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SHORT COMMUNICATION

COVID-19 in hospitalized HIV-positive and HIV-negative patients: A matched study

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Abstract

Objectives: We compared the characteristics and clinical outcomes of hospitalized individuals with COVID-19 with [people with HIV (PWH)] and without (non-PWH) HIV co-infection in Spain during the first wave of the pandemic.

*Members of the the Spanish HIV Research Network Cohort (CoRIS) are given in the Appendix.

Methods: This was a retrospective matched cohort study. People with HIV were identified by reviewing clinical records and laboratory registries of 10 922 patients in active-follow-up within the Spanish HIV Research Network (CoRIS) up to 30 June 2020. Each hospitalized PWH was matched with five non-PWH of the same age and sex randomly selected from COVID-19@Spain, a multicentre cohort of 4035 patients hospitalized with confirmed COVID-19. The main outcome was all-cause in-hospital mortality.

Results: Forty-five PWH with PCR-confirmed COVID-19 were identified in CoRIS, 21 of whom were hospitalized. A total of 105 age/sex-matched controls were selected from the COVID-19@Spain cohort. The median age in both groups was 53 (Q1–Q3, 46–56) years, and 90.5% were men. In PWH, 19.1% were injecting drug users, 95.2% were on antiretroviral therapy, 94.4% had HIV-RNA < 50 copies/mL, and the median (Q1–Q3) CD4 count was 595 (349–798) cells/μL. No statistically significant differences were found between PWH and non-PWH in number of comorbidities, presenting signs and symptoms, laboratory parameters, radiology findings and severity scores on admission. Corticosteroids were administered to 33.3% and 27.4% of PWH and non-PWH, respectively ($P = 0.580$). Deaths during admission were documented in two (9.5%) PWH and 12 (11.4%) non-PWH ($P = 0.800$).

Conclusions: Our findings suggest that well-controlled HIV infection does not modify the clinical presentation or worsen clinical outcomes of COVID-19 hospitalization.

KEYWORDS

Coronavirus, COVID-19, HIV, SARS-CoV-2

INTRODUCTION

Since the beginning of the COVID-19 pandemic, HIV has been uncommonly listed as an underlying condition in case series of hospitalized patients with COVID-19 [1, 2]. This is likely because of the much lower prevalence of HIV among the general population than that of other prevailing diseases and because the number of older individuals is much lower among people with HIV (PWH) than among the HIV-uninfected population (non-PWH). Notwithstanding this, whether HIV increases the risk of acquiring SARS-CoV-2 or the severity or mortality of COVID-19 has stirred substantial research. Many studies have analysed the characteristics and outcomes of COVID-19 in PWH, but to the best of our knowledge, only in eight of these has some comparison been made between PWH and people without HIV (non-PWH) [3–10]. In four of these studies, worse outcomes in PWH *vs*. non-PWH have been reported [3,7,9,10].

We assessed the frequency of COVID-19 within a large prospective cohort of PWH in Spain during the first wave of the pandemic and compared the characteristics and clinical outcomes of hospitalized PWH with COVID-19 with an age/sex-matched control group of non-PWH.

METHODS

We performed a retrospective study of individuals with reverse transcription polymerase chain reaction (PCR)-confirmed COVID-19 among PWH in active follow-up within the Spanish HIV Research Network Cohort (CoRIS) up to 30 June 2020. CoRIS is a prospective cohort of PWH aged > 13 years, naïve to antiretroviral therapy (ART) at study entry, seen for the first time from 1 January 2004, in 46 participating centres from 13 of 17 regions in Spain. The CoRIS database collects demographic and clinical data, HIV transmission category, ART history, previous opportunistic diseases, specific non-AIDS diseases, and serological and immunovirological data. Internal quality controls are done annually [11].

PWH with confirmed COVID-19 in CoRIS were identified by reviewing clinical records and laboratory registries. The data source for demographics, HIV-related characteristics and comorbidities in this study was the CoRIS database. COVID-19-related clinical data were collected from the electronic medical records using an electronic case report form.

Each hospitalized PWH with COVID-19 was matched with five hospitalized non-PWH with COVID-19 of the same age and sex randomly selected from COVID-19@Spain, a multicentre cohort of 4035 patients hospitalized with

TABLE 1 Demographics and comorbidity data of 45 people with HIV (PWH) with COVID-19 stratified according to hospitalization

Characteristic	Non-hospitalized (*N* = 24)	Hospitalized (*N* = 21)	*P*	Total (*N* = 45)
Sex [*n*/*N* (%)]				
Male	20/24 (83.3)	19/21 (90.5)	0.482	39/45 (86.7)
Female	4/24 (16.7)	2/21 (9.5)		6/45 (13.3)
Age (years)				
Median (Q1–Q3)	38 (34–48)	53 (46–56)	0.001	46 (37–56)
Distribution [*n*/no. with data (%)]				
0–20 years	0/23 (0)	0/21 (0)	0.007	0/44 (0)
21–30 years	5/23 (21.7)	0/21 (0)		5/44 (11.4)
31–40 years	9/23 (39.1)	1/21 (4.8)		10/44 (22.7)
41–50 years	4/23 (17.4)	8/21 (38.1)		12/44 (27.3)
51–60 years	4/23 (17.4)	8/21 (38.1)		12/44 (27.3)
61–70 years	1/23 (4.3)	3/21 (14.3)		4/44 (9.1)
71–80 years	0/23 (0)	1/21 (4.8)		1/44 (2.3)
≥ 81 years	0/23 (0)	0/21 (0)		0 (0)
Country of birth [*n*/no. with data (%)]				
Spain	18/24 (75.0)	12/21 (57.1)	0.205	30/45 (66.7)
Other	6/24 (25.0)	9/21 (42.9)		15/45 (33.3)
Transmission category [*n*/no. with data (%)]				
Homo/bisexual intercourse	16/24 (66.7)	7/21 (33.3)	0.051	23/45 (51.1)
Heterosexual intercourse	7/24 (29.2)	8/21 (38.1)		15/45 (33.3)
Injecting drug use	0/24 (0)	4/21 (19.1)		4/45 (8.9)
Other/unknown	1/24 (4.2)	2/21 (9.5)		3/45 (6.7)
Antiretroviral therapy [*n*/no. with data (%)]	24/24 (100.0)	20/21 (95.2)	0.280	44/45 (97.8)
Last median CD4 count (Q1–Q3) (cells/μL)	434 (418–870)	495 (349–798)	0.958	481 (418–823)
HIV-RNA <50 copies/mL [*n*/no. with data (%)]	16/17 (94.1)	17/18 (94.4)	0.967	33/35 (94.3)
Comorbid conditions [*n*/no. with data (%)]				
Hypertension	2/24 (8.3)	9/21 (42.9)	0.007	11/45 (24.4)
Coronary heart disease	0/24 (0)	2/21 (9.5)	0.122	2/45 (4.4)
Prior heart failure	0/24 (0)	2/21 (9.5)	0.122	2/45 (4.4)
Cerebrovascular disease	0/24 (0)	0/21 (0)	—	0/45 (0)
Diabetes	2/24 (8.3)	4/21 (19.0)	0.292	6/45 (13.3)
Chronic lung disease (not asthma)	0/24 (0)	4/21 (19.0)	0.025	4/45 (8.9)
Obesity (BMI ≥ 30 kg/m^2)	0/24 (0)	1/18 (5.6)	0.243	1/42 (2.4)
Epilepsy	0/24 (0)	0/21 (0)	—	0/45 (0)
Other chronic neurological disorder	1/24 (4.2)	0/21 (0)	0.344	1/45 (2.2)
Asthma	3/24 (12.5)	0/21 (0)	0.094	3/45 (6.7)
Solid cancer (active)	0/24 (0)	1/21 (4.8)	0.280	1/45 (2.2)
Haematological cancer (active)	0/24 (0)	0/21 (0)	—	0/45 (0)
Chronic kidney disease (GFR < 60)	1/24 (4.2)	3/21 (14.3)	0.234	4/45 (8.9)
Liver cirrhosis	0/24 (0)	0/21 (0)	—	0/45 (0)
Inflammatory disease	0/24 (0)	0/21 (0)	—	0/45 (0)
Dementia	0/23 (0)	0/21 (0)	—	0/44 (0)

(Continues)

TABLE 1 (Continued)

Characteristic	Non-hospitalized ($N = 24$)	Hospitalized ($N = 21$)	P	Total ($N = 45$)
Concomitant medication [*n*/no. with data (%)]				
ACE inhibitors	2/24 (8.3)	4/21 (19.0)	0.292	6/45 (13.3)
ARBs	1/24 (4.2)	2/21 (9.5)	0.472	3/45 (6.7)
Corticosteroids systemic	0/24 (0)	1/21 (4.8)	0.280	1/45 (2.2)
Statins	3/24 (12.5)	5/21 (23.8)	0.322	8/45 (17.8)
Summary of clinical syndromes				
Mild illness	23/24 (95.8)	2/21 (9.5)	<0.001	25/45 (55.6)
Moderate disease (pneumonia)	1/24 (4.2)	6/21 (28.6)	0.024	7/45 (15.6)
Severe disease (severe pneumonia)	0/24 (0)	12/21 (57.1)	<0.001	12/45 (26.7)
Critical disease (ARDS)	0/24 (0)	1/21 (4.8)	0.280	1/45 (2.2)
Death	0/24 (0)	2/21 (9.5)	0.122	2/45 (4.4)

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; ARDS, acute respiratory distress syndrome; BMI, body mass index; GFR, glomerular filtration rate; PWH, people with HIV; Q1/Q3, first/third quartile.

PCR-confirmed COVID-19 in Spain [2]. The COVID-19 SEIMC score (predictive of 30-day mortality), based on age, sex, dyspnoea, oxygen saturation, neutrophil-to-lymphocyte ratio and estimated glomerular filtration rate, was calculated retrospectively at admission in all patients [12].

The main outcome was all-cause in-hospital mortality. Descriptive analysis of individuals' characteristics was carried out using frequency tables with percentages for categorical variables and median and quartiles for continuous variables. The study was approved by the Ethics Committee of Hospital General Universitario Gregorio Marañón.

RESULTS

Among 10 922 PWH in active-follow-up within CoRIS during the study period, 45 (0.41%) had a recorded diagnosis of COVID-19, 21 of whom (46.7%) were hospitalized. The demographics and clinical characteristics of the 45 PWH with COVID-19 are shown in Table 1, categorized according to whether they were hospitalized.

In comparison with non-hospitalized PWH, those hospitalized were older (median age 38 *vs*. 53 years, $P = 0.001$) and more frequently diagnosed with arterial hypertension (8.3% *vs*. 42.9%, $P = 0.007$) or chronic lung disease, not including asthma (0% *vs*. 19%, $P = 0.025$). No statistically significant differences were found between both groups in the proportion of individuals on ART, CD4 cell counts or the proportion of those with HIV-RNA load < 50 copies/mL. Among non-hospitalized PWH, 23 had a mild illness and one had moderate disease (pneumonia), whereas among hospitalized PWH, two had a mild illness, six had moderate disease, 12 had severe disease (severe pneumonia), and one had critical disease (acute respiratory distress syndrome). Two of the 45 PWH with COVID-19, both hospitalized, died.

The clinical characteristics and outcomes of the 21 hospitalized PWH with COVID-19 and the 105 age/sex-matched non-PWH are shown in Table 2. In both groups, the median [quartile 1 (Q1)–quartile 3 (Q3)] age was 53 (46–56) years, and 90.5% were men. In PWH, 19.1% acquired HIV by injecting drug use, 95.2% were on ART, 94.4% had an HIV-RNA < 50 copies/mL, and the median (Q1–Q3) CD4 count was 495 (349–798) cells/μL.

A higher proportion of PWH than non-PWH were born abroad (42.9% *vs*. 20.4%, $P = 0.028$), particularly in Latin American countries. Likewise, a higher proportion of PWH than non-PWH had chronic kidney disease defined as an estimated glomerular filtration rate (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula of < 60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause (14.3% *vs*. 2.9%, $P = 0.026$). C-reactive protein (CRP) concentrations at baseline were statistically significantly lower in PWH than in non-PWH (median 13 *vs*. 49 mg/L, respectively, $P < 0.001$). No statistically significant differences were found between PWH and non-PWH in the number of comorbidities, presenting signs and symptoms, chest radiology findings, oxygen saturation at room air, other laboratory parameters and COVID-19 SEIMC score on admission.

During the hospital course, 61.9% of PWH and 78.4% of non-PHW received oxygen therapy, and 9.5% and 23.3%, respectively, underwent mechanical ventilation ($P = 0.158$). No statistically significant differences were found between PWH and non-PWH in the percentage of patients receiving corticosteroids (33.3% *vs*. 27.4%, $P = 0.586$), tocilizumab (4.8% *vs*. 16.7%, $P = 0.160$) and remdesivir (0 *vs*. 2.9%, $P = 0.426$). Death during admission was documented in two (9.5%) PWH and 12 (11.4%) non-PWH ($P = 0.800$).

TABLE 2 Clinical characteristics, treatment and outcome of hospitalized patients with COVID-19

	PWH (*N* = 21)	Non-PWH (*N* = 105)	*P*
Sociodemographic characteristics			
Male sex [*n*/*N* (%)]	19/21 (90.5)	95/105 (90.5)	1.00
Age (no. with data)	21	105	
Median (Q1–Q3) (years)	53 (46–56)	53 (46–56)	1.00
Country of birth [*n*/no. with data (%)]			
Spain	12/21 (57.1)	82/103 (79.6)	0.028
Other	9/21 (42.9)	21/103 (20.4)	
Number of comorbidities [*n*/no. with data (%)]			
None	8/18 (44.4)	36/91 (39.6)	0.798
1–2	7/18 (38.9)	43/91 (47.3)	
≥ 3	3/18 (16.7)	12/91 (13.2)	
Types of comorbidity [*n*/no. with data (%)]			
Hypertension	9/21 (42.9)	37/103 (35.9)	0.549
Chronic heart disease	3/21 (14.3)	6/104 (5.8)	0.168
Diabetes	4/21 (19.0)	17/104 (16.3)	0.763
Chronic lung disease (not asthma)	4/21 (19.0)	13/105 (12.4)	0.414
Obesity (BMI ≥ 30 kg/m^2)	1/18 (5.6)	19/94 (20.2)	0.137
Other chronic neurological disorder	0/21 (0)	5/104 (4.8)	0.305
Asthma	0/21 (0)	6/105 (5.7)	0.262
Solid cancer (active)	1/21 (4.8)	2/105 (1.9)	0.433
Haematological cancer (active)	0/21 (0)	2/104 (1.9)	0.522
Chronic kidney disease[a]	3/21 (14.3)	3/104 (2.9)	0.026
Liver cirrhosis	0/21 (0)	3/104 (2.9)	0.431
Inflammatory disease	0/21 (0)	4/105 (3.8)	0.363
Dementia	0/21 (0)	3/105 (2.9)	0.433
Signs and symptoms (>10%) [*n*/no. with data (%)]			
History of fever	19/21 (90.5)	94/105 (89.5)	0.896
Cough	14/21 (66.7)	80/105 (76.2)	0.360
Malaise	12/21 (57.1)	71/102 (69.6)	0.267
Dyspnoea	14/21 (66.7)	59/103 (57.3)	0.426
Upper respiratory tract symptoms	9/21 (42.9)	30/103 (29.1)	0.217
Myalgia/arthralgia	4/21 (19.0)	27/97 (27.8)	0.407
Diarrhoea	4/21 (19.0)	16/103 (15.5)	0.690
Headache	4/21 (19.0)	13/98 (13.3)	0.492
Vomiting/nausea	3/21 (14.3)	16/99 (16.2)	0.831
Chest pain	2/21 (9.5)	13/98 (13.3)	0.639
Chest radiography [*n*/no. with data (%)]			
Infiltrates present at baseline	18/20 (90.0)	86/100 (86.0)	0.631
Bilateral opacities	15/18 (83.3)	62/82 (75.6)	0.481
Capillary O_2 saturation at room air (%)			
No. with data	19	89	
Median (Q1–Q3)	95 (89–97)	95 (92–97)	0.647
Laboratory parameters			
Leukocyte count (*n* with data)	17	103	
Median (Q1–Q3) (cells/μL)	6540 (5590–8120)	6400 (4580–7900)	0.489

(Continues)

TABLE 2 (Continued)

	PWH (*N* = 21)	Non-PWH (*N* = 105)	*P*
Lymphocyte count (*n* with data)	17	102	
Median (Q1–Q3) (cells/μL)	1170 (930–1500)	1100 (820–1450)	0.247
Neutrophil count (*n* with data)	17	104	
Median (Q1–Q3) (cells/μL)	4370 (3780–6730)	4310 (2900–6050)	0.497
Neutrophil-to-lymphocyte ratio [*n* with data (%)]	17	102	
Median (Q1–Q3)	3.6 (2.2–5.9)	3.7 (2.4–6.6)	0.838
D-Dimer [*n* with data]	13	45	
Median (Q1–Q3) (ng/mL)	591 (349–1324)	490 (310–880)	0.508
ALT (*n* with data)	16	93	
Median (Q1–Q3) (U/L)	29 (12–46)	39 (22–58)	0.234
Creatinine (*n* with data)	17	104	
Median (Q1–Q3) (mg/dL)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.932
C-reactive protein (*n* with data)	17	98	
Median (Q1–Q3) (mg/L)	13 (9–17)	49 (21–116)	<0.001
COVID-19 SEIMC score			
No. with data	15	85	
Median (Q1–Q3)	4 (2–7)	5 (3–7)	0.996
Supportive therapy [*n*/no. with data (%)]			
Oxygen therapy (nasal, reservoir, mask)	13/21 (61.9)	88/102 (78.4)	0.108
BiPAP, CPAP, HFNO	0/21 (0)	20/102 (19.6)	0.027
Mechanical ventilation	2/21 (9.5)	24/103 (23.3)	0.158
Inotropes/vasopressors	2/21 (9.5)	17/102 (16.7)	0.409
Renal replacement therapy/dialysis	1/21 (4.8)	3/100 (3.0)	0.681
Treatment [*n*/no. with data (%)]			
Remdesivir	0/21	3/102 (2.9)	0.426
Corticosteroids	7/21 (33.3)	28/102 (27.4)	0.586
Tocilizumab	1/21 (4.8)	17/102 (16.7)	0.160
Outcomes [*n*/no. with data (%)]			
Death	2/21 (9.5)	12/105 (11.4)	0.800

Abbreviations: ALT, alanine, aminotransferase; BiPAP, bilevel positive airway pressure; BMI, body mass index; CPAP, continuous positive airways pressure; HFNO, high-flow nasal oxygen therapy; non-PWH, people not infected with HIV; PWH, people with HIV; Q1/Q3, first/third quartile; SEIMC, Spanish Society of Infectious Diseases and Clinical Microbiology.

[a]Defined as an estimated glomerular filtration rate by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula of <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause.

DISCUSSION

In this retrospective study nested in a large prospective cohort of PWH in Spain, COVID-19 was reported as confirmed in 0.4% of individuals up to 30 June 2020, 46.7% of whom were hospitalized. Most individuals had well-controlled HIV infection; however, those hospitalized were older and more frequently afflicted with underlying comorbidities than those managed ambulatorily. These findings are similar to those reported in two other sizeable multicentre retrospective studies with PWH in Spain and Italy, where 0.4% and 0.3% of PWH developed COVID-19, and 63.9% and 55.1%, respectively, were hospitalized [13,14]. A higher frequency of COVID-19 was found in a population-based study in the West Cape region in South Africa, in which the infection was confirmed in 7.4% of PWH [3].

We also compared the characteristics and outcomes of hospitalized PWH with COVID-19 with age/sex-matched non-PWH controls from a cohort of hospitalized individuals with COVID-19 in Spain [2]. Clinical features and severity score on admission were well matched between the groups. However, serum CRP concentrations indicative of systemic inflammation were lower in PWH than in non-PWH. Notwithstanding this, median serum concentrations of CRP in both groups were

below the cut-off values associated with severe disease and fatal outcomes (50 and 75 mg/L, respectively) [15].

It is notable that a higher proportion of PWH than non-PWH were born abroad, particularly in Latin American countries, most likely because these individuals are overrepresented in CoRIS compared with Spain's general population. Other explanations include increased exposure to SARS-CoV-2 due to differences in societal factors or differences in the genetic background that could influence COVID-19 acquisition. In a single-centre case series from the UK, hospitalized PWH with COVID-19 were more likely to be of black ethnicity [4]. However, no differences in race/ethnicity between hospitalized PWH and non-PWH were found in two multicentre case series from the USA [5,6].

We found that mortality for COVID-19 among PWH was 4.4% overall and 9.5% among those hospitalized, a figure not significantly different from the 11.4% seen in the age/sex-matched non-PWH controls. Of note, approximately a third of hospitalized patients with COVID-19 received corticosteroids, and a smaller proportion received tocilizumab or remdesivir, with no statistically significant differences found between PWH and non-PWH. No significant differences in mortality between PWH and non-PWH have been described in four studies from the UK and the USA [4-6,8], including a large retrospective study of the US Veterans Aging Cohort Study that included all veterans with HIV and 1:2 age-, race/ethnicity-, sex- and site-matched uninfected veterans, in which no evidence was found of increased risk of severe COVID-19 outcomes including death by HIV status [8]. Nevertheless, an association between HIV infection and COVID-19 death has been found in South Africa [3] and two extensive studies from the UK [7,9], although one or more confounding factors (socioeconomic status and type of occupation, comorbidities, body mass index, smoking and markers of HIV control) could not be ruled out in these studies. In a recent cohort study of linked HIV diagnosis, COVID-19 laboratory diagnosis and hospitalization databases in New York State, PWH were more likely to receive a diagnosis of, be hospitalized with, and die in-hospital with COVID-19 compared with non-PWH [10]. In this study, COVID-19 hospitalization and mortality remained significantly elevated for PWH after demographic adjustment; but again, the role played by comorbidities, risk behaviours and socioeconomic status could not be determined.

Our study is limited by retrospective design and by the small number of PWH with COVID-19. Our work is also limited by the absence of critical socioeconomic information about housing, employment and level of education. Strengths include having been carried out in a prospective cohort of PWH, a comparison with age- and sex-matched non-PWH controls, and the use of a validated predictive scoring system.

In conclusion, our findings suggest that well-controlled HIV infection does not modify the clinical presentation or worsen clinical outcomes in patients hospitalized with COVID-19.

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CONFLICT OF INTEREST

JCL reports honoraria for advice or public speaking from Gilead, MSD, Janssen and ViiV Healthcare. JRB reports honoraria for advice or public speaking from Abbvie, Gilead, MSD, Janssen and ViiV Healthcare, and grants from Gilead. LJG-F reports honoraria for advice or public speaking from MSD and grants from GILEAD. FG reports honoraria for advice or public speaking from Janssen and ViiV Healthcare. IS-G reports honoraria for advice or public speaking from Gilead, MSD and ViiV Healthcare. JRA reports honoraria for advice or public speaking from Alexa, Gilead, MSD, Janssen, Serono, Teva and ViiV Healthcare, and grants from Alexa, Gilead, Janssen, MSD, Serono, Teva and ViiV Healthcare. SM reports honoraria for advice or public speaking from Gilead, MSD, Janssen and ViiV Healthcare, and grants from Gilead, MSD and ViiV Healthcare. JG-G reports honoraria for advice or public speaking from Gilead, MSD, Janssen and ViiV Healthcare. IJ reports honoraria for advice or public speaking from Gilead and ViiV Healthcare, and grants from MSD. JB reports honoraria for advice or public speaking from Abbvie, Gilead, MSD, Janssen and ViiV Healthcare, and grants from Abbvie, Gilead, MSD and ViiV Healthcare. CD, JDR-R, RM, SC, GS, JP, LJG-F, JLG-S, CA and MN have nothing to disclose.

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AUTHOR CONTRIBUTIONS

JB conceived the study. CD, JRA, SM, JG and IJ made substantial contributions to the conception and design. JDR and IJ analysed the data. RM, JCL, JRB, SC, GS, JP, LJG-F, FG, JLG, IS, CA and MN made substantial contributions to the acquisition of data. JB drafted the manuscript, and all authors revised it critically and approved the final version.

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APPENDIX

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