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A randomized controlled study of convalescent plasma for individuals hospitalized with COVID-19 pneumonia

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BACKGROUND. Antibody-based strategies for COVID-19 have shown promise in prevention and treatment of early disease. COVID-19 convalescent plasma (CCP) has been widely used but results from randomized trials supporting its benefit in hospitalized patients with pneumonia are limited. Here, we assess the efficacy of CCP in severely ill, hospitalized adults with COVID-19 pneumonia.

METHODS. We performed a randomized control trial (PennCCP2), in 80 adults hospitalized with COVID-19 pneumonia, comparing up to 2 units of locally-sourced CCP plus standard care vs. standard care alone. The primary efficacy endpoint was comparison of a clinical severity score. Key secondary outcomes include 14- and 28-day mortality, 14- and 28-day WHO8 score, duration of supplemental oxygenation or mechanical ventilation, respiratory SARS-CoV-2 RNA, and anti-SARS-CoV-2 antibodies.

RESULTS. 80 hospitalized adults with confirmed COVID-19 pneumonia were enrolled at median day 6 of symptoms and day 1 of hospitalization; 60% were anti-SARS-CoV-2 antibody seronegative. Participants had a median of 3 comorbidities, including risk factors for severe COVID-19 and immunosuppression. CCP treatment was safe and conferred significant benefit by clinical severity score (MED (IQR) 10 (5.5,30) vs. 7 (2.75,12.25), p=0.037) and 28-day mortality (n=10, 26% vs. n=2, 5%; p=0.013). […]

A Randomized Controlled Study of Convalescent Plasma for Individuals Hospitalized with COVID-19 Pneumonia

Running title: Convalescent plasma for COVID-19 pneumonia

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Abstract

Background. Antibody-based strategies for COVID-19 have shown promise in prevention and treatment of early disease. COVID-19 convalescent plasma (CCP) has been widely used but results from randomized trials supporting its benefit in hospitalized patients with pneumonia are limited. Here, we assess the efficacy of CCP in severely ill, hospitalized adults with COVID-19 pneumonia.

Methods. We performed a randomized control trial (PennCCP2), in 80 adults hospitalized with COVID-19 pneumonia, comparing up to 2 units of locally-sourced CCP plus standard care vs. standard care alone. The primary efficacy endpoint was comparison of a clinical severity score. Key secondary outcomes include 14- and 28-day mortality, 14- and 28-day WHO8 score, duration of supplemental oxygenation or mechanical ventilation, respiratory SARS-CoV-2 RNA, and anti-SARS-CoV-2 antibodies.

Results. 80 hospitalized adults with confirmed COVID-19 pneumonia were enrolled at median day 6 of symptoms and day 1 of hospitalization; 60% were anti-SARS-CoV-2 antibody seronegative. Participants had a median of 3 comorbidities, including risk factors for severe COVID-19 and immunosuppression. CCP treatment was safe and conferred significant benefit by clinical severity score (MED (IQR) 10 (5.5,30) vs. 7 (2.75,12.25), p=0.037) and 28-day mortality (n=10, 26% vs. n=2, 5%; p=0.013). All other pre-specified outcome measures showed weak evidence towards benefit of CCP.

Conclusions. Two units of locally-sourced CCP administered early in hospitalization to majority seronegative participants conferred a significant benefit in clinical severity score and 28-day mortality. Results suggest CCP may benefit select populations, especially those with comorbidities who are treated early.

Trial Registration. ClinicalTrials.gov: NCT04397757

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Introduction

Since the identification of the first SARS-CoV-2 infections in late 2019, the COVID-19 pandemic has caused more than 200 million cases and 4.5 million deaths worldwide [1]. Prevention strategies are of paramount importance, but effective treatment approaches are needed for individuals who become infected. SARS-CoV-2 infection leads to widely variable outcomes, with a subset of infected individuals developing severe pneumonia requiring hospitalization. Substantial morbidity and mortality remain for COVID-19 patients hospitalized with pneumonia, and few efficacious therapies exist.

Early in the COVID-19 pandemic, convalescent COVID-19 plasma (CCP) was recognized as a potentially promising intervention. Use of convalescent plasma in other infectious diseases[2-5] and previous coronavirus pandemics [6, 7] provided biological plausibility, and early observational studies suggested possible benefit [8-10]. In the setting of limited treatments and desperate clinical need, CCP was widely used in hospitalized COVID-19 patients in the United States via an expanded access program (EAP) or emergency use authorization (EUA) [3, 11]. These mechanisms enabled access to CCP to more than 500,000 hospitalized individuals, with up to 40% of US COVID-19 inpatients receiving CCP in the fall of 2020 [12]. Observational analyses of subcohorts of hospitalized CCP recipients from the US FDA's EAP suggested possible benefit in recipients of early, high-titer plasma [13]. Yet, results from randomized controlled trials of efficacy are mixed or demonstrate limited benefit [14-19]. Here, we report results of a single health system randomized controlled study of 80 severely ill, hospitalized patients with COVID-19 pneumonia treated with up to two units of CCP and standard of care versus standard of care alone.

Results

Participant demographics. Between May 18, 2020 and January 8, 2021, we enrolled 80 participants, of whom 41 were randomized to the treatment and 39 to the control arm (Figure 1). Two participants in the treatment arm declined CCP administration; one participant who withdrew from the study on day 1 was not included in analyses, while the other was retained in the intent to treat analyses. Baseline characteristics of the 79 analyzed participants are described in Table 1.

Participants' median age was 63 years (IQR 52, 74), with 58% over 60 years old and 25% over 75 years old. Participants were 54% female, with 53% identifying as African American, 5% as Asian, and 38% as Caucasian; 4% reported Hispanic ethnicity. Enrollment fluctuated over the 9-month study period following the local epidemic and hospital admissions, with higher enrollment rates during May and June 2020 and November 2020 through January 2021.

Baseline clinical characteristics. Participants' baseline clinical characteristics are described in Table 2. Participants were enrolled early in their disease course, at a median of 6 days (IQR 4, 9) from COVID-19 symptom onset and 1 day (IQR 1, 2) from hospital admission. 60% of participants were SARS-CoV-2 antibody seronegative at study enrollment.

Baseline clinical severity was similar across study arms. The median WHO8 score was 5 (hospitalized, requiring supplemental oxygen) (IQR 5,6). No participants required mechanical ventilation at enrollment. National Early Warning Severity (NEWS)[20] scores also indicated a range in clinical severity at enrollment.

Participants had a high frequency of baseline comorbidities, with a median of 3 (IQR 2, 4) per participant. We note a high prevalence of disease states associated with poor COVID-19 outcomes, including diabetes, obesity, hypertension, cardiovascular and pulmonary disease [21, 22], as well as conditions associated with immunosuppression, including chronic kidney and liver disease, cancer and immunodeficiency [23]. Participants had frequent use of COVID-19 therapies at the time of enrollment, including remdesivir (81%) and steroids (84%).

Safety. CCP administration was generally safe and well-tolerated. There were few SAEs (MED, IQR) of 0 (0,1) SAEs per participant in both control and treatment arms, with 15 (38%) control and 12 (30%) plasma-recipients with at least 1 SAE (Table 3). There were 3 treatment-related AEs (nausea, pruritis, and an acute allergic reaction; all grade 2). As shown in Table 3, there was weak evidence to suggest a greater number of total AEs (p=0.151) and higher maximum severity of AEs (OR 0.507, p=0.105) per participant in control vs. treatment arms.

Clinical efficacy. Comparing the CSC between study arms, CCP-treated participants ranked significantly better (lower severity) than controls (p=0.037 by Wilcoxon rank-sum test), with median clinical severity score of 7 (IQR 2.75, 12.25) in the treatment arm vs. 10 (IQR 5.5, 30) in the control arm. Figure 2 shows cumulative incidence curves for discharge and mortality by treatment arm, censored at 28 days. While there were limited differences in time to discharge or mortality within the first two weeks, the curves diverge in the second two study weeks for both discharges (more in treatment) and deaths (more in control). The logrank test comparing survival and the cause-specific hazard ratio for discharge were also significant (Figure S1).

CCP treatment showed a significant mortality benefit at day 28, OR 0.156, p=0.013, with 5% (2 of 40) and 25.6% (10 of 39) mortality in treated vs. control participants, respectively. Consistent with the overall lower severity score, several other pre-specified secondary efficacy endpoints provided weak evidence (0.05< p-value <0.20) of benefit of CCP treatment, including WHO8 scores at day 14 and 28, any use of mechanical ventilation or ECMO, duration of mechanical ventilation or ECMO use, and duration of supplemental oxygen use (Table 3).

In exploratory analyses, we examined whether the observed treatment benefit for mortality could be explained by imbalances between study arms at baseline by fitting a series of Cox proportional hazards model for mortality adjusting for treatment and one of the following baseline factors: randomization date, sex, age, race, SARS-CoV-2 Ab seropositivity, blood type, obesity, hypertension, diabetes, congestive heart failure, chronic kidney disease, cancer, immune deficiency, number of comorbidities, steroid use, and anti-thrombotic use (Table S1). For steroid use, models were degenerate as there were no deaths in participants who were not receiving steroids at study enrollment. Otherwise, adjustment for the explored factors did not appreciably change the effect size or significance of the found treatment benefit and no additional independent predictors of mortality were identified(Table S2). We conducted a sensitivity analysis with linear regression models for the CSC ranks, adjusting the treatment effect for the same baseline factors. Only baseline seropositive status and age were associated with CSC. Adjusted treatment effect sizes were

similar to unadjusted and the significance of treatment generally remained in the adjusted models, except with adjustment for hypertension and having two or more comorbidities (p=0.06) (Table S3).

Antibody measures. Anti-SARS-CoV-2 RBD IgG levels were assessed in donor plasmas and in recipients at baseline (pre-plasma administration) on study day 1, and longitudinally throughout the study using a validated in-house assay shown to discriminate between seasonal betacoronavirus infection and correlate with neutralization titers [24, 25]. All donor plasmas had IgG >0.48 au/mL, with median levels of 3.69 (IQR 1.61, 8.56). A total of 76 units of plasma from 53 unique donors were used in the study. Of the 40 participants randomized to receiving plasma in the ITT cohort, 37 received 2 units, 2 received 1 unit, and 1 received 0 units due to participant refusal. The median combined titer of antibody (total the units administered to each recipient) was 8.180 au/mL (IQR 4.195, 20.980)(Figure S2).

In exploratory analyses, we used a distinct set of 22 donor plasmas and compared our assay with two commercial assays currently approved for certifying “high-titer” plasma by the FDA. We found that our anti-RBD IgG assay, which uses a quantitative titration-based read-out, correlated closely with the chemiluminescence-based Beckman Coulter RBD IgG immunoassay and the Euroimmun IgG S1 ELISA (Pearson correlations of 0.960 and 0.890, respectively), Figure S3. If we extrapolate from the log-linear relationship between our assay and the two commercial assay standards and the established cut-offs for high titer (3.3 on Beckman-Coulter and 3.5 on Euroimmun), we estimate that 24 (62%) plasma recipients (using Beckman Coulter levels) and 33 (85%) plasma recipients (Euroimmun levels) received at least one unit of high-titer plasma (Figure S3).

At baseline, 60% (47 of 79) of participants were seronegative, with IgG levels ranging from 0.5 to 19.84 au/mL in seropositive participants (Figure S4). At study days 3 through 60, CCP-treated and control participants appear to have similar antibody levels, though these analyses are limited by increasing numbers of missing samples and the potentially non-random pattern of missing samples. Missing data occurred with increasing frequency at later study days, as participants were either unwilling or unable to

provide samples after discharge. Notably, there were not appreciable differences in longer-term humoral responses in sampled treated vs. control participants at day 60 (n=35).

SARS-CoV-2 quantification of respiratory samples. Quantification of SARS-CoV-2 levels in oropharyngeal swab-derived respiratory samples were assessed by RT-PCR at baseline and longitudinally. At baseline, 77 participants had evaluable samples. 83% (n=64) had detectable virus, with 44% (n=34) having high-titer (>4 Log10 copies) virus levels. To compare viral loads, we considered a composite score of viral load and clinical status, in which those discharged were assigned the lowest score, deaths the highest score, and those in-hospital the observed viral load. Plasma recipients had a lower composite score at day 3 (p=0.0128 by Wilcoxon rank sum test) (Figure 3).

Discussion

Antibody-based strategies for COVID-19 have shown promise in prevention and treatment of early disease[26-28], but data supporting benefit in hospitalized patients with pneumonia are more limited. Observational analyses of a subcohort of hospitalized CCP recipients from the US FDA's EAP suggested possible benefit in recipients of early, high-titer plasma[13]. More recently, reports from larger, randomized controlled trials suggest CCP is not efficacious when given broadly to hospitalized COVID-19 patients [14, 17-19].

In this open-label, randomized controlled trial, we assessed the impact of early administration of multiple units of locally sourced CCP in hospitalized individuals with COVID-19 pneumonia. We found that CCP treatment was safe and conferred significant benefit as measured by our clinical severity score and 28-day mortality. In exploratory analyses, we found a reduction in a composite respiratory virus and clinical status score at study day 3 in plasma recipients. In all other pre-specified outcome measures, including ordinal WHO8 scale at days 14 and 28, 14-day mortality, use and duration of oxygen and mechanical ventilation, and number and max grade of AE, we found weak evidence towards a benefit of CCP treatment.

Given recent large, randomized studies that have not shown benefit in general hospitalized cohorts, it is important to put the positive result of our study in context. This study has several unique characteristics that may have contributed to the demonstrated benefit, including the early administration of two units of locally sourced, plasma in a highly comorbid, majority antibody seronegative population[29, 30]. In addition, we employed a sensitive primary outcome measure enabling a composite characterization of clinical status[31]. First, we posit that relatively early treatment distinguished this study from many others, as we enrolled and administered CCP within a median of day 6 of symptoms and 1 day of hospitalization, in participants in whom 60% were seronegative at entry. Many other reported RCTs enrolled participants later in disease course, as determined by seropositivity and days since symptoms onset. For example, reports describe a median 30 days since symptom onset in the Wuhan study[32], median 10 days of symptoms and 63% seropositivity in RECOVERY[18], 83% seropositive in PLACID[14], median 10 days of symptoms and 79% seropositive in CONCOVID[15], median 8 days of symptoms in PlasmAR[17], and median 8 days of symptoms in CONCOR-1[19]. Benefit from earlier treatment with antibody-based interventions has also been reported, with early treatment with CCP in some high-risk outpatient cohorts [28, 33] and early treatment with monoclonal antibodies[26, 27]. Though potentially confounded and requiring cautious interpretation, multiple subgroup analyses of earlier treated participants also suggest possible benefit[16, 34-36].

Second, we enrolled a highly comorbid population. Our study was conducted within tertiary care referral centers that serve highly complex patient populations. In our experience, the safety profile and permissive entry criteria of this study compared with competing COVID-19 clinical trials led to increased enrollment of higher risk individuals, in terms of both severe COVID-19 outcomes and immunodeficiency. Whereas our participants had a median of 3 comorbidities, and just 4% (3/79) had no reported co-morbidities, many studies enrolled high proportions of participant without comorbidities (*e.g.,* RECOVERY enrolled 44% participants with no comorbidities and PlasmAR enrolled 35% with no comorbidities)[17, 18]. Further, we enrolled substantial numbers of participants with cancer (27%) and immunodeficiency (14%), both of which have high mortality from COVID-19[23, 37, 38], and have been reported to incur benefit from antibody-based therapies[39-41]. Thus, we suspect that early CCP treatment of a higher-risk, highly comorbid

population may have conferred benefit in a way not seen in later-treated, more general hospitalized populations. The hypothesis that baseline clinical characteristics of plasma recipients and timing of CCP administration could substantially impact CCP efficacy is being more formally assessed in large, collaborative studies of treatment benefit index [35, 42].

We propose that our CSC primary endpoint [31] is well suited to detect more subtle distinctions in disease course, which mortality and duration of hospitalization outcomes alone may miss. We pre-specified this validated clinical severity outcome, given the heterogeneity of disease outcomes in COVID-19 patients, the proposed mechanism of antibody-based treatments, an expected modest efficacy of CCP, and the smaller size of our study. Others have advocated for the use of similar disease severity scores in settings where participants may experience multiple outcomes and disease course is heterogenous with a spectrum of disease severity [37, 43]. Further, continuous outcomes that consider time to recovery are advocated in COVID-19 as more robust in detecting differences than an ordinal score at a fixed timepoint because of the potential mismatch between the chosen timepoint of analysis and actual timing of patient recovery[44]. Our sensitive severity score measure enabled us to detect an improvement in clinical disease progression not well detected by the WHO8 score at discrete timepoints. This outcome is also supported by a statistically significant 28-day mortality benefit.

Our study found a significant difference in mortality at 28 days, but less distinction between study arms earlier. Indeed, at day 14 we had fewer events: either discharges or deaths to distinguish between study arms. We note other trials have identified differences in 28-day mortality, without or with less substantial earlier outcomes[16, 45].

High-titer antibodies in donor plasma have also been associated with improved outcomes (12). Our donor and recipient plasmas were tested by a validated, quantitative in-house assay [24], thus titers are not directly comparable to commercial assays currently used in assessment of clinically relevant titer. While our exploratory analyses have limitations, they suggest that more than two-thirds of participants received at

least one unit of “high-titer” plasma and between 20% and 44% received two units of “high-titer” plasma (Figure S3).

Our study has several limitations. It was smaller, open label, and performed at just two hospitals within a single health system. Use of ABO-compatible plasma limited enrollment for some blood types. Over the eight months of study enrollment, the local epidemic shifted in severity and affected populations, approved and emergency use treatments changed, and standard practices for the treatment and infection control of COVID-19 evolved. Strengths of the study included its randomized nature, use of two units of locally-sourced plasma, early enrollment, and permissive entry criteria. We note the inclusion of pregnant and lactating individuals, and the successful enrollment of three pregnant participants.

In summary, our randomized controlled study found that CCP conferred a significant benefit in clinical severity score and 28-day mortality. Results support the heterogeneity of COVID-19, and suggest CCP may benefit select populations, especially those with comorbidities who are treated early.

Methods

Trial Design and Oversight. This open-label, controlled trial assessed the safety and efficacy of CCP in severely-ill, hospitalized participants with pneumonia due to COVID-19 (ClinicalTrials.gov number NCT04397757). This study enrolled adults ≥18 years old, including pregnant women. The study was conducted at two hospitals (Hospital of the University of Pennsylvania (HUP) and Penn Presbyterian Medical Center (PPMC)) within the University of Pennsylvania Health System in Philadelphia, Pennsylvania.

Study Participants. The study enrolled hospitalized adults with RT-PCR-confirmed SARS-CoV-2 infection, radiographic documentation of pneumonia, and abnormal respiratory status, defined as room air saturation of oxygen (SaO2) <93%, or requiring supplemental oxygen, or tachypnea with a respiratory rate ≥30. Participants were excluded if they had a contraindication to transfusion, were participating in other clinical trials of investigational COVID-19 therapy, if there was clinical suspicion that the etiology of acute illness was primarily due to a condition other than COVID-19, or if ABO-compatible CCP was unavailable.

Intervention and Assessments. A total of 80 eligible participants were randomized to receive either 2 units of CCP and standard of care (treatment arm) versus standard of care alone (control arm). Participants were assigned to treatment or control in 1:1 ratio using randomization stratified on the use of remdesivir and mechanical ventilation at entry using block randomization with variable block size. Participants in the treatment arm received up to 2 units of convalescent plasma on study day 1 in addition to standard of care. Participants were assessed on all study days while hospitalized through day 29, and after discharge as outpatients on study days 15, 22, 29, and 60. Blood samples were collected at baseline (prior to CCP administration on study day 1), study days 3, 8, 15, 29, and 60; respiratory samples (oropharyngeal swabs in non-intubated participants or endotracheal aspirates in intubated participants) were collected on study days 1, 3, 5, 8, 11, and 15. The protocol is available in the Supplement.

COVID-19 Convalescent Plasma (CCP). Between April 16th and July 6th, 2020, the Hospital of the University of Pennsylvania apheresis unit collected donor plasma that was further manufactured into Penn CCP by the hospital blood bank/transfusion service. CCP was collected from individuals who would otherwise qualify as blood donors (per FDA), were diagnosed with SARS-CoV-2 RT-PCR testing during acute COVID-19 infection, and were at least 28 days from symptoms. In addition to standard blood donor infectious disease tests, female donors were screened for the presence of anti-HLA antibodies which disqualified plasma donation. CCP was then tested for the presence of anti-SARS-CoV-2 antibodies by ELISA [24]. For each study participant randomized to treatment, two units ABO-compatible CCP with detectable antibodies were randomly selected, with a preference for use CCP from two different donors when available.

Study Objectives and Outcomes. The overall objectives of the study were to evaluate the safety and explore the efficacy of CCP in hospitalized participants with confirmed COVID-19 pneumonia. The primary efficacy outcome was a clinical severity score (CSC), which could effectively rank patients by their disease severity by taking into account multiple endpoints in a prioritized manner, following the procedure similar to Shaw and Fay 2016 [31]. Clinical severity was determined by a participant's survival time, time to recovery,

and disease course while in the hospital (considering max 8-point WHO ordinal score (WHO8), use of supplemental oxygen and AEs)[46]. Detailed CSC methods are in the Supplement. The composite severity score outcome was chosen as primary over a single mortality outcome to enhance power and in recognition that deaths could follow an initial recovery so time to recovery alone was anticipated to inadequately summarize outcomes. Key secondary and exploratory efficacy outcomes include 14- and 28-day mortality, 14- and 28-day WHO8 score, duration of supplemental oxygenation, use and duration of mechanical ventilation, presence and quantity of SARS-CoV-2 RNA in respiratory samples, and anti-SARS-CoV-2 antibody levels. Sample sizes were determined by desire to estimate safety and to provide a preliminary idea of efficacy. We estimated that 40 participants in the CCP arm enabled an 80% chance of observing at least one individual with an AE if the underlying AE rate is 4%. We approximated the power for the CSC primary efficacy comparison by considering the power of the Win Ratio[43] statistic. For 40 matched experimental-control pairs, we had over 80% power to reject the null proportion=50% if the experimental treatment is associated with an 80% or higher probability of having better severity than a control participant.

Plasma anti-SARS-CoV-2 antibody testing. To quantitate anti-SARS-CoV-2 IgG in donor plasma (CCP) and in participants, enzyme-linked immunosorbent assays (ELISAs) were completed using plates coated with recombinant receptor-binding domain and full-length SARS-CoV-2 spike protein, as previously described [24].

SARS-CoV-2 quantification in respiratory samples.

Oropharyngeal swabs were collected for all non-intubated participants and endotracheal aspirates were collected for intubated participants. From each sample, SARS-CoV-2 RNA was quantified by RT-PCR [47].

Statistical Analyses. The primary safety endpoint was cumulative incidence of serious adverse events (SAEs) at Day 29, calculated separately by arm as the percent of individuals who had at least one SAE by Day 29. The SAE rate, treatment-related AE rate, and the number and maximum grade of all AEs at Day 29 were also calculated.

For the primary efficacy outcome, the Wilcoxon rank-sum test was used to assess the difference between arms. This type of prioritized outcome severity score can be interpreted as a weighted average of the log-rank type test statistic for survival. Binary secondary outcomes were analyzed with Fisher's exact, ordinal endpoints by the proportional odds model, and the 28-day censored survival time by the Peto-Peto log-rank (See Supplement). The cumulative incidence of discharge was estimated and the treatment effect on time-to-discharge assessed using a cause-specific proportional hazards model, with death as a competing risk.

Study Approvals. The trial was sponsored by the University of Pennsylvania and approved by its institutional review board, located in Philadelphia, PA. All participants provided informed consent prior to participation in the study. alukeAll authors vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the respective protocol. There was no commercial support for this trial.

Author Contributions.

Author contributions include: designed clinical trial (KJB, PAS, GHC, NA, AF, MC, JLP, ME, IF, SEH, DLS, PT), conducted clinical trial (KJB, PAS, GHC, NA, AF, HS-C, LG, JS, MA, MM, CA, GF, MD, MB, MC, JG, AW, MAM, FM, EL, AM, HB, AP, LI, RT, RE, FD, JLP, WS, ME, JB, NM, KD, IF, DLS, PT), conducted experiments (KJB, LG, AW, MAM, GM, EL, SG, ETLP, SEH, DLS), analyzed data (KJB, PAS, GHC, JY, PT), wrote manuscript (KJB, PAS, GHC, MC, PT).

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Figure Legends.

Figure 1. Consort Diagram

Figure 2. Stacked cumulative incidence curves for the competing risks of remaining hospitalized, death, or discharge are shown over time, censored at 28 days for the control (A) and treatment arm (B) of the 79 participants of the ITT cohort. Deaths are shaded red and discharges blue. One participant who withdrew at day of discharge (day 9) is assumed to have survived 28 days.

Figure 3. Composite endpoint assessing respiratory sample viral load and clinical status, in which those who were discharged had the lowest score and those who died had the highest. Control (red) and plasma (blue) arms are shown for baseline (prior to plasma administration) and study days 3 and 8. Imputed values are shown in filled symbols and measured virus levels are shown in open circles. Values were not significantly different at baseline and were significantly lower in treatment arm at day 3 ($p=0.0128$ by Wilcoxon rank sum test).

Tables.

Table 1. Participant baseline characteristics (N=79)

Characteristic		Control N=39	Plasma N=40	All N=79
Age in years, n (%)				
	<45	2 (5.1)	10 (25.0)	12 (15.2)
	45-60	15 (38.5)	6 (15.0)	21 (26.6)
	61-74	12 (30.8)	14 (35.0)	26 (32.9)
	75+	10 (25.6)	10 (25.0)	20 (25.3)
Sex, n (%)				
	Female	24 (61.5)	19 (47.5)	43 (54.4)
	Male	15 (38.5)	21 (52.5)	36 (45.6)
Race, n (%)				
	African American	21 (53.8)	21 (52.5)	42 (53.2)
	Asian	1 (2.6)	3 (7.5)	4 (5.1)
	Caucasian	16 (41.0)	14 (35.0)	30 (38.0)
	Unknown	1 (2.6)	2 (5.0)	3 (3.8)
Ethnicity, n (%)				
	Hispanic	2 (5.1)	1 (2.5)	3 (3.8)
	Non-Hispanic	37 (94.9)	39 (97.5)	76 (96.2)
Blood Type, n (%)				
	A	15 (38.5)	13 (32.5)	28 (35.4)
	B	6 (15.4)	2 (5.0)	8 (10.1)
	O	18 (46.2)	25 (62.5)	43 (54.4)
Randomization date, n (%)				
	May-Jun 2020	10 (25.6)	9 (22.5)	19 (24.1)
	Jul-Aug 2020	9 (23.1)	10 (25.0)	19 (24.1)
	Sep-Oct 2020	5 (12.8)	5 (12.5)	10 (12.7)
	Nov-Jan 2021	15 (38.5)	16 (40.0)	31 (39.2)

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553 **Table 2. COVID-19 symptoms and comorbidities at baseline**

Characteristic	Control N=39	Plasma N=40	All N=79
Days from Symptoms to Randomization, MED [IQR]	6 [4,9]	6 [4,8.5]	6 [4,9]
Days from Hospitalization to Randomization, MED [IQR]	1 [1,2]	2 [1,2.25]	1 [1,2]
Ab negative[1], n (%)	24 (61.5)	23 (57.5)	47 (59.5)
WHO8 Score[2], n (%)			
4	3 (7.7)	1 (2.5)	4 (5.1)
5	20 (51.3)	22 (55.0)	42 (53.2)
6	16 (41.0)	17 (42.5)	33 (41.8)
NEWS Score, n (%)			
Low risk: <5	17 (43.6)	19 (47.5)	36 (45.6)
Medium risk: 5-6	15 (38.5)	15 (37.5)	30 (38.0)
High risk: 7+	7 (17.9)	6 (15.0)	13 (16.5)
ICU level care, n (%)	2 (5.1)	3 (7.5)	5 (6.3)
Comorbidities, n (%)			
Diabetes (types 1 or 2)[2]	19 (48.7)	13 (32.5)	32 (40.5)
Obesity	20 (51.3)	16 (40.0)	36 (45.6)
Hypertension	30 (76.9)	23 (57.5)	53 (67.1)
Coronary Artery Disease	11 (28.2)	12 (30.0)	23 (29.1)
Congestive Heart Failure	3 (7.7)	9 (22.5)	12 (15.2)
Pulmonary Disease[3]	12 (30.8)	11 (27.5)	23 (29.1)
Chronic Kidney Disease	15 (38.5)	11 (27.5)	26 (32.9)
Chronic Liver Disease	3 (7.7)	3 (7.5)	6 (7.6)
Cancer	11 (28.2)	10 (25.0)	21 (26.6)
Immune Deficiency	6 (15.4)	5 (12.5)	11 (13.9)
Total number of comorbidities, MED [IQR][4]	3 [2.5,4]	3 [1,4]	3 [2,4]
Potential COVID-19 therapies			
Remdesivir, n (%)	32 (82.1)	32 (80.0)	64 (81.0)
Hydroxychloroquine, n (%)	2 (5.1)	0 (0.0)	2 (2.5)
Steroids, n (%)	35 (89.7)	31 (77.5)	66 (83.5)

[1]anti-SARS-CoV-2 RBD IgG interpolated concentration, negatives indicated by IgG <0.4 mg/ml.
[2] WHO 8-point Ordinal score: 4, hospitalized, not requiring supplemental oxygen; 5, hospitalized, requiring supplemental oxygen; 6, hospitalized, on high-flow oxygen or non-invasive ventilation
[3]Asthma, Chronic Respiratory Disease, Chronic Oxygen Requirement.
[4]Possible range from 0 to 9; Using listed comorbidities with Coronary Artery Disease and Congestive Heart Failure considered as one cardiovascular disease category.
MED median; IQR interquartile range 25th and 75th percentile

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555 **Table 3. Clinical outcomes by treatment arm through Day 28 (N=79).**

Outcome	Control N=39	Plasma N=40[1]	P-Value	OR (95%CI)[2]
Clinical Severity Score, MED [IQR]	**10 [5.5,30]**	**7 [2.75,12.5]**	**0.037[a]**	
14-day mortality, n (%)	2 (5.1)	1 (2.5)	0.615[b]	0.479 (0.008,9.558)
28-day mortality, n (%)	**10 (25.6)**	**2 (5.0)**	**0.013 [b]**	**0.156 (0.015,0.814)**
Day 14 WHO8 score, MED [IQR]	2 [1.5,6.5]	2 [1,4]	0.076[c]	0.481 (0.212,1.072)
Day 28 WHO8 score, MED [IQR]	2 [1,7.5]	1 [1,2]	0.174[c]	0.562 (0.243,1.288)
Mechanical ventilation (MV) / ECMO, n (%)	10 (25.6)	5 (12.8)	0.161[b]	0.419 (0.1,1.531)
Days with MV/ECMO, MED [IQR]	0 [0,0.5]	0 [0,0]	0.085[d]	
Days with any O2 support, MED [IQR]	8 [4, 18.5]	7 [2,10.25]	0.169[a]	
Number participants with ≥1 SAE, n(%)	15 (38.5)	12 (30.0)	0.482[b]	0.689 (0.242,1.929)
Max grade AE per subject, MED [IQR]	3 [0,4.5]	1 [0,3]	0.105[c]	0.507 (0.221,1.148)
Number of AEs per subject, MED [IQR]	1 [0,7]	0.5 [0,2.25]	0.151[d]	
Max grade SAE per subject, MED [IQR]	0 [0,4.5]	0 [0,3]	0.204[c]	0.553 (0.218,1.375)
Number of SAEs per subject, MED [IQR]	0 [0,1]	0 [0,1]	0.737[d]	

[1]One subject who withdrew early had WHO8 score at day of discharge (day 9) imputed for day 14 and day 28 outcomes and is assumed to survive 28 days.; [2]Odds ratio (plasma:control) and 95% confidence interval.; [a]Wilcoxon rank sum asymptotic p value; [b]Fisher's exact test; [c]Proportional odds model; [d]Lachenbruch test.

MED, median; IQR, interquartile range 25th and 75th percentile

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Figure 1. Study consort diagram

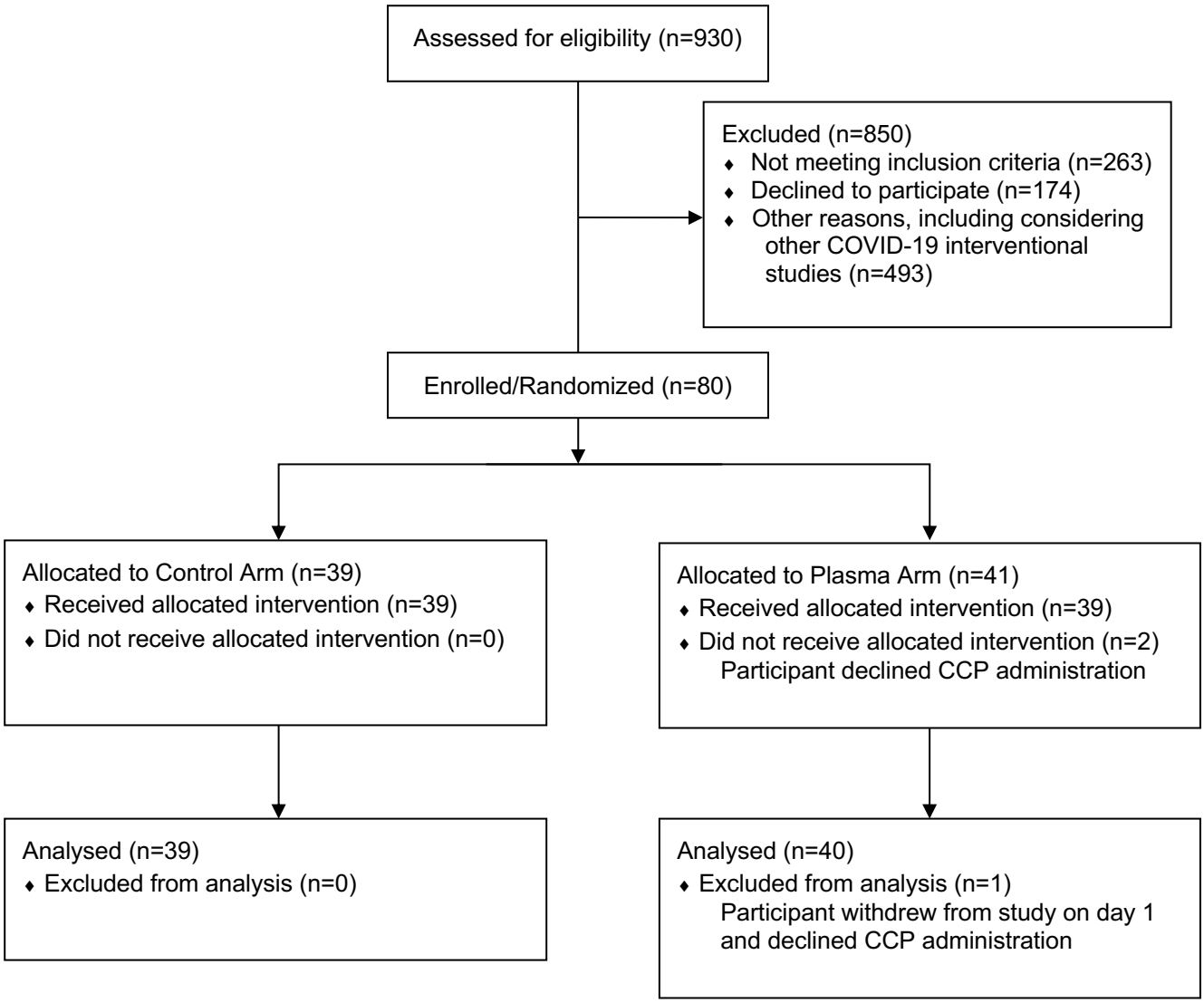
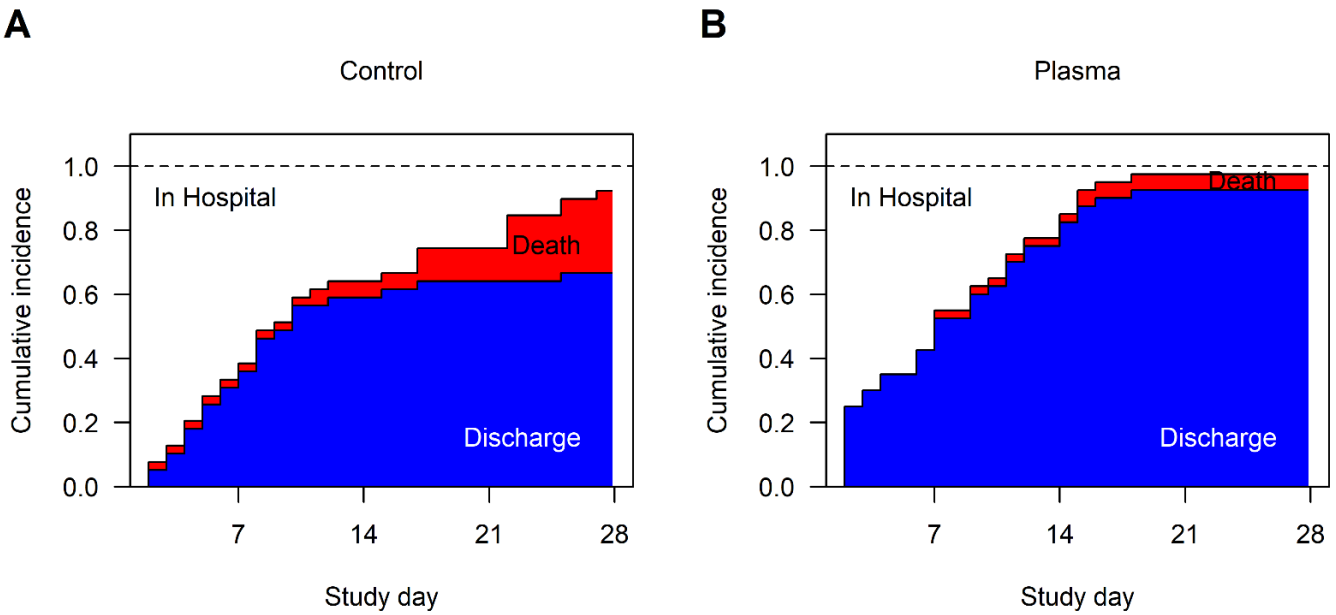
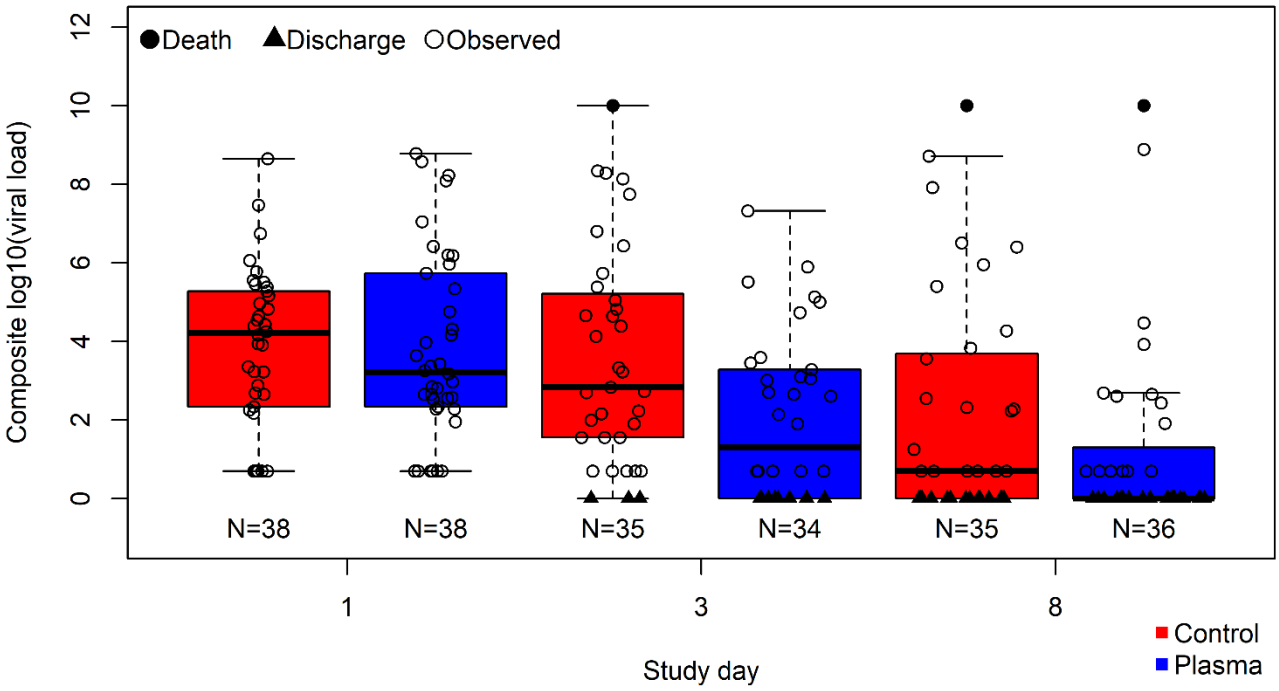


Figure 2. Cumulative incidence of discharge and mortality over 28 days.



Stacked cumulative incidence curves for the competing risks of remaining hospitalized, death, or discharge are shown over time, censored at 28 days for the control (A) and treatment arm (B) of the 79 participants of the ITT cohort. Deaths are shaded red and discharges blue. One participant who withdrew at day of discharge (day 9) is assumed to have survived 28 days.

Figure 2. Composite respiratory viral load and hospital discharge score by treatment arm



Composite endpoint assessing respiratory sample viral load and clinical status, in which those who were discharged had the lowest score and those who died had the highest. Control (red) and plasma (blue) arms are shown for baseline (prior to plasma administration) and study days 3 and 8. Imputed values are shown in filled symbols and measured virus levels are shown in open circles. Values were not significantly different at baseline and were significantly lower in the treatment arm at day 3 (p=0.0128 by Wilcoxon rank sum test).