Hospitalized patients with HIV and COVID-19 receiving convalescent plasma: A case series

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Abstract. The use of convalescent plasma in coronavirus disease 2019 (COVID-19) in the general population has not been shown to have a clear benefit. However, there are limited data available on its use in specific populations, such as in persons with human immunodeficiency virus (HIV; PWH). The present case series study describes 12 hospitalized PWH who received convalescent plasma for severe COVID-19 between March 2020 and July 2020. Demographics, pre-existing comorbidities, HIV status, and COVID-19 management were reported and examined in a multivariate analysis. A high mortality rate of 58%, (7 out of 12 PWH) was observed in those receiving the convalescent plasma. By contrast, a brief review of 13 previously published cohorts of PWH hospitalized with COVID-19 revealed a cumulative mortality of 19% (85 of 439 PWH). In the present case series study, PWH had a significantly higher relative risk for in-hospital COVID-19-associated mortality compared with individuals without HIV (unadjusted range, 2.10-2.52; and adjusted range, 1.79-2.08; P<0.02 in all analyses). Covariate-adjustments were made for patient demographics, pre-existing co-morbidities, and mechanical ventilation needs. The high mortality rate of the present case series may be related to random sampling or an adverse effect of convalescent plasma in PWH and severe COVID-19. Additional research is thus required to investigate the risks and benefits of the use of COVID-19 convalescent plasma in PWH.

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Introduction

The use of convalescent plasma in coronavirus disease 2019 (COVID-19) in the general population has not been found to have a clear benefit (1-3). Persons with human immunodeficiency virus (HIV; PWH) hospitalized with coronavirus disease 2019 (COVID-19) have been reported to experience a similar mortality rate to patients hospitalized for COVID-19 without HIV (4-21). Pooled data from 13 studies revealed a cumulative mortality rate of 19% or (85 out of 439 PWH hospitalized for COVID-19) (Table I). Inpatient COVID-19 therapies remain limited and vary in effectiveness. Convalescent plasma is a potential therapeutic candidate and functions by providing passive immunity with neutralizing antibodies, which may be useful in the acute phase of COVID-19 (22). The effectiveness of convalescent plasma has been widely investigated; however, there is limited evidence available regarding its use in PWH. The present case series reports the outcomes of 12 PWH hospitalized with severe COVID-19 who received convalescent plasma at six hospitals in a New York City health system and compares their clinical outcomes to similar patients without HIV hospitalized with COVID-19 during the same time period.

Patients and methods

Patient information. During the period between March 24 to July 12, 2020, 441 hospitalized patients with severe COVID-19 within the Mount Sinai Health System were treated with convalescent plasma through the Food and Drug Administration (FDA) single-patient emergency investigational new drug (eIND) pathway or the Mayo Clinic Emergency Access Program (EAP) (NCT04338360). Eligibility for the inpatient transfusion of convalescent plasma required laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, age ≥18 years, and respiratory compromise with at least one of the following: dyspnea, blood oxygen saturation ≤93%, respiratory frequency ≥30 breaths/min, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300 mmHg (normal ratio, 400-500 mmHg), or infiltrates in >50% of lung fields on a chest X-ray within 48 h of presentation. Eligible patients received ABO blood type-compatible units of convalescent

Table I. Outcomes of individuals with HIV hospitalized for COVID-19 found in previous studies.

Identified study no.	Authors/(Refs.), year	Location, time-frame	Hospitalized mortality
1	Sigel *et al* (8), 2020	New York NY, USA; March to Arpil, 2020	21%, 18 of 88
2	Shalev *et al* (7), 2020	New York NY, USA; March to Arpil, 2020	26%, 8 of 31
3	Nagarakanti *et al* (6), 2021	Newark, NJ, USA; March to Arpil, 2020	13%, 3 of 23
4	Gudipati *et al* (4), 2020	Detroit, MI, USA; March to Arpil, 2020	38%, 3 of 8
5	Karmen-Tuohy *et al* (5), 2020	New York NY, USA; March to Arpil, 2020	29%, 6 of 21
6	Childs *et al* (11), 2020	South London, UK; not available	28%, 5 of 18
7	Ridgway *et al* (17), 2020	Chicago, IL, USA; March to Arpil, 2020	0%, 0 of 5
8	Collins *et al* (12), 2020	Atlanta, GA, USA; March to Arpil, 2020	15%, 3 of 20
9	Stoeckle *et al* (19), 2020	New York NY, USA; March to May, 2020	7%, 2 of 30
10	Calza *et al* (10), 2020	Bologna, Italy; March to Arpil, 2020	0%, 0 of 5
11	Vizcarra *et al* (20), 2020	Madrid, Spain; not available	7%, 2 of 28
12	Patel *et al* (16), 2021	New York NY, USA; October to November, 2020	22%, 22 of 100
13	Laracy *et al* (14), 2021	New York NY, USA; March to June, 2020	21%, 13 of 62
	Cumulative result		19%, 85 of 439
	The present study	New York NY, USA; March to July, 2020	58%, 7 of 12

plasma derived from donors with known serum antibody titers against SAR-CoV-2 spike protein of ≥1:320 dilutions. Of the 441 total recipients, 436 patients had met the endpoint of a post-transfusion survival of ≥2 weeks, or mortality within 2 weeks, with a median follow-up of 19 days [interquartile range (IQR), 9-22 days]. A retrospective chart review of the 436 plasma recipients identified 12 PWH recipients and 424 recipients without HIV. The present study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB) in conjunction with the Mayo Clinic IRB for the patients enrolled in the Expanded Access Program (EAP). Participants underwent an informed consent process for the receipt of the convalescent plasma, including the discussion of the risks involved, benefits, alternative therapies and the use of medical information for the purposes of research (ISMMS IRB nos. 20-03393, 20-03574 and 20-03759).

Statistical analysis. All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc.). For comparisons between HIV and non-HIV groups, the Chi-squared or Fisher's exact tests were used for categorical variables, Student's t-tests were used for normally distributed continuous variables, and Wilcoxon rank-sum tests for skewed continuous variables, as appropriate. Due to the limited sample size, the primary analysis was based on an unadjusted relative risk assessment for in-hospital mortality comparing convalescent plasma recipients with HIV vs. those convalescent plasma recipients without HIV. A confirmatory secondary analysis of outcomes used a log-binomial regression model adjusted for major covariates of survival based on the well-known risk factors or P-values <0.2 from the univariate group comparison. The major covariates included: hospital site, days from admission until the receipt of first plasma unit, sex, age, race/ethnicity (Caucasian, African-American, Hispanic, Asian, or unknown), valvular disease, chronic kidney disease (including end-stage renal disease), solid organ transplant, a history of chronic viral hepatitis, chronic liver disease, the need for endotracheal intubation and mechanical ventilation, and tracheostomy placement.

At the time of the analysis, 24 recipients without HIV and no recipients with HIV remained hospitalized and met the ≥2 weeks post-transfusion endpoint. To account for the remaining hospitalized recipients, two potential scenarios were constructed to test the veracity of an association between the receipt of convalescent plasma, HIV and mortality. The first scenario assumed that all 24 remaining hospitalized recipients were discharged alive to estimate the largest magnitude association between the receipt of convalescent plasma and mortality among individuals with HIV and SARS-CoV-2. The second scenario estimated the smallest magnitude association by assuming that all 24 remaining patients would succumb to their illness.

Results

The mean age of the 12 PWH recipients was 62 years and 4 PWH (33%) were female. A total of 9 patients were identified as African-American. All 12 PWH had pre-existing medical conditions (Table II). In total, 6 recipients (50%) were either overweight or obese (body mass index >26). Of the 12 PWH, 1 patient had valvular disease (8.3%), 5 patients (41.7%) had diabetes, 4 patients (33.33%) had chronic kidney disease or end-stage renal disease, 4 patients had a history of chronic viral hepatitis (33.3%), 3 patients had chronic liver disease (hepatitis C with or without cirrhosis) (25.0%) and 2 patients (16.7%) had received a solid organ transplant. In total, 11 recipients had long-standing HIV infections and were prescribed antiretroviral therapy prior to admission. Recent median CD4 cell counts prior to presentation with COVID-19 ranged from 446 to 910 cells/mm^3 (Table II). A total of 9 patients (75%) had HIV viral loads <20 copies/mm. In addition, 1 patient was newly diagnosed with HIV during their COVID-19 admission and had a HIV viral load of 472,000 copies/ml.

All 12 PWH recipients received other concurrent treatments for COVID-19 as follows: a total of 9 patients (75%) received therapeutic anticoagulation; 8 patients (66.7%) received azithromycin; 7 patients (58.3%) received hydroxychloroquine;

Table II. Characteristics of hospitalized individuals with HIV who received convalescent plasma for the treatment of COVID-19 (n=12) in New York, NY, USA between March 24 and July 12, 2020.

	Patient no.											
Characteristics	1	2	3	4	5	6	7	8	9	10	11	12
Age, years	65	72	59	68	68	62	51	70	63	38	58	66
Sex	F	F	M	M	M	M	M	F	M	M	F	M
Last HIV viral load[a]	<20	<20	<20	<20	<20	296	<20	<20	<20	472,000	<20	26
Race	AF	AF	AF	AF	AF	AF	Other	AF	AF	Other	AF	Other
Ethnicity	NH	Hisp.	NH	NH	NH	NH	NH	U	U	Hisp.	NH	Hisp.
CD4 count at admission[b]	407	n/a	241	157	218	696	122	240	n/a	4	170	327
Last CD4 cell count before admission[b] (month/year collected)	666 (11/19)	538 (3/20)	615 (3/20)	584 (4/20)	910 (3/19)	n/a	708 (6/17)	n/a	446 (2/13)	n/a	484 (10/19)	508 (4/20)
Antiretroviral therapy	ABC/3TC/ DTG	TDF/FTC + DTG	TAF/FTC + ATV/c	ABC/3TC + ATV/r	TAF/FTC + DRV/c	TAF/FTC + DTG	DTG/RPV	DOR +	DRV/c + DTG	None RAL	TAF/FTC + RAL	3TC + LPV/r + RAL
Body mass index	32.6	22.7	27.7	25.3	26.6	37.4	25.5	27.3	25.5	21.1	33.1	22.2
Underlying medical conditions	Renal SOT, HCV with SVR, HTN, HLD	Hypo-thyroidism, cryptogenic cirrhosis	DM, HLD, HTN	DM, HTN, CKD III, HCV with SVR	HCV with SVR, AUD, cirrhosis	BPH	Renal SOT, HTN, HLD	ESRD on HD, DM, HTN	ESRD on HD, HTN, HLD, DM, CAD, CHF, COPD, Valvular disease	Asthma	HTN, Hypo-thyroidism, AI, MDD	ESRD on HD, CAD, HCV w/cirrhosis, HTN, DM, CVA, PVD
Concurrent non-plasma interventions												
Therapeutic anticoagulation	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Azithromycin	Yes	Yes	Yes	Yes	Yes	No	Yes	No	No	No	Yes	Yes
Hydroxy-chloroquine	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes
Steroids	Yes	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	No
Remdesivir	No	No	No	No	No	No	Yes	No	No	Yes	Yes	No
Mesenchymal stem cells	No	No	No	No	No	No	Yes	No	No	No	No	No
Immunomodulatory therapy	No	No	No	No	No	No	No	No	No	No	No	No
Outcome												
Disposition	Deceased	Deceased	D/C	D/C	Deceased	D/C	Deceased	D/C	Deceased	D/C	Deceased	Deceased

[a]Copies/ml; [b]cells/mm^3. AF, African-American; NH, non-Hispanic; Hisp, Hispanic; AI, adrenal insufficiency; AUD, alcohol use disorder; BPH, benign prostatic hypertrophy; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CVA, cerebral vascular accident; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; HCV, hepatitis C virus; HD, hemodialysis; HIV, human immunodeficiency virus; HLD, hyperlipidemia; HTN, hypertension; M, male; MDD, major depressive disorder; NH, non-Hispanic; PVD, peripheral vascular disease; SOT, solid organ transplant; SVR, sustained virologic response; D/C, discharged as of July 12, 2020.

Table III. Discharged vs. expired analysis of remaining hosptialized patients at time of analysis.

Statistical model	Assumption for the potential outcomes of in-hospital patients (n=24)[a]	Adjusted for covariates[b]	Relative risk of persons with HIV	95% Lower limit	95% Upper limit	P-value
Log-binomial model for relative risk	Discharged	No	2.52	1.52	4.20	0.0004
		Yes	2.08	1.26	3.43	0.004
	Expired	No	2.10	1.27	3.45	0.004
		Yes	1.79	1.11	2.87	0.016

[a]As of July 12, 5 persons with HIV who received convalescent plasma were discharged (41.7%) and 7 expired (58.3%). Among the non-HIV recipients, 302 (71.2%) were discharged, 98 died (23.1%), and 24 (5.7%) were still in hospital. [b]Adjusted covariates included the following: Hospital site, days to plasma, sex, age, race (African or African American, Hispanic or Latino), the need for intubation and mechanical ventilation, and tracheostomy placement.

7 patients (58.3%) received systemic steroids; 3 patients (25%) received remdesivir; and 1 patient (8.3%) received a mesenchymal stem cell transplant (Table II). In total, 11 PWH received 2 units of convalescent plasma during a single administration. Furthermore, 1 patient received a single unit of convalescent plasma. The median time interval between admission and the receipt of convalescent plasma was 2 days (IQR, 1-3 days).

Of note, three severe adverse events were reported shortly following transfusion. In total, 2 patients required an increase in supplemental oxygen delivery within 4 h of transfusion; both had increasing oxygen demands prior to transfusion. The third event involved the self-removal of supplemental oxygen and subsequently that patient expired. The relation of convalescent plasma in this outcome was uncertain. Of the 12 PWH recipients, 5 patients (42%) were discharged alive and 7 patients (58.3%) did not survive. Mortality occurred at a median of 21 days (IQR, 1-32 days) following admission.

Survival at ≥2 weeks from admission that led to subsequent transfusion or mortality within 2 weeks was assessed for 424 convalescent plasma recipients without HIV. The median duration of follow-up from admission was 18 days (IQR, 9-25 days) for individuals with HIV and 12 days (IQR, 7-22 days) for individuals without HIV. As of July 12, 2020, 302 patients with COVID-19 (71.2%) without HIV who had received convalescent plasma had been discharged alive, 98 (23.1%) had succumbed and 24 (5.7%) remained hospitalized at 2 weeks. Among the 12 patients with HIV, 5 patients (41.7%) had been discharged alive and 7 patients (58.3%) had succumbed. Among the recipients with HIV who succumbed, mortality occurred at a median of 21 days (IQR, 10-32 days) and among the recipients without HIV who succumbed, mortality occurred at a median of 16 days (IQR, 9-26 days).

As described above in the Patients and methods section, two scenarios were created for the remaining hospitalized recipients. Assuming that all remaining hospitalized recipients survived, then the unadjusted relative risk (RR) of inpatient mortality for PWH vs. those without HIV would be 2.52 [95% confidence interval (CI), 1.52-4.20, P<0.01). Assuming that all remaining hospitalized recipients expired, then the unadjusted RR among all patients for inpatient mortality for PWH vs. those without HIV would be 2.10 (95% CI, 1.27-3.45, P=0.004). The RRs adjusted for major covariates of survival (as indicated in the Patients and methods section) for all survived and all expired scenarios were 2.08 (95% CI, 1.26-3.43, P=0.004) and 1.79 (95% CI, 1.11-2.87, P=0.016), respectively (Table III). In all models, the RR for mortality among PWH who received convalescent plasma was ~2-fold higher than that among individuals without HIV.

Discussion

The present case series found a high mortality of 58% among PWH who received convalescent plasma, while hospitalized with COVID-19. This mortality rate was higher than that found in previously published literature of PWH hospitalized for COVID-19 (4-21) (Table I); within patients hospitalized for COVID-19 who received convalescent plasma, the RR of mortality was ~2-fold higher in PWH than in individuals without HIV. The present case series study was limited in sample size; however, the findings raise concerns and suggest that further investigations into the potential risks of the use of convalescent plasma among PWH are warranted. There are limitations to this analysis. The present study was a retrospective case series and at risk of selection bias. Patients in the present cohort had numerous pre-existing medical conditions, and it is not certain whether HIV or other medical conditions were responsible for the increased mortality. A comparison of the covariates of convalescent plasma recipients among persons with or without HIV is presented in Table SI. Beyond the presence of HIV, covariates with statistically significant differences (P-values <0.05) included the hospital site of admission, race/ethnicity, chronic kidney disease, end-stage renal disease, solid organ transplantation, chronic viral hepatitis, and liver disease (alcoholic or non-alcoholic). No significant differences in medication administration relating to antibiotics, steroids, anticoagulation, or antiplatelet therapies were observed (data not shown). Although the cohort of PWH is much smaller than the cohort of recipients without HIV these differences may have contributed to the observed outcomes. For example, several patients had hepatitis and chronic liver disease, which may have been compounded by the effect of COVID-19 on liver function (23). The present study cohort had an over-representation of African-American patients and may be at a higher risk of poor outcomes due to historic and ongoing discrimination, which may limit the generalizability of these observations (24). There is no clear biomedical mechanism to explain why convalescent plasma may lead to poorer outcomes in PWH with SARS-CoV-2. One possible etiology may be the HIV-associated platelet

dysfunction and COVID-19 hypercoagulability exacerbating coagulation complications. Since COVID-19 may alter respiratory microbiota (25) and has been shown to be associated with bacterial and fungal co-infections (26), further research is required to investigate whether these pathways play a role in PWH.

In conclusion, the present case series study on 12 PWH hospitalized with severe COVID-19 is very limited and drawing definitive conclusions on the safety of convalescent plasma in individuals with HIV would be premature and inappropriate. A deeper subpopulation analysis of ongoing convalescent plasma studies may enhance the current understanding of the mechanisms through which HIV, race/ethnicity and/or underlying medical conditions, including end-stage renal disease, solid organ transplantation, liver disease, and viral hepatitis may contribute to the excess mortality that was observed in the present case series of 12 patients.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RJS and HML were the equal primary authors of the article. RJS, HML, HLC and STHL performed the data analysis. RJS and STHL performed the literature review. HML and HLC performed data management. FR, NMB and STHL obtained the informed consent from the study participants and collected the data. VA, IB and SAA performed the laboratory analyses. NMB, JAA and STHL managed the convalescent plasma program. NMB, JAA and STHL reviewed the manuscript. RJS, HML and STHL confirm the authencity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB) in conjunction with the Mayo Clinic IRB for the patients enrolled in the Expanded Access Program (EAP). Participants underwent an informed consent process for the receipt of the convalescent plasma, including the discussion of the risks involved, benefits, alternative therapies and the use of medical information for the purposes of research (ISMMS IRB nos. 20-03393, 20-03574 and 20-03759).

Patient consent for publication

Not applicable.

Competing interests

SL receives personal fees from Synairgen. JA receives grants and personal fees from Gilead, Merck, Janssen, and ViiV; personal fees from Theratech, and Medicure; and grants from Atea, Pfizer, Regeneron, Janssen, Emergent BioSolutions, and GigaGen outside of the submitted work. SL and FR are sub-investigators for Atea, Gilead, Pfizer, Janssen, Regeneron, Kinevant, Emergent BioSolutions, and GigaGen outside the submitted work. No other potential competing interests were disclosed.

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