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RESEARCH ARTICLE

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Higher intensive care unit consultations for COVID-19 patients living with HIV compared to those without HIV coinfection in Uganda

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Abstract

Coronavirus disease-2019 (COVID-19) is the leading cause of death worldwide from a single infectious agent. Whether or not HIV infection affects clinical outcomes in patients with COVID-19 remains inconclusive. This study aimed to compare the clinical outcomes of people living with HIV (PLWH) and non-HIV-infected patients hospitalized during the second wave of the COVID-19 pandemic in Uganda. We retrospectively retrieved data on patients with COVID-19 who were admitted to the Mulago National Referral Hospital in Uganda between April 2021 and mid-July 2021. We performed propensity-score-matching of 1:5 to compare outcomes in COVID-19 patients living with and those without HIV coinfection (controls). We included 31 PLWH and 155 non-HIV controls. The baseline characteristics were similar across groups (all p values > 0.05). PLWH had close to threefold higher odds of having ICU consultation compared to controls (odds ratio [OR]: 2.9, 95% CI: 1.2–6.9, $p = 0.015$). There was a trend toward having a severe or critical COVID-19 illness among PLWHIH compared to controls (OR: 1.9, 95% CI: 0.8–4.7, $p = 0.164$). Length of hospitalization was not significantly different between PLWH and non-HIV controls (6 days vs. 7 days, $p = 0.184$). Seven-day survival was 63% (95% CI: 42%–78%) among PLWH and 72% (95% CI: 61%–82%) among controls while 14-day survival was 50% (95% CI: 28%–69%) among PLWH and 65% (95% CI: 55%–73%) among controls ($p = 0.280$). There was another trend toward having 1.7-fold higher odds of mortality among PLWH compared to controls (OR: 1.7, 95% CI: 0.8–3.8, $p = 0.181$). Our data suggest that PLWH may be at an increased risk of severe or critical COVID-19 illness requiring ICU consultation. Further studies with larger sample sizes are recommended.

KEYWORDS

coronavirus disease 2019, COVID-19, HIV, SARS-CoV-2, Uganda

1 | INTRODUCTION

In December 2019, an outbreak of viral pneumonia caused by a novel coronavirus was reported in Wuhan, a city in China's Hubei Province.[1] The virus, now identified as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is the causative agent of the coronavirus disease-2019 (COVID-19). It spread enough to cause an international public health concern[2] and then later a pandemic.[3] COVID-19 is now the leading cause of death from a single infectious agent, killing at least 6.3 million of the over 530 million reported cases as of May 30, 2022.[4]

Majority of people infected with SARS-CoV-2 are asymptomatic. However, people with underlying chronic illnesses such as diabetes mellitus, hypertension, and heart failure are at increased risk of morbidity and mortality.[5] Our understanding of the risk posed by HIV is evolving. Recent systematic reviews have shown that people living with HIV (PLWH) can be infected with COVID-19 and are largely affected by similar features of disease risk and progression as HIV-uninfected people. They have shown that the proportion of reported PLWH with COVID-19, compared with people without HIV, appeared to have higher multimorbidity and severity of the disease. They also had a potentially higher proportion of death, from COVID-19 than people without HIV.[6,7]

Despite the plethora of evidence in support of the increased risk of COVID-19 mortality for PLWH even for those with low CD4 counts, a survey in two districts of Wuhan, China, suggests that HIV-positive-related immunosuppression could actually be protective.[8] The researchers suggest that immunosuppression and low CD4 cell counts might protect PLWH from developing the cytokine storm observed in patients with COVID-19.[8]

To date, however, little work has been done to understand how HIV status moderates the severity of COVID-19 infection and mortality for PLWH on the African continent. A study in South Africa found an independent association between HIV infection and COVID-19 mortality,[9] while another study in Zambia found that HIV status alone was not significantly associated with severe COVID-19 at admission or during hospitalization or COVID-19 mortality.[10] These somewhat conflicting findings lend credence to the need for further work in the subject area. Most other work on the topic from the African continent has largely been small case studies and reports.[11,12] With Africa accounting for two-thirds (25.4 million of the 37.7 million) of PLWH worldwide,[13] it is crucial to characterize the outcomes of COVID-19 such as length of hospitalization, ICU consultation, and death among this group.

Given this knowledge gap, the overall aim of this study was to understand how HIV status affects the clinical manifestations and outcomes for people hospitalized for COVID-19 in Uganda during the country's second wave of the pandemic. We focused on the second wave of the pandemic particularly given the preponderance of the new delta variant of the coronavirus during the second wave.

2 | METHODS

2.1 | Study design

This was a retrospective chart review of medical records of patients with COVID-19 admitted to Mulago National Referral Hospital (MNRH) in Kampala, Uganda during the country's second wave of the COVID-19 pandemic from April 2021 to mid-July 2021.

2.2 | Ethics

The study was approved by Mulago Hospital Research Ethics Committee (MHREC Protocol Number 2030) and received an exemption determination from the Yale University Institutional Review Board (Protocol ID: 2000030645). The study was conducted according to the Declaration of Helsinki.

2.3 | Participants

Patients' records were screened, and only COVID-19 patients diagnosed via an Antigen Rapid Diagnostic Test (RDT), or a Polymerase Chain Reaction (PCR) test were included. Patients with a clinical or radiological diagnosis of COVID-19 infection who did not have a confirmatory RDT Antigen or PCR test were excluded. All eligible PLWH who were admitted to the hospital during this period were included and were matched in a 1:5 ratio with hospitalized patients without HIV using propensity score matching adjusted for age and sex.

2.4 | Study setting

MNRH is a tertiary health facility with 1500 admission beds and 36 adult ICU beds located in the capital city of Uganda, Kampala. It is also a teaching hospital for Makerere College of Health Sciences. MNRH is the largest public hospital in Uganda and serves the larger Kampala metropolitan (Ministry of Health, 2021). MNRH provides specialized inpatient care to patients referred from the district and regional hospitals around the country and various outpatient HIV care centers. The HIV prevalence in the general adult population in Uganda is 6.2%,[14] and approximately 30% of patients hospitalized in MNRH are infected with HIV.[15] Mulago Hospital also serves as the largest COVID-19 treatment center in Uganda.[16]

Uganda started experiencing a second wave of the coronavirus pandemic from April 2021. This new surge was fueled by five variants in the country namely the Alpha, Beta, Delta, Eta, and the A.23.1 variants of local origin. Genomic sequencing made for some samples collected from Kampala and Wakiso indicated that the predominant strain was the Delta variant.[17]

2.5 | Independent variables

The independent variables for this study were the patient's demographic information (such as age, sex, nationality, district of residence, etc.), symptoms at presentation, comorbidities, HIV status, treatments for HIV used, and duration of HIV treatment use.

2.6 | Study outcome measures

The main outcome measures were the following:

1. in-hospital mortality rate;
2. length of hospitalization determined as the number of days a patient was admitted at MNRH until he/she was discharged or passed away;
3. ICU consultation; and
4. severity grade at admission.

ICU consultation was used instead of ICU admissions because we found that for many patient charts, there was a recommendation for ICU admission but remained on the regular floors due to a lack of available beds. COVID-19 severity at admission was adjudged using national guidelines prescribed by the Ugandan Ministry of Health.[18] Mild COVID-19 was indicated by the presentation of uncomplicated upper respiratory tract viral infection, nonspecific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain, or malaise. Moderate COVID-19 was indicated by the presentation of pneumonia and no signs of severe pneumonia. Adolescents and adults were assessed as having severe COVID-19 if they presented with fever or suspected respiratory infection, plus one of respiratory rate > 30 breaths/min, severe respiratory distress, or SpO_2 < 90% on room air. Children with severe COVID-19 presented with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 < 90% on room air. Critical COVID-19 was indicated if the patient continued to show the following signs despite receiving maximum oxygen flow rate using a face mask with a reservoir bag: rapid progression of severe respiratory distress, severe shortness of breath, inability to complete full sentences, tachypnoea, use of accessory muscles of respiration, and cyanosis.

2.7 | Data analysis

Propensity-score-matching (PSM) was performed in a 1:5 ratio based on age and sex using XLSTAT.[19] All demographic and outcome variables were evaluated for normality using Shapiro–Wilk tests and visually using normal QQ plot. Categorical variables were presented as proportions and continuous variables as median with interquartile range (IQR). Hypothesis testing was performed using the Pearson χ^2 test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Case–control analysis was performed using *cc* command in STATA 16.0 and reported as odds ratio at 95% confidence interval. Survival analysis was performed and depicted using Kaplan–Meier curves. Log-rank test was done to compare survival in PLWH across independent variables. All analyses were performed using STATA 16. Statistical significance was maintained at a two-tailed $p \leq 0.05$.

3 | RESULTS

3.1 | Baseline characteristics

This study included 31 PLWH and 155 non-HIV controls. Ninety-seven (62.6%) non-HIV controls were referrals compared to 22 (71%) PLWH ($p = 0.375$). There were no significant differences in baseline characteristics between the two groups (Table 1). The most common comorbidity among both PLWH (29.0%) and controls (27.7%) was hypertension ($p = 0.884$).

3.2 | Clinical presentation and disease severity

The most common symptoms were cough (87.1% in PLWH and 79.4% in control patients), difficulty in breathing (80.6% in PLWH and 80% in control patients), chest pain (19.4% in PLWH and 32.3% in control patients), and fever (29.0% in PLWH and 26.5% in controls). Overall, clinical presentation and baseline vitals were not significantly different across groups (Table 2).

3.3 | Treatment and clinical outcomes

The most common medication treatments received for COVID-19 infection were dexamethasone, enoxaparin, ceftriaxone, and zinc. 77.4% of PLWH and 65.8% of control patients required oxygen supplementation and this difference was not significantly different. The most common oxygen delivery methods were non-rebreather masks and nasal prongs. Only 6.5% of PLWH and 2.6% of control patients received oxygen supplementation from the high flow nasal cannula due to availability limitations (Table 3).

Our study revealed that most PLWH and uninfected controls were assessed to have severe COVID-19 disease (67.7% for PLWH and 58.7% for controls) and thus did not differ significantly in their requirement of the various treatment modalities and oxygen supplementation methods[9] (Table 3). However, PLWH were 2.9 times more likely to require ICU consultation compared to controls (odds ratio: 2.9, 95% CI: 1.2–6.9, $p = 0.015$). Moreover, the odds of having severe/critical COVID-19 were 1.9 times higher in PLWH in a trend toward statistical significance (odds ratio: 1.9, 95% CI: 0.8–4.7, $p = 0.164$) (Table 4). There was another trend toward statistical significance with regard to the odds of mortality which were 1.7 times higher in PLWH (odds ratio: 1.7, 95% CI: 0.8–3.8, $p = 0.181$) (Table 4). Length of hospitalization was not significantly different between PLWH and non-HIV controls (6 days vs. 7 days, $p = 0.184$). Seven-day survival was 63% (95% CI: 42%–78%) among PLWH and

TABLE 1 Baseline characteristics of the patients

Characteristics	Non-HIV (n = 155)	PLWH (n = 31)	p Value
Age			0.985
<18	6 (3.9)	1 (3.2)	
18–50	75 (48.4)	15 (48.4)	
50+	74 (47.7)	15 (48.4)	
Sex			0.511
Female	80 (51.6)	18 (58.1)	
Male	75 (48.4)	13 (41.9)	
Level of education			0.272
None	1 (2)	1 (25)	
Primary	2 (4)	0 (0)	
Tertiary	47 (94)	3 (75)	
Religion			0.065
Christian	76 (73.8)	22 (91.7)	
Muslim	27 (26.2)	2 (8.3)	
Occupation			0.115
Formal	34 (35.1)	3 (15.8)	
Informal	63 (64.9)	16 (84.2)	
Referred to the hospital			0.375
No	58 (37.4)	9 (29)	
Yes	97 (62.6)	22 (71)	
Nationality			1.000
Non-Ugandan	2 (1.3)	0 (0)	
Ugandan	153 (98.7)	31 (100)	
Comorbidity			
Hypertension	43 (27.7)	9 (29)	0.884
Diabetes mellitus	33 (21.3)	5 (16.1)	0.515
Heart failure	1 (0.6)	1 (3.2)	0.300
Pregnancy	4 (2.6)	2 (6.5)	0.600

Abbreviation: PLWH, people living with HIV.

TABLE 2 Presenting complaints and vital signs at admission among PLWH and non-HIV

Presenting complaints	Non-HIV (N = 155) n (%)	PLWH (N = 31) n (%)	p Value
Difficulty in breathing	124 (80)	25 (80.6)	0.935
Cough	123 (79.4)	27 (87.1)	0.456
Chest pain	50 (32.3)	6 (19.4)	0.153
Fever	41 (26.5)	9 (29)	0.767
General body weakness	36 (23.2)	8 (25.8)	0.758
Headaches	14 (9)	2 (6.5)	1.000
Runny nose	10 (6.5)	1 (3.2)	0.694
Abdominal pain	3 (1.9)	1 (3.2)	0.521
Loss of appetite	3 (1.9)	2 (6.5)	0.194
Diarrhea	3 (1.9)	0 (0)	>0.999
Altered mental status	0 (0)	1 (3.2)	0.167
Vitals			
SPO_2, median (IQR)	90.0 (83.5–95.0)	89 (81–96)	0.935
Systolic blood pressure, median (IQR)	133 (121–145)	131 (121–136)	0.411
Diastolic blood pressure, median (IQR)	81 (71–89)	80 (73–86)	0.975
Pulse rate, median (IQR)	101 (87–113)	102 (91–110)	0.968
Respiratory rate, median (IQR)	28 (22–32)	35 (26–42)	0.089

Abbreviations: IQR, interquartile range; PLWH, people living with HIV.

72% (95% CI: 61%–82%) among controls while 14-day survival was 50% (95% CI: 28%–69%) among PLWH and 65% (95% CI: 55%–73%) among controls (p = 0.280) (Figure 1 and Table 5).

4 | DISCUSSIONS

In this study, we investigated how HIV status affects disease severity and outcomes among adult patients hospitalized for COVID-19 during Uganda's second wave of the pandemic. We found that even though most patients hospitalized for COVID-19 at Mulago Hospital presented with severe disease, PLWH were significantly more likely to require an ICU consultation. To buttress this finding, there was also a trend suggesting worse outcomes for PLWH in terms of disease severity and mortality although this was not statistically significant. Given the trend toward statistical significance, we recommend further studies with larger sample sizes.

Our findings are consistent with the results of similar studies looking at HIV-COVID-19 coinfection in South Africa[9] and the United Kingdom.[20] These studies found an independent association between HIV infection and COVID-19 mortality. However other studies in Zambia[10] and the United States[21] did not find that HIV infection was associated with worse outcomes for patients hospitalized for COVID-19. The study from Zambia, however, found that among HIV-positive patients hospitalized for COVID-19, those with advanced HIV disease were more likely to develop severe COVID-19 or to die of COVID-19 compared with those with controlled HIV disease.

TABLE 3 Treatment and clinical outcomes of hospitalized COVID-19 patients with HIV coinfection and matched controls

Variable	Non-HIV (*N* = 155) *n* (%)	PLWH (*N* = 31) *n* (%)	*p* Value
Treatment modalities			
Dexamethasone	124 (80)	22 (71)	0.264
Enoxaparin	110 (71)	22 (71)	>0.999
Oxygen	102 (65.8)	24 (77.4)	0.207
Ceftriaxone	108 (69.7)	20 (64.5)	0.571
Zinc	97 (62.6)	17 (54.8)	0.419
Azithromycin	57 (36.8)	10 (32.3)	0.633
Nebulization	36 (23.2)	7 (22.6)	0.938
Antihypertensives	21 (13.5)	8 (25.8)	0.086
N-acetyl cysteine	13 (8.4)	3 (9.7)	0.733
Vitamin C	7 (4.5)	1 (3.2)	>0.999
Ivermectin	0 (0)	1 (3.2)	0.167
Oxygen delivery methods			
Non-rebreather mask	79 (51)	18 (58.1)	0.470
Nasal prong	32 (20.6)	7 (22.6)	0.809
High flow nasal cannula	4 (2.6)	2 (6.5)	0.262
Disease severity			**0.075**
Mild	11 (7.1)	4 (12.9)	
Moderate	44 (28.4)	3 (9.7)	
Severe	91 (58.7)	21 (67.7)	
Critical	9 (5.8)	3 (9.7)	
ICU consult			
No	133 (85.8)	21 (67.7)	0.015
Yes	22 (14.2)	10 (32.3)	
Length of hospitalization: median (IQR) days	7 (3–13)	6 (2–9)	0.184

Abbreviations: IQR, interquartile range; PLWH, people living with HIV.

TABLE 4 Factors associated with COVID-19 outcomes among PLWH compared to the controls

Outcome	Odds ratio (95% CI)	*p* Value
COVID-19 severity		
Mild-moderate	1.0	
Severe-critical	1.9 (0.8–4.7)	0.164
ICU consult required		
No	1.0	
Yes	2.9 (1.2–6.9)	0.015
Vital status		
Alive	1.0	
Died	1.7 (0.8–3.8)	0.181

Abbreviation: PLWH, people living with HIV.

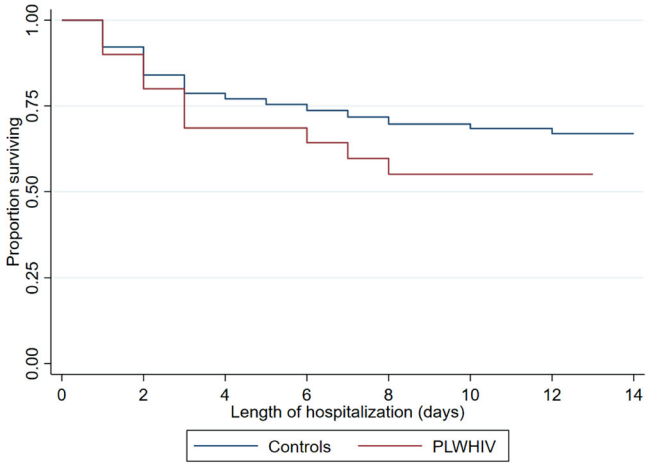

FIGURE 1 Survival analysis between PLWH and matched HIV-uninfected controls. Cox-regression analysis for risk of death due to COVID-19 in those with HIV compared to controls. Hazards ratio: 1.4 (95% CI: 0.7–2.7, $p = 0.297$). Log-Rank test shows no statistically significant difference, $p = 0.280$.

TABLE 5 Survival to 7-day and 14-day for PLWH versus non-HIV control

HIV status	7-day	14-day
PLWH	63% (42%–78%)	50% (28%–69%)
Non-HIV control	72% (64%–79%)	65% (55%–73%)

Abbreviation: PLWH, people living with HIV.

Among the PLWH group, 61.3% patients had at least one comorbidity. The most common comorbidities within our group of PLWH were hypertension (29.6%) and diabetes (16.1%). This is consistent with existing literature on comorbidities among PLWH within other populations.[22] Pre-existing comorbidities, like hypertension, diabetes, and heart failure, have been shown to not only increase the risk of COVID-19 infection but also exacerbate the severity of COVID-19 infection[23] and may have influenced the severity of COVID-19 infection at admission.

Since the pathognomonic feature of HIV is the progressive infection and reduction in the CD4+ T cells, leading to the destruction of both cell-mediated and antibody-mediated immune responses,[24] there is concern that PLWH may be at an increased risk for COVID-19 infection, increased disease severity, increased mortality, and comorbidities.[25] This could explain the increased need for ICU consultation among PLWH compared to the non-HIV controls.

Our study has some limitations. The relatively small sample size may have caused us to miss important differences between PLWH and control patients that might be detected in a larger study.

However, we used propensity-score-matching to try and balance important covariates among PLWH and non-HIV patients with COVID-19. A second limitation was the lack of data on ART use among PLWH which prevented us from investigating how ART use and HIV control could moderate COVID-19 disease severity and outcomes. The last limitation was the lack of radiographic and immunologic laboratory findings including CD4 count and viral load in patient files that could have allowed us to investigate differences in these laboratory measures between PLWH and matched controls. We recommend further studies on this topic, perhaps with a study design approach that is not afflicted with the problem of lack of available data inherent in most retrospective chart reviews especially in this region.

5 | CONCLUSIONS

In conclusion, PLWH hospitalized for COVID-19 at Mulago Hospital during Uganda's second wave of the coronavirus disease pandemic were almost three times more likely to require ICU consultation compared to a matched HIV uninfected control group. There was also a trend that suggests worse outcomes for PLWH. This elicits further studies with higher sample sizes.

AUTHOR CONTRIBUTIONS

Brian Fleischer, Joseph Baruch Baluku, Ronald Olum, Elijah Paintsil, and Felix Bongomin conceived the idea and developed the study design. Brian Fleischer, Ronald Olum, Dianah Rhodah Nassozi, and Ivaan Pitua completed the data extraction from the patient files. Ronald Olum and Brian Fleischer completed the data analysis. Brian Fleischer, Ronald Olum, Frederick Nelson Nakwagala, Elijah Paintsil, Joseph Baruch Baluku, and Felix Bongomin contributed to the interpretation of the results. Brian Fleischer took lead in writing the manuscript. All authors provided critical feedback and helped shaped the research, analysis, and manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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