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Predictors of in-hospital mortality in HIV-infected patients with COVID-19

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Summary

Background: Underlying immunodeficiency is associated with severe COVID-19, but the prognosis of persons with human immunodeficiency virus (HIV) (PWH) with COVID-19 is under debate.
Aim: assessment of the mortality rate and major determinants of death in HIV-infected patients hospitalized with COVID-19 in Spain before vaccine availability.
Design: Retrospective nationwide public database analysis.
Methods: Nationwide, retrospective, observational analysis of all hospitalizations with COVID-19 during year 2020 in Spain. Stratification was made according to HIV status. The National Registry of Hospital Discharges was used with the ICD-10 coding list.
Results: A total of 117 694 adults were hospitalized with COVID-19 during 2020. Only 234 (0.2%) were HIV-positives. More than 95% were on antiretroviral therapy. Compared to HIV-negatives, PWH were younger (mean age 53.2 vs. 66.5 years old; $P<0.001$) and more frequently male (74.8% vs. 56.6%; $P<0.001$). Most co-morbidities predisposing to severe COVID-19 (diabetes, hypertension, dementia and cardiovascular disease) were more frequent in HIV-negatives. In contrast, the rate of baseline liver disease was over 6-fold higher in PWH (27.4% vs. 4.4%; $P<0.001$). In-hospital mortality was lower in PWH (9.4% vs. 16%; $P=0.004$). In multivariate analysis, older age, dementia and especially advanced liver disease (relative risk (RR): 7.6) were the major determinants of death in PWH hospitalized with COVID-19.
Conclusion: HIV-infected patients hospitalized in Spain with COVID-19 during 2020 had better survival than HIV-negatives, most likely explained by younger age and lower rate of co-morbidities. However, advanced liver disease was a major predictor of death in PWH hospitalized with COVID-19.

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Introduction

The surge of Severe acute respiratory syndrome due to coronavirus type 2 (SARS-CoV-2) infection by the end of 2019 in China and its rapid spread worldwide is an unprecedented medical phenomenon.[1] By the end of year 2021, estimates for excess mortality due to Coronavirus disease 2019 (COVID-19) were over 18 million people globally.[2] Although SARS-CoV-2 infection is often asymptomatic or produce only mild symptoms, roughly 5% of infected adults develop clinically overt bilateral pneumonia and require hospitalization.[3] Predictors of severe disease were soon unveiled and included older age, male gender and certain co-morbidities, such as diabetes and obesity.[4–6]

Underlying immunodeficiencies have been associated with worst clinical presentation and increased mortality in patients with COVID-19.[7–9] However, the impact of distinct etiologies of impaired immunity on COVID-19 outcomes is under debate. Since human immunodeficiency virus (HIV) infection is a well-known cause of acquired immunodeficiency and current estimates are of 38 million persons with HIV (PWH) worldwide,[10] we aimed to exam the prognosis of patients with COVID-19 and HIV infection in Spain before the introduction of SARS-CoV-2 vaccines.

Methods

A retrospective study with data from population-based hospital discharge diagnoses at the Minimum Basic Data Set of the Spanish National Registry of Hospital Discharges (SNRHD) was performed. This is a national public registry that belongs to the Spanish Ministry of Health. It records information from all patients discharged at hospitals/clinics across the country since the nineties.[11] Prior studies have been performed on this registry for other illnesses, including infectious diseases, and have recognized its high value for producing estimates of current burden and time trends for different clinical conditions at national level.[12–16]

Our study was conducted with all data included at the SNRHD from 1 January to 31 December of the year 2020. The criteria for diseases and procedures were defined according to the International Classification of Diseases-10th Revision, Clinical Modification (ICD-10-CM). We selected all hospital admissions with the coding list U07.1 (COVID-19) as main diagnosis. All other diagnoses were considered regardless their position in the diagnostic list for each episode of hospital admission. Data about comorbid conditions were retrieved using the enhanced ICD-10-CM tools.[17]

Statistical analysis

Figures are given in absolute numbers and percentages. Quantitative and qualitative variables are described as medians with interquartile ranges, mean with standard deviations or as proportions. Bivariate comparisons of quantitative and qualitative variables were performed using the Kruskal–Wallis test, U Mann–Whitney test and the chi-square test. All statistical analyses were performed using the IBM SPSS package for Windows v25.0 (IBM Corp., Armonk, NY, USA). All tests were two-tailed and only P-values <0.05 were considered as significant.

The incidence rates for COVID-19 admissions with and without COVID-19 were estimated using the total Spanish population in year 2020, as recorded at the public government website (Instituto Nacional de Estadística).[18] The estimated number of PWH in Spain was recorded from the Ministry of Health website that periodically update this information.[19]

The association of distinct co-morbidities with hospitalization and mortality in both HIV-negative and PWH was examined considering all chronic conditions recorded at the Charlson co-morbidity index,[20] which is a well validated composite that predicts clinical outcome in multiple illnesses. Among other medical conditions, it included diabetes, obesity, heart failure, dementia, chronic kidney disease and cancer, most of which have been associated to severe COVID-19. For the purpose of our analysis, we excluded HIV as variable within the index.

Ethical aspects

The database was provided by the Spanish Ministry of Health after removal of all potential patients' identifiers. In accordance with the Spanish legislation, patient's informed consent was not needed for this analysis. The study protocol was approved by the Clinical Research Ethics Committee of Puerta de Hierro University Hospital (Madrid, Spain) (ref. PI_80-21). The procedures described here were carried out in accordance with the ethical standards described in the 2013 Revised Declaration of Helsinki.

Results

A total of 117 694 adults were hospitalized in Spain with COVID-19 during 2020. Only 234 (0.2%) were HIV-positive. More than 95% of them were on antiretroviral therapy. Nationwide estimates for COVID-19 hospitalizations were of 0.25% in the HIV-negative population (47.5 million people were living in Spain in year 2020) compared to 0.16% among PWH (roughly 150 000 HIV-positives living in Spain in year 2020) ($P < 0.001$).

Table 1 depicts the main demographics of the Spanish population hospitalized with COVID-19 during 2020. Compared to HIV-negatives, PWH were younger (mean age 53.2 vs. 66.5 years old; $P < 0.001$), more frequently male (74.8% vs. 56.6%; $P < 0.001$) and non-Caucasian (38.9% vs. 26.9%; $P < 0.001$).

Table 2 records the rate of distinct medical conditions, as recorded using the Charlson co-morbidity index,[20] in patients hospitalized with COVID-19. Most co-morbidities known to predispose to severe COVID-19 (diabetes, hypertension, dementia and cardiovascular disease) were significantly more frequent among HIV-negatives than in PWH. In contrast, the rate of baseline liver disease was higher among PWH than in HIV-negatives (27.4% vs. 4.4%; $P < 0.001$).

Table 3 records the clinical outcome of patients hospitalized with COVID-19. Rates of images of interstitial pneumonia, respiratory insufficiency, admission at the intensive care unit and development of acute respiratory distress syndrome did not differ significantly when comparing PWH and HIV-negatives. Likewise, the length of hospital admission, including time at the intensive care unit, was similar in both groups. Interestingly, in-hospital mortality was significantly lower in PWH compared to HIV-negatives (9.4% vs. 16%; $P = 0.004$).

A multivariate analysis was performed in the whole population hospitalized with COVID-19 in order to characterize the independent predictors of in-hospital mortality. Male gender, high blood pressure, obesity and a composite of co-morbidities as included in the Charlson co-morbidity index were all independently associated with death. In contrast, HIV infection did not (Figure 1).

In order to better characterize the role of HIV and antiretroviral therapy, we identified and compared the subset of HIV-

Table 1. Main demographics of the study population

	Total (*N*, %)	HIV-pos (*n*, %)	HIV-neg (*n*, %)	*P*
COVID-19 hospitalized patients	117 694	234 (0.2)	117 460 (99.8)	
Mean age (SD)	66.5 (18)	53.2 (11.1)	66.5 (18)	<0.001
Male sex	66 685 (56.7)	175 (74.8)	66 510 (56.6)	<0.001
Ethnicity				<0.001
Caucasian	85 977 (73.1)	143 (61.1)	85 834 (73.1)	<0.001
Arabic	2786 (2.4)	0	2786 (2.4)	0.04
Black	1592 (1.4)	25 (10.7)	1567 (1.3)	<0.001
Asian	387 (0.3)	0	387 (0.3)	0.462
Hispanic	9296 (7.9)	39 (16.7)	9257 (7.9)	<0.001
Hindu	156 (0.1)	0	156 (0.1)	0.733
Unknown	17 500 (99.8)	27 (11.5)	17 474 (14.9)	0.09

HIV: human immunodeficiency virus, SD: standard deviation.

Table 2. Distribution of major co-morbidities in the study population

	Total (*N*, %)	HIV-pos (*n*, %)	HIV-neg (*n*, %)	*P*
High blood pressure	**56 701 (48.2)**	**59 (25.2)**	**56 642 (48.2)**	**<0.001**
Diabetes mellitus	**28 094 (23.9)**	**32 (13.7)**	**28 062 (23.9)**	**<0.001**
Uncomplicated	18 595 (15.8)	21 (9)	18 574 (15.8)	0.002
End-organ damage	9499 (8.1)	11 (4.7)	9488 (8.1)	0.038
Obesity	13 966 (11.90)	24 (10.3)	13 942 (11.9)	0.254
Ischemic heart disease	7858 (6.7)	10 (4.3)	7848 (6.7)	0.084
Heart failure	**14 199 (12.1)**	**8 (3.4)**	**14 191 (12.1)**	**<0.001**
Peripheral vascular disease	**5059 (4.3)**	**2 (0.9)**	**5057 (4.3)**	**0.002**
CVA or TIA	7308 (6.2)	9 (3.8)	7299 (6.2)	0.08
Hemiplejia	1717 (1.5)	1 (0.4)	1.716 (1.5)	0.143
Dementia	**10 146 (8.6)**	**6 (2.6)**	**10 140 (8.6)**	**0.001**
Chronic lung disease	16 814 (14.3)	35 (15)	16 779 (14.3)	0.421
Connective tissue disease	2019 (1.7)	2 (0.9)	2017 (1.7)	0.233
Peptic ulcer disease	341 (0.3)	1 (0.4)	340 (0.3)	0.493
Liver disease	**6001 (5.1)**	**70 (30)**	**5931 (5)**	**<0.001**
Mild	**4929 (4.2)**	**57 (24.4)**	**4875 (4.1)**	**<0.001**
Moderate to severe	**1073 (0.9)**	**13 (5.6)**	**1060 (0.9)**	**<0.001**
Chronic kidney disease	13 232 (11.2)	19 (8.1)	13 213 (11.2)	0.079
Tumor				
Localized solid tumor	433 (0.4)	0	433 (0.4)	0.422
Metastatic solid tumor	701 (0.6)	2 (0.9)	699 (0.6)	0.407
Leukemia	697 (0.6)	0	697 (0.6)	0.249
Lymphoma	**610 (0.5)**	**6 (2.6)**	**604 (0.5)**	**<0.001**
CCI (mean, SD)	**3.5 (2.6)**	**8.2 (2)**	**3.5 (2.6)**	**<0.001**
CCI excluding HIV (mean, SD)	**3.5 (2.6)**	**2.2 (2)**	**3.5 (2.6)**	**<0.001**

HIV: human immunodeficiency virus, CVA: cerebrovascular accident, TIA: transient ischemic attack, CCI: Charlson co-morbidity index.
Values with statistical significance in bold.

Table 3. Clinical outcomes in patients hospitalized with COVID-19 according to HIV status

	Total (*N*, %)	HIV-pos (*n*, %)	HIV-neg (*n*, %)	*P*
Interstitial pneumonia	75 739 (64.4)	144 (61.5)	75 595 (64.4)	0.203
Respiratory insufficiency	47 529 (40.4)	90 (38.5)	47 439 (40.4)	0.297
ICU admission	11 449 (9.7)	26 (11.1)	11 423 (9.7)	0.273
ARDS	3811 (3.2)	3 (1.3)	3808 (3.2)	0.053
Mortality	**18 858 (16)**	**22 (9.4)**	**18 836 (16)**	**0.004**
Admission length	10.6 (11.7)	11.6 (12.1)	10.6 (11.7)	0.193
ICU admission length	15.6 (17.6)	12 (13.1)	15.6 (17.6)	0.297

HIV: human immunodeficiency virus, ICU: intensive care unit, ARDS: acute respiratory distress syndrome.
Values with statistical significance in bold.

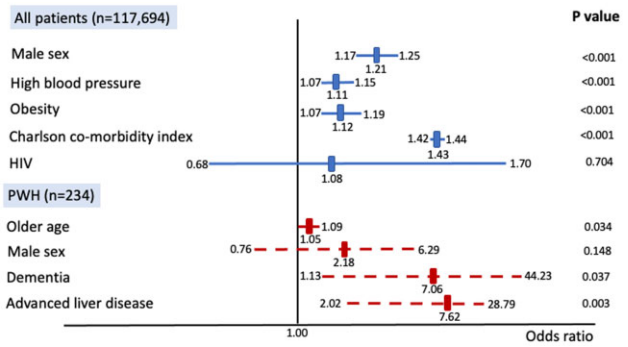

Figure 1. Predictors of COVID-19 in-hospitality mortality; multivariate analysis (odds ratio, 95% confidence interval).

positives on antiretroviral therapy ($n = 223$; 95.2%) and a control group of HIV-negatives matched for age, sex and co-morbidities. Overall, very few HIV-negative patients met these criteria and then their survival did not differ significantly when a comparison was made with HIV-positive patients hospitalized with COVID-19 (data not shown). These results reinforce that older age and co-morbidities are the major determinants of the increased death rate seen in HIV-negatives with COVID-19 compared to HIV-positives.

Predictors of in-hospital mortality were specifically examined in PWH. Overall 22 HIV-positives died compared to 212 survivors (Table 4). Besides older age, baseline dementia and the Charlson co-morbidity index, a significant association with death was recognized for advanced liver disease in PWH hospitalized with COVID-19. In multivariate analysis, advanced liver disease was the most significant predictor of in-hospital mortality among PWH with COVID-19 (Figure 1). Interestingly, chronic viral hepatitis B and/or C was the main etiology of liver disease among PWH. In contrast, non-alcoholic fatty liver disease was the major cause of hepatic damage among HIV-negatives (Table 5).

Discussion

The role of HIV infection as predictor of severe COVID-19 is under debate.[21–28] Differences in study design and patient populations largely explain discordant results. A recent meta-analysis concluded that there is an increased risk of hospitalization, severe disease and death in PWH with COVID-19.[29] In contrast, a systematic review of 25 published studies showed no increased risk for incident SARS-CoV-2 infection or disease progression for individuals with HIV receiving antiretroviral therapy and virally suppressed as compared to HIV-negative individuals.[30] In our nationwide study of all patients hospitalized with COVID-19 during year 2020, before vaccines became available, PWH experienced an overall lower rate of hospital admission and improved survival compared to HIV-negatives. The younger age and the lower rate of co-morbidities in PWH largely accounted for this better outcome. It is worth to acknowledge that most PWH in Spain are under antiretroviral therapy and show high CD4 counts and undetectable viremia.[19,25]

Several reviews have pointed out that co-morbidities seem to be the major determinant of COVID-19 severity in PWH.[31–33] However, none of these studies has highlighted that advanced liver disease could be a major predictor of death in this population. In other studies, chronic liver disease, either due to viral hepatitis, alcohol abuse or non-alcoholic steatohepatitis, has already been associated with an increased risk of severe COVID-19,[34,35] with evidence supporting that mortality could be directly linked to the extent of liver fibrosis[36] or hepatic insufficiency.[37] In our study, underlying advanced liver disease associated to chronic viral hepatitis B and/or C was the most significant predictor of mortality among PWH hospitalized with COVID-19.

The prevalence of chronic viral hepatitis, either B or C, among PWH in Spain has traditionally been considered elevated compared to other European countries, largely as result of the

Table 4. Determinants of in-hospital mortality in PWH with COVID-19

	Total (N, %)	Non-survivors	Survivors	P
	234	22 (9.4)	212 (90.6)	
Mean age (SD)	**53.2 (11.1)**	**58.9 (15.7)**	**52.6 (10.4)**	**0.01**
Male sex	175 (74.8)	15 (68.2)	160 (75.5)	0.303
High blood pressure	59 (25.2)	4 (18.2)	55 (25.9)	0.304
Diabetes mellitus	32 (13.7)	4 (18.2)	28 (13.2)	0.353
Uncomplicated	21 (9)	3 (13.6)	18 (8.5)	0.314
End-organ damage	11 (4.7)	1 (4.5)	10 (4.7)	0.723
Obesity	24 (10.3)	2 (9.1)	22 (10.4)	0.602
Ischemic heart disease	10 (4.3)	1 (4.5)	9 (4.2)	0.635
Heart failure	8 (3.4)	1 (4.5)	7 (3.3)	0.552
Peripheral vascular disease	2 (0.9)	0	2 (0.9)	0.820
CVA or TIA	9 (3.8)	1 (4.5)	8 (3.8)	0.595
Hemiplejia	1 (0.4)	0	1 (0.5)	0.906
Dementia	**6 (2.6)**	**3 (13.6)**	**3 (1.4)**	**0.012**
Chronic lung disease	35 (15)	5 (22.7)	30 (14.2)	0.216
Connective tissue disease	2 (0.9)	0	2 (0.9)	0.820
Peptic ulcer disease	1 (0.4)	0	1 (0.5)	0.906
Liver disease	70 (29.9)	7 (31.8)	63 (29.7)	0.505
Mild	57 (24.4)	2 (9.1)	55 (25.9)	0.08
Moderate to severe	**13 (5.6)**	**5 (22.7)**	**8 (5.6)**	**0.004**
Chronic kidney disease	19 (8.1)	3 (13.6)	16 (7.5)	0.259
Tumor				
Localized solid tumor	0	0	0	
Metastatic solid tumor	2 (0.9)	1 (4.5)	1 (0.5)	0.180
Leukemia	0	0	0	
Lymphoma	6 (2.6)	1 (4.5)	5 (2.4)	0.451
CCI (mean, SD)	**8.2 (2)**	**9.7 (2.5)**	**8 (1.9)**	**0.005**

PWH: persons living with HIV, SD: standard deviation, CVA: cerebrovascular accident, TIA: transient ischemic attack, CCI: Charlson co-morbidity index.
Values with statistical significance in bold.

Table 5. Baseline liver disease in patients hospitalized with COVID-19 in Spain

	Total (N, %)	HIV-pos (n, %)	HIV-neg (n, %)	P
Any liver disease	**6001 (5.1)**	**70 (30)**	**5931 (5)**	**<0.001**
Moderate to severe	**1073 (0.9)**	**13 (5.6)**	**1060 (0.9)**	**<0.001**
Etiology:				
Alcohol abuse	664 (11.1)	5 (7.1)	659 (11.1)	0.198
Toxic	151 (2.5)	2 (2.9)	149 (2.5)	0.530
Viral	**1204 (20.1)**	**49 (70)**	**1155 (19.5)**	**<0.001**
Hepatitis B	**533 (8.9)**	**14 (20)**	**519 (8.8)**	**0.003**
Hepatitis C	**673 (11.2)**	**35 (50)**	**638 (10.8)**	**<0.001**
Autoimmune	124 (2.1)	1 (1.4)	123 (2.1)	0.573
NAFLD	**2609 (43.5)**	**8 (11.4)**	**2601 (43.9)**	**<0.001**
Others/unknown	**1407 (23.4)**	**9 (12.8)**	**1398 (23.5)**	**0.01**

HIV: human immunodeficiency virus, HBV: hepatitis B virus, HCV: hepatitis C virus, NAFLD: non-alcoholic fatty liver disease.
Values with statistical significance in bold.

large epidemic of injection drug use during the eighties and nineties.[38,39] Thereafter, men having sex with men became the most frequent risk group for HIV acquisition.[40] During the last decade, the high success of oral antivirals as curative treatment for hepatitis C and as suppressive therapy for hepatitis B has benefited most PWH with chronic viral hepatitis. Although regression of liver fibrosis has been reported following hepatitis C as well as in HIV–hepatitis B virus-coinfected patients under long-term tenofovir-based antiretroviral therapy, severe hepatic fibrosis may persist in a large subset of patients with prior liver cirrhosis.[41–43] In this regard, liver disease accounts for between 13% and 18% of all-cause mortality in PWH.[44,45]

Several limitations of our study should be acknowledged. First, we could not recognize whether a patient had been hospitalized at different hospitals within the same calendar year, given that the SNRHD data are anonymous. Thus, a slight overestimation of patients hospitalized with COVID-19 might have occurred, because we interpreted re-admissions due to late complications or SARS-CoV-2 reinfections as new admissions. Second, the retrospective design of our study and the lack of access to patient's clinical charts precluded to clarify any doubtful information and/or collect more specific clinical information. Third, we did not assess the impact of ethnicity on clinical outcomes and mortality. Prior studies have shown that COVID-19 may evolve worst in the black race.[35] However, our population was mostly represented by Caucasians and blacks were <1.5%. Fourth, we did not take into account differences in clinical outcomes in patients hospitalized during distinct COVID-19 waves. Three waves of COVID-19 were recognized in Spain during 2020, with improvements in clinical management in the most recent waves.[46,47] Fifth, the susceptibility of HIV- infected individuals to severe COVID-19 might differ in those with and without antiretroviral therapy. Although most PWH in Spain are under antiretroviral therapy, we did not check the extent of viral suppression or CD4 counts in those hospitalized with COVID-19. Despite all these limitations, the SNRHD has proved to be useful for epidemiological investigations,[12–16] since this database covers over 98% of hospital admissions in Spain. The accuracy of this register has been guaranteed by periodic audits conducted by the Ministry of Health.[17] Therefore, our results must be considered as fully representative of the clinical impact of COVID-19 hospital admissions in Spain during year 2020, before SARS-CoV-2 vaccines became available.

Conclusion

Despite a well-established association between immunodeficiency and COVID-19 severity following SARS-CoV-2 infection, hospitalizations in Spain during 2020 were significantly more frequent among HIV-negative than HIV-positive adults. Furthermore, PWH hospitalized in Spain with COVID-19 showed an improved survival compared to HIV-negatives. Younger age and having less co-morbidities most likely contributed to the improved survival of PWH. Interestingly, advanced liver disease was a major predictor of death in PWH with COVID-19. Whereas chronic viral hepatitis B and/or C was the main etiology of hepatic damage among PWH, non-alcoholic fatty liver disease was the major cause of hepatic damage among HIV-negatives.

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Author's contribution

V.M.-T., C.d.M. and V.S. designed the study. V.M.-T. built the database and did the statistical analyses. V.M.-T., C.d.M. and V.S. wrote the first draft. All authors participated in the interpretation of results and contributed with comments to the draft. All authors approved the final submission.

Conflict of interest: None declared.

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