Coronavirus disease 2019 hospitalization outcomes in persons with and without HIV in Spain

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Objective: To compare coronavirus disease 2019 (COVID-19) hospitalization outcomes between persons with and without HIV.

Design: Retrospective observational cohort study in 150 hospitals in Spain.

Methods: Patients admitted from 1 March to 8 October 2020 with COVID-19 diagnosis confirmed by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 positive) PCR test in respiratory tract samples. The primary data source was the COVID-19 Sociedad Española de Medicina Interna's registry (SEMI-COVID-19). Demographics, comorbidities, vital signs, laboratory parameters, and clinical severity as well as treatments received during admission, treatment duration, ICU admission, use of invasive mechanical ventilation, and death were recorded. Factors associated with mortality and the composite of ICU admission, invasive mechanical ventilation, and death, were analyzed.

Results: Data from 16 563 admissions were collected, 98 (0.59%) of which were of persons with HIV infection. These patients were younger, the percentage of male patients was higher, and their Charlson comorbidity index was also higher. Rates of mortality and composite outcome of ICU admission, invasive mechanical ventilation or death were lower among patients with HIV infection. In the logistic regression analysis, HIV infection was associated with an adjusted odds ratio of 0.53 [95% confidence interval (CI) 0.29-0.96] for the composite outcome.

Conclusion: HIV infection was associated with a lower probability of ICU admission, invasive mechanical ventilation, or death.

AIDS 2022, **36**:683–690

Keywords: coronavirus disease 2019, HIV, mortality, prognosis, severe acute respiratory syndrome coronavirus 2

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Received: 15 April 2021; revised: 28 July 2021; accepted: 9 August 2021.

DOI:10.1097/QAD.0000000000003056

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Introduction

Since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were declared in China at the end of 2019, close to 100 million individuals have been infected, and by the end of January 2021 more than two million deaths had been reported [1]. Age, male sex, and comorbidities, such as high blood pressure (HBP), obesity, and diabetes, among others, have been associated with a poorer prognosis in different series [2–4]. In addition, several observational studies have reported an increased mortality in persons with HIV (PWH) compared with persons without HIV [5–7] but other studies have not detected worse outcomes in PWH [8–10], suggesting that controlled HIV infections are not associated with an increased mortality. HIV infection is associated with an immune dysfunction despite effective antiretroviral therapy (ART) [11,12] and, except in cases of severe immunodepression, it remains to be seen whether this immune dysfunction could have a paradoxical effect on the clinical course of COVID-19. It has further been speculated that some agents of ART regimens could be active against SARS-CoV-2 [13], which would lead to better results in COVID-19 management [14]. Again, however, not all studies point in the same direction [15].

The aim of our study was to compare the profile of patients admitted for COVID-19 and the outcomes of their hospitalizations according to whether they had HIV infection or not, using a large registry (SEMI-COVID-19) held by the Sociedad Española de Medicina Interna (SEMI).

Methods

A retrospective analysis of the SEMI-COVID-19 registry [16] was performed. The SEMI-COVID-19 registry contains most COVID-19 admissions of at least 18-year-old patients in 150 hospitals distributed throughout Spain since the beginning of the pandemic. Confirmation of SARS-CoV-2 infections was obtained in all cases by means of a PCR test of nasopharyngeal specimens, sputum, or bronchoalveolar lavage.

Sociodemographics and previously diagnosed comorbidities were collected as well as regular medications, clinical and radiological presentations of the COVID-19 episodes, in-hospital treatments and laboratory test results, and length of hospitalizations and outcomes in terms of death or discharge. Data obtained from medical records were entered in an electronic platform. Comorbidities and the Charlson comorbidity index were recorded.

Persons with a medical history of HIV infection or with HIV positive serology (western blot) prior to their COVID-19 admission were identified as PWH.

Qualitative variables were described using percentages, and quantitative variables were described using means and 95% confidence intervals (CIs). Qualitative variables were compared using the χ^2 test and quantitative ones using Student's t test after confirming data normality. A statistically significant association was considered when P less than 0.05, and the association was expressed as an odds ratio (OR) with a 95% CI. A logistic regression analysis was performed for the death outcome variable and for the composite outcome variable consisting of ICU admission or invasive mechanical ventilation or death. Variables with a P less than 0.01 in the univariate analysis were included. Association values were expressed in this analysis as adjusted ORs (AORs) with 95% CIs. Variables with missing values greater than 25% were excluded from the logistic regression analysis.

Results

From 1 March to 8 October 2020, 16 563 COVID-19 admissions were recorded, of which 98 were PWH (0.59%). Of these 98 patients, 76 (77.55%) were admitted in March, 18 (18.36%) in April, only two in May, and a further two in October. Among persons without HIV, 79% of admissions occurred in March and 17.7% in April 2020. The main demographic characteristics of admitted patients according to their HIV status are summarized in Table 1.

Duration of symptoms was shorter in PWH than in persons without HIV (5.64 vs. 6.54 days) but the difference was not statistically significant. SARS-CoV-2 PCR was positive in nasopharyngeal specimens in 93.9% of persons with HIV compared with 98.1% in persons without HIV ($P < 0.005$), although positivity was higher in sputum (3.1 vs. 1.6%) and bronchoalveolar lavage (3.1 vs. 0.4%) samples in PWH.

The mean Charlson comorbidity index score was 2.59 in PWH compared with 1.29 in those without HIV ($P < 0.0005$). Symptoms experienced by patients are shown in Table 2.

At their arrival at the emergency department, there were no differences between patients with and without HIV infection in terms of presence of tachypnea (27.7 vs. 31.6%), SBP or DBP, or temperature. However, oxygen saturation was higher in PWH (94.24 vs. 92.87%, $P = 0.025$), with a higher proportion having had their initial blood test performed breathing room air (83 vs. 71.3%, $P =$ n.s.). For patients with data enabling the calculation of the arterial oxygen pressure/fraction of inspired oxygen ratio, this was also higher in PWH, without reaching statistical significance (313.37 vs. 285.48, $P = 0.055$). Lower levels of troponin I were

Table 1. Main patient characteristics.

Parameter	HIV-positive	HIV-negative	*P*
Sex (male %)	74.5	57.1	0.001
Age (mean in years)	57.9	67.4	<0.001
BMI (mean, kg/m^2)	27.4	28.7	n.s.
Obesity (BMI ≥30 kg/m^2, %)	34.5	29.4	n.s.
Excessive alcohol consumption (%)	9.3	4.6	0.028
Active tobacco use (%)	16.3	5.1	<0.001
High blood pressure (%)	35.7	51.3	0.002
Dyslipidemia (%)	37.8	39.7	n.s.
Diabetes mellitus (%)	21.5	19.8	n.s.
Atrial fibrillation (%)	11.1	5.2	n.s.
Anxiety disorder (%)	8.2	7.8	n.s.
Depression (%)	7.1	10.5	n.s.
Acute myocardial infarction (%)	6.1	5.8	n.s.
Heart failure (%)	0.3	0.6	n.s.
Ischemic stroke (%)	1	2.8	n.s.
Peripheral arterial disease (%)	1.2	4.6	0.033
Chronic obstructive pulmonary disease (%)	5.1	6.8	n.s.
Asthma (%)	3.1	7.2	n.s.
Obstructive sleep apnea/hypopnea syndrome	6.1	6	n.s.
Dementia (%)	6.1	10	n.s.
Moderate–severe liver disease (%)	5.1	1	<0.001
Moderate–severe chronic renal failure (%)	9.2	6.1	n.s.
Malignancy (%)	6.1	6.2	n.s.
Lymphoma (%)	5.1	1.3	0.001

n.s., not significant.

observed in patients with HIV infection, which could reflect less myocardial damage in these individuals.

Table 3 shows the main laboratory parameters tested upon arrival at the emergency department.

HIV serostatus was determined in 9019 patients with unknown HIV status. Of these, 54 (0.59%) tested positive. Chest X-rays showed no differences in the percentage of patients with alveolar consolidation (54.25% in PWH vs. 52.2% in persons without HIV) or pleural effusion (2.1 vs. 4.7%) but the presence of interstitial pattern was less common (55.2 vs. 74%, respectively, $P = 0.034$).

A lower percentage of PWH received lopinavir–ritonavir for the treatment of COVID-19 (37.5 vs. 59%, $P < 0.0005$) but no differences were found in the use of interferon beta (7.2 vs. 10.6%), remdesivir (0 vs. 0.9%), hydroxychloroquine (86.7 vs. 84.5%), chloroquine (4.1 vs. 4.2%), azithromycin (52 vs. 60.3%), colchicine (0 vs. 0.9%), tocilizumab (9.2 vs. 8.9%), immunoglobulins (0 vs. 0.5%), anakinra (2.1 vs. 0.6%), baricitinib (0 vs. 0.7%), low-molecular-weight heparin (80.6 vs. 82.8%), or intravenous corticosteroids (27.6 vs. 35.9%). Seventy-three percent of persons with HIV were receiving ART.

Table 2. Percentage of different symptoms experienced by patients.

Symptom	HIV-positive	HIV-negative	*P*
Cough			0.014
Dry	58.1	52	
Productive	15	25.5	
Muscle and joint pain	30.5	28.6	n.s.
Ageusia	12.2	8.4	n.s.
Anosmia	11.5	7.5	n.s.
Asthenia	42.9	43.3	n.s.
Anorexia	18.4	29.8	n.s.
Sore throat	14.4	9.7	n.s.
Headache	19.4	11.7	0.019
Fever/low-grade fever	88.8	83.9	n.s.
Dyspnea	53.6	57.6	n.s.
Diarrhea	30.9	23.9	n.s.
Nausea	14.4	12.3	n.s.
Vomiting	11.2	7.8	n.s.
Abdominal pain	6.1	6.6	n.s.
Confusion	7.2	12	n.s.

n.s., not significant.

No differences were found between PWH and persons without HIV in the need for noninvasive mechanical ventilation (8.2 vs. 5.1%, mean duration of 3 vs 4.8 days, $P =$ n.s.) or invasive mechanical ventilation (5.1 vs. 7%, mean duration of 8.25 vs 14.33 days $P =$ n.s.). With regard to complications during admission, PWH had a lower frequency of bacterial pneumonia (2.1 vs. 11%, $P = 0.005$), sepsis (1 vs. 6.2%, $P = 0.034$), and shock (0 vs. 4.6%, $P = 0.031$) but no differences were found for adult respiratory distress syndrome (28.9 vs. 33.9%), heart failure (2.1 vs. 5.9%), arrhythmias (2.1 vs. 4.1%), acute myocardial infarction (0 vs. 0.8%), renal failure (7.25 vs. 13.9%), or venous thromboembolic disease (0 vs. 2.3%). No differences were found in antibiotic prescription during admission (89 vs. 82%, $P =$ n.s.).

Table 3. Laboratory parameters upon arrival at the emergency department (mean).

Parameter	HIV infection	No HIV infection	*P*
Hemoglobin (g/dl)	13.8	13.68	n.s.
Platelets (cells/μl)	187 259	207 224	0.03
Lymphocytes (cells/μl)	1182	1161	n.s.
C-reactive protein (mg/dl)	85.68	88.36	n.s.
Creatinine (mg/dl)	1.23	1.1	n.s.
LDH (IU/l)	379.28	371.25	n.s.
Alanine aminotransferase (IU/l)	40.34	41.26	n.s.
Glucose (mg/dl)	118.27	128.44	n.s.
Creatine phosphokinase (IU/l)	135.57	199.5	n.s.
Ferritin (mg/dl)	1115.93	944.79	n.s.
Lactate (mg/dl)	3.39	3.86	n.s.
Troponin I (mg/dl)	0.44	3.96	<0.001
Interleukin 6 (mg/dl)	30.43	70.62	n.s.
Procalcitonin (mg/dl)	1.86	0.49	n.s.
D-dimers (mg/dl)	965.45	1997.24	n.s.

LDH, lactate dehydrogenase; n.s., not significant.

Of the PWH, 6.1% were transferred to the ICU compared with 8.7% of persons without HIV (P = n.s.), and there were no differences in the length of stay in the ICU (13.17 vs. 15.81 days). Hospital length of stay was 13.73 vs. 11.16 days, respectively (P = n.s.), and mortality was 12.4 vs. 21.3% ($P = 0.044$).

With regard to the composite outcome, ICU admission, invasive mechanical ventilation, or death occurred in 15.5% of persons with HIV and 26.5% of persons without HIV ($P = 0.019$).

In the mortality logistic regression analysis, HBP, Charlson comorbidity index, sex, and age were included in addition to HIV infection. These variables had shown statistically significant associations with mortality and with the composite outcome of ICU admission or invasive mechanical ventilation or death. HIV infection was not significantly associated with lower mortality but the association of male sex (AOR: 1.62, 95% CI: 1.48–177), age (AOR: 1.08, 95% CI: 1.07–1.09), HBP (AOR: 1.16, 95% CI: 1.06–1.28), and Charlson index (AOR: 1.20, 95% CI: 1.18–1.23) with a higher mortality remained.

When the logistic regression analysis of the composite outcome of ICU admission or invasive mechanical ventilation or death was performed, including the same variables as in the previous analysis, HIV infection (AOR: 0.53, 95% CI: 0.29–0.96), male sex (AOR: 1.57, 95% CI: 1.45–1.69), age (AOR: 1.04, 95% CI: 1.04–1.05), HBP (AOR: 1.14, IC 95%: 1.05–1.24), and Charlson index (AOR: 1.14, 95% CI: 1.12–1.16) remained in the model.

Discussion

In line with other similar registries [6], PWH represented 0.59% of patients recorded in the SEMI-COVID-19 registry. This group had a higher male/female ratio, a mean age 10 years younger, and a higher burden of comorbidities (as measured by the Charlson comorbidity index) than persons without HIV. Although alcohol consumption and tobacco use were significantly higher in PWH, HBP (a known risk factor for poor COVID-19 clinical outcomes) was less prevalent.

Duration of symptoms prior to admission was shorter in PWH, with no differences in the type of symptoms presented except for a higher occurrence of headaches and dry cough. This, together with a better respiratory status when presenting to the emergency department, may be an indirect reflection of a greater awareness of vulnerability in the context of the pandemic, leading these patients to seek medical advice or be referred from primary care earlier than other patients on presentation of suspicious clinical signs and symptoms. Among the analytical findings, troponin I levels were significantly lower in patients with HIV infection, who also suffered heart failure, arrhythmias, acute myocardial infarction, or renal failure less frequently.

Treatments received for COVID-19 were similar except in the case of lopinavir–ritonavir, which was given less frequently to PWH probably as a measure to avoid potential undesirable interactions with background ART. Likewise, the proportion of patients requiring noninvasive mechanical ventilation, invasive mechanical ventilation, or ICU admission did not differ between the two groups of patients. It can, therefore, be inferred that there was no difference in terms of resource allocation in the context of the pandemic between PWH and HIV-negative patients.

The proportion of patients with bacterial pneumonia, shock, or sepsis was lower in PWH. However, antibiotic consumption was prescribed more frequently (without reaching statistical significance), a likely indication that broader criteria to initiate antibiotic treatment were applied. The initial difference in mortality between PWH and HIV-negative patients did not persist in the logistic regression analysis controlling for age, sex, HBP, and Charlson comorbidity index but for the composite outcome of ICU admission or invasive mechanical ventilation or death, the difference persisted in the logistic regression analysis controlling for the same variables, with a risk of presenting these events reduced by almost half. The characteristics of PWH at the time of hospital admission seem to show a better clinical status, although differences did not reach statistical significance because of the small group size. However, they had higher arterial oxygen pressure/fraction of inspired oxygen ratio, lower levels of IL-6, D-dimers, troponin I, and very similar levels of C-reactive protein or lymphocytes, which again seems to indicate that COVID-19 clinical features and inflammatory response were less severe in HIV patients. Another possible reason that may have contributed to this may be the existence of a higher alert threshold in PWH compared with persons without HIV, leading to a shorter time period between symptom onset and arrival to the emergency department.

A significant increase in mortality in PWH was found in a large register of hospitalized patients in the United Kingdom [6], in which almost half of the patients were black and persons with HIV had fewer comorbidities than PWH. Other studies have linked black ethnicity with an increased risk of COVID-19 mortality [7]. In our cohort, non-Caucasian individuals represented less than 10% of the total patient population, and ethnicities were not specified in this group [16]. The Charlson comorbidity index was significantly higher in PWH but prevalence of HBP was significantly lower. HBP is known to be associated with worse COVID-19 outcomes so that, in our series, this could have acted in favor of the prognosis

of PWH although this condition was controlled for in the logistic regression analysis. Another study with similar characteristics conducted in South Africa showed an increased mortality associated with HIV infection [5]. In this study, PWH accounted for 18% of the total number of COVID-19 patients and most were black. In contrast, the findings of three other studies are consistent with ours in terms of the absence of a higher mortality in PWH [8,10,17]. However, in these studies, which were conducted in the United States of America, mortality was shown to be higher than in our study, and mean patient age and burden of comorbidities, such as HBP or diabetes mellitus were also higher [8,17].

Neither $CD4^+$ cell counts nor data on the different ART agents used prior to admission were recorded in the SEMI-COVID-19 registry. However, there is no firm evidence to date associating any ART agent with a lower severity or better outcomes of COVID-19 [15,18] and, in addition, 66.7% of PWH who died in our study were receiving ART prior to their admission.

In conclusion, in this study, HIV infection has been associated with a lower rate of ICU admissions, invasive mechanical ventilation, or death. Cohort studies providing updated COVID-19 results are essential as new specific treatments are implemented for its management.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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