

Fattori associati con il ricovero ospedaliero per COVID-19 in 80 pazienti HIV-positivi italiani.

Factors associated with hospital admission for COVID-19 in 80 Italian HIV patients.

Lucia Taramasso,¹ Leonardo Calza,² Nicola Squillace,³ Barbara Menzaghi,⁴ Stefano Rusconi,⁵ Andrea Parisini,⁶ Giancarlo Orofino,⁷ Olivia Bargiacchi,⁸ Roberto Gulminetti,⁹ Molteni Chiara,¹⁰ Laura Valsecchi,¹¹ Giovanni Cenderello,¹² Sergio Ferrara,¹³ Paolo Maggi,¹⁴ Annalisa Saracino,¹⁵ Katia Falasca,¹⁶ Antonio Di Biagio,¹ Paolo Bonfanti,³ for the CISAI Study group.

¹ Infectious Diseases, University of Genoa, San Martino Hospital Genoa, Genoa

² Clinic of Infectious Diseases, S.Orsola Hospital, Department of Medical and Surgical Sciences, University of Bologna, Italy

³ Infectious Diseases Unit ASST-Monza, San Gerardo Hospital-University of Milano-Bicocca, Monza, Italy

⁴ Unit of Infectious Diseases, ASST della Valle Olona - Busto Arsizio (MI), Italy

⁵ Infectious Diseases Unit, DIBIC "Luigi Sacco", University of Milan, Milan, Italy

⁶ Unit of Infectious Diseases, SS.Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy

⁷ Division I of infectious and Tropical Diseases, ASL Città di Torino, Italy

⁸ Infectious Diseases Unit, AOU Maggiore della Carità, Novara, Italy

⁹ Division of Infectious Diseases and Immunology, Department of Medical Sciences and Infectious Diseases, Fondazione IRCCS San Matteo, Pavia, Italy

¹⁰ Unit of Infectious Diseases, A. Manzoni Hospital, ASST Lecco, Italy

¹¹ Department of Infectious Diseases, ASST Fatebenefratelli Sacco, Milan, Italy

¹² Unit of Infectious Diseases, Department of Graduated Medical Care, Sanremo Hospital, Sanremo, Italy

¹³ S.C. Malattie Infettive Universitarie AOU OO.RR. Foggia, Italy

¹⁴ Infectious Diseases Clinic University of Campania "Luigi Vanvitelli", Naples,

¹⁵ Infectious Disease Clinic, University of Bari, Bari, Italy

¹⁶ Clinic of Infectious Diseases, Department of Medicine and Science of Aging, University "G. d'Annunzio" Chieti-Pescara, Italy

Corresponding author:

Lucia Taramasso
Clinica Malattie Infettive,
Università degli Studi
di Genova
Ospedale Policlinico
San Martino di Genova
Padiglione Patologie
Complesse
Piano-2
Largo R. Benzi, 10

taramasso.lucia@gmail.com

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Riassunto

Questo studio analizza i ricoveri ospedalieri e l'outcome di 80 pazienti HIV-positivi, con diagnosi di infezione da SARS-CoV-2 effettuata tra febbraio e settembre 2020, in una rete di centri di Malattie Infettive italiani.

Sesso, etnia e durata dell'infezione da HIV e dei trattamenti antiretrovirali (ART) erano simili nei soggetti ricoverati e non, mentre i 45 pazienti ricoverati erano più vecchi, avevano valori più bassi sia per quanto riguarda il nadir dei CD4 che la conta dei linfociti al momento della diagnosi.

Questi due valori erano anche correlati ad un esito peggiore della COVID-19.

Durante il periodo di osservazione, 10 (12.3%) pazienti sono morti. La terapia ART non sembrava associata con la severità della malattia da SARS-CoV-2.

Abstract

This study reports on hospital admission and outcomes of 80 HIV-infected subjects who were diagnosed with SARS-CoV-2 infection between February and September 2020, in a network of Italian centers.

Sex, ethnicity and duration of HIV infection and antiretroviral therapy (ART) were similar in admitted and non-admitted subjects, whereas 45 admitted patients were older, had lower nadir CD4 cells and current lymphocytes count.

These values were also correlated to worse COVID-19 outcome.

Ten (12.3%) patients died over the observation period. ART drugs did not seem associated with disease severity.

Introduction

As of 22 November 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected more than 55 million people on five continents, and more than 1,272,000 infections, causing 47,000 deaths in Italy. Prognosis for Coronavirus disease 2019 (COVID-19) is worse for older people and those with comorbidities (hypertension, diabetes, cardiovascular diseases, lung diseases) (1). It was recently observed, in a large cohort of unselected COVID-19 patients, admitted to 30 different clinical centers all over Italy, that the major predictors of in-hospital death were impaired renal function, elevated C reactive protein and advanced age (2). Regarding people living with HIV (PLWH), the emergence of COVID-19 created another health burden for a group that may already be at heightened risk for other comorbidities (3), because maintaining adequate standard of HIV care may be hard during this pandemic (4). Besides these potential extra burdens, few information is available on COVID-19 severity and prognosis in patients with HIV coinfection (5,6). In Italy, an early report on 47 patients with HIV and SARS-CoV-2 coinfection (7) suggested a lower death toll (about 4%) as compared to the HIV-negative patients in the same hospital (about 17%). As data piled up, new observations emerged. For example, characteristics of PLWH with COVID-19 did not differ from the rest of the HIV population, in Barcelona HIV cohort (8). Clinical presentation, severity rate, and mortality were not dependent on any HIV-related or antiretroviral (ART)-related factor. COVID-19 standardized incidence rate was lower in PLWH than in the Barcelona general population, although no comparison of mortality rate was performed between the two groups, thus confirming the previous results from Gervasoni et al. (7). In a paper by Hadi JB et al. (9), crude COVID-19 mortality resulted higher in PLWH. However, propensity matched analyses revealed no difference in outcomes, showing that higher mortality is driven by higher burden of comorbidities rather than HIV infection *per se*. This finding was further confirmed in a study where 42 HIV-negative and 21 HIV-positive COVID-19 patients (10) were matched by admission date, age, body mass index, gender, tobacco history, and a history of chronic kidney disease, hypertension,

asthma, chronic obstructive pulmonary disease, and heart failure. HIV coinfection did not significantly impact presentation, hospital course, or outcomes of patients infected with SARS-CoV-2. To offer further information on HIV characteristics potentially affecting COVID-19 outcome, we present the update of a multi-center experience in patients infected with HIV-1 in Italy and diagnosed with SARS-CoV-2 infection (11).

Methods

The purpose of this study was to describe the epidemiological and clinical features, as well as the outcomes of 80 HIV patients with confirmed SARS-CoV-2. They were observed in a network of Infectious Diseases Departments participating in the CISA (*Coordinamento Italiano per lo Studio dell'Infezione da HIV e Allergie*) Study Group (AIDS) between March and September 2020. Using a standard collection form, we collected information on patients' and HIV infection characteristics and history, ART at SARS-CoV-2 infection diagnosis, hospital admission and COVID-19 clinical outcome. When diagnosed with SARS-CoV-2 infection, patients signed the consent to the use of their anonymized information for clinical studies. Twenty-five Infectious Diseases Clinics participated in this survey and 17 collected data of patients with COVID-19. Eight of them did not record infections, with or without subsequent hospitalization, among their HIV patients, mainly in the Southern and Central Italy.

Among over 23,000 individuals referring to the centers of our network, 80 were diagnosed with SARS-CoV-2 infection and 45 were admitted to hospital due to moderate to severe COVID-19 (3 of them because their housing situation prevented isolation) between February, 21 and September, 10. A diagnosis of SARS-CoV-2 infection was based on a throat swab positive for viral nucleic acid in all patients, irrespectively of their needing of hospital admission.

Results

Hospitalized PLWH were slightly older, with CDC stage C more frequently B and C than A, lower nadir CD4 count and last lymphocytes count. Using proc logistic to evaluate the risk of requiring hospitalization for COVID-19, we found that the sex- and age-adjusted odds ratio (aOR) for nadir CD4 cells was 0.86 (by 50 cells/mm³, 95% confidence

Patient's characteristics	No hospital admission		Hospital admission		P [§]
	N*=35	%*	N*=45	%*	
Male sex	23	65.7	37	82.2	0.09
Age at hospital admission, years (median, IQR)	52	45-58	56	51-62	0.03
Caucasian ethnicity	31	88.6	37	82.2	0.54
Risk factor for HIV acquisition					
MSM	15	42.9	14	31.1	0.48
Heterosexual	13	37.1	16	35.6	
IDU	7	20.0	14	31.1	
Other	0	0	1	2.2	
CDC stage					
A	20	57.1	16	35.6	0.03
B	7	20.0	10	22.2	
C	7	20.0	18	40.0	
Unknown	1	2.9	1	2.2	
Nadir CD4 T, cells/mm ³ (median, IQR)	378	159-519	167	60-355	0.008
HIV infection duration, years (median, IQR)	11	6-20	16	7-20.5	0.19
ART duration, years (median, IQR)	8	4-20	13	6-19	0.29
At last control					
HIV-RNA <50 copies/mm ³	29	82.9	40	88.9	0.44
CD4, cells/mm ³ (median, IQR)	598	508-765	536	351-726	0.23
CD8, cells/mm ³ (median, IQR)	688	655-844	689	502-811	0.36
CD4/CD8 ratio (median, IQR)	0.84	0.71-1.09	0.86	0.67-1.06	0.91
Leucocytes, cells/mm ³ (median, IQR)	5190	4620-6110	5210	4070-6270	0.81
Lymphocytes, cells/mm ³ (median, IQR)	1927	1250-2160	1320	760-1800	0.001
ART at SARS-CoV-2 diagnosis					
PI based	9	25.7	9	20.0	0.54
NNRTI based	11	31.4	12	26.7	0.64
INSTI-based	15	42.9	24	53.3	0.35
Tenofovir-containing	23	65.7	23	51.1	0.19
Comorbidities					
Hypertension	12	34.3	23	51.1	0.13
Diabetes	4	11.4	9	20.0	0.30
Cardiovascular diseases	4	11.4	10	22.2	0.25
Other	17	48.6	24	53.3	0.67
Days from symptoms to diagnosis (median, IQR)	4	3-6	7	3-8	0.02
Pneumonia	2	5.7	34	75.6	<0.0001
Outcome (N=79)					
Death	1	2.9	9	20.4	
Recovered w/o hospitalization	34	97.1	-	-	-
Discharged	-	-	33	41.8	
Still in hospital			2	4.6	

Table. Characteristics of 80 HIV-infected patients diagnosed with COVID-19, according to hospital admission.

* if not otherwise specified; § P refers to Pearson or Fisher exact or Mantel-Haenszel chi-square test, as appropriate, for frequencies, and to Mann-Whitney test for continuous variables. **IQR:** interquartile range; **MSM:** males having sex with males; **IDU:** intravenous drug use; **ART:** antiretroviral therapy; **PI:** protease inhibitors; **NNRTI:** non-nucleoside reverse transcriptase inhibitors; **INSTI:** integrase strand transferase inhibitors

interval (CI) 0.76-0.98) and 0.90 for lymphocytes count (by 100 cells/mm³, 95% CI 0.82-0.98). Including both variables in the model, we found that risk estimates did not change for lymphocytes count (aOR 0.89, 95% CI 0.81-0.98), whereas aOR for nadir CD4 level got closer to 1 and lost significance (0.94, 95% CI 0.91-1.08).

In the non-hospitalized group, one patient in an assisted-living facility died, as well as 9 in the hospitalized group. Two patients were still admitted at the time of this analysis and 33 had been discharged. Among 45 hospitalized subjects with known outcome, 38 were treated with hydroxychloroquine (with azithromycin in 12 patients), 14 with PI (added to non-PI-including ART in 13), 10 took heparin, 6 steroids, 2 tocilizumab and 6 other antimicrobials. Among those who were admitted to hospital, lower nadir CD4 and lymphocyte count were associated with death, but not significantly: 82 versus 180 cells/mm³ for nadir CD4 ($p=0.08$), and 700 versus 1360 cells/mm³ ($p=0.22$). The median hospital stay length was 13 days (interquartile range 7-20).

Discussion

Since the start of this pandemic, HIV patients' management was an issue, and evidence regarding coinfection with SARS-CoV-2 was episodic and forcibly limited. Beside the above cited studies from Barcelona (8) and the USA (9), two case series do not support the case for higher risk of death in PLWH than in the general population: in a multicentric study on hospitalized subjects in 12 German centers, 3 patients out of 33 died (9%) (12), whereas 2 deaths out of 13 (15%) patients needing hospital admission were observed in an Italian study (7), for an overall death rate of 4% (2/47). In our study, 20.4% of hospitalized patients died over the study period.

Due to the different testing strategies performed in the centers of our network, we cannot infer the proportion of subjects who experienced moderate to severe COVID-19, or even death, in the general population of PLWH. However, we could compare the characteristics of those who did or did not need hospital admission.

First, nadir CD4 cells count was significantly associated with hospital admission, irrespectively of the CD4 cells count at last visit before diagnosis. This suggests that, as well as for other conditions

such as non-AIDS events, a lower nadir CD4 cells seems to be a factor strongly associated with the development of severe cases of COVID-19 (13).

Second, despite almost all patients were treated with hydroxychloroquine and/or other agents suggested for COVID-19 treatment, the outcomes were not significantly better than in previous case-series (7,12), where a not negligible part of subjects did not receive these treatments.

Lastly, all PLWH included in this study were on antiretroviral treatments. Although the sample size is too small to draw any significant conclusions, we did not observe any association, significant or not, between need for hospital admission and class of ART drugs.

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