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Convalescent plasma treatment of severe COVID-19: a propensity score–matched control study

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a new human disease with few effective treatments[1]. Convalescent plasma, donated by persons who have recovered from COVID-19, is the acellular component of blood that contains antibodies, including those that specifically recognize SARS-CoV-2. These antibodies, when transfused into patients infected with SARS-CoV-2, are thought to exert an antiviral effect, suppressing virus replication before patients have mounted their own humoral immune responses[2,3]. Virus-specific antibodies from recovered persons are often the first available therapy for an emerging infectious disease, a stopgap treatment while new antivirals and vaccines are being developed[1,2]. This retrospective, propensity score–matched case–control study assessed the effectiveness of convalescent plasma therapy in 39 patients with severe or life-threatening COVID-19 at The Mount Sinai Hospital in New York City. Oxygen requirements on day 14 after transfusion worsened in 17.9% of plasma recipients versus 28.2% of propensity score–matched controls who were hospitalized with COVID-19 (adjusted odds ratio (OR), 0.86; 95% confidence interval (CI), 0.75–0.98; chi-square test *P* value = 0.025). Survival also improved in plasma recipients (adjusted hazard ratio (HR), 0.34; 95% CI, 0.13–0.89; chi-square test *P* = 0.027). Convalescent plasma is potentially effective against COVID-19, but adequately powered, randomized controlled trials are needed.

SARS-CoV-2 is a positive-sense, single-stranded RNA virus belonging to the family *Coronaviridae*. Humans infected with SARS-CoV-2 may develop COVID-19, which manifests across a wide spectrum of clinical severity ranging from a mild upper respiratory tract illness to a diffuse viral pneumonia causing acute respiratory failure, with sequelae including acute lung injury, multiorgan dysfunction syndrome and death[4–6]. Although protection from COVID-19 infection or disease has yet to be directly correlated with levels of circulating antibodies against SARS-CoV-2 (ref. [7]), providing virus-neutralizing antibodies in the form of convalescent plasma may expedite disease resolution before the maturation of a patient's own humoral response[1,8,9]. Historical evidence supports the potential of convalescent plasma transfusions to treat a variety of infectious diseases, including influenza, Argentine hemorrhagic fever and SARS[10–12]; however, their effectiveness in treating other infectious diseases, such as Ebola[13], remains inconclusive.

To date, published clinical data regarding convalescent plasma transfusions as treatment for COVID-19 include single-arm, observational studies from China, the United States, Italy[5,7,14–16] and, most recently, two randomized open-label trials that were terminated before full enrollment[17,18]. In respiratory infections specifically, the strongest evidence suggests that the benefit of passive antibody transfer is most demonstrable in patients who were treated within days of symptom onset[11,19–21]. Therefore, we hypothesized that treatment of patients with convalescent plasma early in the disease course would reduce morbidity and mortality associated

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Table 1 | Demographics and clinical parameters of convalescent plasma recipients before transfusion

Characteristic[a]	Patients ($n = 39$)
Demographics	
Age (years), mean ± s.d.	55 ± 13
Sex	
Male versus female, *n* (%)	25 (64) versus 14 (36)
BMI, mean ± s.d.[b]	31.7 ± 6.0
Coexisting disorder, *n* (%)	
Asthma	3 (8)
Cancer[c]	2 (5)
Chronic kidney disease	1 (3)
Chronic obstructive pulmonary disease	1 (3)
Current or former smoker	7 (18)
Diabetes mellitus	8 (21)
Hemorrhagic or ischemic stroke	0
Human immunodeficiency virus	0
Obstructive sleep apnea	2 (5)
Duration (d) of symptoms before admission, median (range)	7 (0–14)
Presenting symptoms, *n* (%)	
Fever	26 (67)
Shortness of breath	26 (67)
Cough	24 (62)
Diarrhea	8 (21)
Sputum production	3 (8)
Sore throat	2 (5)
Vital signs on admission, *n* (%)	
Temperature >100.4 °F or 38 °C	13 (33)
Heart rate >100 beats per min	22 (56)
Respiratory rate ≥20 breaths per min	28 (72)
Imaging, *n* (%)	
Chest radiography	38 (97)
Chest computed tomography	3 (8)
Clinical parameters	
Laboratory data before transfusion	
White-cell count	
Cells per mm^3 field, median (range)	7,600 (3,900–22,600)
Distribution, *n* (%)	
≥10,000 cells per mm^3 field	10 (26)
≤4,000 cells per mm^3 field	2 (5)
Aspartate aminotransferase >40 U l^{-1}, *n* (%)	26 (67)
Alanine aminotransferase >40 U l^{-1}, *n* (%)	18 (46)
Lactate ≥1.5 mmol l^{-1}, *n* (%)	23 (59)
D-dimer, median (range) (μg ml^{-1} fibrinogen equivalent units)	2.33 (0.27–28.28)
Fibrinogen, mean ± s.d. (mg dl^{-1})	684 ± 140
Ferritin, median (range) (ng ml^{-1})	1,135 (107–7,441)
C-reactive protein, median (range) (mg l^{-1})	161.4 (19.8–339.8)
IL-6, mean ± s.d. (pg ml^{-1})	178 ± 348
Length of stay before transfusion	
Duration (d), median (range)	4 (0–7)
Supplemental oxygen requirement before initiation of transfusion	
Room air, *n* (%)	1 (3)
Standard nasal cannula, *n* (%)	7 (18)
2 l, *n* (%)	0
3 l, *n* (%)	2 (5)
4 l, *n* (%)	2 (5)
≥5 l, *n* (%)	3 (8)
High-flow oxygen[d], high-flow nasal cannula or BiPAP, *n* (%)	27 (69)
Mechanical ventilation, *n* (%)	4 (10)

Thirty-nine patients received convalescent plasma. Baseline demographics, comorbid conditions, symptoms and duration before admission, initial vital signs, initial laboratory parameters and initial imaging studies are described. Length of stay before transfusion and oxygen device at the time of transfusion are also provided. [a]Percentages may not total 100% because of rounding. [b]BMI is the weight in kilograms divided by the square of the height in meters. [c]One patient with thyroid cancer after resection and one patient with Gleason 6 prostate cancer. [d]High-flow oxygen included venti-mask and non-rebreather mask; BiPAP, bilevel positive airway pressure.

patients with severe to life-threatening COVID-19 who received convalescent plasma transfusions at a single center, The Mount Sinai Hospital (MSH), in New York City.

Adult patients admitted to MSH between 24 March 2020 and 8 April 2020 were screened for eligibility to receive a COVID-19 convalescent plasma transfusion under the criteria established for the U.S. Food and Drug Administration (FDA) single-patient emergency investigational new drug (eIND) process (Supplementary Text 1). Forty-five applications requesting individual patient eIND authorization to administer COVID-19 convalescent plasma were submitted to and approved by the FDA. Four patients improved and two patients withdrew consent before receipt of plasma, leaving 39 evaluable patients who received COVID-19 convalescent plasma under compassionate-use guidelines. The average age of convalescent plasma recipients was 55 (standard deviation (s.d.) ± 13) years (Table 1). Approximately two-thirds of the cohort were male and one-third were female, similar to the proportions of men and women with severe disease in previous studies[4]. Convalescent plasma recipients were, on average, obese (mean body mass index (BMI), 31.7 ± 6.0 kg m^{-2}) but generally had few other baseline comorbidities. The median duration of symptoms before initial presentation was 7 d (range, 0–14 d). The median time between admission and transfusion was 4 d (range, 0–7 d). On the day of transfusion, the majority of the convalescent plasma recipients (34 patients; 87%) required supplemental oxygen via a noninvasive delivery device. Four convalescent plasma recipients (10%) were mechanically ventilated at the time of transfusion.

Convalescent plasma recipients were retrospectively propensity-score matched to control patients who were admitted during the same period, between 24 March 2020 and 8 April 2020. Analyses were performed at 1:4 and 1:2 ratios (convalescent plasma recipients to controls), with and without replacement. In sampling without replacement, each untreated control can be matched to only one treated case, while sampling with replacement allows each untreated control to be matched by similarity in propensity score to more than one treated case. Each method has distinct advantages[22]; thus, we used both methods for sensitivity analyses. After matching was established, control patients were retrospectively chart reviewed

by a medical data team who were blinded to information about the matched convalescent plasma recipient. Predictors not readily available in the system database, such as duration of symptoms before hospital admission and exposures to specific pharmacotherapies (azithromycin, hydroxychloroquine, broad-spectrum antibiotics, therapeutic-dose anticoagulation, corticosteroids, remdesivir, mesenchymal stem cells and interleukin (IL)-1 and IL-6 inhibitors), were manually collected after matching. Subsequently, duration of symptoms before hospital admission was not significantly different between the controls and convalescent plasma recipients for both the 1:2 (Wilcoxon rank-sum test, $P=0.307$) and 1:4 (Wilcoxon rank-sum test, $P=0.968$) analyses. There were also no significant differences between convalescent plasma recipients and control patients in exposures to the aforementioned pharmacotherapies, except for therapeutic anticoagulation ($P=0.004$ for the 1:4 ratio and $P=0.018$ for the 1:2 ratio, chi-square test; Supplementary Table 1). Overall, the distribution of the logit propensity score–matched controls was within range of the convalescent plasma recipients, as opposed to the logit propensity score of all patients with COVID-19 system wide who were admitted during the same period (Extended Data Fig. 1).

The day of convalescent plasma transfusion was defined as 'day 0' for convalescent plasma recipients. For each control patient, 'day 0' was defined as the same hospital day (number of days into their admission) that corresponded to the hospital day on which their matched convalescent plasma recipient received the transfusion (Supplementary Table 2). Although matching was not enforced by admission date, the 156 controls in the 1:4 matched analysis were admitted to the hospital within a median of 4 d (interquartile range (IQR), 2–6 d) of the convalescent plasma recipients to whom they were matched. Control patients were admitted slightly earlier (median, 1 d before; IQR, 5 d before to 4 d after) than the convalescent plasma recipients.

Convalescent plasma recipients and control patients in the 1:4 analysis were 100% matched on their supplemental oxygen requirement on day 0; 69.2% of patients in both groups received high-flow oxygen and 10.3% received invasive mechanical ventilation (Supplementary Table 3). By day 14, clinical conditions had worsened in 17.9% of the convalescent plasma recipients and in 28.2% of the control patients. The covariates-adjusted OR for worsening oxygenation on day 14 was 0.86 (95% CI, 0.75–0.98; chi-square test, $P=0.025$). The effect of plasma on oxygenation status appeared to be confounded by the use of therapeutic anticoagulants (unadjusted versus adjusted anticoagulation versus fully adjusted OR: 0.90 versus 0.84 versus 0.86) but not by other drug classes or by duration of symptoms before admission (OR, 0.90–0.91). The plasma group also showed a reduction in the proportion of patients with worsened oxygenation status earlier in hospitalization, but the group differences did not reach statistical significance on day 1 (OR, 0.98; 95% CI, 0.92–1.04; chi-square test, $P=0.443$) or day 7 (OR, 0.95; 95% CI 0.84–1.08; chi-square test, $P=0.435$).

As of the end of the study (1 May 2020), 12.8% of convalescent plasma recipients and 24.4% of the 1:4 matched control patients had died (21.6% in the 1:2 matched dataset), and 71.8% and 66.7% (68.9%) had been discharged alive, respectively. The median follow-up time was 11 d (range, 1–28 d) for the plasma group and 9 d (range, 0–31 d) for the control group. Overall, survival probability was greater in convalescent plasma recipients than controls (Fig. 1). Without covariate adjustment, the survival benefit of convalescent plasma was significant in the 1:4 matched dataset (HR, 0.39; 95% CI 0.15–0.99; chi-square test $P=0.048$; Fig. 2), with potential benefit in the 1:2 matched dataset (HR, 0.47; 95% CI 0.17–1.28; chi-square test $P=0.14$). No evidence of confounding was found for any covariates in the survival analysis. Following covariate adjustment (adjusting for duration of symptoms before admission and for exposure to therapeutic anticoagulation and broad-spectrum antibiotics), the

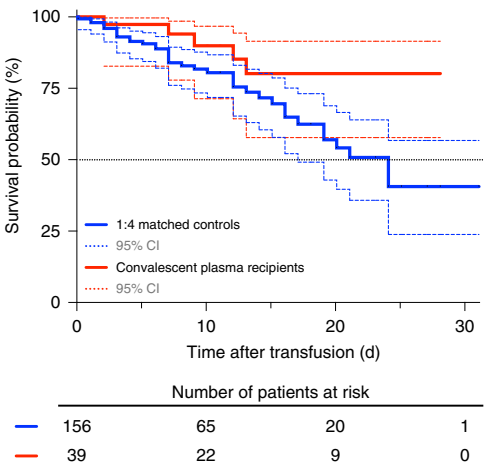
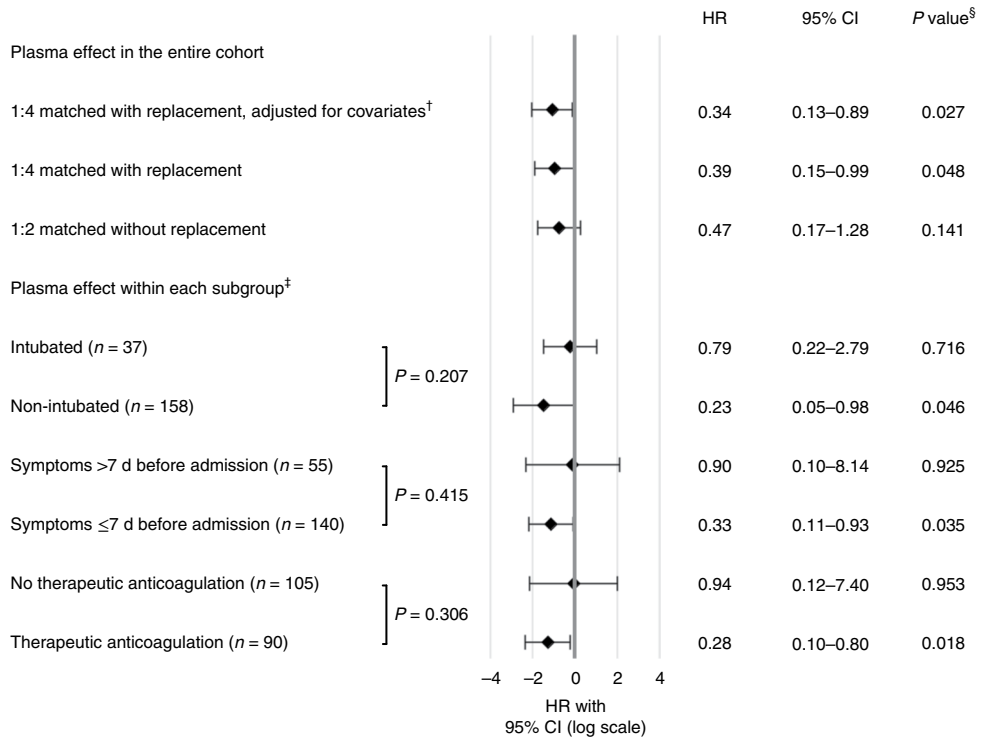


Fig. 1 | Survival probability. As of 1 May 2020, 5 (12.8%) of 39 convalescent plasma recipients and 38 (24.4%) of 156 1:4 matched control patients had died. The median follow-up time was 11 d (range 1–28 d) for the plasma group and 9 d (0–31 d) for the control group. Overall, improved survival was observed for the plasma versus the control group.

1:4 matched model continued to show significant survival benefit of convalescent plasma (HR, 0.34; 95% CI, 0.13–0.89; chi-square test, $P=0.027$). When aggressively adjusting for additional covariates, including mechanical ventilation, corticosteroids, azithromycin, interventional antivirals and IL-6 inhibitors, convalescent plasma remained significantly associated with improved survival (HR, 0.31; 95% CI, 0.12–0.82; chi-square test, $P=0.018$). Subgroup analyses showed significant survival benefits of convalescent plasma within the subgroups of patients who were not intubated, had a shorter duration of symptoms and received therapeutic anticoagulation, in comparison to the matched untreated control groups (Fig. 2). However, the effects of convalescent plasma within these subgroups were not significantly different from its effects within the complementary subgroups (chi-square tests for homogeneity for intubated versus non-intubated, $P=0.207$; symptoms >7 d versus ≤7 d before admission, $P=0.415$; and treated versus not treated with therapeutic anticoagulation, $P=0.306$). Because the effects of convalescent plasma were not significantly different within these subgroup pairs, its effect on survival in patients who were not intubated, had a shorter duration of symptoms and received therapeutic anticoagulation also should not be interpreted as significantly better than its effect on survival in those who were intubated, had a longer symptom duration and did not receive anticoagulation therapy. Therefore, these results suggest but do not confirm a benefit of convalescent plasma in non-intubated patients, those with less than a week of symptoms and those also receiving therapeutic anticoagulation. These subgroup findings remain inconclusive, potentially due to a lack of statistical power.

Before donation, potential convalescent plasma donors were prescreened for SARS-CoV-2-specific serum antibodies with the MSH-ELISA anti-IgG COVID-19 assay, a research assay[23,24] that was transitioned to clinical use in the Mount Sinai Laboratory[25]. Only donors with an MSH-ELISA serum IgG titer of ≥1:320 ($n=25$) were referred for plasmapheresis.

Donors presented for plasma donation at a median of 4 d (IQR, 1–5 d) after their screening antibody test was performed. Stored samples of donor serum and plasma were available for 24 of 25 donors, who provided a total of 76 units of plasma to 38 recipients (Fig. 3). We assessed the total anti-spike IgG titers in transfused plasma units in a lab-based ELISA. We also performed a microneutralization assay to quantify the capacity of donor serum antibodies



§*P* value by chi-square test
†Covariates: duration of symptoms before admission, therapeutic anticoagulation and broad-spectrum antibiotics
‡*P* value by chi-square test for homogeneity

Fig. 2 | HRs for in-hospital mortality. In a covariates-adjusted Cox model, convalescent plasma transfusion was significantly associated with improved survival (HR, 0.34; 95% CI, 0.13–0.89; chi-square test, $P=0.027$). Subgroup analyses showed significant survival benefits of convalescent plasma in patients who were not intubated, had a shorter duration of symptoms and received therapeutic anticoagulation. However, these subgroups were not significantly different from their complementary subgroups (chi-square test for homogeneity $P=0.207$, $P=0.415$ and $P=0.306$, respectively). All statistical tests are two-sided.

to inhibit the replication of authentic SARS-CoV-2; 50% neutralization titers are expressed as the reciprocal serum dilution at which in vitro virus infectivity was halved, relative to a serum-free control infection. We observed a correlation between the total anti-spike IgG titer of the donor serum samples, as measured by the clinical MSH-ELISA assay, and both the total anti-spike IgG titers of the plasma units (Spearman correlation coefficient (ρ), 0.83; $P<0.001$; Fig. 3a) and the 50% neutralizing titers of the donor serum samples (Spearman ρ, 0.65; $P<0.001$; Fig. 3b). Donor serum samples with an MSH-ELISA titer of 1:320 had a geometric mean 50% neutralizing titer (GM-NT) of 1:46 (95% CI, 1:18–1:120); for sera with an MSH-ELISA titer of 1:960, GM-NT was 1:174 (95% CI, 1:71–1:427); and sera measured at an MSH-ELISA titer of ≥1:2,880 had a GM-NT of 1:338 (95% CI, 1:91–1:1,252). However, we observed no correlation between donor neutralization titers and convalescent plasma-recipient outcomes at the end of the study period (Spearman ρ, 0.083; $P=0.62$; Fig. 3c). Analysis of variance demonstrated a nonsignificant trend toward higher neutralizing titers in the sera of donors who provided convalescent plasma to the group of recipients that remained hospitalized at the end of the study (Kruskal–Wallis test, $P=0.07$; Dunn's multiple-comparisons test, adjusted $P=0.17$ for hospitalized versus discharged and adjusted $P=0.10$ for hospitalized versus expired). The majority of convalescent plasma recipients were discharged by 1 May 2020 ($n=28$), with few ($n=11$) who died or remained hospitalized at the end of the study for comparison. This small sample size limits our ability to draw robust conclusions about the level of neutralizing antibodies necessary to improve convalescent plasma-recipient outcomes. During this time frame, all available MSH-ELISA testing capacity was prioritized for the screening of potential convalescent plasma donors; thus, we were not able to measure anti-SARS-CoV-2 antibody titers before or after transfusion in convalescent plasma recipients.

Among the 39 convalescent plasma recipients, no serious adverse events were judged to be directly caused by convalescent plasma transfusion. One patient died within 7 d of transfusion, on day 3 after transfusion, of cardiac arrest in the setting of progressive hypoxemia due to COVID-19. The other four deaths during the study period, all due to COVID-19 complicated by multiorgan failure and shock, occurred on days 8, 9, 13 and 14 after transfusion. No suspected occurrences of transfusion-associated adverse events, such as transfusion-associated circulatory overload or transfusion-related acute lung injury were reported.

This initial assessment offers evidence in support of convalescent plasma transfusion as an effective intervention in COVID-19. Preliminary data suggest a mortality benefit, but greater numbers and a randomized trial design are needed to draw definitive conclusions about the efficacy of convalescent plasma for the treatment of COVID-19.

Although controls were retrospectively identified by propensity score matching, the conclusions drawn from these data are not as robust as those from a prospective, randomized, placebo-controlled trial. An important potential confounder in our analysis is the higher proportion of convalescent plasma recipients who were anticoagulated compared to their matched controls. We cannot exclude the possibility that convalescent plasma recipients benefited from generally more assertive clinical management by their primary physican

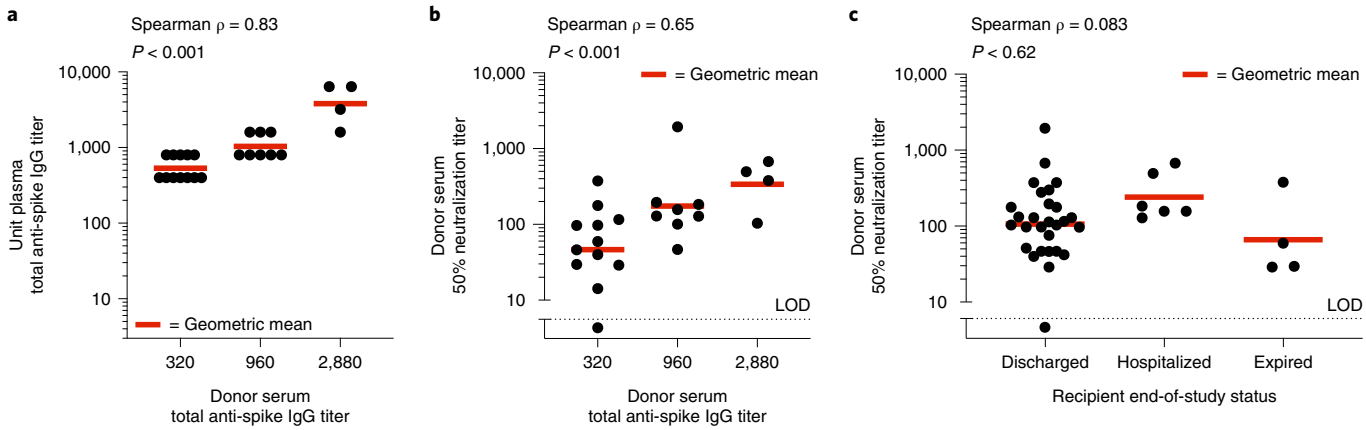


Fig. 3 | Donor antibody levels and convalescent plasma-recipient outcomes. a, Total anti-SARS-CoV-2 spike protein IgG titers in serum, obtained from plasma donors by clinical MSH-ELISA assay, positively correlate with the total anti-spike IgG titers in plasma units, measured by a lab-based ELISA (Spearman ρ, 0.83; $P < 0.001$). **b**, Total anti-spike IgG titers from donors also correlate with the reciprocal serum dilution required to neutralize virus infectivity by 50%, as measured by microneutralization assay (Spearman ρ, 0.65; $P < 0.001$). **c**, No correlation was observed between donor neutralization titers and convalescent plasma-recipient outcomes at the end of the study period (Spearman ρ, 0.083; $P = 0.62$). Plasma ELISAs (**a**) were performed once ($n = 1$ replicate per plasma sample), and microneutralization assays (**b** and **c**) were performed in duplicate ($n = 2$ replicates per serum sample). Data from $n = 24$ donors (**a** and **b**) and $n = 38$ recipients (**c**) were used to calculate Spearman correlation coefficients and P values. One serum sample showed no measurable neutralization activity in vitro; this point is shown below the dotted line indicating the limit of detection (LOD) (**b** and **c**). Donor serum neutralization titer was unavailable for one convalescent plasma recipient who expired; donor titers for the remaining four deceased recipients are shown (**c**). All statistical tests are two-sided.

teams. However, the requirement for informed consent should mitigate provider bias to some extent, given that patients who were offered convalescent plasma could and did decline to give consent. Our analyses also did not show that convalescent plasma recipients received any other therapies, including several investigational agents, at a higher rate than controls. Ultimately, our retrospective data cannot address the underlying reason for this discrepancy, and our analysis must be viewed with this caveat in mind.

As in our retrospective study, a prospective, open-label, randomized trial conducted by Li et al.[18] also found a trend toward the benefit of convalescent plasma only in the subgroup of less severely ill patients, in which convalescent plasma recipients were significantly more likely to improve clinically than controls (HR, 2.15; 95% CI, 1.07–4.32; $P = 0.03$). However, no significant difference was observed in the subgroup with life-threatening disease (HR, 0.88; 95% CI, 0.30–2.63; $P = 0.83$), and the interaction by disease severity failed to reach statistical significance (P value for interaction = 0.17); thus, Li et al. concluded that the findings for the severe and life-threatening subgroups should not be interpreted as significantly different[18]. Similarly, in our cohort, we found that convalescent plasma recipients who were not mechanically ventilated at the time of transfusion were significantly less likely to die than their matched controls (HR, 0.23; 95% CI, 0.05–0.98; chi-square test, $P = 0.46$), whereas we were unable to observe an effect of convalescent plasma in recipients who were mechanically ventilated at the time of transfusion (HR 0.79; 95% CI, 0.22–2.79; chi-square test, $P = 0.716$). While these results are consistent with past literature demonstrating that passive antibody-transfer therapies are most efficacious early in disease[11,19–21], the effect of convalescent plasma was not significantly different in the non-intubated and intubated recipient groups (chi-square test for homogeneity, $P = 0.207$), and thus, like Li et al.[18], we conclude that the effect of convalescent plasma in these two subgroups should not be interpreted as significantly different. Importantly, the number of mechanically ventilated convalescent plasma recipients in our study is small, and larger randomized trials are still needed to address uncertainties about the effect of convalescent plasma and to define more clearly the patient populations in whom convalescent plasma may have benefit.

This study has many unique strengths. Data from three different time frames (baseline, before transfusion and the day of transfusion) informed the matching of controls to cases to maximize their similarity. New York City has a large and very diverse population, and its metropolitan area was among the earliest and hardest hit by the COVID-19 pandemic in the United States. Over this study's 16-d enrollment period (24 March 2020 to 8 April 2020), the Mount Sinai Health System (MSHS) admitted 4,152 patients with confirmed COVID-19. This large pool from which to draw control patients permitted an aggressive matching algorithm based on treatment propensity and enabled 1-to-4 matching of cases to controls.

In addition, the efficacy of passive antibody transfer relies heavily on the quality of the donor convalescent plasma. We show that the serum neutralizing antibody titers, measured against a clinical isolate of wild-type SARS-CoV-2, correlate well with the serum antibody titers measured by the MSH-ELISA assay used to prioritize the convalescent donors that we referred for plasmapheresis, both in the donor group presented here (Fig. 3b) and in a larger cohort of individuals screened for serum antibodies within our health system[25]. Others have reported similar findings[26–28]. We did not observe a correlation between donor serum neutralizing titers and convalescent plasma-recipient outcomes (Fig. 3c), with the caveats that, (1) all of our donors were prescreened to have relatively high anti-SARS-CoV-2 antibody titers before donation and, (2) the sample size is small.

No significant transfusion-related morbidity or mortality was observed in this convalescent plasma-recipient cohort, nor in a much larger national, multicenter cohort[29,30]; however, potential harms are associated with plasma transfusion. Allergic reactions to plasma are typically mild and self-limited, but anaphylaxis, while rare, can occur. Plasma contains procoagulants, whose additive effects are unknown in COVID-19. Given that COVID-19 is independently associated with hypercoagulability, additional caution should be exercised in patients with acute thrombotic events[31]. Keeping these risks in mind, additional studies are needed to confirm these findings and draw more definitive conclusions about the efficacy of convalescent plasma transfusion for the treatment of COVID-19 in different populations.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-1088-9.

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Methods

Ethics and regulatory oversight. Both convalescent plasma treatment and retrospective analysis of data from our electronic medical record database were performed with the oversight of the Icahn School of Medicine at Mount Sinai (ISMMS) Institutional Review Board (IRB nos. 20-03574 and 20-03489). Convalescent plasma recipients were treated under compassionate use, via single-patient eIND applications to the FDA. As required by federal law, the ISMMS IRB was notified of every eIND application, FDA authorization was sought and received for each treated patient before transfusion, and all patients, or their legally authorized representatives, gave informed consent. As a retrospective analysis of compassionate-use treatment data, the study was neither prospectively designed nor registered on clinicaltrials.gov, nor was a data safety monitoring board prospectively convened to oversee this study.

Eligibility and selection of convalescent plasma recipients. Between 24 March 2020 and 8 April 2020, 4,152 patients were hospitalized for COVID-19 in the MSHS. During this period, adult patients admitted to MSH were screened for eligibility to receive a COVID-19 convalescent plasma transfusion under the criteria established for the FDA single-patient eIND process, published 24 March 2020 (Supplementary Text 1). FDA eIND criteria included: age ≥18 years, severe or immediately life-threatening COVID-19 and patient or proxy ability to provide informed consent. Severe disease included at least one of the following: dyspnea; respiratory frequency ≥30 per min; blood oxygen saturation ≤93%; partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300; and/or progression of lung infiltrates by >50% within 24–48 h. Life-threatening disease included at least one of the following: respiratory failure, septic shock and multiple-organ dysfunction or failure. There were no published exclusion criteria. As required by federal law (Code of Federal Regulations; 21CFR312.305 and 21CFR312.310), all patients treated under eIND criteria met the expanded access use requirements as documented on FDA form 3926, which was submitted for each individual patient and reviewed and approved by the FDA before transfusion. Initially, convalescent plasma inventory was limited relative to the number of eligible convalescent plasma recipients under eIND criteria; thus, patients were further prioritized by the following considerations, which were flexible according to plasma supply: (1) ABO blood type; (2) duration of symptoms; (3) length of stay, inclusive of admission at a transferring hospital; and (4) baseline functional status and comorbidities.

Forty-five applications requesting individual patient eIND authorization to administer COVID-19 convalescent plasma were submitted to and approved by the FDA between 28 March and 8 April 2020. Sample size was not determined prospectively. The first eIND application was submitted upon receipt of the first convalescent plasma units from the New York Blood Center, and the last was submitted immediately before the MSHS joined the national Expanded Access Protocol (www.uscovidplasma.org/). Six patients consented to receive convalescent plasma and were granted FDA authorization under eIND criteria, but were not treated; four improved without convalescent plasma and two withdrew consent before transfusion. These six eINDs were withdrawn. Between the end of the study period (1 May 2020) and now (24 July 2020), two additional convalescent plasma recipients died of complications of multiorgan failure due to COVID-19, on days 42 and 88 after transfusion, for an overall death rate of 17.9%. The FDA was notified of all seven deaths and these eINDs were withdrawn. Thirty convalescent plasma patients were discharged from the hospital, for an overall discharge rate of 76.9%; these eINDs were withdrawn. One convalescent plasma recipient remains hospitalized as of 24 July 2020, and this eIND remains open.

Convalescent plasma transfusion. Convalescent plasma donors were screened for SARS-CoV-2 antibody titers with the MSH-ELISA anti-IgG COVID-19 assay, a two-step, spike-protein-directed ELISA[23,24] adapted for emergency clinical use and performed by the Mount Sinai Laboratory[25]. Donors with total anti-spike IgG titers of ≥1:320 on the MSH-ELISA were referred for blood collection at the New York Blood Center, which performed the plasmapheresis and then returned convalescent plasma units and segments (apheresis tubing containing residual plasma) to MSH. Segments were frozen at −20 °C for research use. Convalescent plasma recipients were transfused with two units of ABO type-compatible convalescent plasma. The majority of recipients received both units from a single donor. Each unit, approximately 250 ml in volume, was infused over 1–2 h. Convalescent plasma recipients were monitored every 15 min for signs of transfusion-related reactions and then followed for outcomes after the transfusion.

Propensity score matching of controls to convalescent plasma recipients. A propensity score–matched analysis was conducted within Epic electronic health records from the MSHS from 24 March 2020 to 8 April 2020. Analyses of patient data were performed using SAS 9.4. A logistic regression was fit to predict the potential for plasma therapy based on three sources of information: (1) baseline data, including age, gender, smoking status, obesity, diabetes, chronic obstructive pulmonary disease or sleep apnea and D-dimer and C-reactive protein at admission; (2) data from the day of transfusion (day 0), including supplemental oxygen requirement, length of hospital stay, minimal oxygen saturation, heart rate, respiratory rate and systolic and diastolic blood pressure; and (3) chronological data up to the day of transfusion, including the use of hydroxychloroquine or azithromycin, intubation status and, if intubated, the duration of intubation. Day 0 for convalescent plasma recipients was defined as the day on which they received plasma transfusion. For control patients, day 0 was defined as the day of hospitalization corresponding to the length of stay of their matched convalescent plasma recipient before transfusion. Two sets of matched data were generated based on 1:4 and 1:2 ratios for cases versus controls using the nearest neighbor matching algorithm, with and without replacement, respectively (SAS package: PROC PSMatch). Among the predictors, exact matching was enforced on oxygen requirement on the day of transfusion, length of hospital stay from the day of admission to the day of transfusion, the administration of hydroxychloroquine and azithromycin, and intubation status and duration (Supplementary Table 3). Other medications were administered too infrequently to enforce exact matching.

The distribution of the logit propensity score–matched controls was within range of the convalescent plasma recipients, as opposed to the logit propensity score of the data from patients with confirmed COVID system wide (Extended Data Fig. 1). Balance was well achieved between the plasma and control groups, as all predictors had a standardized mean difference of less than 0.2 (Extended Data Fig. 2). Descriptive results for matched datasets are shown in Supplementary Table 3.

Assessment of respiratory status. Patients were evaluated for their supplemental oxygen requirements and survival at three time points: days 1, 7 and 14 after transfusion. Four categories of supplemental oxygen use status were collected for both cases and controls (Supplementary Tables 2 and 3). These included, in order of increasing severity: room air, without supplemental oxygen; low-flow oxygen delivery by standard nasal cannula; high-flow oxygen delivery, including non-rebreather mask, high-flow nasal cannula or BiPAP noninvasive ventilation; and mechanical ventilation. A patient's oxygenation status at the three time points was considered to have worsened if they changed from a lower- to a higher-severity category compared to day 0, or if they had died before the time point. A generalized estimating equations approach with a logit link for binary data was used to model the effect of plasma on the odds of oxygenation improvement on days 1, 7 and 14 following transfusion, controlling for oxygen status on day 0. An independent working correlation structure was assumed for the patients within each cluster; however, *P* values were calculated based on the empirical standard errors. Since some patients with COVID-19 were being discharged with continued home oxygen supplementation during the study period, but this information was not easily obtainable from the database, the oxygen status of all discharged patients was assumed to be no worse than low-flow oxygen by standard nasal cannula. Adjusted covariates included duration of symptoms, use of pharmacotherapies (such as broad-spectrum antibiotics, therapeutic anticoagulation, azithromycin, corticosteroids, hydroxychloroquine and investigational antivirals) and laboratory values, specifically IL-6 levels.

Assessment of outcomes. Kaplan–Meier survival curves were used to depict the overall survival following transfusion. A Cox model was fit to estimate the HR for in-hospital mortality for the plasma group, with matched clusters treated as random effects and onset of intubation as a time-varying covariate. In addition, interactions between convalescent plasma administration and intubation duration were tested to see if the plasma effects were the same in subgroups.

Both survival models were adjusted for duration of symptoms before admission and other therapies administered during admission, as these data were only ascertained by manual chart review after the matching was completed. The initial list of therapies consisted of those used for COVID-19 during the study period, which included azithromycin, broad-spectrum antibiotics, hydroxychloroquine, therapeutic anticoagulants, corticosteroids and investigational therapies, including directly acting antivirals, mesenchymal stem cells and IL-1 and IL-6 inhibitors. Only those that had a chi-square test *P* value < 0.5, however, were included in the final model for adjustment. A liberal *P* value was used here to be inclusive of any potential confounders. As a sensitivity analysis, the 1:2 matching data without replacement data were also analyzed, where the balance between the matched pairs was enhanced but the study power was reduced.

Antibody assays and analyses. *The MSH anti-IgG COVID-19 enzyme-linked immunosorbent assay.* The MSH-ELISA anti-IgG COVID-19 assay[23–25] is an orthogonal immune assay specific for anti-SARS-CoV-2 spike protein IgG in clinical serum or plasma specimens. It measures the relative concentration of IgG and reports the result as the reciprocal of the highest dilution of serum or plasma giving a positive signal. The assay received FDA emergency use authorization for clinical use on 15 April 2020 (https://www.fda.gov/media/137032/download/) and was also independently authorized as a laboratory developed test for clinical application by the New York State Department of Health at the Mount Sinai Laboratory, Center for Clinical Laboratories, a division of the Department of Pathology, Molecular and Cell-Based Medicine, New York (Clinical Laboratory Improvement Amendments no. 33D1051889).

Enzyme-linked immunosorbent assay. Plasma unit samples were retrieved from frozen apheresis segments, and antibody titers were determined by ELISA, performed in 96-well microtiter plates (Thermo Fisher) coated with 50 µl of

recombinant full-length spike protein at a concentration of 2 μg ml^{-1} overnight at 4 °C. The next day, the plates were washed three times with PBS (Gibco) containing 0.1% Tween-20 (T-PBS; Fisher Scientific). The plates were blocked with 200 μl of blocking solution (T-PBS with 3% wt/vol milk powder (American Bio)) and incubated for at least 1 h at room temperature. Plasma samples were serially diluted in 1% milk prepared in T-PBS and added to the plates after the blocking solution was removed, and then the plates were incubated for 2 h at room temperature. The plates were washed three times with T-PBS using an automatic plate washer (BioTek) and 50 μl of anti-human IgG (Fab-specific) horseradish peroxidase antibody (produced in goat; Sigma, A0293), diluted 1:3,000 in T-PBS containing 1% milk powder, was added to all wells. After 1 h, the plates were washed three times with T-PBS, 100 μl of SigmaFast *o*-phenylenediamine dihydrochloride (Sigma) was added to all wells, and the reaction stopped after 10 min by adding 50 μl per well of 3 M hydrochloric acid (Thermo Fisher). The plates were read at a wavelength of 490 nm using a plate reader (BioTek), and the endpoint titer was calculated, defined as the last dilution before the signal dropped below an OD490 of 0.15.

Microneutralization assay. Donor serum samples were heat inactivated at 56 °C for 1 h before use. Vero.E6 cells from the American Type Culture Collection (ATCC no. CRL-1586) were seeded at a density of 20,000 cells per well in a 96-well cell culture plate (Corning, 3595) 1 d before the assay was performed. Cells were maintained in culture in complete DMEM (Gibco), and the medium used for the neutralization assay was 1× MEM (Gibco) supplemented with 2% FBS (Corning). Starting with 1:10, serial dilutions of each sample in duplicate were prepared in a 96-well plate. Six wells in each plate were used as no-virus negative controls, and six wells were used as serum-free, virus-only positive controls. Next, 80 μl of each respective dilution was mixed with 600 median tissue culture doses ($TCID_{50}$) of SARS-CoV-2 isolate USA-WA1/2020 (BEI Resources, NR-52281) in 80 μl. The virus–serum mixture was incubated for 1 h. The medium was removed from cells, and 120 μl of virus–serum mixture was added. After 1 h of incubation at 37 °C, the virus–serum mixture was removed, and 100 μl of MEM and 100 μl of each serum dilution was added to the cells. The cells were incubated at 37 °C for 2 d. The medium from the cells was removed, and 150 μl of 10% formaldehyde (Polysciences) was added for 24 h to fix cells and inactivate the virus. The next day, cells were permeabilized and stained using a mouse monoclonal anti-SARS-CoV-2 nucleocapsid antibody (clone 1C7, generated in-house by T. Moran, Center for Therapeutic Antibody Discovery at ISMMS). For each dilution, the inhibition of virus growth, relative to the controls, was calculated. A nonlinear regression was performed in Prism version 7.0 (GraphPad Software) to calculate the 50% inhibitory dilution (ID_{50}), the serum dilution at which virus growth was halved relative to the serum-free, virus-only controls. The 50% neutralizing titer was defined as the reciprocal of the ID_{50}.

Data analysis. Donor serum antibody titers (total IgG against recombinant SARS-CoV-2 full-length spike protein, measured by the clinical MSH-ELISA) were available for all 25 donors who provided the convalescent plasma to this recipient cohort. Stored samples of donor serum, drawn on the same day as the antibody screening test, and unit plasma, retrieved from plasma segments, were available from 24 of 25 donors. The donor for whom these samples were not available had a screening antibody titer of 1:960 and donated both units of plasma to recipient number 15, who expired during the study period. The serum from one donor, who had a screening antibody titer of 1:320, showed no detectable neutralization of SARS-CoV-2 in the microneutralization assay; the 50% neutralization titer of this sample was set at 1 for the purposes of calculating geometric means and correlation coefficients. These data are provided as source data. For recipients who received plasma units from two different donors, the GM-NT of the serum samples from the two donors is presented in Fig. 3c. Spearman's rank correlation coefficients (ρ) and GM-NTs were calculated in Prism version 8.0 (GraphPad).

Statistical analyses. We did not perform a priori sample size calculations. The convalescent plasma-recipient cohort ($n = 39$) was a sample of convenience that included all adult patients treated with convalescent plasma under FDA eIND at MSH. The untreated control sample size was determined by matching at 1:2 and 1:4 ratios (cases to controls) by propensity score analysis. Group differences were evaluated by chi-square and Wilcoxon rank-sum tests for categorical and ordinal data, respectively. ORs and HRs are presented with 95% CIs and chi-square *P* values. Spearman's rank correlation was used to test for monotonous relationships between plasma donors' antibody titers and plasma recipients' clinical outcomes, and analysis of variance was assessed by the Kruskal–Wallis test, followed by Dunn's multiple-comparison test. All tests were two-sided, and statistical significance was defined as a P value < 0.05, unless otherwise indicated. Descriptive data are reported as number (percent), mean ± s.d., geometric mean (95% CI) or median (range or IQR), as appropriate.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Data will be shared in accordance with ISMMS policy on access to and use and disclosure of Mount Sinai data. This process can be initiated upon request to the corresponding author. Source data are provided with this paper.

Code availability

No custom code is associated with this manuscript. The SAS code for these analyses can be downloaded from https://www.researchgate.net/project/Convalescent-plasma-treatment-of-severe-COVID-19-A-propensity-score-matched-control-study/.

Acknowledgements

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Author contributions

J.A.A., A.C., N.M.B., S.T.H.L., H.-M.L., B.K.C. and D.L.R. conceived and designed the study. S.T.H.L., H.-M.L., P.T., M.A.L., E.B., A.D., C.S. and A.Z. analyzed the data. S.T.H.L., N.M.B., J.A.A., J.P.G., F.R., D.R.A., I.B., D.R.M., A.F.B., C.C.-C., J.S.J., S.A.A., A.W., J.B., D.R., A.B.-M. and F.K. participated in the donor plasma collection program and the transfusion of convalescent plasma recipients. Mount Sinai laboratory technicians performed the clinical MSH-ELISA assay, developed by F.A., D.S. and F.K. and transitioned to clinical use by D.R.M., A.F.-B. and C.C.-C. on donor serum samples. F.T.N., F.A. and D.S. performed the lab-based ELISA and microneutralization assays on donor serum and plasma samples, and N.M.B. analyzed the antibody titer data. S.T.H.L., H.-M.L. and N.M.B. wrote the manuscript.

Competing interests

F. Krammer has filed patent applications for the assay used to select plasma donors, and Mount Sinai has licensed its use to several companies. All other authors have nothing to disclose.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-020-1088-9.

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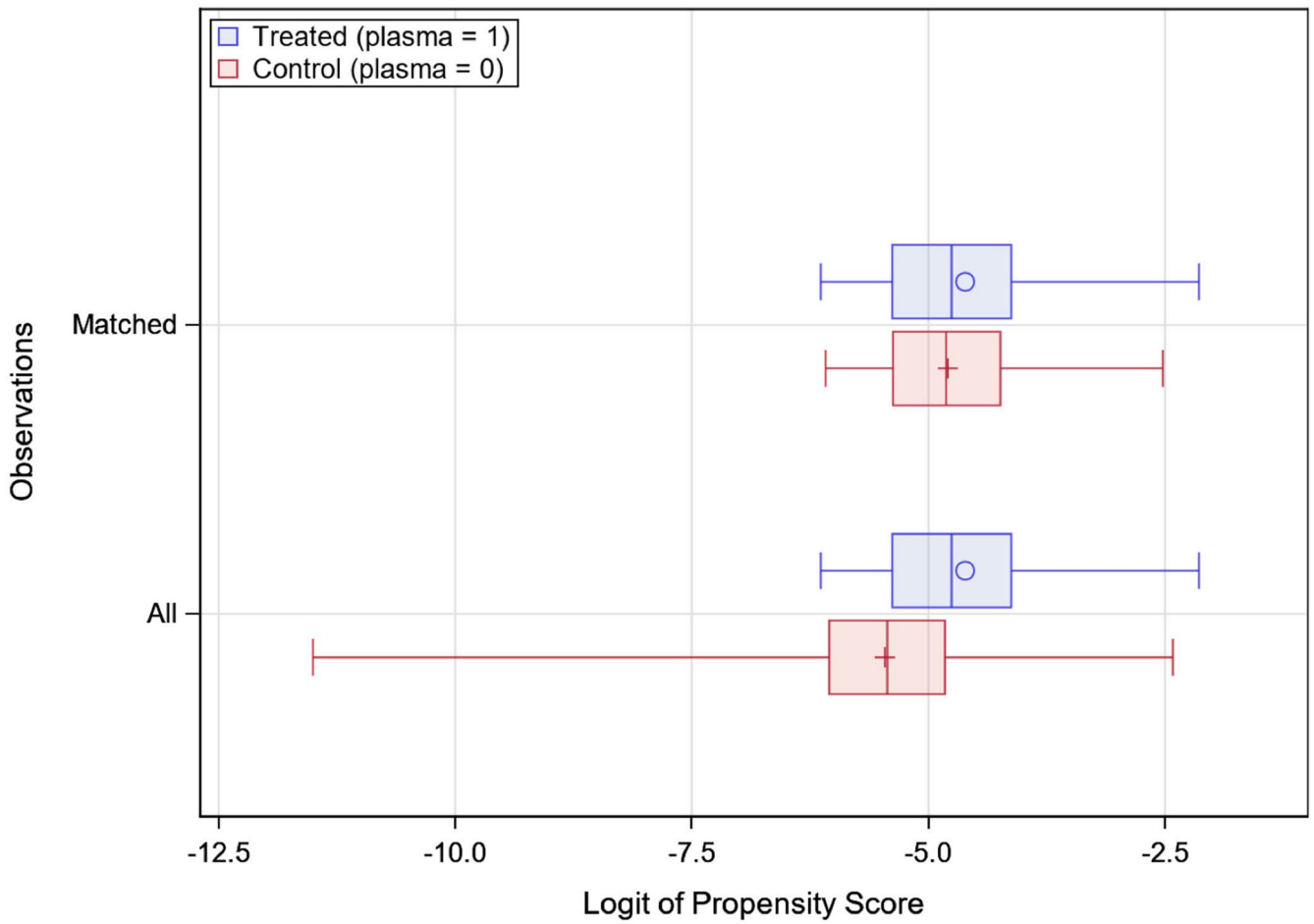
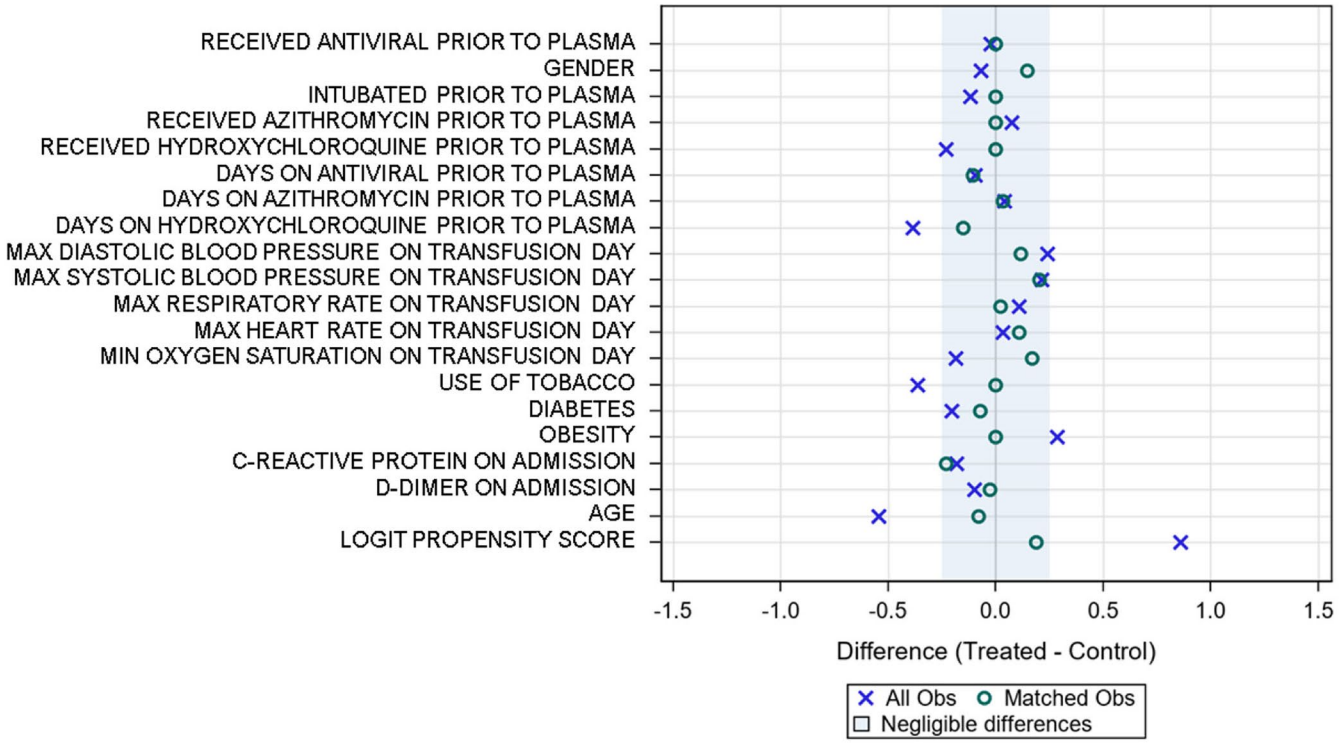
Correspondence and requests for materials should be addressed to N.M.B.

Peer review information Alison Farrell is the primary editor on this article and managed its editorial process and peer review in collaboration with the rest of the editorial team.



Extended Data Fig. 1 | Propensity scoring of matched controls and all COVID-positive patients versus convalescent plasma recipients. The logits of propensity scores were more similarly distributed for convalescent plasma recipients (n=39) and their propensity score-matched controls (n=156) than for all COVID-19 patients admitted to the Mount Sinai Health System between 24 March 2020 and 8 April 2020 (n=4,152). The means are represented by open circles (for convalescent plasma recipients) or plus signs (for matched controls and all COVID patients). The box represents the interquartile range, the center line is the median value, and the whiskers delineate the range between minimum and maximum values.



Extended Data Fig. 2 | Standardized mean differences of matched controls and all COVID-positive patients. Balance was well achieved between the groups of convalescent plasma recipients (n=39) and matched controls (n=156). For each predictor listed on the y-axis, the observed standardized mean difference is represented by green circles for matched controls and by blue X symbols for all COVID-19 patients in the Mount Sinai Health System (n=4,152). Between plasma recipients and matched controls, all treatment predictors had a standardized mean difference of less than 0.2, represented by the blue shading.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Data were collected from the Mount Sinai Health System electronic medical record (Epic Systems Corporation, Verona, WI).
Data analysis	Data analysis was performed using SAS 9.4 (SAS Institute Inc., Cary, NC) and Prism versions 7.0 & 8.0 (GraphPad Software, San Diego, CA). The SAS script file can be downloaded from https://www.researchgate.net/project/Convalescent-plasma-treatment-of-severe-COVID-19-A-propensity-score-matched-control-study.

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Data

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All figures/tables have associated raw data. The de-identified and aggregated data used for plotting all figures are provided as Source Data files. Individual patient records in our Electronic Medical Record (EMR) contain Protected Health Information (PHI), as defined in the Health Insurance Portability and Accountability Act (HIPAA). As such, the EMR database cannot be made freely and publicly available without any restrictions. However, individuals not affiliated with the Mount Sinai Health System who have a research interest in these data can request that they be shared in accordance with Icahn School of Medicine at Mount Sinai (ISMMS) Policy on Access to and Use and Disclosure of Mount Sinai Data. This process can be initiated upon reasonable request to the corresponding author.

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Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The treated sample size was not determined prospectively but was rather a sample of convenience, determined retrospectively. It includes all adult patients treated with convalescent plasma under FDA single-patient eIND ("compassionate use") at the Mount Sinai Hospital. Convalescent plasma transfusions under FDA single-patient eIND began as soon as convalescent plasma became available at Mount Sinai Hospital, and ended when the FDA Expanded Access Protocol (EAP), under lead institution the Mayo Clinic, opened as an alternative to the single-patient eIND pathway. The untreated control sample size was determined by matching at 1:2 and 1:4 ratios (cases to controls) by propensity score analysis. A lower matching ratio (e.g., 1:2) decreases variability by maximizing propensity score similarity between cases and controls but also reduces statistical power because the control group is smaller. A higher matching ratio (e.g., 1:4) increases power for the parameter estimates but also increases propensity score variability between cases and controls; the statistical literature suggests that matching ratios should not exceed 1:5. We analyzed control data at both 1:2 and 1:4 matching ratios as a sensitivity analysis, to demonstrate that both control group sample sizes (one with less variability but also less power, and the other with more variability but also more power) yield similar results, which suggests that the control group sample sizes were sufficient for these analyses from a statistical perspective. References: Linden A, Samuels SJ. Using balance statistics to determine the optimal number of controls in matching studies. J Eval Clin Pract. 2013;19(5):968-975. doi:10.1111/jep.12072 Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol. 2010 Nov 1;172(9):1092-7. doi: 10.1093/aje/kwq224. Epub 2010 Aug 28. PMID: 20802241; PMCID: PMC2962254.
Data exclusions	No data of patients transfused under eIND or their matched controls were excluded.
Replication	This study is a retrospective data analysis; as such, no replicates were performed.
Randomization	No treatment randomization was performed. COVID-19 patients meeting criteria established by the FDA were offered investigational treatment with COVID-19 convalescent plasma. Forty-five patients, or their legally authorized representatives, provided informed consent for treatment under the FDA's single-patient eIND pathway. Four patients improved and two patients withdrew consent prior to receipt of plasma, leaving n=39 evaluable patients who received COVID-19 convalescent plasma. Controls (n=156) were retrospectively matched 4-to-1 to plasma recipients by propensity score analysis. Covariates were controlled through exact matching and propensity score matching.
Blinding	Chart review for clinical data unobtainable from the database was performed by a data team who were blinded to the cases to whom controls were matched. Laboratory assays (plasma ELISAs and serum microneutralization assays) were performed by individuals who were blinded to the donor's identity and serum IgG titer, as measured by the MSH-ELISA performed by the Mount Sinai Laboratory.

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Materials & experimental systems

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☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Anti–human IgG (Fab-specific)–horseradish peroxidase (HRP) labeled secondary antibody produced in goat (Sigma #A0293). Mouse monoclonal anti-SARS-CoV-2 Nucleocapsid [clone 1C7] (generated by Dr. Thomas Moran, Center for Therapeutic Antibody Discovery at the Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Pl Box 1124, New York, NY 10029; https://icahn.mssm.edu/research/ddi/capabilities/ctad).

Validation

No validation was performed for the commercial Anti-human IgG-HRP secondary. Citations for the anti-SARS-CoV-2 antibody: Blanco-Melo D, Nilsson-Payant BE, Liu WC, et al. Imbalanced Host Response to SARS-CoV-2 Drives Development of COVID-19. Cell. 2020;181(5):1036-1045.e9; Amanat F, Stadlbauer D, Strohmeier S, et al. A serological assay to detect SARS-CoV-2 seroconversion in humans. Nat Med. 2020;26(7):1033-1036; Amanat F, White KM, Miorin L, et al. An In Vitro Microneutralization Assay for SARS-CoV-2 Serology and Drug Screening. Curr Protoc Microbiol. 2020;58(1):e108.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)

Vero.E6 cells were sourced from ATCC

Authentication

No authentication was performed.

Mycoplasma contamination

The cell lines were not tested for mycoplasma.

Commonly misidentified lines
(See ICLAC register)

No commonly misidentified cell lines were used.

Human research participants

Policy information about studies involving human research participants

Population characteristics

Population characteristics of the convalescent plasma recipients are presented in Table 1. The propensity for plasma therapy was predicted by fitting a logistic regression based on time-series data obtained at baseline (upon admission), prior to transfusion, and the day of transfusion. The treatment predictors identified by the regression analysis and considered in the propensity score model, and the control matching results of the propensity score model, are presented the Supplementary Information. In selecting controls to propensity-score match to treated cases, exact matching was enforced on the administration of hydroxychloroquine and azithromycin, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion; results of the matching are shown in the Supplementary Information. Details of the matching method and results are described in the Methods.

Recruitment

Between 24 March 2020 and 8 April 2020, a total of 4,152 patients were hospitalized for COVID-19 in the Mount Sinai Health System. From that group, forty-five adult patients hospitalized at The Mount Sinai Hospital were identified as eligible for COVID-19 convalescent plasma transfusion under the criteria established for the U.S. Food and Drug Administration (FDA) single patient emergency investigational new drug (eIND) pathway, including age ≥18 years old; severe or immediately life-threatening COVID-19; and patient or proxy ability to provide informed consent. Severe disease included at least one of the following: dyspnea; respiratory frequency ≥30/min; blood oxygen saturation ≤93%; partial pressure of arterial oxygen to fraction of inspired oxygen (PaO2/FiO2) ratio <300; and/or progression of lung infiltrates >50% within 24 to 48 hours. Life-threatening disease included at least one of the following: respiratory failure; septic shock; and multiple organ dysfunction or failure. Plasma inventory was limited relative to the number of eligible recipients under eIND criteria; thus, patients were further prioritized by the following considerations, which were flexible according to plasma supply: (1) ABO blood type; (2) duration of symptoms; (3) length of stay, inclusive of admission at a transferring hospital; and (4) baseline functional status and comorbidities.

As a non-randomized, retrospectively analyzed study, these results may be confounded by a number of unintended biases. Because of the requirement for informed consent under the FDA eIND pathway, there were patients who were offered convalescent plasma and opted not to receive it; thus, plasma recipients were those who self-selected to be treated with an investigational therapy. However, more patients were eligible to receive convalescent plasma than we had plasma to give them, so it is likely that the much larger group of untreated patients includes individuals who would have consented to convalescent plasma treatment, had they been offered it. Selection bias is also a potential confounder, though propensity score matching was utilized to attempt to reduce selection bias by specifically selecting untreated controls with a similar propensity for treatment as those who were ultimately treated. The patients to whom plasma was offered were, by design, those who had been symptomatic for a short time and who were early in their hospital admissions, so they were, as a group, possibly less sick than other patients in the hospital at the same time. However, the matched control patients' "day 0" was defined as the day in their hospital admission that corresponded to the hospitalization day on which their matched plasma recipient was transfused, so that duration of admission before "day 0" was equivalent in cases and controls. Although we could not include duration of symptomatic illness in the matching algorithm (because this information was not recorded in a discrete data field), we retrospectively assessed the duration of symptoms prior to admission and found it to be not significantly different between cases and controls (Wilcoxon rank-sum test P = 0.307 for the 1:2 matched analysis and P = 0.968 for the 1:4 matched analysis). Observer bias may also confound these results. To the extent possible, EMR data were analyzed objectively by computer algorithm without human involvement. Data that could not be obtained from discrete data fields was chart abstracted by individuals blinded to the case-control matches, and laboratory analyses were similarly performed by individuals blinded to the source of the serum/plasma samples being assayed.

Ethics oversight	Both convalescent plasma treatment and retrospective data analysis research were performed with the oversight of the Icahn School of Medicine at Mount Sinai Institutional Review Board (ISMMS IRB) and the Food and Drug Administration (FDA). All patients were treated under compassionate use, via single-patient eIND applications. As required by federal law, the ISMMS IRB was notified of every eIND application; FDA authorization was sought and received for each treated patient before transfusion, and all patients or their legally authorized representatives gave informed consent for investigational treatment with convalescent plasma. The use of matched control data from our electronic medical records was reviewed by our IRB (# 20-03574) and determined to be exempt human research. Donor antibody titer analyses were also performed under IRB oversight (#20-03489).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	As per ICJME guidelines, the study was not registered as a clinical trial because it was not designed as a prospective trial. It is a retrospective analysis of patients treated under FDA eIND ("compassionate use") of an investigational therapy.
Study protocol	No study protocol exists for this retrospective analysis of data from compassionate use treatments with convalescent plasma performed under FDA eIND. As required by federal law, the ISMMS IRB was notified of every eIND application; FDA authorization was sought and received for each treated patients before transfusion; and all patients or their legally authorized representatives gave informed consent for investigational treatment with convalescent plasma.
Data collection	Data were collected at the Mount Sinai Hospital. Patients in the study were admitted between 24 March 2020 and 8 April 2020. Convalescent plasma recipients were recruited between 28 March and 8 April 2020 and treated between 28 March and 9 April 2020. Outcomes were analyzed through 1 May 2020.
Outcomes	As a retrospective analysis of compassionate use treatment data, no outcomes were pre-defined.