Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study

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Objective: We studied clinical outcomes of COVID-19 infection in patients living with HIV (PLH) in comparison to non-HIV population.

Design: Analysis of a multicentre research network TriNETX was performed including patients more than 10 years of age diagnosed with COVID-19.

Methods: Outcomes in COVID-19 positive patients with concurrent HIV (PLH) were compared with a propensity-matched cohort of patients without HIV (non-PLH).

Results: Fifty thousand one hundred and sixty-seven patients with COVID-19 were identified (49,763 non-PLH, 404 PLH). PLH were more likely to be men, African–American, obese and have concurrent hypertension, diabetes, chronic kidney disease and nicotine dependence compared with non-PLH cohort (all P values <0.05). We performed 1 : 1 matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence and sex. In unmatched analysis, PLH had higher mortality at 30 days [risk ratio 1.55, 95% confidence interval (95% CI): 1.01–2.39] and were more likely to need inpatient services (risk ratio 1.83, 95% CI: 1.496–2.24). After propensity score matching, no difference in mortality was noted (risk ratio 1.33, 95% CI: 0.69–2.57). A higher proportion of PLH group needed inpatient services (19.31 vs. 11.39%, risk ratio 1.696, 95% CI: 1.21–2.38). Mean C-reactive protein, ferritin, erythrocyte sedimentation rate and lactate dehydrogenase levels after COVID-19 diagnosis were not statistically different and mortality was not different for PLH with a history of antiretroviral treatment.

Conclusion: Crude COVID-19 mortality is higher in PLH; however, propensity-matched analyses revealed no difference in outcomes, showing that higher mortality is driven by higher burden of comorbidities. Early diagnosis and intensive surveillance are needed to prevent a 'Syndemic' of diseases in this vulnerable cohort.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related disease (COVID-19) has emerged as the major health crisis of 2020 [1]. Its impact on patients with preexisting infection with HIV has hitherto not been studied extensively. Recently, the Centers for Disease Control and Prevention (CDC) highlighted that patients living with HIV may be at a heightened risk of severe illness from SARS-CoV-2 as compared to the general population [2]. This postulated increased risk was attributed to both biological immune compromise and comorbidities as well as socially produced burdens. However, others have suggested that the use of antivirals in this population may confer relative protection from the virus [3].

Considering the large global burden of patients living with HIV, data on COVID-19 infection in these patients are scarce and are limited to case reports and small case series, which do not allow for comparison of outcomes with non-HIV populations [4,5]. We aimed to utilize a multicentre research network to study outcomes in patients with COVID-19 with preexisting HIV infection in comparison to those without HIV coinfection.

Materials and methods

We conducted an analysis of all patients diagnosed with COVID-19 who were more than 10 years of age at the time of diagnosis, using the multicentre research network TriNETX (Cambridge, Massachusetts, USA). Validated COVID-19 specific diagnosis terminology recommended by the WHO and CDC and purported by TriNETX network was used to identify patients with COVID-19 in the USA. This research network provides real-time access to de-identified electronic health records of more than 50 million patients from more than 35 healthcare organizations that are primarily large urban centres. The structure of the research network is discussed in more detail in Supplementary file 1.

The COVID-19 population was then divided into two cohorts based on the presence or absence of infection with HIV. The HIV-positive cohort was identified using ICD codes B20-B24 and Z21 and was then further stratified for subgroup analysis into HIV disease cohort (B20-B24) and the asymptomatic HIV infection without associated illness cohort (Z21).

The HIV cohort was compared with a propensity-matched cohort of patients without HIV to account for confounding. 1 : 1 propensity score matching was performed using nearest neighbour algorithms with a caliper width of 0.1 pooled standard deviations. For the purposes of this study, a two-sided alpha of less than 0.05 was defined *a priori* for statistical significance and risk ratios were calculated for all study outcomes to compare HIV and non-HIV groups.

In analyses with counts less than 10, TriNetX software obfuscates counts to protect patient health information by rounding to the nearest 10. Any such rounding in the analysis conducted for our study was identified and noted, when applicable.

Study outcomes included mortality (within 30 days of COVID-19 diagnosis), hospitalization (within 30 days of COVID-19 diagnosis) and laboratory data (within 30 days of COVID-19 diagnosis).

Further details of methodology are discussed in supplementary study material.

Results

Study population

Using our inclusion criteria, we identified a total of 50 167 patients with COVID (49 763 without concurrent diagnosis of HIV, 404 with preexisting diagnosis of HIV). Among the patients with HIV, 370 had HIV disease, while the rest carried the diagnosis of asymptomatic HIV infection without any HIV associated disease.

Characteristics of COVID-positive patients with HIV

The HIV cohort was predominantly male (285 patients, 71%) with a mean age of 48.2 years (SD 14.2). A majority of HIV patients diagnosed with COVID were nonwhite, with African–American being the most common race (49%). Regarding geographical distribution of the HIV cohort, a majority was derived from the southern USA (177 patients, 44%), followed by the northeast (90 patients, 22%). Most patients had a history of treatment with antiretroviral agents (284 patients, 70%), and many patients had documentation of antiretroviral treatment within 6 months of COVID diagnosis (187 patients, 46%).

Seventy-eight (19.3%) patients with HIV required inpatient services, and 27 patients (6.7%) required critical care services in the 30-day period from the COVID diagnosis.

Among the 404 patients with HIV, 25 received hydroxychloroquine (6.2%), while 57 patients (14.1%) received azithromycin. A total of 52 patients received glucocorticoids (12.9%).

Comparison of characteristics of the HIV-positive and negative cohorts

Patients with HIV were more likely to have concurrent diagnoses of hypertension, diabetes, chronic kidney disease and personal history of nicotine dependence (all

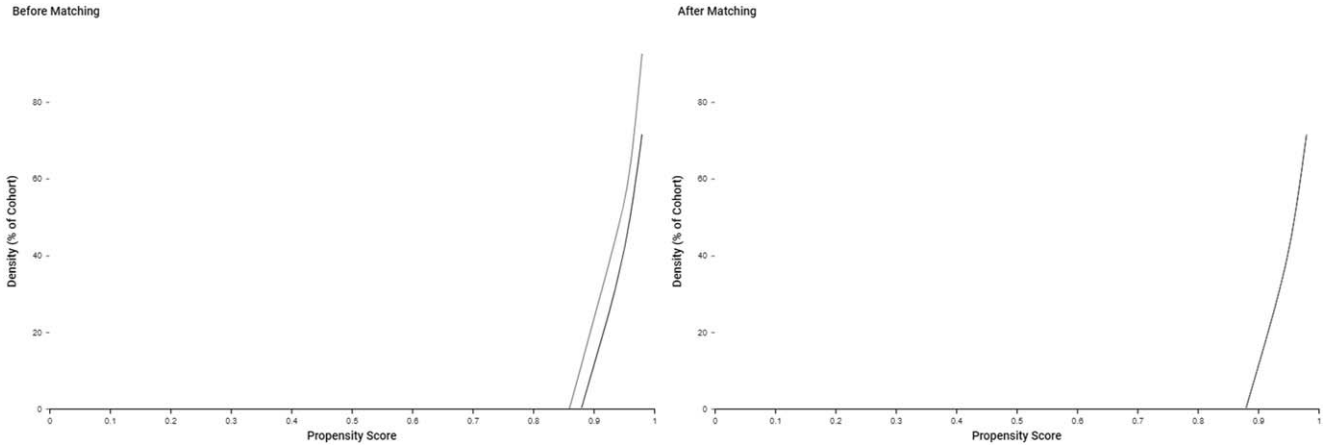

Fig. 1. Propensity score density in the HIV-positive and negative cohorts before and after propensity score matching in the HIV-positive (purple) and non-HIV (blue) cohorts.

P values <0.001). A greater proportion of patients in HIV group were men (70.6 vs. 44.9%, $P < 0.001$). Mean age was similar between the two groups ($P = 0.52$). African–American race was more common in the HIV cohort when compared with the non-HIV cohort (49.8 vs. 25.2%, $P < 0.001$). A greater proportion of patients in the HIV group were obese (BMI >30 kg/m^2) compared with non-HIV group ($P = 0.03$).

Clinical outcomes

We performed 1 : 1 matching for BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence and sex. The HIV and non-HIV groups (404 each) were well matched after the propensity score matching, as described in Fig. 1 and Table 1.

In unmatched analysis of the whole cohorts, patients with HIV had higher mortality at 30 days from COVID diagnosis [4.95 vs. 3.2%, risk ratio 1.55, 95% confidence interval (95% CI): 1.01–2.39] and were significantly more likely to need inpatient services (19.3 vs. 10.6%, risk ratio 1.83, 95% CI: 1.50–2.24).

After the propensity score matching, no difference in mortality was noted in the HIV and non-HIV groups (5.0 vs. 3.7%, risk ratio 1.33, 95% CI: 0.69–2.57). A significantly higher proportion of patients in HIV group needed inpatient services (19.3 vs. 11.4%, risk ratio 1.70,

Table 1. Comparison of demographic characteristics and clinical variables before and after propensity score matching.

	Before matching					After matching				
	HIV cohort		Non-HIV cohort		*P*	HIV cohort		Non-HIV cohort		*P*
Variable	Number	Percentage/ SD	Number	Percentage/ SD		Number	Percentage/ SD	Number	Percentage/ SD	
Demographics										
Age (mean)	48.18	14.17	48.80	19.24	0.52	48.18	14.17	47.75	15.89	0.69
Male	285	70.55%	22351	44.92%	<0.001	285	70.55%	284	70.30%	0.94
Female	119	29.46%	27309	54.88%	<0.001	119	29.46%	120	29.70%	0.94
BMI (30 and above)	103	25.50%	10468	21.04%	0.03	103	25.50%	116	28.71%	0.30
Black or African–American	201	49.75%	12528	25.18%	<0.001	201	49.75%	215	53.22%	0.32
White	137	33.91%	23418	47.06%	<0.001	137	33.91%	126	31.19%	0.41
Hispanic or Latino	53	13.12%	7609	15.29%	0.23	53	13.12%	35	8.66%	0.04
Asian	10	2.48%	1332	2.68%	0.8	10	2.48%	10	2.48%	1
Comorbidities										
Hypertension	187	46.29%	13839	27.81%	<0.001	187	46.29%	196	48.52%	0.53
Chronic lower respiratory diseases	101	25%	7784	15.64%	<0.001	101	25%	97	24.01%	0.74
Diabetes mellitus	89	22.03%	7260	14.59%	<0.001	89	22.03%	95	23.52%	0.61
Chronic kidney disease	67	16.58%	3376	6.78%	<0.001	67	16.58%	49	12.13%	0.07
Ischemic heart disease	57	14.11%	4135	8.31%	<0.001	57	14.11%	49	12.13%	0.4
History of nicotine dependence	56	13.86%	3619	7.27%	<0.001	56	13.86%	53	13.12%	0.76

Table 2. Outcomes in the two cohorts.

Outcome	HIV group	Percentage	Non-HIV group	Percentage	Risk ratio	95% CI Lower	95% CI Upper
Before propensity score matching							
Mortality within 30 days	20	4.95	1585	3.19	1.55	1.01	2.39
Inpatient services	78	19.31	5254	10.56	1.83	1.50	2.24
After propensity score matching							
Mortality within 30 days	20	4.95	15	3.71	1.33	0.69	2.57
Inpatient services	78	19.31	46	11.39	1.70	1.21	2.38

95% CI, 95% confidence interval.

95% CI: 1.21–2.38). These outcomes are detailed in Table 2. The Kaplan–Meier curves for the two propensity score matched cohorts are plotted in Fig. 2.

Mean C-reactive protein, ferritin, erythrocyte sedimentation rate and lactate dehydrogenase levels after COVID-19 diagnosis were also not significantly different in the two matched groups (Table 3).

A subgroup analysis of only patients who had HIV-associated disease [excluding patients with asymptomatic infection without acquired immunodeficiency syndrome (AIDS)] revealed similar results. There was no difference in mortality in this HIV disease group when compared with patients without HIV on propensity-matched analysis (5.1 vs. 4.6%, risk ratio 1.12, 95% CI: 0.59–2.12).

A second subgroup analysis was conducted for patients with HIV with a history of treatment with antiretroviral agents. No difference in 30-day mortality was found when compared with non-HIV group in the unmatched analysis (3.9 vs. 3.2%, risk ratio 1.22, 95% CI: 0.68–2.18).

Discussion

Data on COVID-19 disease in HIV patients are scarce; this study analyses the largest cohort of HIV-positive COVID patients thus far. Our analysis provides some novel insights into this unique subgroup of COVID patients. We found a large burden of comorbidities and high-risk features in patients with HIV presenting with COVID-19. This finding is similar to a study by Meyerowitz *et al.* [5], which included 34 COVID-19 patients with HIV in their cohort. Another recent small study by Gervasoni *et al.* [6], which included 47 HIV patients with proven or probable COVID-19, did not observe worse outcomes when compared with those without HIV and COVID.

Chronic inflammation due to the immune system dysregulation, and the immune deficiency that is the hallmark of HIV disease can be postulated to elevate the risk of severe COVID-19 disease in HIV patients. Conversely, antiretroviral treatment that many persons living with HIV are taking may confer some protection against SARS-COV-2 [3,7], thus reducing the severity of

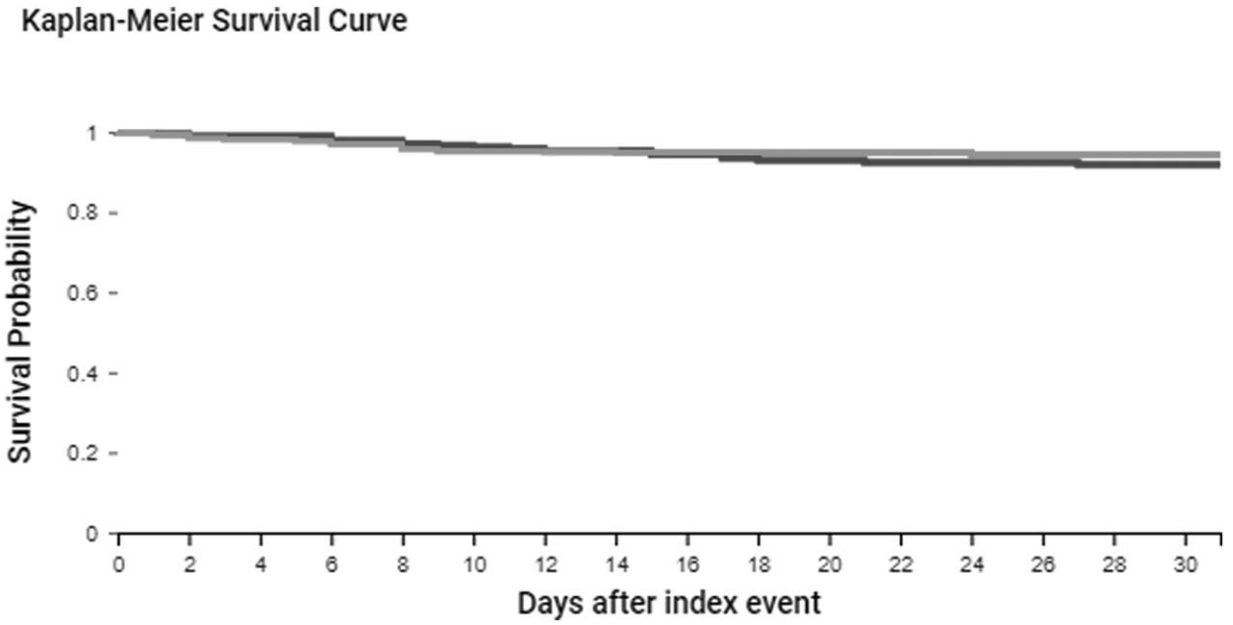

Fig. 2. Survival probability after COVID-19 in the HIV-positive (purple) and non-HIV (blue) cohorts in the matched analysis.

Table 3. Laboratory values after COVID 19 episodes in the two groups.

	Before propensity matching							After propensity matching						
	HIV			Non-HIV				HIV			Non-HIV			
Outcome	Patients with Outcome	Mean	SD	Patients with Outcome	Mean	SD	*P*	Patients with Outcome	Mean	SD	Patients with Outcome	Mean	SD	*P*
C-reactive protein (mg/l)	96/404	71.15	95.33	9968/49763	64.39	81.02	0.42	96/404	71.15	95.33	85/404	52.57	71.50	0.14
Lactate dehydrogenase (U/l)	92/404	372.45	291.05	8315/49763	420.78	740.16	0.53	92/404	372.45	291.05	67/404	373.88	245.18	0.97
Erythrocyte sedimentation rate (mm/h)	19/404	52.89	40.17	2792/49763	49.31	32.05	0.63	19/404	52.89	40.17	26/404	57.62	35.29	0.68
Alanine aminotransferase (U/l)	151/404	37.20	42.08	13455/49763	55.64	245.55	0.36	151/404	37.20	42.08	119/404	47.97	69.76	0.12
Aspartate aminotransferase (U/l)	150/404	48.43	108.14	13421/49763	80.76	684.74	0.56	150/404	48.43	108.14	120/404	59.49	154.59	0.49
Bilirubin (mg/dl)	149/404	0.84	2.34	13346/49763	0.66	1.33	0.11	149/404	0.84	2.34	118/404	0.67	1.58	0.5
Ferritin (ng/ml)	82/404	23646.94	78275.49	7969/49763	24507.81	82894.97	0.93	82/404	23646.94	78275.49	64/404	22619.86	83931.79	0.94

the disease [2]. Our analysis finds that outcomes of COVID in HIV populations are no different than HIV-negative population, even in patients with a history of treatment with antiretrovirals.

Comorbidities, including diabetes, hypertension and chronic kidney disease, exist irrespective of HIV status, as they result from similar physiological or pathological processes. Therefore, we performed propensity matching to assess for independent associations in our study.

The propensity-matched analysis revealed no difference in mortality after controlling for comorbidities implying that the increase in COVID mortality is likely mediated by the high comorbidity burden prevalent in this HIV-positive population. Many of the comorbidities that have been associated with severe COVID disease have also been associated with HIV or its treatment as well [8]. Chronic kidney disease, chronic lung disease and diabetes mellitus were more prevalent in the HIV cohort in our study. Previous data have also shown a higher prevalence of these noncommunicable comorbidities in patients living with HIV when compared with the general population [9,10]. Chronic inflammation caused by the viral illness and/or antiretroviral therapy have been proposed as putative mechanisms [5]. In our analysis, HIV patients were more likely to need inpatient evaluation even after robust controlling of these risk factors with propensity matching. Patients living with HIV, thus, represent a high-risk group for adverse outcomes related to COVID-19.

Our study is limited by its retrospective design, and the biases and limitations inherent to electronic medical record (EMR) based network studies. However, we used standardized criteria to identify cases, and limited the studied variables and outcomes to ones that are logically less likely to suffer from documentation errors. Moreover, the inclusion of a relatively large sample with robust control of confounders should mitigate any 'pollution' resulting from documentation errors. The research network used is primarily based on large academic centres in the USA, which may limit generalizability to other specific HIV populations in other communities. Patients who had an asymptomatic course of infection and did not undergo testing for COVID-19 remain uncaptured in this study, and thus, one can infer that our analysis included a more 'severe' form of disease spectrum.

In conclusion, COVID crude mortality is higher in HIV-positive patients when compared with non-HIV patients; however, propensity-matched analyses revealed no difference in outcomes, showing that this high mortality is driven by the higher burden of risk factors for severe COVID in the HIV patients. Thus, patients living with HIV represent a cohort of patients with many risk factors for severe disease that needs special consideration in public health efforts. Early diagnosis and intensive surveillance may be needed to prevent a 'Syndemic' of diseases in this vulnerable cohort.

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Conflicts of interest

There are no conflicts of interest.

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