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Original Article

Risk factors for progressing to severe COVID-19 among people living with HIV in Japan: A hospital claims database study

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ABSTRACT

Introduction: Risk factors for severe COVID-19 associated with people living with HIV (PLWH) have not been well studied in Japan. In this study, we aim to reveal how having AIDS and comorbidities affect adverse COVID-19 outcomes.

Methods: This observational, retrospective study examined the clinical outcomes for PLWH hospitalized as COVID-19 inpatients in Japan, using data extracted from hospitals with the Diagnosis Procedure Combination (DPC) system between January 2020 and December 2021. From 4672 records of HIV patients receiving antiretroviral therapy, 85 adult PLWH became hospitalized with COVID-19. The associations between patients' AIDS diagnosis, comorbidities, and their adverse COVID-19 outcomes (mild/moderate and severe/death) were analyzed.

Results: Among 85 studied patients, 78 were male (91.8%) with mean (SD) age of 48 (14.4) years. 75 (88.2%) were found to be COVID-19 mild/moderate; 9 (10.6%) were severe; 1 (1.2%) died. Older age ($p = 0.002$) and hypertension ($p = 0.032$) were significantly associated with progressing to severe COVID-19 or death. AIDS and other AIDS-defining illnesses were not found to be significant risk factors in this study.

Conclusions: While interpretation of the results from this hospital claim database study warrants caution, we found that among PLWH hospitalized as COVID-19 inpatients in Japan, those who are older or with hypertension have a higher risk for progression to severe COVID-19 outcomes, suggesting a careful monitoring of clinical course for these patients.

1. Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has thrown the world into the midst of a new pandemic. In Japan, COVID-19 has become a severe public health crisis, causing large numbers of hospitalizations and deaths since the first case was reported in January 2020 [1]. During the past three years, people living with HIV (PLWH) have also experienced SARS-CoV-2 infection, although reports of COVID-19 in PLWH in Japan have remained scarce.

PLWH have been studied worldwide to determine if they are at a higher risk for COVID-19 compared to the general population. While some reported that PLWH had no elevated risk of severe COVID-19 compared to the general population [2–4], other studies reported PLWH showed severity with COVID-19 infection and hospitalization, including mortality [5–8]. In two large meta-analysis studies of COVID-19 in PLWH, Hariyanto et al. reported higher mortality for COVID-19 in PLWH (28 studies) (OR = 1.19; 95% CI [1.01–1.39]), and Mellor et al. also reported PLWH had a higher risk of COVID-19 mortality compared to people without HIV (5 studies) (hazard ratio = 1.95; 95% CI [1.62–2.34]) [9,10]. Organizations such as CDC (Centers for Disease Control and Prevention) and WHO (World Health Organization) also demonstrated that immunodeficient individuals, including PLWH, may have a higher risk for severe COVID-19 [11,12].

PLWH tend to have more comorbidities than the general population, including hypertension, diabetes, cardiovascular diseases, and ischemic

Abbreviations: ART, antiretroviral therapy; ICD-10, International Statistics Classification of Diseases and Related Health Problems, 10th Revision; PLWH, people living with HIV.

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cerebrovascular diseases [13–15]. Additionally, as they age, they remain disproportionately burdened with multimorbidity [16,17]. Due to PLWH's multiple long-term conditions, in addition to being immunodeficient, they may be vulnerable to severe COVID-19. Examining risk factors for severe COVID-19 in PLWH, therefore, is important to support this vulnerable population. As of the end of 2021, the cumulative number of reported HIV infections in Japan was approximately 33,000 people [18]. While risk factors in PLWH for progression to severe COVID-19 have been studied in other countries [19–21], this population has remained unstudied in Japan.

When the first edition of treatment guidelines for COVID-19 was established in March 2020 in Japan, options such as steroids with or without lopinavir/ritonavir or favipiravir were often chosen clinically [22]. In Japan, remdesivir was fast-track approved in May 2020; later, dexamethasone was officially recommended in the guidelines in July 2020 [23], and these two became the standard therapy for COVID-19 pneumoniae requiring oxygen inhalation [24].

Japan has a relatively low rate of COVID-19 mortality, which is less than one-tenth of COVID-19 mortality in the United State and Europe [25]. One of the likely reasons is good public compliance with infection control measures such as wearing face masks and strict personal hygiene [26]. Given these special circumstances, studies addressing risk factors associated with severe COVID-19 among Japanese PLWH will be a valuable addition to the existing literature.

In this hospital claims database study, we aim to analyze PLWH hospitalized with COVID-19 to examine risk factors associated with adverse COVID-19 outcomes. HIV-infected individuals experience a progressive decline in CD4-positive cells over time, resulting in the development of severe cellular immunodeficiency leading to AIDS diagnosis within approximately 7–10 years after infection [27,28]. Because immunodeficient AIDS patients are generally considered to be vulnerable to severe COVID-19 outcomes, our examination of other comorbidities as risk factors can elucidate the possible association between AIDS diagnosis and severe COVID-19 outcomes.

2. Methods

2.1. Study design and data source

This observational, retrospective, database study examined the clinical outcomes in COVID-19 inpatients of PLWH in Japan. The hospital claims database that we analyzed was compiled and provided by Medical Data Vision Co., Ltd. (MDV) [29]. Data were extracted from hospitalization records at Diagnosis Procedure Combination (DPC) hospitals in Japan during January 2020 and December 2021. DPC is a comprehensive payment system first introduced in Japan in 2003 [30], using a per-diem payment system (PDPS) for inpatient medical care services. There are approximately 1,750 hospitals who adopted the DPC system by the end of 2021 [31], mainly large and advanced medical centers, including all government certified "Advanced Treatment Hospitals" that meet criteria such as having more than 400 beds and ICUs (Intensive Care Units) [32]. For clarification, although the DPC system indicates a per-diem payment system for inpatient care services, hospitals that adopt the DPC system provide both outpatient and inpatient services.

The MDV database contains information on 460 hospitals, accounting for approximately 26% of all Japanese hospitals that use the DPC/PDPS (as of December 2021). Patient information on age, sex, departments visited, date of medical service, diagnosis codes, hospitalization, medical procedures, and prescriptions are included.

2.2. Study population

Hospitalized patients who were aged ≥18 years with a diagnosis record of both HIV under antiretroviral therapy (ART) and COVID-19 were included in this study. According to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD–10) codes B20−24 were included: HIV disease resulting in infectious and parasitic diseases (B20), malignant neoplasms (B21), other specified diseases (B22), other conditions (B23), and unspecified HIV disease (B24). In addition, patients who had a prescription record of ART between January 2020 and December 2021 were selected. ART includes nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, integrase strand transfer inhibitors, and entry inhibitors.

The COVID-19 infection is coded U071. To ensure accurate classification, we excluded the code B342 (coronavirus infection), which includes not only COVID-19 but also severe acute respiratory syndrome (SARS) and/or Middle East respiratory syndrome (MERS). Because the aim of this study is to examine how having AIDS and comorbidities affected adverse COVID-19 outcomes, we included hospitalized COVID-19 patients of PLWH only. COVID-19 patients who were treated in outpatient settings with light symptoms were not included in the study population.

2.3. Main outcome and definitions

Main outcomes of this study are the severity of COVID-19 clinical outcomes among hospitalized PLWH patients. We used the severity classification method for COVID-19 patients by the Ministry of Health, Labor, and Welfare (MHLW) of Japan: Mild is $SpO_2 \geqq 96\%$ with no respiratory symptoms or only cough without dyspnea; Moderate I is $93\% < SpO_2 < 96\%$, with dyspnea or pneumonia; Moderate II is $SpO_2 \leqq 93\%$ requiring oxygen supplementation; Severe is admission to intensive care unit or requiring mechanical ventilation [24]. In the studied MDV database, patients with codes of oxygen inhalation (receipt code 140005610) were defined as moderate II. The patients with codes of artificial respiration (140009310, 140023510, 140023750), high-flow therapy (140057410) or extracorporeal membrane oxygenation (ECMO) (150262910, 150275710) were defined as severe. Patients without these codes were categorized as mild or moderate I.

Patient information such as demographic characteristics (age and sex), body mass index (BMI), smoking index, pregnancy, present diagnosis of AIDS and other AIDS-defining illnesses, comorbidities, COVID-19 treatment, duration of hospitalization, condition at discharge, and size of admitted hospital were extracted from the MDV database. The disease diagnosis codes include those identified during outpatient visits as well as during hospitalization.

Any studied patients with code B24 (including any of the receipt codes of 2793011, 7712015, 8830055, 2793007) were classified as AIDS patients. Other AIDS-defining illnesses include *pneumocystis carinii* pneumonia (*pneumocystis jirovecii* pneumonia included) (B20.6/B59), cytomegalovirus infection (B20.2/B25), HIV disease resulting in encephalopathy (B22.0 with receipt code 8830098), HIV disease resulting in other specified conditions (B23.8), candidiasis (B204/B378), mycobacterial infection (A31), and other viral infections (B20.3).

The non-cancer comorbidities investigated included diabetes, dyslipidemia, hypertension, hepatitis B/C co-infection, psychiatric disorders, bone disorder, vascular diseases, kidney disease, syphilis, chronic obstructive pulmonary disease (COPD), asthma, interstitial pneumonia, Parkinson disease, anemia, liver disease and rheumatoid arthritis. Patients who had associated ICD-10 codes of investigated comorbidities during the study period, whether diagnosed before or after the HIV diagnosis, were considered to have comorbidities. Detailed ICD-10 codes are listed in Table 1; a similar method was applied in our previous MDV database study for HIV patients [29].

Cancers were classified as AIDS-defining and non-AIDS-defining cancers. AIDS-defining cancers included Burkitt lymphoma (B21.1/C83.7), Kaposi sarcoma (B21.0/C46), non-Hodgkin lymphoma (B21.2/C82−85 except for C83.7), and cancer of the cervix uteri (C53). All other cancers were defined as non-AIDS-defining cancers, which included prostate cancer (C61), rectosigmoid junction cancer (C19), rectal cancer

Table 1
ICD-10 codes of comorbidities.

Category	Included pathologies	ICD-10 codes
Diabetes	Diabetes type II	E11—14
Dyslipidemia	Hypercholesterolemia or hyperlipidemia	E78.0–78.5
Hypertension	–	I10, I12, I14—15
Hepatitis B infection	–	B18.1
Hepatitis C infection	–	B18.2
Psychiatric disorders	Mania and depression	F30—32
	Psychosis	F2
	Anxiety	F40—41
	Insomnia	F51
	Dementia	F01, F03
Bone disorder	–	M80—81
Vascular diseases	Angina	I20
	Myocardial infarction	I21—22
	Stroke (excluding venous veins-related strokes)	I60—69
	Hypertensive heart and renal diseases	I11, I13
Kidney disease	Chronic kidney disease	N18—19
	Urolithiasis	N20—21
Syphilis	–	A51—53
COPD	–	J44
Asthma	–	J45
Interstitial pneumonia	–	J84
Parkinson disease	–	G20—22
Anemia	–	D50—59, D60—64
Liver diseases	–	K70—77
Rheumatoid arthritis	–	M05—06

(C20), breast cancer (C50.9), bladder cancer (C67.9), secondary malignant neoplasm of bone and bone marrow (C79.5), and multiple myeloma (C90).

2.4. Statistical analysis

Patient information was summarized descriptively by COVID-19 outcome groups. Characteristics of mild/moderate cases and severe/death cases were analyzed. The patients' comorbidities and COVID-19 adverse outcomes (mild/moderate and severe/death) were analyzed using the *t*-test for continuous variables and Fisher's exact test for categorical variables. The level of significance was $< p < 0.05$. All statistical analyses were performed using R 4.2.2 (R Core Team, 2022).

3. Results

There were 4,672 patients who had diagnostic codes of HIV receiving ART from 2020 January to 2021 December. Among these patients, 93 patients were confirmed with COVID-19. 8 patients were excluded because they were treated as outpatients. As a result, 85 hospitalized PLWH with COVID-19 were included in the study. (Fig. 1).

The monthly number of hospitalized COVID-19 patients in PLWH vs. monthly number of hospitalized COVID-19 patients in Japan from January 2020 until December 2021 are shown in Fig. 2.

3.1. Patient characteristics

Characteristics of the 85 studied patients are described in Table 2. The majority of the patients were male (91.8%). The mean age of the participants was 48 years [SD; range ±14.4]. As for the COVID-19 severity, 75 (88.2%) were found in the mild/moderate group, including 55 (64.7%) as mild/moderate I and 20 (23.5%) as moderate II; 9 patients (10.6%) were severe; 1 patient (1.2%) died.

We made further evaluations of the characteristics of the COVID-19 severe cases and the death case. Table 3 summarizes the details of these

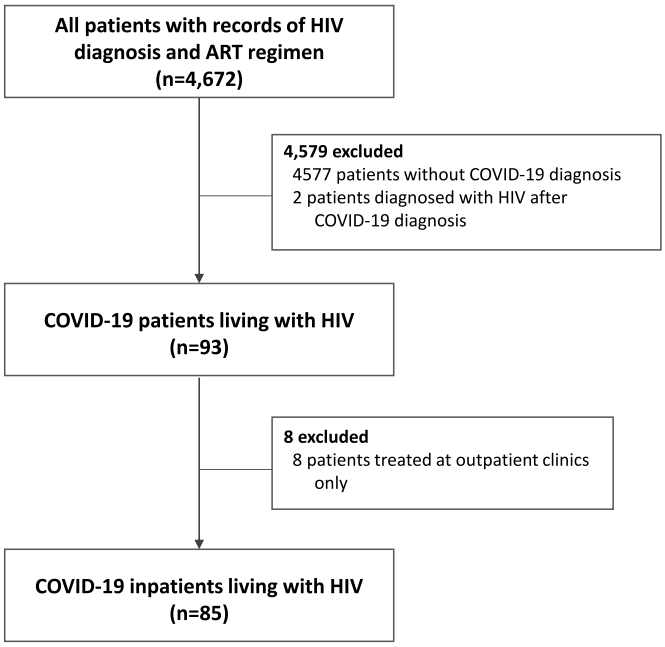

Fig. 1. Diagram of studied patient selection
MDV (Medical Data Vision) database was used for data collection; Studied period was from January 2020 to December 2021; ART is antiretroviral therapy.

cases. Among the 9 severe patients, 5 received artificial respiration, 3 received high-flow therapy and 1 received both artificial respiration and extracorporeal membrane oxygenation. As for COVID-19 treatments, 4 patients received lopinavir/ritonavir; 3 patients received dexamethasone. We could not derive the data of remdesivir usage because the records were managed individually by the central government of Japan, which was not registered in the DPC system, and therefore not available in this MDV database.

Among the 9 severe COVID-19 patients, 2 patients had AIDS, and 2 patients had *pneumocystis carinii* pneumonia (including 1 previous AIDS-coded patient). 8 of 9 patients had non-AIDS-defining comorbidities. The most frequent comorbidities in this group were hypertension (5 patients), followed by diabetes (4 patients), liver diseases (3 patients), dyslipidemia (3 patients), and interstitial pneumonia (3 patients). Only one severe patient had a comorbidity of malignancy—breast cancer. For the only death case, no comorbidities were declared.

3.2. AIDS-defining illnesses and comorbidities

AIDS-defining illnesses and comorbidities of the patients are described in Table 4. Among 85 studied patients, AIDS-defining illnesses were confirmed in 28 patients (32.9%) including 12 patients (14.1%) coded as AIDS and 16 patients (18.8%) with other AIDS-defining illnesses. Besides AIDS-defining illnesses, 68 patients (80.0%) had comorbidities. The most frequent comorbidity was syphilis (40.0%), followed by diabetes (34.1%) and dyslipidemia (24.7%).

For cancer specifically, there were 9 patients who had cancer, including 4 with AIDS-defining cancer (all non-Hodgkin lymphoma) and 6 with non-AIDS-defining cancer (Table 5). Among non-AIDS-defining cancer cases, 2 had prostate cancer, and 1 each with breast cancer, rectal cancer, bladder cancer, secondary malignant neoplasm of bone and bone marrow, and multiple myeloma, respectively. 1 patient had both non-Hodgkin lymphoma and multiple myeloma, and 1 patient had both prostate cancer and secondary malignant neoplasm of bone.

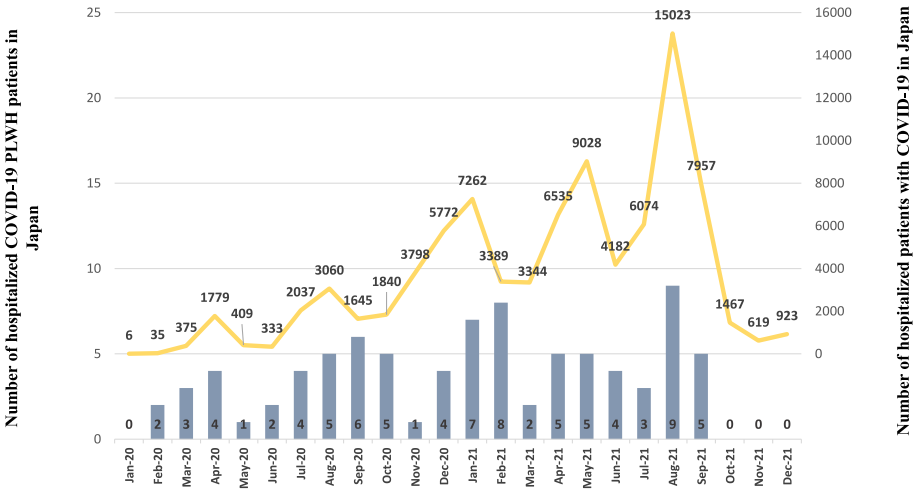

Fig. 2. Number of hospitalized COVID-19 patients of PLWH vs. number of hospitalized COVID-19 patients, by month from January 2020 to December 2021 in Japan
The blue bars indicate the number of hospitalized COVID-19 of PLWH while the yellow line indicates the number of hospitalized COVID-19 patients in Japan. Data were extracted from MDV (Medical Data Vision) database. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Characteristics of studied hospitalized COVID-19 patients in PLWH (n = 85).

	No. of Patients		Mild/Moderate COVID-19 group[a]		Severe COVID-19 and Death group		
	n = 85	(%)	n = 75	(%)	n = 10	(%)	p-value
Sex							0.19
Male	78	(91.8%)	70	(93.3%)	8	(80.0%)	
Female	7	(8.2%)	5	(6.7%)	2	(20.0%)	
Age, Mean (SD)	48	(14.4)	46	(13.0)	65	(14.5)	0.002
Age group (years)							
<20	0	(0.0%)	0	(0.0%)	0	(0.0%)	
20–29	9	(10.6%)	9	(12.0%)	0	(0.0%)	
30–39	15	(17.6%)	15	(20.0%)	0	(0.0%)	
40–49	25	(29.4%)	23	(30.7%)	2	(20.0%)	
50–59	20	(23.5%)	18	(24.0%)	2	(20.0%)	
60–69	8	(9.4%)	5	(6.7%)	3	(30.0%)	
≥70	8	(9.5%)	5	(6.7%)	3	(30.0%)	
BMI (Body Mass Index), Mean (SD)	25	(4.5)	25	(4.6)	25	(2.3)	0.811
BMI							
<18.5	4	(4.7%)	4	(5.3%)	0	(0.0%)	
18.5–25	39	(45.9%)	36	(48.0%)	3	(30.0%)	
≥25	32	(37.6%)	29	(38.7%)	3	(30.0%)	
Unknown	10	(11.8%)	6	(8.0%)	4	(40.0%)	
Smoking (pack-years)[b]							>0.999
Never	45	(52.9%)	40	(53.3%)	5	(50.0%)	
<10	5	(5.9%)	5	(6.7%)	0	(0.0%)	
10–30	16	(18.8%)	15	(20.0%)	1	(10.0%)	
≥30	5	(5.9%)	5	(6.7%)	0	(0.0%)	
Unknown	14	(16.5%)	10	(13.3%)	4	(40.0%)	

[a] 1 patient who was found to be COVID-19 Moderate II died, and therefore was included into "severe COVID-19 and death group".
[b] Pack-years is defined as the multiplication of the number of packages of cigarettes smoked daily and the number of years of smoking.

3.3. Risk factors for COVID-19 in PLWH

We analyzed the risk factors for progression to severe COVID-19 between 75 mild/moderate patients and 10 severe/death patients. We found statistically significant higher risk in older age (p = 0.002), hypertension (p = 0.032), and interstitial pneumonia (p = 0.049) in the severe/death group (Tables 2 and 4). Because interstitial pneumonia can be caused by COVID-19, further analysis was performed to determine whether interstitial pneumonia should be considered as a significant risk factor in this study. Among 8 patients diagnosed with interstitial pneumonia, 5 were diagnosed on the same day or right before their COVID-19 admission, while 3 were diagnosed years before they were hospitalized for COVID-19 (Supplementary Table 1).

BMI and smoking index (pack per years) were not statistically related to severe COVID-19 outcomes (Table 2). Diabetes and hepatic disorders were not found as risk factors either (Table 4). Syphilis was found only in the mild/moderate group (p = 0.005) (Table 4).

AIDS and other AIDS-defining illnesses were not statistically related to severe COVID-19 progression or death for all age groups (**Tables 2 and 4**). However, for PLWHs aged 60 or below and with severe COVID-19 outcomes, we found 3 out of 5 were diagnosed with AIDS or AIDS-defining illnesses (Table 3).

4. Discussion

To our knowledge, this is the first large observational study on risk factors for progressing to severe COVID-19 among PLWH in Japan.

Studies of risk factors for severe COVID-19 in PLWH have been conducted in other countries. A previous prospective observational study revealed that older age, diabetes, and obesity had higher rate for 28-day mortality among hospitalized COVID-19 patients in PLWH [8]. Additionally, in a large survey of WHO Global Clinical Platform (n = 15, 522), PLWH who were aged 65 or above [OR = 1.62; 95% CI [1.41–18.7)], male [OR = 1.21; 95% CI [1.23–1.31)], with diabetes [OR

Table 3
Characteristics of severe COVID-19 and death cases (n = 10).

	Case1	Case2	Case3	Case4	Case5	Case6	Case7	Case8	Case9	Case10
Age	78	69	87	83	44	68	56	56	49	60
Sex	Female	Male	Male	Female	Male	Male	Male	Male	Male	Male
BMI	Unknown	27.8	Unknown	25.2	23.5	26.9	Unknown	23.7	Unknown	21.8
Smoking (Pack-years)	Never	Unknown	Never	Never	Never	28	Never	Unknown	Unknown	Unknown
Duration of hospitalization (days)	94	31	43	41	16	24	16	28	25	18
Admitted hospital size	200–499 beds	≥500 beds	200–499 beds	200–499 beds	≥500 beds	200–499 beds	≥500 beds	≥500 beds	200–499 beds	≥500 beds
Condition at the time of discharge	Recovery	Recovery	Death	Recovery	Recovery	Recovery	Recovery	Transfer to another hospital	Recovery	Recovery
Therapy										
Oxygen inhalation	yes	yes	yes	yes	yes	yes	–	yes	yes	yes
Artificial respiration	yes	yes	–	–	yes	yes	yes	yes	–	–
High-flow therapy	–	–	–	yes	–	–	–	–	yes	yes
ECMO	–	–	–	–	–	–	yes	–	–	–
Medication[a]	Lopinavir Ritonavir	Lopinavir Ritonavir	Lopinavir Ritonavir	Lopinavir Ritonavir	–	Dexamethasone	–	Dexamethasone	–	Dexamethasone
AIDS/AIDS-defining illnesses	–	–	–	–	AIDS	–	–	*Pneumocystis* pneumonia/ AIDS	*Pneumocystis* pneumonia	–
Comorbidities (excluding cancers)										
Diabetes	yes	–	–	–	yes	yes	–	yes	–	–
Dyslipidemia	yes	–	–	–	–	–	–	–	yes	yes
Hypertension	yes	–	–	yes	–	yes	yes	–	yes	–
Hepatitis B infection	–	–	–	–	–	–	–	–	–	–
Hepatitis C infection	–	–	–	–	–	–	–	–	–	–
Psychiatric disorder (Mania and depression)	–	–	–	–	–	–	–	–	yes	–
Psychiatric disorder (Psychosis)	–	–	–	–	–	–	–	–	yes	–
Bone disorder	–	–	–	–	–	–	–	–	–	–
Vascular disease (Hypertensive heart and renal diseases)	–	–	–	–	yes	–	–	–	–	–
Kidney disease	–	–	–	–	–	–	–	–	–	–
Syphilis	–	–	–	–	–	–	–	–	–	–
COPD	–	–	–	–	–	–	–	–	–	–
Asthma	–	–	–	–	yes	–	–	–	–	–
Interstitial pneumonia	–	–	–	–	yes	–	–	yes	yes	–
Parkinson disease	–	–	–	–	–	–	–	–	–	–
Anemia	–	–	–	–	–	–	–	–	–	–
Liver diseases	–	–	–	–	yes	–	–	yes	yes	–
Rheumatoid arthritis	–	–	–	–	–	–	–	–	–	–
Cancers	–	–	–	Breast cancer	–	–	–	–	–	–

AIDS stands for Acquired Immunodeficiency Syndrome; ECMO stands for Extracorporeal Membrane Oxygenation.

[a] remdesivir, an important drug for treating patients with moderate or severe COVID-19, was managed and supplied to hospitals by the government through a special channel separate from the health insurance system, not registered in the DPC system; therefore, the information pertaining to remdesivir use for COVID-19 inpatients of PLWH was not available in this study.

Table 4
Risk Factors for COVID-19 severity in PLWH (n = 85).

	No. of patients		Mild/Moderate COVID-19 group		Severe COVID-19 and Death group		
	n = 85	(%)	n = 75	(%)	n = 10	(%)	p-value
AIDS/AIDS-defining illnesses[a,b]	28	(32.9%)	25	(33.3%)	3	(30.0%)	>0.999
AIDS[c]	12	(14.1%)	10	(13.3%)	2	(20.0%)	0.628
Other AIDS-defining illnesses[d]	16	(18.8%)	15	(20.0%)	1	(10.0%)	–
Pneumocystis carinii pneumonia	12	(14.1%)	10	(13.3%)	2	(20.0%)	0.628
Cytomegalovirus infection	4	(4.7%)	4	(5.3%)	0	(0.0%)	>0.999
Non-Hodgkin's lymphoma	4	(4.7%)	4	(5.3%)	0	(0.0%)	>0.999
HIV disease resulting in encephalopathy	4	(4.7%)	4	(5.3%)	0	(0.0%)	>0.999
HIV disease resulting in other specified conditions	4	(4.7%)	4	(5.3%)	0	(0.0%)	>0.999
Candidiasis	2	(2.4%)	2	(2.7%)	0	(0.0%)	>0.999
HIV disease resulting in mycobacterial infection	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999
HIV disease resulting in other viral infections	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999
Comorbidities (excluding cancer)[e]	68	(80.0%)	60	(80.0%)	8	(80.0%)	–
Diabetes	29	(34.1%)	25	(33.3%)	4	(40.0%)	0.729
Dyslipidemia	21	(24.7%)	18	(24.0%)	3	(30.0%)	0.703
Hypertension	18	(21.2%)	13	(17.3%)	5	(50.0%)	0.032
Hepatitis B infection	14	(16.5%)	14	(18.7%)	0	(0.0%)	0.203
Hepatitis C infection	12	(14.1%)	12	(16.0%)	0	(0.0%)	0.344
Psychiatric disorders	18	(21.2%)	17	(22.7%)	1	(10.0%)	0.681
Bone disorder	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999
Vascular diseases	8	(9.4%)	7	(9.3%)	1	(10.0%)	>0.999
Kidney disease	6	(7.1%)	6	(8.0%)	0	(0.0%)	>0.999
Syphilis	34	(40.0%)	34	(45.3%)	0	(0.0%)	0.005
COPD	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999
Asthma	7	(8.2%)	6	(8.0%)	1	(10.0%)	>0.999
Interstitial pneumonia	8	(9.4%)	5	(6.7%)	3	(30.0%)	0.049
Parkinson disease	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999
Anemia	10	(11.8%)	10	(13.3%)	0	(0.0%)	0.599
Liver diseases	16	(18.8%)	13	(17.3%)	3	(30.0%)	0.390
Rheumatoid arthritis	1	(1.2%)	1	(1.3%)	0	(0.0%)	>0.999

[a] 1 patient had both AIDS-defining illness and comorbidities.
[b] There were patients who had multiple AIDS-defining illnesses.
[c] Patients with AIDS diagnosis (but without a specific diagnosis for AIDS-defining illnesses) were classified as "AIDS".
[d] Patients with specific diagnosis of AIDS-defining illnesses were classified as "other AIDS-defining illnesses" with specific diagnoses listed.
[e] There were patients who had multiple comorbidities.

Table 5
Studied patients with cancers.

Malignancy type (Cancers)	No. of patients	(%) out of 85 studied patients
Overall[a]	9 patients	(10.6%)
AIDS-defining cancers	4	(4.7%)
Non-Hodgkin lymphoma	4	(4.7%)
Non-AIDS-defining cancers	6	(7.1%)
Prostate cancer	2	(2.4%)
Others[b,c]	4	(4.7%)

[a] 1 patient had both non-Hodgkin lymphoma and multiple myeloma.
[b] Other non-AIDS-defining cancers include rectal cancer, breast cancer, bladder cancer, secondary malignant neoplasm of bone and bone marrow, and multiple myeloma.
[c] 1 patient had both prostate cancer and secondary malignant neoplasm of bone.

= 1.10; 95% CI [1.03–1.22]), or hypertension [OR = 1.54; 95% CI [1.41–1.68]) were found to have an increased risk for severe or critical COVID-19 condition at hospital admission [12]. Older age [19,33], hypertension [19,20,33,34], obesity [35], diabetes [20,33,35], chronic respiratory diseases [19,20,33], cardiovascular disease [20,34], chronic kidney disease [20,33], and organ transplantation [36] were also reported to be related risk factors for severity or mortality of COVID-19 in other previous studies. In our study, we found older age and hypertension as risk factors for progressing to severe COVID-19, which are consistent with previous studies.

While interstitial pneumonia alone has not been reported as a risk factor in PLWH in previous studies in other countries, in our study we initially found interstitial pneumonia was associated with severe COVID-19 progression in PLWH (p = 0.049). However, when the date of interstitial pneumonia diagnosis was further examined, we found 5 of the 8 patients with interstitial pneumonia were diagnosed on the same day or right before their COVID-19 admission. These 5 patients' diagnosis of interstitial pneumonia, therefore, can be considered as COVID-19-related pneumonia. Due to our limited sample size, whether interstitial pneumonia is a risk factor associated with severe COVID-19 cannot be concluded. Further study is warranted.

On the other hand, syphilis was found significantly associated with mild or moderate COVID-19 outcomes. Since syphilis is generally connected with sexual activity, it is likely that the samples with syphilis were of relatively younger age, which is considered to be a lower risk factor for severe COVID-19 outcomes [37].

CD4 count, a major indicator for AIDS diagnosis, was found to be associated with adverse COVID-19 outcomes in previous studies [4,33,38,39]. HIV primarily causes a cellular immune deficiency, and the CD4 count serves as an indicator of immune deficiency in HIV patients. Parker et al. showed CD4 count of < 200 cells/mm^3 as a predictor of inpatient mortality in the multicenter cohort data of South Africa [4]. Dandachi et al. demonstrated poor COVID-19 outcomes in PLWH and higher risks in those with comorbidities and lower CD4 cell counts [33]. Hoffmann et al. showed a CD4$^+$ T cell nadir of $< 200/\mu L$ or current CD4$^+$ T cells $< 350/\mu L$ with the presence of at least one comorbidity were associated with severe COVID-19 in PLWH [38]. In addition, Kamis KF et al. reported decreased CD4 count associated with increased hospitalizations [39]. In our study, we could not obtain data for CD4 cell counts or viral load. However, AIDS and other AIDS-defining illnesses were not found to be statistically related to progression to severe COVID-19 outcomes. In our study, only 28 participants had the diagnosis of AIDS or other AIDS-defining illnesses (Table 4). The small sample size may have contributed to the lack of statistically significant

results regarding the risk of severe COVID-19 progression, which was shown in previous studies in other countries [4,33,38,39]. However, we found 3 out of 5 cases with severe COVID-19 and aged 60 or below were diagnosed with AIDS or AIDS-defining illnesses (Table 3), which may indicate that the diagnosis of AIDS or other AIDS-defining illnesses as a risk factor associated with severe COVID-19 outcomes for younger PLWHs.

For patients with malignant tumors, we did not observe any significant association with severe COVID-19 outcomes. However, patients with malignant tumors were shown to be vulnerable to severe COVID-19 outcomes due to poor health conditions and immunodeficiency caused by both cancer and therapies in previous studies, with increased mortality rate and ICU admission [40–43]. Limited sample size might explain why our study did not reveal any significant association for severe COVID-19 outcomes. Further investigation is warranted among this population.

Among the studied patients, one died. From the perspective of COVID-19 severity, the patient was originally found to be moderate II. Although detailed information was unavailable from this hospital claims database, one of the possible reasons was that the 87-year-old male patient might have preferred not to receive artificial respiration or high-flow oxygen support.

As the first large observational database study on risk factors for progressing to severe COVID-19 among PLWH in Japan, we also examined the occurrence of COVID-19 hospitalization among PLWH vs. the overall COVID-19 hospitalization in the Japanese population. Five waves—March 2020 to May 2020, July 2020 to September 2020, October 2020 to January 2021, March 2021 to June 2021, July 2021 to September 2021—were seen for the general population. For PLWH, five waves were experienced, but the number of hospitalized with COVID-19 remained small in Japan.

Our study has several limitations. First, since we collected the clinical information from the hospital claims database, registered patient data of characteristics, comorbidities, and treatments based on codes were applied for analysis, which may not completely reflect actual patient conditions; no severity of comorbidities was considered when assessing the association with severe COVID-19 outcomes. Second, remdesivir, an important drug for treating patients with moderate or severe COVID-19, was managed and supplied to hospitals by the government through a special channel separate from the health insurance system, not registered in the DPC system; therefore, the information pertaining to remdesivir use for COVID-19 inpatients of PLWH was not available in this study; whether mild/moderate COVID-19 outcomes were driven by remdesivir remains unknown. Third, due to the small sample size, there is a possibility that our study was unable to identify significant risks for severe COVID-19 outcomes, such as being diagnosed with AIDS or AIDS-defining illnesses and/or malignant tumors. Lastly, the information of each patient's CD4 count, ART drugs, and COVID-19 vaccination records were not available; therefore, we could not perform confounding analysis with consideration of patients' immune deficiency and the impact of COVID-19 vaccination. Overall, interpretation should be made with caution because this is a hospital claims database study, without examination of individual cases based on detailed medical records.

5. Conclusion

In this first study examing risk factors for severe COVID-19 outcomes among Japanese PLWH, older age and hypertension were found to be significantly associated with severe COVID-19. Our findings support that HIV patients with high risk comorbidities require close clinical course monitoring to prevent progression to severe outcomes. Further studies are required to determine the risk factors of CD4 cell counts and antiviral treatments for severe COVID-19 outcomes among PLWH.

Authorship statement

All authors meet the ICMJE authorship criteria.

Ethics statement

Informed consent was waived because this is an observational study using de-identified data. The Japanese Ethical Guidelines for Medical and Health Research Involving Human Subjects do not apply to studies exclusively using de-identified data.

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Author contributions

Prof Naito had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kanazawa,Yan.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Yuda, Fukui.

Administrative, technical, or material support:Yuda, Fukui.

Supervision: Saita, Mori, Naito.

All authors meet the ICMJE authorship criteria.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2023.09.009.

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