International Journal of Infectious Diseases 135 (2023) 49–56

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Risk of COVID-19 hospitalization in people living with HIV and HIV-negative individuals and the role of COVID-19 vaccination: A retrospective cohort study

Joseph H. Puyat[1,2,3,*], Adeleke Fowokan[1], James Wilton[1], Naveed Z. Janjua[1,2,3], Jason Wong[1,2], Troy Grennan[1,2], Catharine Chambers[4], Abigail Kroch[5], Cecilia T. Costiniuk[6], Curtis L. Cooper[7], Darren Lauscher[8], Monte Strong[9], Ann N. Burchell[4,10,11], Aslam H. Anis[2,3,8], Hasina Samji[1,12,*], COVAXHIV Study Team

[1] *British Columbia Centre for Disease Control, Vancouver, Canada*
[2] *School of Population and Public Health, University of British Columbia, Vancouver, Canada*
[3] *Centre for Health Evaluation and Outcome Sciences, St Paul's Hospital, Vancouver, Canada*
[4] *Dalla Lana School of Public Health, University of Toronto, Toronto, Canada*
[5] *The Ontario HIV Treatment Network, Toronto, Canada*
[6] *Department of Medicine, Division of Infectious Diseases and Chronic Viral Illness Service, McGill University Health Centre, Montreal, Canada*
[7] *Department of Medicine, University of Ottawa, Ottawa, Canada*
[8] *CIHR Canadian HIV Trials Network, Vancouver, Canada*
[9] *PAN, Vancouver, Canada*
[10] *Department of Family and Community Medicine, Faculty of Medicine, University of Toronto, Toronto, Canada*
[11] *MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Canada*
[12] *Faculty of Health Sciences, Simon Fraser University, Burnaby, Canada*

ARTICLE INFO

Article history:
Received 11 May 2023
Revised 28 June 2023
Accepted 30 June 2023

Keywords:
SARS-CoV-2
COVID-19 outcomes
Canada
HIV infection
Epidemiology

ABSTRACT

Objective: To examine the risk of hospitalization within 14 days of COVID-19 diagnosis among people living with HIV (PLWH) and HIV-negative individuals who had laboratory-confirmed SARS-CoV-2 infection.
Methods: We used Cox proportional hazard models to compare the relative risk of hospitalization in PLWH and HIV-negative individuals. Then, we used propensity score weighting to examine the influence of sociodemographic factors and comorbid conditions on risk of hospitalization. These models were further stratified by vaccination status and pandemic period (pre-Omicron: December 15, 2020, to November 21, 2021; Omicron: November 22, 2021, to October 31, 2022).
Results: The crude hazard ratio (HR) for risk of hospitalization in PLWH was 2.44 (95% confidence interval [CI]: 2.04-2.94). In propensity score-weighted models that included all covariates, the relative risk of hospitalization was substantially attenuated in the overall analyses (adjusted HR [aHR]: 1.03; 95% CI: 0.85-1.25), in vaccinated (aHR 1.00; 95% CI: 0.69-1.45), inadequately vaccinated (aHR: 1.04; 95% CI: 0.76-1.41) and unvaccinated individuals (aHR: 1.15; 95% CI: 0.84-1.56).
Conclusion: PLWH had about two times the risk of COVID-19 hospitalization than HIV-negative individuals in crude analyses which attenuated in propensity score-weighted models. This suggests that the risk differential can be explained by sociodemographic factors and history of comorbidity, underscoring the need to address social and comorbid vulnerabilities (e.g., injecting drugs) that were more prominent among PLWH.

Introduction

The COVID-19 outbreak, which is caused by the novel coronavirus (SARS-CoV-2) [1] was declared a pandemic by the World Health Organization on March 11, 2020. To date, over 760 million infections have been recorded, which have resulted in over

* Corresponding authors.
E-mail addresses: jpuyat@cheos.ubc.ca (J.H. Puyat), Hasina.Samji@bccdc.ca (H. Samji).

https://doi.org/10.1016/j.ijid.2023.06.026

6.9 million deaths [2]. Findings from epidemiologic studies suggest that older adults, individuals who belong to certain ethnic minority groups (often a proxy for social and structural factors such as poor access to healthcare and racism), those with existing comorbidities, individuals with substance use disorders, immunocompromised individuals such as transplant patients and people living with HIV (PLWH) are at increased risk of SARS-CoV-2 infection and adverse COVID-19 outcomes [3–6].

Although the exact mechanism that accounts for greater COVID-19 risk among PLWH is relatively unclear, it is well established that HIV is marked by impairments to the immune system, even among active antiretroviral therapy users [7]. While the immune system impairments experienced by PLWH might in part explain their increased risk for severe COVID-19 outcomes, PLWH may experience other compounding vulnerabilities that are known to be associated with increased risk of SARS-CoV-2 acquisition and COVID-19 illness severity. They typically comprise a higher proportion of individuals with lower socioeconomic status, older adults, those with substance use disorders, and individuals experiencing multimorbidity, resulting in a syndemic of infections, comorbidities, and social conditions that could further exacerbate health outcomes [8–10].

Among studies that have sought to explore the impact of HIV status on clinical outcomes from COVID-19, it remains unclear whether HIV status is an independent risk factor for severe COVID-19 outcomes or if known social determinants or biological vulnerabilities that intersect with HIV infection might explain the increased risk for severe COVID-19 outcomes among PLWH [11]. Additionally, given significant heterogeneity in the prevalence of HIV and the composition of populations living with HIV between and within countries [12], there is a need to explore this relationship in a Canadian context, which is currently lacking. Further, given the integral role COVID-19 vaccines have played in the control of the pandemic, particularly among at-risk populations such as PLWH, it is important to know if the association of HIV and poorer SARS-CoV-2 outcomes exists independently of vaccination receipt. This information is particularly salient for informing COVID-19 vaccine policies for PLWH going forward.

Consequently, we utilized population-level data to examine the risk of hospitalization related to COVID-19 infection in PLWH and HIV-negative individuals among laboratory-confirmed cases of SARS-CoV-2. As a secondary objective, we sought to determine if the risk of hospitalization differs by vaccination status and pandemic period.

Methods

Study population and data sources

This was a retrospective cohort study using the British Columbia (BC) COVID-19 Cohort (BCC19C) dataset to examine the risk of hospitalization among PLWH and HIV-negative individuals. The BCC19C was established as a collaboration among the BC Centre for Disease Control (BCCDC), the Data, Analytics Reporting and Evaluation (DARE), the Provincial Health Services Authority (PHSA), and the BC Ministry of Health (MoH) to support the COVID-19 pandemic response. The BCC19C includes population-level province-wide COVID-19 datasets including SARS-CoV-2 testing, COVID-19 case surveillance, hospitalizations, and vaccinations, which are integrated with data from other provincial administrative data holdings and registries including (1) data on physician visits as covered by the publicly funded health insurance plan known as the Medical Services Plan (MSP); (2) Chronic Disease Registry (CDR); (3) Death Records (Vital Stats); (4) Client Roster; (5) hospitalizations as recorded in the Discharge Abstract Database (DAD); and (6) emergency department visits as recorded in the National Ambulatory Care Reporting System (NACRS). Detailed information related to the datasets is included in Supplemental File 1.

Study cohort

The study cohort included all individuals who tested positive for SARS-CoV-2 between December 15, 2020, when COVID-19 vaccination first started in BC, and October 31, 2022, when data analysis started. Those who were under 19 years of age as of December 15, 2020, not residents of BC, had unknown place of residence, had missing data on income, or invalid date of deaths were excluded.

Study outcome and follow-up

The primary outcome of interest is COVID-19 hospitalization, defined as a hospital admission occurring 2 days before or 14 days after a positive laboratory collection date [13]. Follow-up time was calculated starting from either the laboratory positive collection or hospital admission date, whichever is earlier. Follow-up was censored at hospitalization, death, or at 14 days.

Study variables

The primary explanatory variable is PLWH status, which was ascertained using a previously developed algorithm [14]. Other covariates include sex, age, regional health authority, neighborhood income quintile, history of injecting drugs, number of other comorbid medical conditions, vaccination status, and biweekly testing periods (to account for time variations in COVID-19 case counts throughout the length of the study). Income quintiles as an area-level measure of socioeconomic status were derived from census data and postal codes. The health authorities delineate important geographic distinctions relating to healthcare service delivery that might provide insight into disparities, particularly among PLWH (see Supplemental File 2 for detailed information about health regions). History of injecting drugs was ascertained using previously published and validated algorithm that looks for International Classification of Diseases-9 and International Classification of Diseases-10 codes in physician claims and hospitalization data [15]. Number of comorbid medical conditions was ascertained from diagnostic codes in physician claims and hospitalization data using the Elixhauser Comorbidity Index, which we modified to exclude HIV and substance use from the list of medical comorbidities. We used a categorical version of the index to identify people who have zero (not counting HIV and history of injecting drugs), one, two, and three or more comorbid conditions.

Vaccination status at the beginning of the follow-up period was determined based on the date of vaccination and the number of days between positive laboratory collection date and the start of the follow-up period. Using an approach to determining vaccination status used by other researchers [16], we regarded those with no recorded immunization date at the start of follow-up as unvaccinated. Those that received one dose only or that received their second and subsequent doses more than 180 days since the beginning of the follow-up period were regarded as inadequately vaccinated [16]. Adequately vaccinated individuals were those who received their second or subsequent doses $\leq$180 days before the start of the follow-up period [16].

Ethics statement

This study was performed using de-identified data routinely collected as part of public health surveillance and/or routine healthcare encounters. Patient consent was not required in accordance with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans article 5.5B. This study was re-

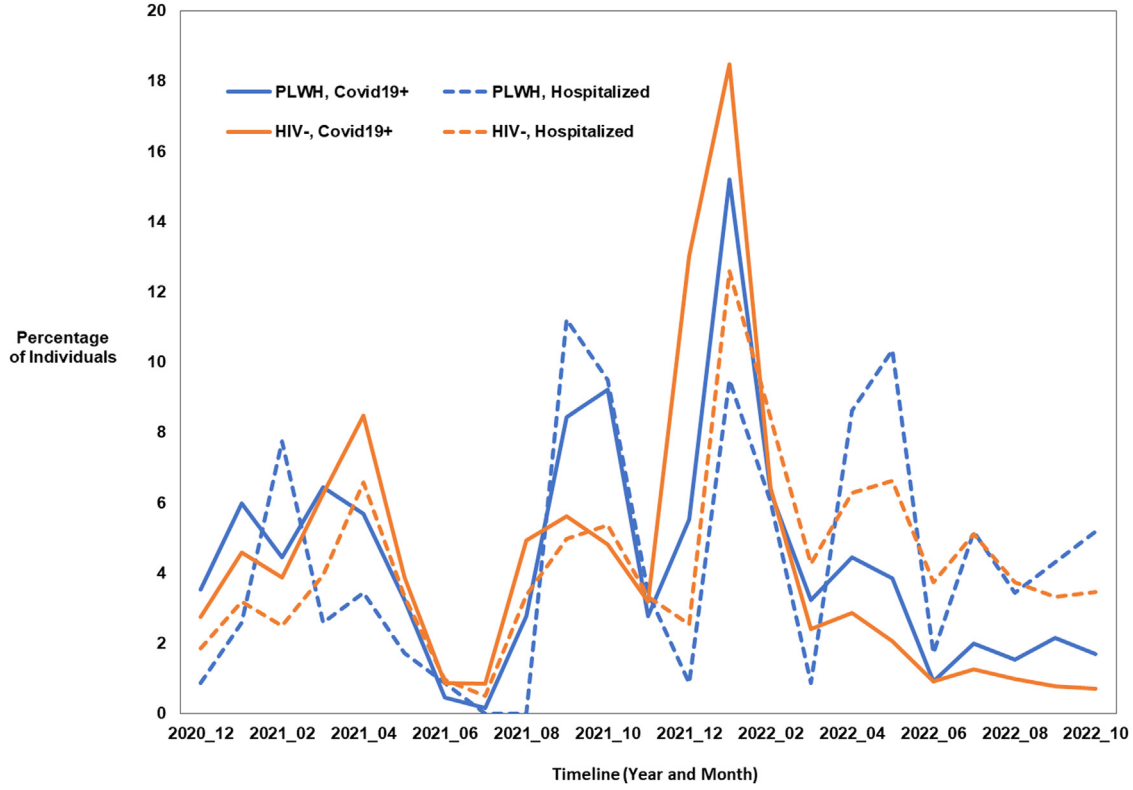

Figure 1. Percentage distribution of COVID-19 cases and hospitalizations throughout the study period. PLWH, people living with HIV.

viewed and approved by the University of BC Research Ethics Board (#H20-02097).

Statistical analyses

The sociodemographic and clinical characteristics of the overall sample and of the study cohorts were summarized using counts, proportions, and median values. We described the distribution of cases and outcomes by plotting monthly percentages of COVID-19 infection and hospital admissions. The crude risk of hospitalization between PLWH and HIV-negative individuals was obtained by calculating the proportion of individuals in each cohort that had COVID-19 hospitalization. We estimated the unadjusted relative hazard of hospitalization by running Cox proportional hazard models with only the indicator for PLWH or HIV-negative individuals as predictor, and we ran these models on the overall data and on data stratified by vaccination status and pandemic period (pre-Omicron: December 15, 2020, to November 21, 2021; Omicron: November 22, 2021, to October 31, 2022).

We used propensity score weighting to determine whether the observed difference in risk of COVID-19 hospitalization between PLWH and HIV-negative individuals could be explained by differences in sociodemographic characteristics, comorbid conditions, or a combination of both. Hence, we derived three sets of propensity scores. The first set was obtained from a logistic regression model containing the full set of baseline covariates that included sociodemographic characteristics, such as sex, age, area-level income, regional health authority, and, comorbid conditions such as history of injecting drugs and number of other comorbid medical conditions regressed on HIV status. The second set was similar to the first except only sociodemographic characteristics were included, while the third set was based solely on comorbid conditions.

We used overlap weights to achieve balance in baseline covariates between the two cohorts. Overlap weighting is a type of propensity score weighting that ensures an exact balance on the mean of every included covariate when the propensity score model is based on logistic regression [17]. This type of weighting overcomes some of the limitations associated with inverse probability of treatment weighting and matching on propensity scores, such as failure to achieve good balance, loss of precision, and poor alignment with the target population [17]. In our analysis, we performed overlap weighting by assigning every individual in the PLWH cohort weights equal to the probability of not being a PLWH (1 – propensity score); all individuals in the HIV-negative cohort were assigned weights equal to the probability of being a PLWH (propensity score). We checked for covariate balance by calculating the absolute standardized difference before and after weighting and used <0.1 as the threshold for good balance.

We applied the overlap weights in the calculation of the adjusted hazard ratios (aHR) using Cox proportional hazard models with month and year of COVID-19 infection and pandemic waves as additional covariates. We ran separate regression analyses using the three different sets of overlap weights. We calculated aHRs overall and as stratified by vaccination status and by pandemic period (pre-Omicron: December 15, 2020, to November 11, 2021, and Omicron: November 11, 2021, to October 31, 2022). We evaluated whether the hazard ratios (HRs) were proportional over time using Schoenfeld test and by plotting the Cox regression coefficient for PLWH status over time.

Sensitivity analyses based on propensity scores estimated from generalized boosted models that use the full set of covariates were also performed. All data preparation and statistical analyses were performed using SAS version 9.4, R version 4.1.0, and PSweight for R version 1.1.8.

Table 1
Study characteristics by PLWH status.

Characteristics	PLWH N = 658 n (%)	HIV-negative individuals N = 252,471 n (%)	Total N = 253,129 n (%)
Female	221 (33.6)	136432 (54.0)	136653 (54.0)
Age			
Median (IQR)	50 (19.0)	42 (28.0)	42 (28.0)
19-29	36 (5.5)	59898 (23.7)	59934 (23.7)
30-39	120 (18.2)	55940 (22.2)	56060 (22.1)
40-49	164 (24.9)	43160 (17.1)	43324 (17.1)
50-59	180 (27.4)	35538 (14.1)	35718 (14.1)
60-69	114 (17.3)	24377 (9.7)	24491 (9.7)
70-79	35 (5.3)	15489 (6.1)	15524 (6.1)
≥80	9 (1.4)	18069 (7.2)	18078 (7.1)
Neighborhood income			
Lowest quintile	276 (41.9)	55817 (22.1)	56093 (22.2)
Second	129 (19.6)	52357 (20.7)	52486 (20.7)
Third	110 (16.7)	50930 (20.2)	51040 (20.2)
Fourth	89 (13.5)	49343 (19.5)	49432 (19.5)
Highest quintile	54 (8.2)	44024 (17.4)	44078 (17.4)
Regional health authority			
Fraser	183 (27.8)	104250 (41.3)	104433 (41.3)
Interior	44 (6.7)	48024 (19.0)	48068 (19.0)
Northern	36 (5.5)	21536 (8.5)	21572 (8.5)
Vancouver Coastal	335 (50.9)	50182 (19.9)	50517 (20.0)
Vancouver Island	60 (9.1)	28479 (11.3)	28539 (11.3)
Persons who inject drugs	282 (42.9)	10752 (4.3)	11034 (4.4)
Elixhauser comorbidity index			
None	94 (14.3)	77411 (30.7)	77505 (30.6)
1	100 (15.2)	62560 (24.8)	62660 (24.8)
2	129 (19.6)	41843 (16.6)	41972 (16.6)
3 or more	335 (50.9)	70657 (28.0)	70992 (28.0)
Pandemic Ws			
W2: 15 December 2020-6 February 2021	71 (10.8)	21009 (8.3)	21080 (8.3)
W3: 07 February 2021-03 July 2021	123 (18.7)	57420 (22.7)	57543 (22.7)
W4: 04 July 2021-04 December 2021	153 (23.3)	49166 (19.5)	49319 (19.5)
W5: 05 December 2021-22 October 2022	311 (47.3)	124876 (49.5)	125187 (49.5)
Vaccination status[a]			
Unvaccinated	245 (37.2)	103779 (41.1)	104024 (41.1)
Non-adequately vaccinated	167 (25.4)	53419 (21.2)	53586 (21.2)
Adequately vaccinated	246 (37.4)	95273 (37.7)	95519 (37.7)
Hospitalized within ≤14 days	115 (17.5)	19166 (7.6)	19281 (7.6)
Received critical care	17 (2.6)	4319 (1.7)	4336 (1.7)
Died ≤ 28 days	8 (1.2)	3734 (1.5)	3742 (1.5)

PLWH, people living with HIV; W, wave.
[a] Vaccination status was determined at the date of testing positive for Covid-19 as follows: unvaccinated if no recorded immunization date; inadequately vaccinated if only one dose was received or if the second and subsequent doses were received >180 days; adequately vaccinated if second subsequent doses were received < 180 days.

Results

Study population

From the linked health data, we identified 663 PLWH and 266,569 HIV-negative individuals, 19 years of age and older, who tested positive for SARS-CoV-2 from December 15, 2020, to October 31, 2022. We excluded 11,585 individuals (1 PLWH; 11,584 HIV-negative) who were not residents of BC, and 2249 individuals with unknown residency status (2 PLWH; 2247 HIV-negative). Lastly, those with missing income data (0 PLWH; 147 HIV-negative) and invalid dates of death (2 PLWH; and 156 HIV-negative) were also excluded. The final study cohorts consisted of 658 PLWH and 252,471 HIV-negative. Figure 1 describes the distribution of COVID-19-positive cases and hospitalizations throughout the study duration. The bi-monthly case and hospitalization patterns across both PLWH and the HIV-negative groups were relatively comparable, except for between August and October 2021 and April and June 2022, where noticeable spike in the proportion of COVID-19 cases and hospitalizations for PLWH was observed.

The cohort of PLWH was predominantly male (66.4%), had a median age of 50, and a relatively higher proportion of people living in the poorest neighborhood (41.9%) and in the Vancouver Coastal Health region (50.9%) (see Supplemental File 2 for detailed information about BC health regions). In contrast, the HIV-negative cohort had a larger proportion of females (54%), a median age of 42, an even distribution of individuals across neighborhood income quintiles, and a relatively larger proportion of people living in the Fraser Health regions. The PLWH cohort had a substantially larger proportion of persons with a history of injecting drugs (42.9% vs 4.3% in the HIV-negative cohort) and with three or more comorbid conditions (50.9% vs 28.0% in the HIV-negative cohort) (Table 1).

The distribution of individuals across pandemic waves was similar in both cohorts, with nearly half of the individuals in both cohorts having recorded COVID-19 infection during the fifth wave of the pandemic. In terms of vaccinations status, about 37% were adequately vaccinated overall in both cohorts; the proportion of unvaccinated individuals was slightly lower in the PLWH cohort (37.2%) than in the HIV-negative cohort (41.1%), whereas there were more inadequately vaccinated individuals in the PLWH cohort (25.4%) than in the HIV-negative cohort (21.2%) (Table 1).

Crude risk of hospitalization

Overall, there was a higher proportion of people hospitalized within 14 days in the PLWH (17.5%) than in the HIV-negative (7.6%)

Table 2
HR of COVID-19 hospitalization by PLWH, stratified by vaccination status.

Propensity score weighting and stratification	Group	n/N	Crude HR (95% CI)	Adjusted HR (95% CI)
Full, pre-Omicron, and Omicron				
All	PLWHIV	115/658	2.44 (2.04, 2.94)	1.03 (0.85, 1.25)
	HIV-negative	19,166/252,471		
Unvaccinated	PLWHIV	43/245	2.39 (1.77, 3.23)	1.15 (0.84, 1.56)
	HIV-negative	8110/103,779		
Inadequately Vaccinated	PLWHIV	40/167	2.90 (2.12, 3.96)	1.04 (0.76, 1.41)
	HIV-negative	4839/53,419		
Adequately Vaccinated	PLWHIV	32/246	2.07 (1.46, 2.92)	1.00 (0.69, 1.45)
	HIV-negative	6217/95,273		
Full, pre-Omicron only				
All	PLWHIV	49/343	2.52 (1.90, 3.33)	1.07 (0.80, 1.43)
	HIV-negative	7523/124,730		
Unvaccinated	PLWHIV	34/216	2.65 (1.89, 3.71)	1.17 (0.83, 1.67)
	HIV-negative	5884/92,547		
Inadequately Vaccinated	PLWHIV	11/65	2.75 (1.52, 4.97)	0.95 (0.52, 1.72)
	HIV-negative	1057/15,974		
Adequately Vaccinated	PLWHIV	<5/62	1.84 (0.69, 4.92)	0.77 (0.28, 2.16)
	HIV-negative	582/16,209		
Full, Omicron only				
All	PLWHIV	66/315	2.46 (1.93, 3.13)	1.01 (0.78, 1.29)
	HIV-negative	11,643/127,741		
Unvaccinated	PLWHIV	9/29	1.64 (0.85, 3.16)	0.95 (0.53, 1.70)
	HIV-negative	2226/11,232		
Inadequately Vaccinated	PLWHIV	29/102	3.14 (2.18, 4.52)	1.07 (0.75, 1.54)
	HIV-negative	3782/37,445		
Adequately Vaccinated	PLWHIV	28/184	2.23 (1.54, 3.24)	1.04 (0.70, 1.55)
	HIV-negative	5635/79,064		
Sociodemographic, pre-Omicron, and Omicron				
All	PLWHIV	115/658	2.44 (2.04, 2.94)	1.57 (1.30, 1.91)
	HIV-negative	19,166/252,471		
Unvaccinated	PLWHIV	43/245	2.39 (1.77, 3.23)	1.69 (1.25, 2.28)
	HIV-negative	8110/103,779		
Inadequately Vaccinated	PLWHIV	40/167	2.90 (2.12, 3.96)	1.57 (1.16, 2.13)
	HIV-negative	4839/53,419		
Adequately Vaccinated	PLWHIV	32/246	2.07 (1.46, 2.92)	1.55 (1.07, 2.26)
	HIV-negative	6217/95,273		
Comorbidities, pre-Omicron, and Omicron				
All	PLWHIV	115/658	2.44 (2.04, 2.94)	1.33 (1.10, 1.60)
	HIV-negative	19,166/252,471		
Unvaccinated	PLWHIV	43/245	2.39 (1.77, 3.23)	1.52 (1.13, 2.05)
	HIV-negative	8110/10,3779		
Inadequately Vaccinated	PLWHIV	40/167	2.90 (2.12, 3.96)	1.44 (1.06, 1.96)
	HIV-negative	4839/53,419		
Adequately Vaccinated	PLWHIV	32/246	2.07 (1.46, 2.92)	1.22 (0.85, 1.75)
	HIV-negative	6217/95,273		

CI, confidence interval; HR, hazard ratio; PLWH, people living with HIV. Pre-Omicron period was from December 15, 2020, to November 21, 2021; Omicron period was from November 22, 2021, to October 31, 2022. In the full model, baseline differences between PLWH and HIV- cohorts were balanced using overlap propensity score weights derived from logistic regression models containing the following covariates: sex, age, income quintile, health region, history of injecting drugs, and comorbidities as measured by Elixhauser comorbidity index. The sociodemographic model was similar to the full model except only sex, age, health region, and income quintile were included as covariates in the propensity score model. The comorbid model was similar to the full model except only the history of injection drug use and Elixhauser comorbidity index was included as covariates in the propensity score model. Vaccination status was determined at the date of testing positive for COVID-19 as follows: unvaccinated if no recorded immunization date; inadequately vaccinated if only one dose was received or if the second and subsequent doses were received >180 days; adequately vaccinated if second subsequent doses were received < 180 days. All adjusted HR estimates were also adjusted for the month and year COVID-19 infection occurred.

cohort. Similarly, the proportion of people who received critical care during hospitalization was higher in the PLWH (2.6%) than in the HIV-negative cohort (Table 1). Unweighted Cox regression results indicate that the hazard of hospitalization within 14 days was more than two-fold higher in the PLWH than in the HIV-negative cohort. The crude HR was 2.44 (95% confidence interval [CI]: 2.04-2.94) for the overall sample and is nearly the same during the pre-Omicron (crude HR: 2.52, 95% CI: 1.90-3.30) and Omicron era (crude HR: 2.46, 95% CI: 1.93-3.13) (Table 2). Across vaccination status, there was a consistently higher risk of hospitalization among PLWH relative to HIV-negative individuals, although the smallest and highest relative difference was found among those that were adequately (crude HR: 2.07, 95% CI: 1.46-2.92) and inadequately vaccinated (crude HR: 2.90; 95% CI: 2.12-3.96), respectively. This pattern was similar before and during the Omicron period, except that the highest unadjusted HR was observed among individuals with inadequate vaccination during the Omicron wave (crude HR: 3.14; 95% CI: 2.18-4.52) (Table 2).

Adjusted risk of hospitalization

Before applying the propensity score weights, examination of absolute standardized differences (ASD) between the PLWH and HIV-negative cohorts show covariate imbalances ranging from 0.03-1.02 (Figure 2). In particular, there were moderate to large imbalances with respect to history of injection drug use (ASD = 1.02),

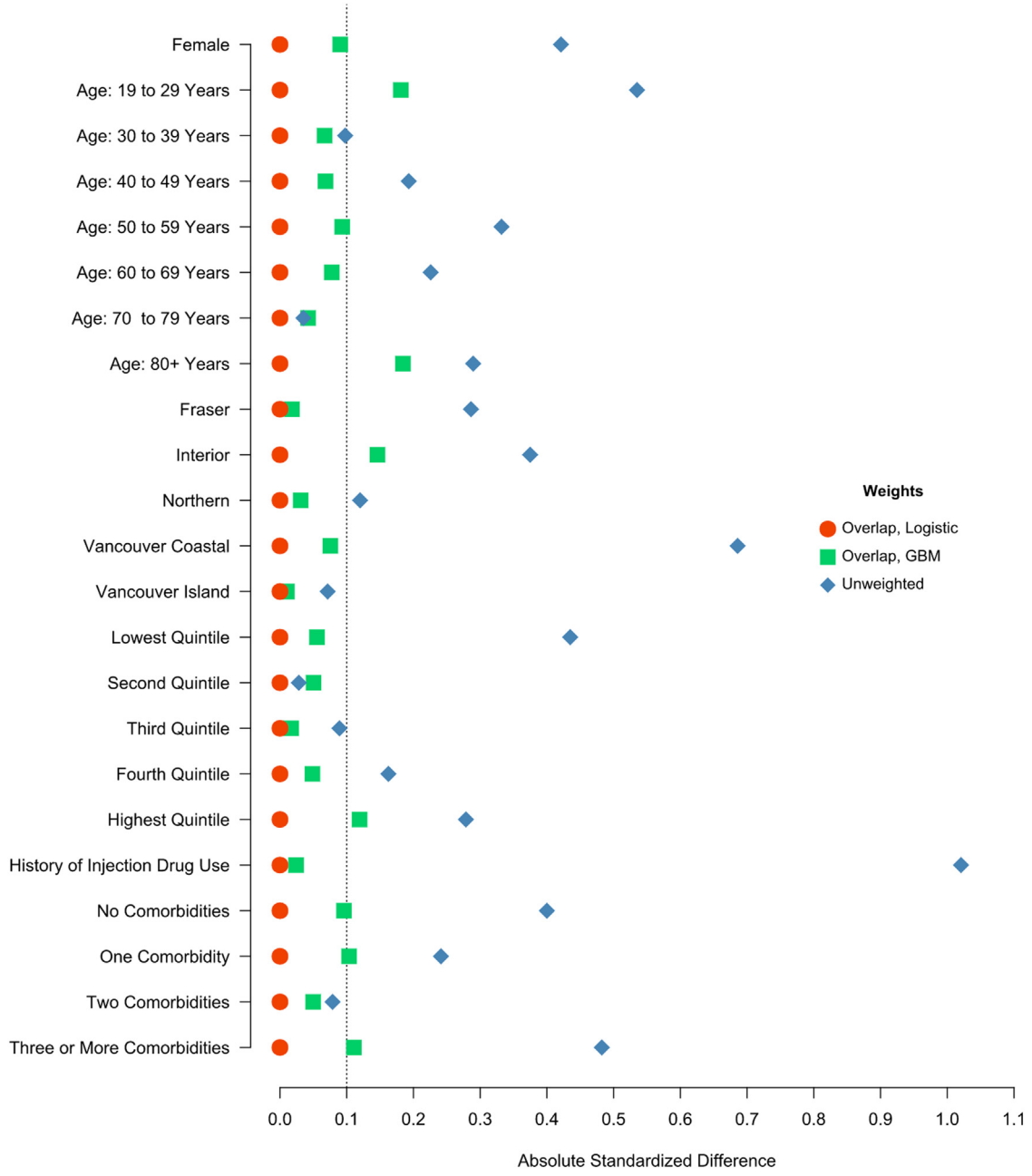

Figure 2. Balance across covariates between people living with HIV and HIV-negative individuals before and after overlap weighting using logistic regression and GBMs. GBM, generalized boosted model.

number of comorbidities (ASD = 0.48), residence in health regions (ASD = 0.69), and sex (0.42). Exact balance was achieved after applying the overlap weights obtained from a propensity score model based on logistic regression model with the full set of adjustment variables.

In propensity score-weighted models that used the full set of covariates for adjustment, the relative risk of hospitalization was substantially attenuated and became statistically non-significant in the overall analyses (aHR: 1.03; 95% CI: 0.85-1.25). The aHR among the unvaccinated (aHR: 1.15; 95% CI: 0.84-1.56) was comparable to the inadequately vaccinated (aHR: 1.04; 95% CI: 0.76-1.41) group, while in the adequately vaccinated group, the adjusted HR was 1.00. Analyses stratified by pandemic period also show similar pattern of attenuation in the adjusted HRs before and during the Omicron wave.

In propensity score-weighted models that balanced differences in sociodemographic variables only, the relative differences in hospitalization risk were reduced in both the overall (aHR: 1.57) and stratified analyses (unvaccinated aHR: 1.69; inadequately vaccinated aHR: 1.57; adequately vaccinated aHR: 1.55). There were similar, albeit more pronounced, reductions in the relative risk of hospitalization in propensity score-weighted models that balanced differences in injection drug use history and number of comorbid conditions, as indicated by adjusted HRs of 1.33, overall, and 1.52, 1.44, and 1.22 for the unvaccinated, inadequately vaccinated and adequately vaccinated groups. Neither model that account for differences in sociodemographic or comorbid conditions, exclusively, yielded results that indicate complete attenuation of the relative differences in risk of hospitalization between PLWH and HIV-negative individuals.

Sensitivity analyses that use propensity score weights derived from using generalized boosted models show similar results based on logistic regression models as reported above (See Supplemental File 3).

Discussion

In this retrospective analysis of linked health data, we found that PLWH has about two times the risk of COVID-19 hospitalization than HIV-negative individuals, with the relative risk more pronounced in the unvaccinated or inadequately vaccinated groups. The elevated risk was observed before and during the Omicron wave of the COVID-19 pandemic. Importantly, most of the increase in risk of COVID-19 hospitalization appears to be driven by differences in sociodemographic characteristics and comorbid conditions, including history of injection drug use given the null differences upon adjustment using propensity score-weighted models.

Evidence is mixed on whether HIV is an independent risk factor for adverse COVID-19 outcomes. One meta-analysis which pooled odds ratio from six studies found that PLWH were more likely to be hospitalized from COVID-19 than their HIV-negative counterparts (pooled odds ratio = 1.49, 95% CI 1.01-2.21), with individual odds ratio from included studies ranging from 0.69-2.19 [18]. Systematic reviews conducted by Mellor *et al.* [19] and Barbera *et al.* [20], exploring the links between HIV and risk of hospitalization, however, appear conflicting. Two of the studies included [21,22] in these review studies reported increased risk for HIV relative to a propensity score matched comparator groups. Two others [23,24], including a large cohort of n = 107,636 veterans found risk of hospitalizations to not vary by PLWH status. It should be noted that the studies included in the review papers differed on the list of covariates accounted for and the specific methods used (i.e., propensity score methods vs covariate adjustment), raising important questions regarding the lack of methodological standardizations to allow for meaningful comparisons across the range of studies included. In studies that have additionally taken into account variables indicative of HIV progression such as viral suppression and/or clusters of differentiation 4 counts, findings suggest those without viral suppression and lower clusters of differentiation 4 counts consistently had increased risk for hospitalizations [25–27]. Given the interrelatedness between sociodemographic factors, prevalence of comorbidities, and HIV clinical parameters and considering the lack of standardization in the selection and assessment of sociodemographic variables and comorbidity history in these studies, it is possible that clinical measures of HIV care might be more reliable for consideration in future analyses.

In the full study sample and pre-Omicron pandemic period (i.e., December 15, 2020, to November 21, 2021), patterns based on point estimates from vaccination-stratified, propensity score-weighted models alone showed that any level of vaccination receipt also attenuated the differences in hospitalization risk between PLWH and HIV-negative individuals. These patterns may affirm the importance of vaccines in this population at mitigating risk for hospitalization and are confirmed by previous work from our group which showed that two doses of COVID-19 vaccines were highly effective against SARS-CoV-2 infection [28] and hospitalizations among PLWH in a pre-Omicron period [29]. Given overlapping confidence intervals, however, caution is warranted in interpreting the findings, as it is possible that this link might be inflated. Consequently, studies with larger sample sizes will be needed to fully confirm what impact vaccines may have in addressing risk of adverse outcomes in PLWH.

The disproportionate prevalence of injection drug use (IDU) among the cohort of PLWH is noteworthy and could represent an area of focus for potential intervention in this cohort. We recently reported that IDU history was associated with slower buildup and faster waning of vaccine effectiveness among PLWH in a pre-Omicron era. Given findings from IDU-adjusted models that showed substantial attenuation, it is plausible that PLWH with IDU might represent a sub-group at increased risk of COVID-19 hospitalizations, as has been reported in the larger BC population [30].

Our study has some limitations. First, low hospitalization counts among the PLWH cohort resulted in imprecise estimates which restricts our ability to make meaningful inferences. Second, although our use of overlap weights based on logistic regression ensured balance on the mean of every included covariate, our results may still be subject to residual confounding due to unmeasured covariates. Third, there were changes in COVID-19 testing policy during the study period, specifically during the Omicron wave when people infected with COVID-19 were less likely to get tested in BC. These people were not represented in our data, and it is currently not known if the proportion of these people differed by HIV or vaccination status. However, the results of the analyses stratified by the pandemic period suggest that the impact of this potential limitation on study results is probably minimal. Lastly, our use of validated algorithms to ascertain PLWH status and history of IDU, like any other case-finding algorithms developed for health administrative data, is likely associated with potential misclassification errors.

Conclusion

We found that PLWH who tested positive for SARS-CoV-2 had about two times the risk of COVID-19 hospitalization than HIV-negative individuals but that this difference can likely be explained by sociodemographic factors and history of comorbidities. This underscores the need for public health programs and interventions to address social and comorbid vulnerabilities—particularly the high rates of IDU among PLWH—and the importance of vaccinations in mitigating the morbidity impacts of the COVID-19 pandemic.

Declarations of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Joseph H. Puyat: Writing – original draft, Investigation, Formal analysis, Methodology, Visualization. **Adeleke Fowokan:** Writing – original draft, Project administration, Methodology. **James Wilton:** Writing – review & editing, Methodology, Conceptualization. **Naveed Z. Janjua:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Troy Grennan:** Conceptualization, Writing – review & editing. **Catharine Chambers:** Conceptualization, Writing – review & editing. **Abigail Kroch:** Conceptualization, Writing – review & editing. **Cecilia T. Costiniuk:** Conceptualization, Writing – review & editing. **Curtis L. Cooper:** Conceptualization, Writing – review & editing. **Darren Lauscher:** Conceptualization, Writing – review & editing. **Monte Strong:** Conceptualization, Writing – review & editing. **Ann N. Burchell:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Aslam H. Anis:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Hasina Samji:** Conceptualization, Funding acquisition, Project administration, Supervision, Writing – review & editing, Methodology.

Funding

This project was supported by funding from the Public Health Agency of Canada, through the Vaccine Surveillance Reference Group and the COVID-19 Immunity Task Force (#2122-HQ-000075), and the Canadian Institutes for Health Research Canadian HIV Trials Network. Joseph Puyat is supported by the Michael

Smith Health Research British Columbia (Scholar Awards). Ann N. Burchell is a Canada Research Chair in Sexually Transmitted Infection Prevention; she is also a recipient of a Non-Clinician Scientist Award from the Department of Family and Community Medicine, Faculty of Medicine, University of Toronto. CTC is supported by a Fonds de Recherche du Québec-Santé Chercheur boursier clinicien Junior 2 salary award. CC is a Vanier scholar.

Ethical approval

This study was reviewed and approved by the University of British Columbia Research Ethics Board (REB) (REB#: H20-02097).

Acknowledgments

The authors acknowledge the assistance of the Provincial Health Services Authority, British Columbia (BC) Centre for Disease Control, BC Ministry of Health, and the Regional Health Authority staff involved in data access, procurement, and management. We would also like to thank staff at the Canadian HIV Trials Network for their support. The authors gratefully acknowledge the population of people living with HIV in BC whose data have been used in this manuscript. The BC COVID-19 cohort was established and is maintained through operational support from Data Analytics, Reporting, and Evaluation and BC Centre for Disease Control at the Provincial Health Services Authority.

Disclaimer

All inferences, opinions, and conclusion drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the data steward(s).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2023.06.026.

References

[1] Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther* 2020;**5**:128. doi:10.1038/s41392-020-00243-2.
[2] World Health Organization *WHO Coronavirus (COVID-19) Dashboard*; 2022. [accessed 17 March 2023] https://covid19.who.int/.
[3] Stainer A, Amati F, Suigo G, Simonetta E, Gramegna A, Voza A, et al. COVID-19 in immunocompromised patients: a systematic review. *Semin Respir Crit Care Med* 2021;**42**:839–58. doi:10.1055/s-0041-1740110.
[4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–62. doi:10.1016/S0140-6736(20)30566-3.
[5] Qiu P, Zhou Y, Wang F, Wang H, Zhang M, Pan X, et al. Clinical characteristics, laboratory outcome characteristics, comorbidities, and complications of related COVID-19 deceased: a systematic review and meta-analysis. *Aging Clin Exp Res* 2020;**32**:1869–78. doi:10.1007/s40520-020-01664-3.
[6] Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. *Mol Psychiatry* 2021;**26**:30–9. doi:10.1038/s41380-020-00880-7.
[7] Deeks SG. Immune dysfunction, inflammation, and accelerated aging in patients on antiretroviral therapy. *Top HIV Med* 2009;**17**:118–23.
[8] Weiser JK, Tie Y, Beer L, Neblett Fanfair RN, Shouse RL. Racial/ethnic and income disparities in the prevalence of comorbidities that are associated with risk for severe COVID-19 among adults receiving HIV care, United States, 2014–2019. *J Acquir Immune Defic Syndr* 2021;**86**:297–304. doi:10.1097/QAI.0000000000002592.
[9] Hochstatter KR, Akhtar WZ, Dietz S, Pe-Romashko K, Gustafson DH, Shah DV, et al. Potential influences of the COVID-19 pandemic on drug use and HIV care among people living with HIV and substance use disorders: experience from a pilot mhealth intervention. *AIDS Behav* 2021;**25**:354–9. doi:10.1007/s10461-020-02976-1.
[10] McKee G, Butt ZA, Wong S, Salway T, Gilbert M, Wong J, et al. Syndemic characterization of HCV, HBV, and HIV co-infections in a large population based cohort study. *EClinicalmedicine* 2018;**4–5**:99–108. doi:10.1016/j.eclinm.2018.10.006.
[11] Lesko CR, Bengtson AM. HIV and COVID-19: intersecting epidemics with many unknowns. *Am J Epidemiol* 2021;**190**:10–16. doi:10.1093/aje/kwaa158.
[12] Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. *BMJ Glob Heal* 2016;**1**:e000010. doi:10.1136/bmjgh-2015-000010.
[13] Harrigan SP, Wilton J, Chong M, Abdia Y, Velasquez Garcia H, Rose C, et al. Clinical severity of severe acute respiratory syndrome coronavirus 2 Omicron variant relative to Delta in British Columbia, Canada: a retrospective analysis of whole-genome sequenced cases. *Clin Infect Dis* 2023;**76**:e18–25. doi:10.1093/cid/ciac705.
[14] Nosyk B, Colley G, Yip B, Chan K, Heath K, Lima VD, et al. Application and validation of case-finding algorithms for identifying individuals with human immunodeficiency virus from administrative data in British Columbia, Canada. *PLoS One* 2013;**8**:e54416. doi:10.1371/journal.pone.0054416.
[15] Janjua NZ, Islam N, Kuo M, Yu A, Wong S, Butt ZA, et al. Identifying injection drug use and estimating population size of people who inject drugs using healthcare administrative datasets. *Int J Drug Policy* 2018;**55**:31–9. doi:10.1016/j.drugpo.2018.02.001.
[16] Najjar-Debbiny R, Gronich N, Weber G, Khoury J, Amar M, Stein N, et al. Effectiveness of Paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients. *Clin Infect Dis* 2023;**76**:e342–9. doi:10.1093/cid/ciac443.
[17] Thomas LE, Li F, Pencina MJ. Overlap weighting: a propensity score method that mimics attributes of a randomized clinical trial. *JAMA* 2020;**323**:2417–18. doi:10.1001/jama.2020.7819.
[18] Danwang C, Noubiap JJ, Robert A, Yombi JC. Outcomes of patients with HIV and COVID-19 co-infection: a systematic review and meta-analysis. *AIDS Res Ther* 2022;**19**:3. doi:10.1186/s12981-021-00427-y.
[19] Mellor MM, Bast AC, Jones NR, Roberts NW, Ordóñez-Mena JM, Reith AJM, et al. Risk of adverse coronavirus disease 2019 outcomes for people living with HIV. *AIDS* 2021;**35**:F1–F10. doi:10.1097/QAD.0000000000002836.
[20] Barbera LK, Kamis KF, Rowan SE, Davis AJ, Shehata S, Carlson JJ, et al. HIV and COVID-19: review of clinical course and outcomes. *HIV Res Clin Pract* 2021;**22**:102–18. doi:10.1080/25787489.2021.1975608.
[21] Hadi YB, Naqvi SFZ, Kupec JT, Sarwari AR. Characteristics and outcomes of COVID-19 in patients with HIV: a multicentre research network study. *AIDS* 2020;**34**:F3–8. doi:10.1097/QAD.0000000000002666.
[22] Karmen-Tuohy S, Carlucci PM, Zervou FN, Zacharioudakis IM, Rebick G, Klein E, et al. Outcomes among HIV-positive patients hospitalized with COVID-19. *J Acquir Immune Defic Syndr* 2020;**85**:6–10. doi:10.1097/QAI.0000000000002423.
[23] Geretti AM, Stockdale AJ, Kelly SH, Cevik M, Collins S, Waters L, et al. Outcomes of coronavirus disease 2019 (COVID-19) related hospitalization among people with human immunodeficiency virus (HIV) in the ISARIC World Health Organization (WHO) clinical characterization protocol (UK): a prospective observational study. *Clin Infect Dis* 2021;**73**:e2095–106. doi:10.1093/cid/ciaa1605.
[24] Park LS, Rentsch CT, Sigel K, Rodriguez-Barradas M, Brown ST, Goetz MB, et al. COVID-19 in the largest US HIV cohort *Conference Reports for NATAP: IAC2020. National AIDS Treatment Advocacy Project*; 2020. [accessed 10 March 2023] https://www.natap.org/2020/IAC/IAC_115.htm.
[25] Tesoriero JM, Swain CE, Pierce JL, Zamboni L, Wu M, Holtgrave DR, et al. COVID-19 outcomes among persons living with or without diagnosed HIV infection in New York State. *JAMA Netw Open* 2021;**4**:e2037069. doi:10.1001/jamanetworkopen.2020.37069.
[26] Yang X, Sun J, Patel RC, Zhang J, Guo S, Zheng Q, et al. Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data. *Lancet HIV* 2021;**8**:e690–700. doi:10.1016/S2352-3018(21)00239-3.
[27] Lang R, Humes E, Coburn SB, Horberg MA, Fathi LF, Watson E, et al. Analysis of severe illness after postvaccination COVID-19 breakthrough among adults with and without HIV in the US. *JAMA Netw Open* 2022;**5**:e2236397. doi:10.1001/jamanetworkopen.2022.36397.
[28] Fowokan A, Samji H, Puyat JH, Janjua NZ, Wilton J, Wong J, et al. Effectiveness of COVID-19 vaccines in people living with HIV in British Columbia and comparisons with a matched HIV-negative cohort: a test-negative design. *Int J Infect Dis* 2023;**127**:162–70. doi:10.1016/j.ijid.2022.11.035.
[29] Chambers C, Samji H, Cooper CL, Costiniuk CT, Janjua NZ, Kroch AE, et al. Coronavirus disease 2019 vaccine effectiveness among a population-based cohort of people living with HIV. *AIDS* 2022;**36**:F17–26. doi:10.1097/QAD.0000000000003405.
[30] Velásquez García HA, Wilton J, Smolina K, Chong M, Rasali D, Otterstatter M, et al. Mental health and substance use associated with hospitalization among people with COVID-19: a population-based cohort study. *Viruses* 2021;**13**:2196. doi:10.3390/v13112196.