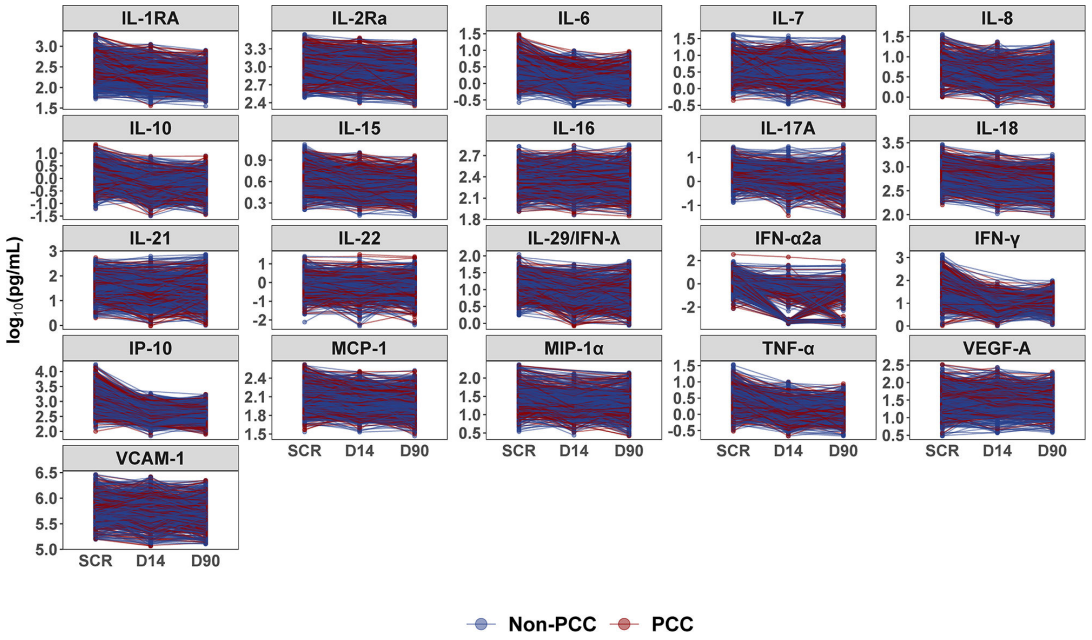

FIG 2 Trajectory of the cytokines during study period. Abbreviations: PCC, post-COVID-19 condition; SCR, screening visit; D14, day 14 visit; D90, day 90 visit. Note: each dot represents a sample, and each line represents a person.

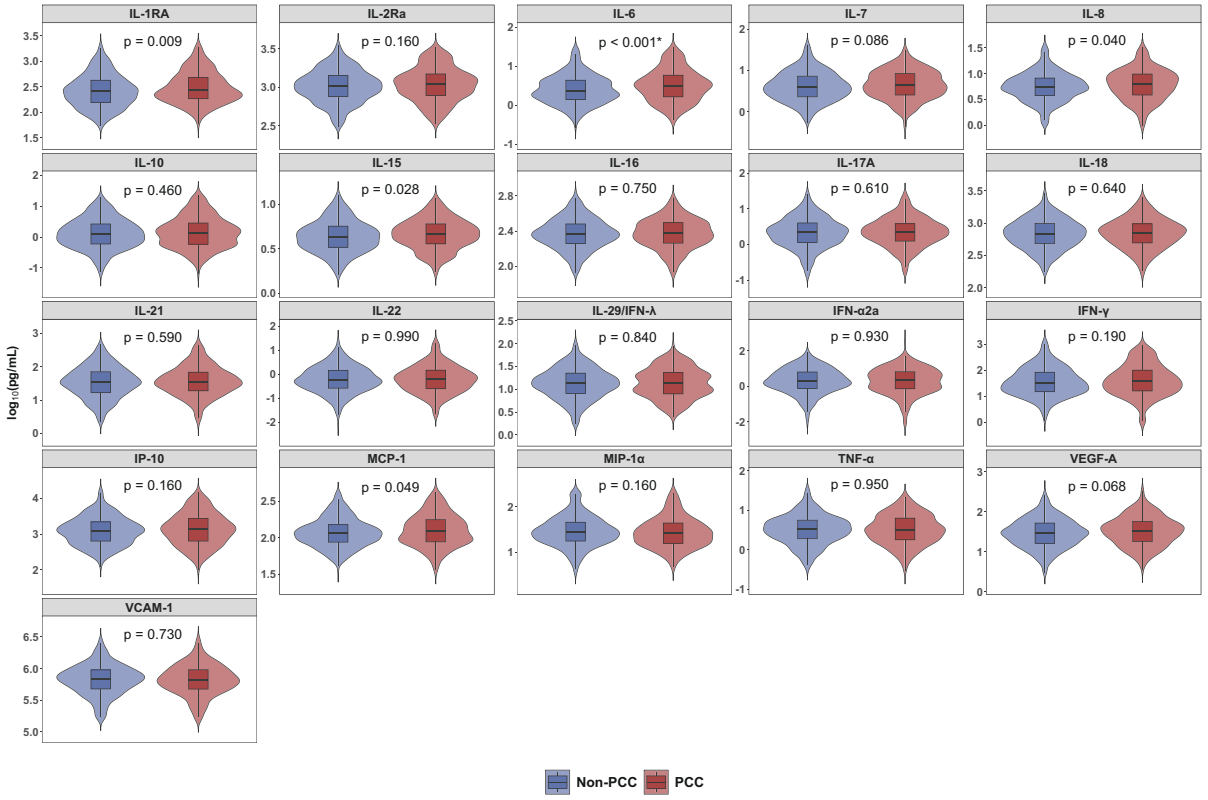

FIG 3 Comparison of cytokines at screening between study participants with PCC and without PCC. PCC, post-COVID-19 condition. Note: *P* values were determined by Wilcoxon rank sum test. *IL-6 was significantly different after adjusting multiple comparison using Benjamini-Hochberg correction with a false discovery rate of 0.05.

TABLE 3 Logistic regression model assessing demographic and clinical factors and PCC among the study population

Characteristic	OR (95% CI), *N* = 882		
	Univariate	Model 1	Model 2
Age, scaled to 10 years	**1.31 (1.18, 1.46)**	**1.35 (1.20, 1.51)**	**1.32 (1.17, 1.50)**
Sex			
Male	Ref.	Ref.	Ref.
Female	**2.26 (1.68, 3.06)**	**2.38 (1.74, 3.28)**	**2.69 (1.93, 3.81)**
Race			
White	Ref.	Ref.	Ref.
Non-white	0.84 (0.58, 1.20)	0.81 (0.55, 1.20)	0.85 (0.56, 1.28)
BMI[b]			
<30	Ref.	Ref.	Ref.
≥30	**1.39 (1.04, 1.87)**	1.21 (0.88, 1.66)	1.19 (0.85, 1.67)
Vaccine status			
None	Ref.	Ref.	Ref.
Partially or fully	0.83 (0.58, 1.16)	0.87 (0.60, 1.25)	0.87 (0.59, 1.26)
Diabetes			
No	Ref.	Ref.	Ref.
Yes	**1.69 (1.03, 2.75)**	1.24 (0.72, 2.14)	1.23 (0.69, 2.21)
Plasma transfused			
Control ≤5 days since symptom onset	Ref.	Ref.	Ref.
CCP ≤5 days since symptom onset	0.77 (0.50, 1.19)	0.85 (0.53, 1.34)	0.75 (0.46, 1.23)
Control >5 days since symptom onset	1.13 (0.76, 1.68)	1.08 (0.70, 1.67)	1.05 (0.66, 1.67)
CCP >5 days since symptom onset	1.13 (0.76, 1.68)	1.30 (0.85, 1.99)	1.21 (0.77, 1.92)
Log_{10} IL-6, pg/mL	–	–	**1.59 (1.02, 2.47)**

[a]*P* values <0.05 are highlighted in bold. Model 1 includes age, sex, race, BMI, vaccine status, diabetes, and the time between CCP transfusion and illness onset. Model 2 additionally includes log_{10} IL-6.
[b]BMI, body mass index; CCP, COVID-19 convalescent plasma; PCC, post-COVID-19 condition at day 90; Ref., reference group; –, not applicable.

to nirmatrelvir with either the prevalence or severity of PCC (32). Studies of remdesivir have also been had conflicting data as the randomized SOLIDARITY trial did not show a benefit of remdesivir against PCC (33), while an observational study in Italy demonstrated a positive effect of remdesivir on PCC (34). CCP has been shown to reduce hospitalizations and prevent morbidity and mortality when provided early and at high-titer (35–42). In this early treatment trial, CCP reduced COVID-19-related hospitalizations by 54% and demonstrated a trend toward lower odds of PCC overall, and even lower PCC odds among those treated with CCP within 5 days (27). Given that CCP functions primarily as an antiviral therapy, this observation is consistent with results of small molecule antivirals and suggests that antibody therapies could reduce PCC incidence when instituted early in the course of COVID-19. The observation that early antibody administration was associated with reduced likelihood of PCC is consistent with the finding that vaccines that elicit antibodies to SARS-CoV-2 also reduce PCC (43). With larger sample size, it may be possible to identify patient populations or clinical phenotypes of PCC that may benefit from early treatment to prevent PCC. Additional studies are needed to better understand the impact of early treatment with monoclonals, CCP, remdesivir, and other oral antivirals among those with outpatient SARS-CoV-2 infection.

IL-6 plays a critical role during infections; this proinflammatory cytokine leads to an acute-phase response, B-cell maturation and also T-cell expansion (44). Notably, elevated levels of IL-6 at screening were associated with the development of PCC after adjusting for demographic factors and comorbidities. While cytokine levels decreased from baseline screening to day 90, they remained elevated during the COVID-19 recovery phase, which likely contributes to PCC.

This study had several notable strengths. First, the study population was large, geographically and demographically diverse, and entirely outpatient (27). Second, biospecimens and data on symptoms were actively ascertained in real time from participants through in-person visits early in the onset of illness and on day 90 after

TABLE 4 Logistic regression model assessing demographic and clinical factors and PCC among the people transfused with CCP[a]

Characteristic	OR (95% CI), $n = 445$		
	Univariate	Model 1	Model 2
Age, scaled to 10 yr	**1.30 (1.13, 1.51)**[b]	**1.36 (1.16, 1.60)**	**1.33 (1.12, 1.58)**
Sex			
Male	Ref.	Ref.	Ref.
Female	**1.96 (1.30, 2.98)**	**2.32 (1.49, 3.66)**	**2.54 (1.59, 4.14)**
Race			
White	Ref.	Ref.	Ref.
Non-white	0.82 (0.49, 1.33)	0.78 (0.45, 1.31)	0.72 (0.41, 1.24)
BMI			
<30	Ref.	Ref.	Ref.
≥30	1.49 (0.98, 2.25)	1.45 (0.92, 2.26)	1.30 (0.81, 2.09)
Vaccine status			
None	Ref.	Ref.	Ref.
Partially or fully	0.71 (0.42, 1.15)	0.69 (0.40, 1.16)	0.71 (0.40, 1.20)
Diabetes			
No	Ref.	Ref.	Ref.
Yes	1.41 (0.72, 2.71)	0.95 (0.44, 1.99)	1.10 (0.49, 2.44)
CCP transfused			
>5 days since symptom onset	Ref.	Ref.	Ref.
≤5 days since symptom onset	0.69 (0.46, 1.03)	**0.64 (0.41, 0.98)**	**0.60 (0.38, 0.95)**
Log_{10} IL-6, pg/mL	–	–	**1.91 (1.03, 3.56)**

[a]BMI, body mass index; CCP, COVID-19 convalescent plasma; PCC, post-COVID-19 condition at day 90; Ref., reference group; –, not applicable.
[b]*P* values <0.05 are highlighted in bold. Model 1 includes age, sex, race, BMI, vaccine status, diabetes, and the time between CCP transfusion and illness onset. Model 2 additionally includes log_{10} IL-6.

transfusion. In addition to the presence or absence of symptoms over time, we collected samples at each visit to allow for cytokine analysis. Finally, study data on symptoms were collected uniformly across all sites, including pre-Omicron COVID-19 variants, thus increasing the generalizability of our findings.

This study has several important limitations. First, participants were asked about 17 symptoms identified early in the trial as important symptoms of COVID-19. During the pandemic, knowledge of PCC expanded to include more neurocognitive symptoms; however, we could not conduct additional validated measurements of sleep or neurologic function as many participants had completed follow-up. Also, while day 90 follow-up was excellent (90%), it was not complete. However, those who did not complete the study did not differ demographically from those who did. Also, samples were not available from all patients at all visits. Sometimes during the sample collection for each patient, insufficient samples were collected due to participant specific factors (patient became pre-syncopal or vein collapsed), or rarely a loss of specimen between the collection site and the laboratory. Any loss of specimen should be considered at random. In addition, COVID-19 has disproportionately affected the elderly and people of color. Within our sample, only a small proportion were age ≥65 years or of minority ethnicity or race, though the proportions were similar to those in the general American population. Fatigue was a common complaint during the pandemic. Our study did not have an uninfected control group to ascertain if our reported rate of fatigue was different than in the general population, and fatigue was not measured using a standardized reporting instrument for quantification. Our study was also limited by sample size in trying to understand the impact of early treatment on the various clinical phenotypes associated with PCC. We could not further delineate PCC phenotype beyond the presence or absence of symptoms at a fixed time. More inclusive phenotyping including exacerbation of a chronic condition or development of a new comorbid condition during recovery may yield different results. Also, this study was done early in the pandemic when relatively few participants were fully vaccinated. Results may differ among participants who have immunity from prior infection or vaccination.

In summary, this study demonstrated high rates of PCC symptoms at day 90, particularly among those with higher baseline levels of IL-6 at the time of infection or who did not receive early CCP treatment. Future studies might examine the impact of anti-IL6 agents and the development of PCC among outpatients. Despite increasing vaccination uptake, PCC risk does not disappear, and IL-6 modulation may be a possible therapeutic intervention to reduce the burden of long-term symptoms among those with SARS-CoV-2 infection.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the plasma donors and study participants who generously gave of their time and biological specimens to the CSSC-001 and CSSC-004 trials and the passionate study personnel who facilitated these studies.

This study was funded principally by the US Department of Defense's (DOD) Joint Program Executive Office for Chemical, Biological, Radiological, and Nuclear Defense (JPEO-CBRND), in collaboration with the Defense Health Agency (DHA) (contract number: W911QY2090012) with additional support from Bloomberg Philanthropies, State of Maryland, the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) 3R01AI152078-01S1 and 3R01AI120938-05S1, National Institute on Drug Abuse (NIDA) F31DA054849, NIH National Center for Advancing Translational Sciences (NCATS) U24TR001609, Division of Intramural Research NIAID NIH, Mental Wellness Foundation, Moriah Fund, Octapharma, HealthNetwork Foundation, and the Shear Family Foundation. The study sponsors did not contribute to the study design, the collection, analysis, and interpretation of data, or the decision to submit this manuscript for publication.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funders.

Kelly Gebo- Consults for the Aspen Institute, Teach for America, served as a non-paid member of scientific advisory board for Pfizer and writes COVID management guidelines for UpToDate which are out of scope of paper. Sonya L. Heath- Nothing to disclose. Yuriko Fukuta- Nothing to disclose. Xianming Zhu- Nothing to disclose. Sheriza Baksh- Nothing to disclose. Alison G. Abraham- Consultant for Implementation Group Inc, Hirslanden Klinik, Zurich CH, & ELSEVIER. Feben Habtehyimer- Nothing to disclose. David Shade- Nothing to disclose. Jessica Ruff- Nothing to disclose. Malathi Ram- Nothing to disclose. Oliver Laeyendecker- Nothing to disclose. Reinaldo E. Fernandez- Nothing to disclose. Eshan U. Patel- Nothing to disclose. Owen R. Baker- Nothing to disclose. Shmuel Shoham- Served on a CCP guideline panel. Edward R. Cachay- has received unrestricted research grants from Gilead and Merck paid to the Regents of the University of California. He also participated in an advisory board to Theratechnologies for an unrelated topic. Judith S. Currier- Consulted for Merck and Company in 2021, currently not on any guidelines panel. Jonathan M. Gerber- Nothing to disclose. Thomas J. Gniadek- Currently employed by Fenwal, Inc., a Fresenius Kabi Company. Barry Meisenberg- Nothing to disclose. Donald N. Forthal- nothing to disclose. Laura L. Hammitt- research funding to my institution from AstraZeneca, CDC, Merck, NIH, and Pfizer. Moises A. Huaman reports contracts from Gilead Sciences Inc, Insmed Inc, AN2 Therapeutics, Inc to the University of Cincinnati, outside the submitted work. Adam Levine- Nothing to disclose. Giselle S. Mosnaim- Received research grant support from Teva, Alk-Abello, and Genentech and currently receives research grant support from Novartis, GlaxoSmithKline, and Sanofi-Regeneron. Serves as Immediate Past President of the American Academy of Allergy Asthma and Immunology and Co-Chair of the Continuous Assessment Program Examination for the American Board of Allergy and Immunology Bela Patel- Part of COVID trials and PAH trials, no disclosures relevant to CP. James H. Paxton- Research funding from MindRhythm, Inc. Jay S. Raval- Consultant and Advisor with Sanofi Genzyme; Board of Directors Member with the American Society for Apheresis, no overlap with CP. Catherine G. Sutcliffe- Nothing to disclose. Shweta Anjan- Nothing to disclose. Seble Kassaye- Helped to produce educational materials related to

HIV with Integritas Communications, LLC and Vindico Medical Education, LLC. Janis E. Blair- Nothing to disclose. Karen Lane- nothing to disclose. Nichol A. McBee- Nothing to disclose. Amy L. Gawad- Nothing to disclose. Piyali Das- Nothing to disclose. Sabra L. Klein- Nothing to disclose. Andrew Pekosz- Nothing to disclose. Arturo Casadevall- Serves on the scientific advisory board of SAB Therapeutics. Evan M. Bloch- reports personal fees and non-financial support from Terumo BCT, Abbott Laboratories, Tegus and UptoDate, outside of the submitted work. E.M.B. is a member of the United States Food and Drug Administration (FDA) Blood Products Advisory Committee. Served on a CCP guideline panel Daniel Hanley- reports personal fees from Neurelis, Neurotrope, and medicolegal consulting. Aaron A.R. Tobian- Served on a CCP guideline panel. David J. Sullivan- Founder and Board member with stock options (macrolide for malaria). D.J.S. reports AliquantumRx, Hemex Health malaria diagnostics consulting and royalties for malaria diagnostic test control standards to Alere- all outside of submitted work.

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FUNDING

Funder	Grant(s)	Author(s)
U.S. Department of Defense (DOD)	W911QY2090012	David J. Sullivan
HHS | NIH | National Institute of Allergy and Infectious Diseases (NIAID)	R01AI152078	Arturo Casadevall
HHS | NIH | National Institute on Drug Abuse (NIDA)	F31DA054849	Eshan U. Patel
HHS | NIH | National Center for Advancing Translational Sciences (NCATS)	U24TR001609	Daniel Hanley
HHS | NIH | National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)	R01DK131926	Aaron A. R. Tobian
HHS | NIH | National Institute of Allergy and Infectious Diseases Division of Intramural Research		Oliver Laeyendecker
HHS | NIH | National Institute of Allergy and Infectious Diseases (NIAID)	R01AI120938S1	Aaron A. R. Tobian

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Project administration, Supervision | Judith S. Currier, Writing – review and editing, Project administration, Supervision | Jonathan M. Gerber, Writing – review and editing, Project administration, Supervision | Barry Meisenberg, Writing – review and editing, Project administration, Supervision | Donald N. Forthal, Writing – review and editing, Project administration, Supervision | Laura L. Hammitt, Project administration, Supervision, Writing – review and editing | Moises A. Huaman, Project administration, Supervision, Writing – review and editing | Adam Levine, Project administration, Supervision, Writing – review and editing | Giselle S. Mosnaim, Project administration, Supervision, Writing – review and editing | Bela Patel, Project administration, Supervision, Writing – review and editing | James H. Paxton, Project administration, Supervision, Writing – review and editing | Jay S. Raval, Project administration, Supervision, Writing – review and editing | Catherine G. Sutcliffe, Methodology, Writing – review and editing, Project administration, Supervision | Shweta Anjan, Project administration, Supervision, Writing – review and editing | Seble Kassaye, Project administration, Supervision, Writing – review and editing | Janis E. Blair, Project administration, Supervision, Writing – review and editing | Karen Lane, Project administration, Supervision, Writing – review and editing | Nichol A. McBee, Project administration, Supervision, Writing – review and editing | Amy L. Gawad, Project administration, Supervision, Writing – review and editing | Piyali Das, Project administration, Supervision, Writing – review and editing | Sabra L. Klein, Project administration, Supervision, Writing – review and editing | Andrew Pekosz, Project administration, Supervision, Writing – review and editing | Evan M. Bloch, Project administration, Supervision, Writing – review and editing | Daniel Hanley, Project administration, Supervision, Writing – review and editing | Arturo Casadevall, Conceptualization, Funding acquisition, Supervision, Writing – review and editing, Project administration | Aaron A. R. Tobian, Conceptualization, Funding acquisition, Project administration, Supervision, Writing – original draft, Writing – review and editing | David J. Sullivan, Conceptualization, Funding acquisition, Supervision, Writing – review and editing, Project administration, Writing – original draft.

ETHICS APPROVAL

All study activities were approved by the Johns Hopkins University single Institutional Review Board, the Navajo Nation Human Research Review Board, the Indian Health Service National Institutional Review Board, and the Human Research Protection Office of the United States Department of Defense. All study activities followed the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonization, and all applicable regulatory requirements. Written informed consent was obtained from all study participants.

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental material (mBio00618-23 S0001.docx). Supplemental tables and figures.

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