COVID-19 in Hospitalized Adults With HIV

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Background. The spread of SARS-CoV-2 and the COVID-19 pandemic have caused significant morbidity and mortality worldwide. The clinical characteristics and outcomes of hospitalized patients with SARS-CoV-2 and HIV co-infection remain uncertain.

Methods. We conducted a matched retrospective cohort study of adults hospitalized with a COVID-19 illness in New York City between March 3, 2020, and May 15, 2020. We matched 30 people with HIV (PWH) with 90 control group patients without HIV based on age, sex, and race/ethnicity. Using electronic health record data, we compared demographic characteristics, clinical characteristics, and clinical outcomes between PWH and control patients.

Results. In our study, the median age (interquartile range) was 60.5 (56.6–70.0) years, 20% were female, 30% were black, 27% were white, and 24% were of Hispanic/Latino/ethnicity. There were no significant differences between PWH and control patients in presenting symptoms, duration of symptoms before hospitalization, laboratory markers, or radiographic findings on chest x-ray. More patients without HIV required a higher level of supplemental oxygen on presentation than PWH. There were no differences in the need for invasive mechanical ventilation during hospitalization, length of stay, or in-hospital mortality.

Conclusions. The clinical manifestations and outcomes of COVID-19 among patients with SARS-CoV-2 and HIV co-infection were not significantly different than patients without HIV co-infection. However, PWH were hospitalized with less severe hypoxemia, a finding that warrants further investigation.

Keywords. coronavirus disease 2019; HIV; severe acute respiratory syndrome coronavirus 2.
delayed development SARS-CoV-2 antibody response, which may have implications for longer recovery periods and clinical outcomes [19, 20].

There is an absence of controlled data about the clinical characteristics and natural history of COVID-19 among individuals with HIV. Herein, we compare the clinical characteristics and outcomes of COVID-19 between hospitalized PWH and matched controls without HIV in a diverse population at the world’s epicenter of the COVID-19 pandemic.

METHODS

Study Design
We conducted a matched retrospective cohort study of adults hospitalized with a COVID-19 illness at New York-Presbyterian/Weill Cornell Medical Center and its affiliate Lower Manhattan Hospital between March 3, 2020, and May 15, 2020. We included all PWH admitted to the hospital during this period and matched them in a 1:3 ratio to patients without HIV (control group) based on age, sex, and race/ethnicity.

Data Collection
We collected demographic data including age, sex, race/ethnicity, body mass index, medical comorbidities, and concomitant medications, as well as data on presenting symptoms. For all patients, we collected absolute lymphocyte counts upon presentation as well as peak values within 7 days of presentation of the following laboratory markers: C-reactive protein (CRP), procalcitonin, D-dimer, and lactate dehydrogenase. HIV-specific data included antiretroviral therapy regimens, CD4 nadir (if available in outpatient records), and most recent CD4 T-cell count, CD8 T-cell count, CD4:CD8 ratio, and HIV-1 viral load obtained during hospitalization. We collected radiographic reports of initial chest x-ray studies and COVID-19 treatments received during hospitalization. All data were manually abstracted from the electronic health record by trained reviewers with a calibrated abstraction process that has been previously described and was demonstrated to have high inter-rater reliability [5].

Study Outcomes
We assessed respiratory status upon presentation and other hospital course events. Respiratory status upon presentation was determined by presence of hypoxemia and highest level of oxygen support within 3 hours of arrival to the emergency department. Levels of oxygen support included ambient air, nasal cannula, nonrebreather, noninvasive ventilation (bilevel or continuous positive airway pressure), and invasive mechanical ventilation. Other hospital course events included death, hospital discharge, hospital length of stay, admission to the intensive care unit, need for invasive mechanical ventilation during hospitalization, need for vasopressors, initiation of dialysis, and do not resuscitate/do not intubate (DNR/DNI) orders.

Statistical Analysis
Three-to-one matching was performed using the gmatch SAS macro, which is a greedy nearest neighbor matching algorithm [21, 22]. Matching was performed using the following characteristics: gender, age (+/- 5 years), and race. Descriptive statistics were calculated, and means, standard deviations, medians, interquartile ranges, and percentages were reported. Bivariate analyses were performed using chi-square and Fisher exact tests for categorical variables, the Student t test for normally distributed continuous variables, and Wilcoxon tests for skewed continuous variables. Statistical significance was determined using an alpha of .05. All analyses were performed using Stata, version 14.

Patient Consent Statement
The design of this work was approved by the Weill Cornell Medicine Institutional Review Board. Written informed consent was waived, as it was an observational and retrospective analysis of our usual clinical practice. All patient data were anonymized for the purpose of analysis, and confidential data were protected in accordance with the ethical standards of the Helsinki Declaration.

RESULTS

Baseline Characteristics
Our study included PWH (n = 30) and a control group (n = 90) matched by age, sex, and race/ethnicity, as shown in Table 1. There were more active smokers (17% vs 4%) and former smokers (33% vs 22%; P = .02) among PWH compared with control patients. In addition, PWH more commonly had chronic obstructive lung disease as a comorbid diagnosis (13% vs 3%; P = .07). Chronic hepatitis B virus infection was significantly higher among PWH (20% vs 1%; P <.001). There were no significant differences between groups in body mass index, hypertension, diabetes mellitus, coronary artery disease, heart failure, stroke, chronic kidney disease, end-stage renal disease, asthma, cirrhosis, or chronic hepatitis C infection.

HIV Characteristics
In the PWH group, 29 of 30 patients were on antiretroviral therapy; 9 (31%) of the 29 were on regimens that contained a protease inhibitor (Table 2). Three patients did not have an HIV viral load or CD4 count recorded. Among the 27 PWH who had a recent HIV viral load and CD4 count available, all patients had undetectable viral loads (<20 copies/mL), and the median CD4 count (interquartile range [IQR]) was 332 (123–526)
Presenting symptoms did not differ significantly between the 2 groups (Table 3). Similar to prior studies of COVID-19 patients, the most common symptoms across both groups were fever (57% in PWH and 73% in control patients), cough (70% and 76%), and dyspnea (67% and 64%). Sputum production was uncommon (3% in PWH, 11% in control patients). Diarrhea occurred in approximately one-third of patients in both groups.

Laboratory and Radiographic Findings

Initial absolute lymphocyte counts and peak values of procalcitonin, D-dimer, and lactate dehydrogenase did not differ significantly between groups (Table 3). Both groups were found to have absolute lymphopenia, elevated D-dimer, and elevated lactate dehydrogenase. Although the difference in CRP between groups was not statistically significant, the median peak value in the control group was notably higher than in the PWH group (16.0 mg/dL vs 7.6 mg/dL; \(P = .07\)). Initial chest x-ray patterns were not significantly different between PWH and control patients. Approximately three-quarters of patients in both groups had either unilateral or bilateral infiltrates on initial chest x-ray.

COVID-19 Treatments

There were no significant differences in COVID-19 treatments received between PWH and control patients, including hydroxychloroquine (67% vs 50%; \(P = .14\)), systemic corticosteroids (13% vs 21%; \(P = .43\)), and remdesivir (0% vs 3%; \(P = .57\)).

Clinical Outcomes

Frequencies of clinical outcomes are reported in Table 4. Upon arrival at the hospital, 50% of all patients were hypoxemic, and there was no significant difference between the PWH and control groups. However, PWH were significantly less likely than the control group to require supplemental oxygen via nonrebreather (3% vs 14%) and invasive mechanical ventilation.
upon hospital arrival. There was no significant difference between intensive care unit admission, requirement of vasopressor support, initiation of dialysis, or death during hospitalization between the 2 groups. There were no differences in documented code status between groups. Most patients in both cohorts were full code (96% in PWH vs 78% in controls).

**DISCUSSION**

Our study is one of the largest reported observational cohort studies of hospitalized COVID-19 patients comparing the clinical manifestations and clinical outcomes of patients with HIV infection and matched controls. We found that there were significantly more active and former smokers, more patients with chronic obstructive pulmonary disease, and a significantly higher proportion of chronic hepatitis B viral infection in PWH compared with matched controls. These data are consistent with existing data on higher rates of smoking and HBV infection in HIV-positive individuals compared with the general population [23, 24]. We did not find significant differences between the PWH and control groups in presenting symptoms, laboratory parameters, radiographic findings, or clinical outcomes including death, need for invasive mechanical ventilation, length of stay, or frequency of hospital discharge.

Our study found that PWH co-infected with COVID-19 share similar laboratory derangements as the general COVID-19

| Table 3. Clinical Manifestations of Hospitalized COVID-19 Patients With HIV Co-infection and Matched Controls |
|--------------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------|
| Presenting symptoms | PWH (n = 30), No. (%) or Median (IQR) | Control (n = 90), No. (%) or Median (IQR) | P Value |
| Time of illness onset (days from symptom onset to hospital presentation), median (IQR) | 7 (3–10) | 7 (4–10) | .89 |
| Fever | 17 (57) | 66 (73) | .11 |
| Cough | 21 (70) | 68 (76) | .63 |
| Sputum production | 1 (3) | 10 (11) | .29 |
| Dyspnea | 20 (67) | 58 (64) | 1.00 |
| Sore throat | 0 (0) | 11 (12) | .63 |
| Rhinorrhea or nasal congestion | 1 (3) | 8 (9) | .45 |
| Headache | 3 (10) | 6 (7) | .69 |
| Myalgias | 4 (13) | 23 (26) | .21 |
| Nausea or vomiting | 5 (17) | 18 (20) | .79 |
| Diarrhea | 10 (33) | 24 (27) | .49 |
| Abdominal pain | 3 (10) | 6 (7) | .69 |
| Anosmia | 1 (3) | 5 (6) | 1.00 |
| Ageusia | 2 (7) | 4 (4) | .64 |
| Laboratory markers* | | | |
| Absolute lymphocyte count, median (IQR), x10^3/µL | 0.9 (0.6–1.5) | 0.9 (0.6–1.1) | .23 |
| C-reactive protein, median (IQR), mg/dL | 7.6 (2.8–16.5) | 16.0 (6.8–25.0) | .07 |
| Procalcitonin, median (IQR), ng/mL | 0.16 (0.08–0.3) | 0.24 (0.1–0.67) | .18 |
| D-dimer, median (IQR), ng/mL | 1021 (427–3145) | 954 (340–4455) | .96 |
| Lactate dehydrogenase, median (IQR), U/L | 410 (283.5–535) | 453 (366–587) | .15 |
| CD4 count, median (IQR), cells/µL | 332 (123–526) | N/A | .16 |
| CD4:CD8 ratio, median (IQR) | 0.7 (0.3–1.0) | N/A | .16 |
| HIV viral load, median (IQR), copies/mL | 0 (0–0) | N/A | .16 |
| Radiographic findings | | | |
| Initial chest x-ray | | | .63 |
| No infiltrates | 9 (30) | 22 (24) | |
| Unilateral or bilateral infiltrates | 21 (70) | 68 (76) | |
population, including lymphopenia and elevated inflammatory markers [25, 26]. Peak CRP levels were lower in PWH compared with controls, which could suggest that PWH, given their relative state of immunodeficiency, do not mount as strong of an immune response to SARS-CoV-2.

Notably, we found that PWH were significantly less likely than control patients to require nonrebreather and invasive mechanical ventilation. This is despite no differences in initial chest x-ray findings, presenting symptoms, time of illness onset, prognostic markers such as lymphopenia or elevated D-dimer, or code status. Other case reports and studies have found similarly low morbidity in patients with HIV and SARS-CoV-2 co-infection [27, 28]. In our study, the PWH group had very well-controlled disease. One possible explanation could be that PWH are more likely to be hospitalized with less severe disease than patients without HIV due to concern from admitting physicians about underlying immunosuppression. Another possible contributing factor could be that PWH have an increased connection with our health care system given the need for primary care or infectious diseases specialists to be intimately involved in their care and disease management, and therefore earlier recognition and triage of symptoms.

It is also possible that PWH had lower rates of severe respiratory failure because many were already on antiretroviral therapy, which could have a protective effect against SARS-CoV-2 infection [29–31]. One-quarter of PWH were on protease inhibitors, including lopinavir/ritonavir, which has been shown to have activity against SARS-CoV-2 in vitro [32]. Although the pharmacodynamics of lopinavir/ritonavir are challenging and a randomized controlled trial of 2 protease inhibitors, lopinavir and ritonavir, did not show benefit beyond standard of care, 19 of 29 (66%) PWH in our study were taking tenofovir (either a disoproxil fumarate or alafenamide formulation), which has demonstrated in vitro activity against SARS-CoV-2 [33–36].

Lastly, it is possible that the relative immune-altered status in HIV infection may allow for less severe forms of COVID-19 and potentially favorable recovery outcomes. Persons with HIV who are well controlled on antiretroviral therapy have heightened levels of T-cell exhaustion, persistent immune activation with inversion of the CD4/CD8 ratio, and impaired immune responses that either collectively or independently may impact COVID-19 pathogenesis. There is emerging evidence that some patients with severe manifestations of COVID-19 develop a hyperactive immune response similar to cytokine release syndrome [37]. This phenotype is characterized by high fevers, elevated inflammatory markers, multi-organ failure, and high mortality rates. In particular, the hyperactivity of T cells may play a role in SARS-CoV-2-mediated lung injury. In peripheral blood flow cytometry analysis of postmortem tissue sampling of a patient who died from severe SARS-CoV-2 infection, there was an increased concentration of proinflammatory CCR6+ Th17 in CD4 T cells, as well as CD8 T cells with cytotoxic granules, suggesting that hyperactive and inflammatory T cells played a key role in lung injury [38].

Our study has limitations. First, our study has a relatively small sample size. Important differences between PWH and control patients might be detected with a larger study. Second,
the majority of PWH in our cohort were on antiretroviral therapy and were virally suppressed, which may limit our ability to comment on outcomes of COVID-19 in PWH who have uncontrolled HIV or advanced disease.

In conclusion, the clinical manifestations and outcomes of COVID-19 among patients with SARS-CoV-2 and HIV co-infection were not significantly different than patients without HIV co-infection. However, more PWH were current and former smokers and were admitted to the hospital with less severe hypoxemia. Levels of CRP among PWH compared with matched controls may indicate that relative immune dysfunction plays a protective role in COVID-19. Future studies should evaluate the role of the host immune system, antiretroviral agents, and immunomodulating agents in the setting of co-infection with SARS-CoV-2 and HIV.

Acknowledgments

This work was made possible through data provided by the Cornell COVID-19 Registry, led by Parag Goyal, MD, Justin Choi, MD, Laura Pinheiro, PhD, and Monika Safford, MD, of Weill Cornell Medicine. We would like to acknowledge Arthur Evans, MD, and Lishomwa Ndhlouvo, MD, PhD, for their valuable feedback and review of this manuscript. We also acknowledge the commitment, resilience, and sacrifice of all frontline health care workers and our patients during this pandemic.

Financial support.

This work was supported by the National Institutes of Health/National Center for Advancing Translational Sciences (grant numbers UL1TR00047, KL2-TR-002385 to J.J.C.) and the National Institute of Allergy and Infectious Diseases (grant number T32 AI007613 to C.D.J.). S.C.W. was supported by a Medical Scientist Training Program grant from the National Institute of General Medical Sciences of the National Institutes of Health (grant number T32GM007739 to the Weill Cornell/Rockefeller/ Sloan Kettering Tri-Institutional MD-PhD Program).

Potential conflicts of interest.

J.J.C. received research support from Roche Diagnostics and consulting fees from Allergan. M.J.G. received research support to Weill Cornell Medicine from Gilead Sciences and Regeneron Diagnostics and consulting fees from Allergan. None of these activities relate to the current work.

Author contributions.

K.S. and C.D.J. contributed equally to drafting the manuscript. K.S., S.C.W., and J.J.C. collected the data. D.P.J. did the statistical analysis. T.M.E., M.A.V., and R.M.G. made substantial contributions to the interpretation of the data. C.D.J., M.J.G., and J.J.C. contributed equally to conceiving the study and supervising the data collection and analysis. All coauthors provided critical revisions to the intellectual content of the manuscript and final approval of the version to be published.

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