




Clinical Presentation and Outcome of COVID-19 in a Latin American Versus Spanish Population: Matched Case-Control Study

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ABSTRACT

Introduction: Increased mortality has been reported in the Latin American population. The objective is to compare the clinical

characteristics and outcome of Latin American and Spanish populations in a cohort of patients hospitalized with COVID-19 during the first year of the pandemic.

Methods: We retrospectively analysed all the Latin American patients (born in South or Central America) hospitalized in our centre from February 2020 to February 2021 and compared them with an age- and gender-matched group of Spanish subjects. Variables included were demographics, co-morbidities, clinical and analytical parameters at admission and treatment received. The primary outcomes were ICU admission and mortality at 60 days. A conditional regression analysis was performed

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to evaluate the independent baseline predictors of both outcomes.

Results: From the 3216 patients in the whole cohort, 216 pairs of case-controls (Latin American and Spanish patients, respectively) with same age and gender were analysed. COPD was more frequent in the Spanish group, while HIV was more prevalent in the Latin American group. Other co-morbidities showed no significant difference. Both groups presented with similar numbers of days from symptom onset, but the Latin American population had a higher respiratory rate (21 vs. 20 bpm, $P = 0.041$), CRP (9.13 vs. 6.22 mg/dl, $P = 0.001$), ferritin (571 vs. 383 ng/ml, $P = 0.012$) and procalcitonin (0.10 vs. 0.07 ng/ml, $P = 0.020$) at admission and lower cycle threshold of PCR (27 vs. 28.8, $P = 0.045$). While ICU admission and IVM were higher in the Latin American group (17.1% vs. 13% and 9.7% vs. 5.1%, respectively), this was not statistically significant. Latin American patients received remdesivir and anti-inflammatory therapies more often, and no difference in the 60-day mortality rate was found (3.2% for both groups).

Conclusion: Latin American patients with COVID-19 have more severe disease than Spanish patients, requiring ICU admission, antiviral and anti-inflammatory therapies more frequently. However, the mortality rate was similar in both groups.

Keywords: COVID-19; Latin American population; Mortality; Spanish population

Key Summary Points

Comparison between Latin American and Spanish patients hospitalized with COVID-19 was made.

Does the Latin American population have higher mortality due to SARS-CoV-2 infection?

The Latin American population had higher inflammatory parameters and more severe disease at admission, and they needed more ICU time and treatments than the Spanish group, but the mortality rate was the same.

Further investigation is needed to clarify whether this increased inflammatory response is due to genetic differences or related to higher viral exposure.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been detected worldwide, with > 4 million related deaths [1]. Several risk factors have been associated with worse outcome including host-dependent factors including age, gender and co-morbidities (chronic heart disease, chronic kidney disease and obesity), genetic traits of the immune response pathway responsible for control respiratory virus replication and virological factors such as the infecting variant or exposure to a high viral load from the index case [2]. These factors are associated with the development of a dysregulated immune response leading to complications such as pneumonia, acute respiratory distress syndrome (ARDS), pulmonary thrombosis and finally death [3]. Recently, three reports from the US described a significant increase in the mortality rate among the Latin American population. One, from Los Angeles County, described an age-adjusted mortality rate (AAMR) due to COVID-19 among Latinx individuals of 160.1 deaths per 100,000 patients

compared with 51.7 deaths per 100,000 patients among White individuals [4]. Another, performed in Florida, presented death rates of 86.8 and 39.3 per 100,000 patients for Latinx and White individuals, respectively [5]. The third, from 99 counties within 14 US states, compared non-Hispanic white persons with other populations. The Latin American population had a higher hospitalization, ICU admission and death rates [6]. These results suggest a role in the origin in COVID-19 outcomes, although it could also just be an association due to poor resources of this population compared to the White one. Indeed, a larger study from Veteran Affairs Hospitals across the US did not observe different mortality rates among the Latin American population compared to White individuals, although the clinical presentation and biomarkers were not evaluated, and consequently it was not possible to adjust the mortality rate according to the severity of the infection [7].

The Latinx population living in Spain is large, and they receive the same quality of care from the Public Health Services as that provided for the native Spanish people. Accordingly, we have performed a matched case-control study to compare the clinical presentation and outcome of Latin American and Spanish patients with COVID-19 admitted to our tertiary university hospital from February 2020 to February 2021. We hypothesized that Latin Americans have higher inflammatory response than Spaniards.

METHODS

Study Design and Patients

This matched case-control study was performed at the Hospital Clinic in Barcelona, Spain, a 700-bed university centre that provides care for an urban population of 500,000 adults. All patients admitted for ≥ 48 h with confirmed rRT-PCR tests performed with nasopharyngeal throat swabs or clinical pictures highly suggestive of COVID-19 between 18 February 2020 and 24 February 2021 were included. Deaths occurring within the first 48 h were included in the analysis. The Institutional Ethics

Committee of the Hospital Clinic of Barcelona approved the study, and due to the nature of the retrospective data review, they waived the need for informed consent from individual patients (HCB/2020/0273). This corresponds to the same number as in previous articles from our group because the project included the analysis of different variables associated with COVID-19 outcomes. The Institutional Ethics Committee of Hospital Clinic of Barcelona approved the study and, due to the nature of the retrospective data review, waived the need for informed consent from individual patients (HCB/2020/0273). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments.

Patients who were born in any country from South or Central America were identified as members of the Latin American group, whereas those born in Spain were considered Spaniards.

Data Collection

Data were retrospectively collected for all patients included in the study from the electronic health records (EHRs). An intelligent system was used to retrieve the high-quality data from EHRs (SILDv1.0 system, S34M[®]) as previously described [8]. Variables included were: age, gender, pre-admission duration of symptoms in days, co-morbidities (hypertension, chronic heart disease, diabetes mellitus, chronic liver disease, chronic kidney disease, chronic obstructive pulmonary disease, haematological and solid neoplasia), respiratory rate and ambient air arterial oxygen saturation (SaO₂) measured with a pulse oximeter at admission, creatinine, lymphocyte count, C-reactive protein (C-RP), lactate dehydrogenase (LDH), D-dimer, ferritin and procalcitonin within the first 24 h from hospital admission. Body mass index was not available. When it was available, the cycle threshold (Ct) of the diagnostic RT-PCR test was gathered. Data on the need for ICU admission and invasive mechanical ventilation were also gathered. Data on treatment with remdesivir, tocilizumab and dexamethasone during the hospitalization were

Table 1 Characteristics of patients according to study groups

Variable	Latin American group (<i>n</i> = 216)	Spanish group (<i>n</i> = 216)	<i>P</i> - value ^m
Median (IQR) age in years	48 (40–58)	48 (40–58)	1
Male gender, <i>n</i> (%)	114 (52.8)	114 (52.8)	1
Comorbidity, <i>n</i> (%)			
Chronic heart disease	21 (9.7)	18 (8.3)	0.615
Hypertension	51 (23.6)	55 (25.5)	0.655
Diabetes mellitus	27 (12.5)	22 (10.2)	0.448
Chronic kidney disease	10 (4.6)	13 (6)	0.520
Chronic liver disease	19 (8.8)	17 (7.9)	0.728
COPD	3 (1.4)	11 (5.1)	0.030
Haematological malignancy	7 (3.2)	11 (5.1)	0.336
Solid neoplasm	5 (2.3)	12 (5.6)	0.083
Solid organ transplantation	5 (2.3)	7 (3.2)	0.558
HIV infection	16 (7.4)	5 (2.3)	0.014
Parameters at admission			
Days from symptom onset ^a	7 (5–9)	7 (5–9)	0.943
Median (IQR) respiratory rate, breaths per min ^b	21 (18–24)	20 (18–24)	0.041
Median (IQR) temperature, °C ^c	37 (36.5–37.8)	37.1 (36.5–38)	0.716
Median (IQR) percentage of oxygen saturation ^d	95 (93–96)	95 (93–96)	0.537
Median (IQR) Ct ^e	27 (22.9–30)	28.8 (24.6–31.4)	0.045
Median (IQR) creatinine, mg/dl ^f	0.82 (0.66–0.99)	0.81 (0.67–0.96)	0.678
Median (IQR) C-reactive protein, mg/dl ^g	9.13 (4.67–15)	6.22 (2.87–10.28)	0.001
Median (IQR) LDH, IU/ml ^h	310 (258–388)	301 (242–358)	0.082
Median (IQR) ferritin, ng/ml ⁱ	571 (258–1142)	383 (189–962)	0.012
Median (IQR) D-dimer, IU/l ^j	500 (300–900)	500 (400–975)	0.079
Median (IQR) procalcitonin, ng/ml ^k	0.10 (0.05–0.21)	0.07 (0.04–0.15)	0.020
Median (IQR) lymphocyte count, cells/mm ^{3,l}	1000 (800–1300)	1000 (700–1325)	0.201
Treatment			
Remdesivir	56 (25.9)	34 (15.7)	0.009
Tocilizumab	50 (23.1)	36 (16.7)	0.092

Table 1 continued

Variable	Latin American group (<i>n</i> = 216)	Spanish group (<i>n</i> = 216)	<i>P</i> - value ^m
Dexamethasone	74 (34.3)	54 (25)	0.035

COPD chronic obstructive pulmonary disease, *HIV* human immunodeficiency virus, *Ct* cycle threshold

^aThis value was available in 193 cases in the Latin American group and 199 in the Spanish group

^bThis value was available in 182 cases in the Latin American group and 167 in the Spanish group

^cThis value was available in 214 cases in the Latin American group and 213 in the Spanish group

^dThis value was available in 215 cases in the Latin American group and 211 in the Spanish group

^eThis value was available in 93 cases in the Latin American group and 86 in the Spanish group

^fThis value was available in all cases in the Latin American group and 214 in the Spanish group

^gThis value was available in all cases in the Latin American group and 213 in the Spanish group

^hThis value was available in 211 cases in the Latin American group and 207 in the Spanish group

ⁱThis value was available in 194 cases in the Latin American group and 176 in the Spanish group

^jThis value was available in 207 cases in the Latin American group and 196 in the Spanish group

^kThis value was available in 190 cases in the Latin American group and 177 in the Spanish group

^lThis value was available in all cases in the Latin American group and 214 in the Spanish group

^mCategorical variables were compared using the chi-squared test and continuous variables with the Mann-Whitney *U* test

collected. The primary endpoints were ICU admission and mortality at 60 days.

Statistical Analysis

We looked for controls born in Spain with the same age and gender among the 3216 patients recorded in our previously described database [8]. No other variables were used for matching patients. The matching was performed using the SPSS tool (SPSS Inc., Chicago, IL). Categorical variables were described using the absolute number and percentage and continuous variables using the median and interquartile range (IQR). Categorical variables were compared using a chi-squared test or Fisher exact test when necessary. Continuous variables were compared using Mann-Whitney *U* test. A conditional regression analysis was performed to evaluate the independent baseline predictors of ICU admission and mortality at 60 days. Baseline variables included demographics, co-morbidities and biochemical parameters within the first 24 h from admission. Continuous variables were dichotomized by the median value to be included in the uni- and multivariate analyses.

Variables with a *P*-value < 0.2 in the univariate analysis were included in the regression analysis. Only variables with < 10% missing values were considered for the analysis. The origin group (Latin American or Spanish) was forced to enter in the model to evaluate its potential independent influence on the outcomes. There was no imputation for missing data. Statistical significance was defined as a two-tailed *P*-value < 0.05. The analysis was performed in SPSS version 26 (SPSS Inc., Chicago, IL).

RESULTS

A total of 3216 patients were admitted, and 222 (6.9%) of these were born in a South or Central American country and were identified as the Latin American group. A total of 216 pairs of cases (Latin American group) and controls (Spanish group) with the same age and gender were identified and included in the study. The main demographic variables and co-morbidities are shown in Table 1. The rate of co-morbidities was similar between the two groups except for chronic obstructive pulmonary disease (COPD),

which was more frequent among the Spanish patients (5.1% [11 out of 216] vs. 1.4% [3 out of 216], $P = 0.030$), and HIV infection (7.4% [16 out of 216] vs. 2.3% [5 out of 216], $P = 0.014$), which was more prevalent in the Latin American group. Although the number of days from symptom onset to admission was the same between the two groups, the Latin American group had a significantly higher respiratory rate (21 versus 20 breaths per minute, $P = 0.041$), and there were significant differences in the main inflammatory parameters. The median CRP (9.13 mg/dl vs. 6.22 mg/dl, $P = 0.001$), ferritin (571 ng/ml vs. 383 ng/ml, $P = 0.012$) and procalcitonin (0.10 ng/ml versus 0.07 ng/ml, $P = 0.020$) were significantly higher in the Latin American group. The Ct value was available in 179 patients (93 from the Latin American group and 86 from the Spanish group), and its median value was significantly lower in the Latin American group (27 versus 28.8, $P = 0.045$), suggesting a higher viral load.

In terms of outcome, the Latin American group required ICU admission (17.1% vs. 13%, $P = 0.226$) and invasive mechanical ventilation (9.7% vs. 5.1%, $P = 0.066$) more frequently, although these differences were not statistically significant. No difference in the mortality at 30 (2.8% for both groups) and 60 days (3.2% for both groups) was observed.

Variables associated with ICU admission were age, male gender, co-morbidities, oxygen saturation and inflammatory parameters (Supplementary material, Table S1). Repeating the analysis for ICU admission without age and gender showed no changes in the final model. Conditional regression analysis identified as independent baseline variables, oxygen saturation (OR, 1.424; CI 95% 1.253–1.681, $P < 0.001$), creatinine > 0.82 mg/dl (OR, 1.927; CI 95% 1.007–3.690, $P = 0.048$), CRP > 7.5 mg/dl (OR, 2.920; CI 95% 1.430–5.962, $P = 0.003$) and D-dimer > 500 IU/l (OR, 2.047; CI 95% 3.066–1.934, $P = 0.031$). The Latin American origin variable was not entered in any of the models as an independent variable. Variables associated with mortality at 60 days are shown in supplementary material (Table S2). Age and co-morbidities were the most important factors, and the conditional regression analysis selected

age > 66 years (OR, 9.823; CI 95% 1.091–88.461, $P = 0.042$), chronic renal failure (OR, 23.386; CI 95% 5.496–99.511, $P < 0.001$) and chronic liver disease (OR, 5.420; CI 95% 1.111–26.441, $P = 0.037$) as independent variables.

DISCUSSION

A worse outcome of COVID-19 among Latin American patients has been suggested in recent articles that compare the mortality rate in this population versus others [4]. In our hospital, 6.9% (222 out of 3216) patients were from Latin America, which is more than double the rate of officially recognized Latin American natives living in Barcelona (3%). This finding suggests that this population has a higher exposure or susceptibility to SARS-CoV-2 infection. We identified 216 pairs matched by age and gender, and the main conclusion is that Latin American patients, at the time of hospital admission, had a higher viral load (low Ct values), higher respiratory rate and higher serum concentration of inflammatory markers (C-RP, LDH, ferritin, D-dimer and procalcitonin). These differences existed even when the duration of symptoms prior to admission was the same in both origin groups. Potential explanations for a higher viral load in the Latin American group include a particular genetic trait in any of the innate immune system pathways responsible for controlling the viral replication, as has been demonstrated in adults with worse outcomes [9], or a higher frequency of autoantibodies against interferon- 2α among the Latin American population [10]. Indeed, autoimmunity is more frequent and the clinical expression is more severe in this population [11]. Other explanations could be related to the exposure to a higher viral load. The exposure to an index case with a high viral load in respiratory secretions has been associated with a higher risk of developing symptomatic COVID-19 [12, 13]. The analysis of three clusters of COVID-19 that occurred in close environments showed that the severity of the new infections was inversely associated with the house size [14]. The Latin American population, according to their social

status, usually lives in small, poorly ventilated apartments, with more family members; this could explain our results in part. Of course, both hypotheses are not mutually exclusive and can be combined in the Latin American population.

The viral load of SARS-CoV-2 correlates with the inflammatory response, severity of the infection and death [15]. Inflammatory markers were significantly higher in the Latin American group, but their mortality rate, adjusted by age and gender, was not different from that of the control group. It sounds reasonable to attribute this finding to the fact that the protocol of our institution includes remdesivir [16] and anti-inflammatory therapies including tocilizumab and dexamethasone [17] from the beginning. In agreement with the clinical presentation of Latin American patients, they received remdesivir, tocilizumab and dexamethasone more frequently.

The main limitation of our study is the lack of information about anthropometric variables of the included population. The influence of obesity on the outcome of COVID-19 is well recognized, but unfortunately, we did not collect this information. The second limitation is that the Ct value was only available in approximately 40% of the included patients. However, the significantly higher inflammatory response observed in Latin Americans makes this finding reasonable. The third limitation is that we divided the group by the place of birth but not according to the ethnic group. The fourth limitation is that we included the number of days from symptom onset to hospitalization in the analysis, and the interpretation of this variable could be difficult in the elderly or it could be biased by socioeconomic factors.

CONCLUSIONS

Latin American patients living in Spain and admitted to the hospital because of SARS-CoV-2 infection had a higher viral load and inflammatory response than native Spaniards even when they had the same duration of symptoms prior to admission. Consequently, they required ICU admission, invasive mechanical

ventilation, and the prescription of antiviral and anti-inflammatory therapies more frequently. Nonetheless, there were no differences in mortality in this population. In the future, to clarify the potential influence of genetics on the outcome of Latin American patients, it will be necessary to include this population in larger studies. While waiting for these results, it is important to advise the at-risk populations to implement isolation measures and room ventilation at home when an index case is declared, particularly in a crowded environments, to avoid exposure to higher viral loads and to implement adequate protocols of treatment to reduce the mortality rate.

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Data availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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