ORIGINAL ARTICLE

# FACTORS ASSOCIATED WITH COVID-19 LETHALITY IN A HOSPITAL IN THE CAJAMARCA REGION IN PERU

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## ABSTRACT

**Objective.** To identify the clinical and epidemiological characteristics related to lethality in patients hospitalized for COVID-19 at the Simón Bolívar Hospital in Cajamarca, during June-August 2020. **Materials and Methods.** This was a retrospective cohort, that used information collected from clinical records and official epidemiological surveillance systems (NOTIWEB, SISCOVID and SINADEF), on hospitalized patients with confirmed COVID-19 diagnosis. Information was collected on sociodemographic and clinical factors, considering discharge (death/survival) and days of hospitalization as outcomes. **Results.** The in-hospital fatality rate was 39.6%, and significant differences were found between hospitalization time and status at discharge in people over 60 years of age ($p<0.001$). Age older than 60 years (HR: 2.87; 95% CI: 1.76-4.68),) unattended ICU bed request (HR: 3.49; 95% CI: 2.02-6.05), oxygen saturation less than 80% at admission (HR: 2.73; 95% CI: 1.35-5.53) and the use of ivermectin (HR: 1.68; 95%CI 1.06-2.68) were factors associated with lethality. The chosen ML model considered that the most important variables were oxygen saturation, age over 60 years, time of hospitalization and time of the onset of symptoms. **Conclusion.** The factors that could increase lethality in patients hospitalized for COVID-19 were age, oxygen saturation less than 80%, use of ivermectin as part of hospital treatment and unattended request for ICU beds. Future studies with better representativeness could confirm these possible relationships at the regional or national level.

**Keywords:** COVID-19; Hospitalization; Case Fatality Rate; Hypertension; Obesity; Ivermectin; Hypoxia; Therapeutics; Intensive Care Units; Medical Records (Source: MeSH).

## INTRODUCTION

COVID-19 (Coronavirus Disease 2019) is the name assigned by the World Health Organization (WHO) to the disease produced by a type of coronavirus called SARSCoV-2 [(1)]; it was officially declared a pandemic on March 2020 [(2)]. One of the most outstanding characteristics of this disease is its high transmissibility, with a high basic reproduction number (R0) ranging between 2.2 and 3.5, which explains its rapid spread around the world [(3)].

At the same time, the clinical course of this disease represents a challenge for healthcare systems. In humans, the same infectious agent can cause, an asymptomatic, mild/moderate condition; a severe condition requiring mechanical ventilation, intensive care unit beds, and finally, death [(4)]. In this sense, it is important to know what type of factors could influence the clinical presentation and the possibility of death among patients with COVID-19. Most studies agree that the presence of some comorbidities (arterial hypertension, type 2 diabetes, chronic kidney disease or chronic obstructive pulmonary disease), age and some laboratory parameters are related to the possibility of dying from COVID-19 [(5)].

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Peru is one of the countries most affected by the COVID-19 pandemic, and one of those with the highest excess mortality reported worldwide [6]. Although there are previous studies that have attempted to study factors associated with lethality in cases of COVID-19 in Peru [7-9], and some examples in Asian countries [10], it is necessary to conduct or expand studies in other regions, considering the geographical context and the measurement of operational aspects, because regional hospital capacity is much lower compared to the country's capital [11].

As of June 23, 2021, the Cajamarca region reported 61,613 cases, with a mortality rate of 266.9 per 100,000 inhabitants and a case fatality rate of 6.3% [12]. It is also the second department in the northern region with the highest percentage of excess mortality (72.5%), surpassed only by Tumbes (87.5%) [13]. Therefore, the aim of this research was to identify the clinical and epidemiological characteristics related to lethality in patients hospitalized for COVID-19 at the Hospital Simón Bolívar in Cajamarca, during June-August 2020.

## KEY MESSAGES

**Motivation for the study:** The Cajamarca region had one of the highest excess mortality rates during the first wave of the COVID-19 pandemic.

**Main findings:** Age older than 60 years, arterial hypertension, oxygen saturation less than 80% on admission, use of ivermectin in the hospital therapeutic scheme, and unattended ICU bed request increased the risk of lethality in COVID-19 patients.

**Implications:** Timely recognition of clinical and epidemiological risk factors can help determine patient prognosis and implement strategies to reduce the risk of death.

## MATERIALS AND METHODS

### Design and Study type

This was a quantitative, observational, retrospective cohort, analytical, quantitative research on patients discharged or deceased after hospitalization due to confirmed SARS-CoV-2 infection at the Hospital Simón Bolívar, during the period from June 1 to August 31, 2020.

### Population and sample

The Hospital II-E Simón Bolívar (HSB), of the Cajamarca Health Network, was declared as the COVID Hospital of Cajamarca since April 2020, thus expanding its capacity for the care of patients affected by this disease, from diagnosis, medicinal oxygen supply, hospitalization, intensive care unit and mechanical ventilation.

The study population consisted of all patients hospitalized at HSB between June 1 and August 31, 2020. Records of patients aged 14 years or older, who were admitted to hospitalization with confirmed SARS-CoV-2 infection by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test result from a nasopharyngeal swab, or a positive rapid serological test result (lateral flow immunochromatography), were selected. Exclusion criteria were: (a) incomplete records according to the study variables; (b) pregnant women; (c) patients referred to another hospital, and (d) patients with a hospital stay of less than 24 hours.

Data collection was carried out retrospectively from medical records; we found 248 records from the study period. These records were complemented with information recorded in official epidemiological surveillance systems. Finally, under the aforementioned selection criteria, 225 clinical records were included, by means of a non-probabilistic census-type selection.

Similar to the study by Hueda-Zavaleta *et al.* [9], we calculated the statistical power of the study considering oxygen saturation ($SpO_2$) as an independent variable. In the aforementioned research, 57.8% of the people with $SpO_2$ < 80% died and a unexposed/exposed ratio of 2.22 was reported. With this information, assuming a confidence level of 95% and 225 participants, we determined a statistical power of 81.8%.

### Study variables

Regarding the independent variables, we considered sociodemographic information: age, sex, marital status, educational level, health insurance, province and districts of origin; comorbidities: arterial hypertension, type 2 diabetes, chronic kidney disease, cardiovascular disease, chronic obstructive pulmonary disease (COPD), cancer, and human immunodeficiency virus-HIV infection; clinical information: symptomatology, oxygen saturation on admission, self-medication, ICU admission, mechanical ventilation, treatment received, and unattended ICU bed request, defined as the presence in the clinical record of a response from the ICU service informing that there was no available bed for the patient. The nutritional status of the patients was also evaluated by using the body mass index (BMI), categorized as follows: normal (BMI<25 kg/m$^2$); overweight (25 kg/m$^2$≥BMI<30 kg/m$^2$); grade


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I obesity (30 kg/m$^2$≥BMI<35 kg/m$^2$); grade II obesity (35 kg/m$^2$≥BMI<40 kg/m$^2$), and grade III obesity (BMI≥40 kg/m$^2$). Likewise, temporal variables such as time of hospitalization, time of symptoms, time spent in ICU-mechanical ventilation were also reported.

The dependent variable was fatality due to COVID-19, operationalized as: survivor (discharge) or deceased. For survival analysis purposes, time zero was considered to be hospital admission, and follow-up was considered to be completed in two situations: a) when the event of interest occurred (hospital death) or b) when the patient was discharged from hospital (survived).

A data collection form was initially prepared, where most of the necessary information was recorded. As a complement, and to corroborate some epidemiological data, other reporting systems were used, such as the National Epidemiological Surveillance System (NOTIWEB); the Integrated System for COVID-19 (SISCOVID) and the National Computer System for Deaths (SINADEF). All the information was consolidated in a Microsoft Excel 2019 ® database.

### Statistical analysis

Statistical analyses and graphs were constructed and plotted using Stata Statistical Software: Release 16 (StataCorp, 2019 ®). Continuous and categorical variables are summarized as frequencies, percentages and medians with interquartile ranges (Q1-Q3). We used hypothesis tests (chi-square test, Fisher's exact test or Mann-Whitney test) to perform bivariate analysis on the independent variables and the dependent variable. We calculated crude and adjusted hazard ratios (HR) and their respective 95% confidence intervals (95% CI) by performing a multivariate analysis using the Cox proportional hazards model. For the construction of the model, we chose to categorize some quantitative variables (dummies) using some cut-off points (age over 60 years, seven days of symptom time, BMI≥30 for obesity, BMI ≥25 for overweight and oxygen saturation: >=90%, 85%-89%, 80%-84%, <80%). We considered variables that had a p-value <0.05 in the crude model to enter the adjusted model. The proportionality assumption was evaluated using Schoenfeld residuals. Subsequently, Kaplan-Meier plots were prepared and the log-rank test was applied to the variables that were statistically significant in the adjusted model.

Additionally, supervised classification algorithms were evaluated using machine learning (ML) to establish the importance of the studied factors in the study outcome. First, a logistic regression (LR) and decision tree (DT) model were used, in which we evaluated the area under the curve (AUC) as a performance indicator of the initial models. Ensemble learning methods were used in the best performing model, as well as hyperparameter optimization using Grid search. With the final optimized model, we carried out a feature importance evaluation, which showed which factors are the most important in the classification prediction according to the lethality by COVID-19 variable. These models were made with the help of Google Colab ®, using the pandas, numpy, sklearn and matplotlib libraries with python programming language.

### Ethical considerations

This study was approved by the Research Ethics Committee of the Hospital Regional Docente Cajamarca, by Letter R034-2020-GRC/DRS/HRCAJ-UAD. It was also registered in the PRISA platform of the Instituto Nacional de Salud (https://www.ins.gob.pe/prisa/ver_investigacion.aspx?FE456A89-5065-42F7-9E51-82983BE4F019) in strict compliance with current regulations.

## RESULTS

Records of 225 patients with a confirmatory diagnosis of COVID-19, either by RT-PCR (n=4) or by serological test (n=221), were included. We found that the evaluated persons had a median age of 59 (48-72) years and that there were significant differences between the ages of the patients who died and those who survived (p<0.001). There were 66.2% male patients, 63.1% were single and 41.3% had completed high school (Table 1). Of the cases, 80.3% resided in the district of Cajamarca. Of those hospitalized, 61.8% had at least one comorbidity, the most frequent being: obesity to any degree (39.1%), arterial hypertension (27.6%), and type 2 diabetes (19.6%). In addition, the most frequently encountered signs and symptoms were dyspnea (77.8%), cough (67.1%), general malaise (53.3%), fever (36.0%), and sore throat (21.3%) (Table 2).

There were 89 cases of hospital deaths due to COVID-19, representing a case-fatality rate of 39.6%. A median time of symptoms at admission of 9 (6-11) days was found in all patients, while the median was 9 (7-11) days in those who survived and 8 (5.5-11) days in those who died, with no significant differences between these groups.

Self-medication was reported in 34.7% of patients, mostly antibiotics (27.1%) and ivermectin (18.7%). Of those hospitalized, 9.8% were admitted to the ICU and 10.2% used mechanical ventilation. Within the therapeutic schemes,

**Table 1.** Sociodemographic and clinical characteristics of patients hospitalized due to COVID-19 at the Simón Bolívar Hospital (Cajamarca). June-August, 2020

| Characteristics | Survives (n=136) | Dies (n=89) | p-value |
|---|---|---|---|
| Age (years) * | 54 (43.5-63.5) | 70 (58-78) | <0.001[a] |
| <18 | 0 (0.0) | 1 (100.0) | |
| 18-40 | 28 (84.8) | 5 (15.1) | |
| 41-60 | 66 (75.9) | 21 (24.1) | <0.001[b] |
| >60 | 42 (40.3) | 62 (59.6) | |
| Sex | | | |
| Female | 48 (63.2) | 28 (36.8) | |
| Male | 88 (59.1) | 61 (40.9) | 0.568[c] |
| Marital status | | | |
| Single | 84 (59.1) | 58 (40.8) | |
| Married | 38 (57.6) | 28 (42.4) | |
| Cohabitant | 2 (100.0) | 0 (0.0) | |
| Widower | 1 (25.0) | 3 (75.0) | 0.020[c] |
| Divorced | 1 (100.0) | 0 (0.0) | |
| Doesn't mention | 10 (100.0) | 0 (0.0) | |
| Level of education | | | |
| No education | 12 (46.1) | 14 (53.9) | |
| Primary school | 27 (46.5) | 31 (53.5) | |
| Secondary school | 72 (77.4) | 21 (22.5) | <0.001[b] |
| University | 15 (71.4) | 6 (28.6) | |
| Doesn't mention | 10 (37.0) | 17 (63.0) | |
| Health insurance | | | |
| Ministry of Health | 117 (59.7) | 79 (40.3) | |
| Social Health Insurance | 14 (60.9) | 9 (39.1) | |
| Peruvian National Police | 1 (100.0) | 0 (0.0) | 0.894[c] |
| Doesn't mention | 4 (80.0) | 1 (20.0) | |

(*) Median (interquartile range).
[a] Mann-Whitney U test; [b] Chi-square test; [c] Fisher's exact test.

almost all patients received antibiotics, enoxaparin, and corticoids, and to a lesser extent, ivermectin.

The median hospitalization length was 6 (3-12) days, with significant differences between those who died and those who survived ($p<0.001$). In addition, significant differences were also found between the median length of stay in the ICU between patients who died and those who survived ($p=0.009$), with a median of 3.5 (3-22) days in the first group.

The bivariate analysis showed significant differences between the study outcome and age ($p<0.001$), educational level ($p=0.020$), marital status ($p=0.020$), presence of arterial hypertension ($p=0.014$), the $SpO_2$ at admission ($p<0.001$), admission to ICU ($p=0.001$), mechanical ventilation ($p=0.001$), request for admission to ICU not attended ($p<0.001$), as well as the use of ivermectin and corticoids during hospitalization ($p=0.038$ and 0.031, respectively). There was no statistically significant relationship with nutritional status or its dummy variables (obesity or overweight) (Table 2).

In the Cox proportional hazards model, the crude analysis found a statistically significant association with age over 60 years, arterial hypertension, having had an unattended ICU bed request, oxygen saturation on admission less than 80%, and use of ivermectin as in-hospital treatment. When calculating adjusted Hazard ratios (HR), arterial hypertension ceased to have a statistical association with case fatality ($p=0.230$). In the evaluation of the proportionality assumption, all factors and the overall model were found to have p-values greater than 0.05 (Table 3).

Statistically significant differences were found between the survival functions of the variables associated with lethality using adjusted HRs by log-rank test: age ($p<0.001$), unattended ICU request ($p>0.001$), oxygen saturation at admission ($p>0.001$) and use of ivermectin in hospitalization ($p=0.014$) (Figure 1).

When applying supervised ML models, we observed that the RL model obtained an AUC of 0.765, while the DT model showed an AUC of 0.99. Therefore, we aimed to optimize the latter model using the Random Forest Classifier as an ensemble method by bagging; as well as the optimization of hyperparameters by means of Grid Search. This optimized model obtained an AUC of 1.000. When evaluating the importance of attributes, oxygen saturation on admission was the most important factor, followed by hospitalization time, time of symptoms on admission, age over 60 years and the number of comorbidities (Figure 2).

## DISCUSSION

The 225 patients in this cohort were all the patients hospitalized with COVID-19 in the Simón Bolívar Hospital during the months of June, July and August. The lethality rate for COVID-19 was 39.6%. This result is very similar to that reported by Hueda-Zavaleta *et al.* (2021), who found a death rate of 32.9% in a hospital cohort in Tacna [9]. However, it is higher than the 18.8% reported in a preliminary report by Benites-Goñi *et al.* (2020) in a hospital cohort in Lima [14].


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**Table 2.** Clinical characteristics of patients hospitalized due to COVID-19. Simón Bolivar Hospital. Cajamarca. June-August 2020

| **Characteristics** | **Survives** N (%) | **Dies** N(%) | **p-value** |
|---|---|---|---|
| Symptomatology | | | |
| Dyspnea | 100 (57.1) | 75 (42.9) | 0.071 |
| Cough | 97 (64.2) | 54 (35.8) | 0.111 |
| General malaise | 76 (63.3) | 44 (36.7) | 0.412 |
| Fever | 56 (69.1) | 25 (30.9) | 0.048 |
| Sore throat | 32 (66.7) | 16 (33.3) | 0.406 |
| Crackles | 21 (58.3) | 15 (41.7) | 0.853 |
| Diarrhea | 11 (73.3) | 4 (26.7) | 0.414 |
| Dysgeusia | 7 (50.0) | 7 (50.0) | 0.413 |
| Nasal congestion | 8 (66.7) | 4 (33.3) | 0.768 |
| Muscle pain | 10 (90.9) | 1 (9.1) | 0.053 |
| Anosmia | 8 (80.0) | 2 (20.0) | 0.322 |
| Sensorium alteration | 5 (3.7) | 3 (3.4) | 1.000 |
| Rhinorrhea | 6 (100.0) | 0 (0.0) | 0.084 |
| Odynophagia | 3 (75.0) | 1 (25.0) | 1.000 |
| Stertors | 0 (0.0) | 2 (100.0) | 0.155 |
| Comorbidities | | | |
| None | 52 (60.5) | 34 (39.5) | |
| 1 | 60 (63.8) | 34 (36.2) | 0.496 [a] |
| 2 or more | 24 (53.3) | 21 (46.7) | |
| Arterial hypertension | | | |
| Yes | 29 (46.8) | 33 (53.2) | 0.014 |
| No | 107 (65.6) | 56 (34.4) | |
| Type 2 diabetes | | | |
| Yes | 25 (56.8) | 19 (43.2) | 0.609 |
| No | 111 (61.3) | 70 (38.7) | |
| Chronic kidney disease | | | |
| Yes | 1 (25.0) | 3 (75.0) | 0.303 |
| No | 135 (61.1) | 86 (38.9) | |
| Cardiovascular disease | | | |
| Yes | 1 (33.3) | 2 (66.7) | 0.564 |
| No | 135 (60.8) | 87 (39.2) | |
| COPD | | | |
| Yes | 1 (33.3) | 2 (66.7) | 0.564 |
| No | 135 (60.8) | 87 (39.2) | |
| Cancer | | | |
| Yes | 0 (0.0) | 2 (100.0) | 0.155 |
| No | 136 (61.0) | 87 (39.0) | |
| HIV | | | |
| Yes | 1 (100.0) | 0 (0.0) | 1.000 |
| No | 135 (60.3) | 89 (39.7) | |
| Nutritional status | | | |
| Normal | 36 (52.9) | 32 (47.1) | 0.479 [a] |

COPD: chronic obstructive pulmonary disease. HIV, human immunodeficiency virus infection. ICU: intensive care unit. MV: mechanical ventilation. SpO2: oxygen saturation on admission. (*) Median (interquartile range). [a] Chi-square test; [b] Mann-Whitney U test. Without superscript: Fisher's exact test *(continued on page 508).*

**Table 2.** Clinical characteristics of patients hospitalized for COVID-19. Simón Bolivar Hospital. Cajamarca. June-August 2020 *(Continued from page 507)*

| Characteristics | SurvivesN (%) | Dies N (%) | p-value |
|---|---|---|---|
| Overweight | 44 (63,8) | 25 (36,2) | |
| Grade I obesity | 41 (61,2) | 26 (38,8) | |
| Grade II obesity | 10 (66,7) | 5 (33,3) | |
| Grade III obesity | 5 (83,3) | 1 (16,7) | |
| $SpO_2$ at admission* | 87 (82-91,5) | 73,5 (61-85) | <0,001 [b] |
| >=90 | 51 (83,6) | 10 (16,4) | |
| 85-89 | 35 (70,0) | 15 (30,0) | <0,001 [a] |
| 80-84 | 28 (70,0) | 12 (30,0) | |
| <80 | 22 (29,7) | 52 (70,3) | |
| Self-medication | | | |
| Yes | 47 (60,3) | 31 (39,7) | 1,000 |
| No | 89 (60,5) | 58 (39,5) | |
| Antibiotics | 36 (59,0) | 25 (41,0) | 0,878 |
| Corticoids | 18 (56,3) | 14 (43,7) | 0,697 |
| Anticoagulant | 9 (64,3) | 5 (35,7) | 1,000 |
| Ivermectin | 26 (61,9) | 16 (38,1) | 0,863 |
| Hydroxychloroquine | 1 (25,0) | 3 (75,0) | 0,303 |
| Chlorine dioxide | 2 (66,7) | 1 (33,3) | 1,000 |
| Admission to ICU | | | |
| Yes | 6 (27,3) | 16 (72,7) | 0,001 |
| No | 130 (64,0) | 73 (36,0) | |
| Mechanical ventilation | | | |
| Yes | 6 (4,4) | 17 (19,1) | 0,001 |
| No | 130 (95,6) | 72 (80,9) | |
| Hospitalization (days) * | 8 (4-16) | 4 (2-8) | <0,001 [b] |
| ICU (days) * | 21 (18-26) | 3,5 (1-14) | 0,009 [b] |
| MV (days) * | 9,5 (7-20) | 4 (2-16) | 0,309 [b] |
| Yes | 1 (4,5) | 21 (95,5) | <0,001 |
| No | 135 (66,5) | 68 (33,5) | |
| Received treatment | | | |
| Antibiotics | 129 (59,7) | 87 (40,3) | 0,489 |
| Ivermectin | 74 (54,8) | 61 (45,2) | 0,038 |
| Hydroxychloroquine | 0 (0,0) | 1 (100,0) | 0,396 |
| Corticoids | 122 (58,4) | 87 (41,6) | 0,031 |
| Enoxaparin | 120 (59,7) | 81 (40,3) | 0,660 |

ICU: intensive care unit. MV: mechanical ventilation. SpO2: oxygen saturation on admission. (*) Median (interquartile range). [a] Chi-square test; [b] Mann-Whitney U test. Without superscript: Fisher's exact test.

Additionally, the case fatality rate obtained in this study is much higher than that reported by a systematic review (17.1%), published by Macedo *et al*. (2021) [15]. These results contrast with the hypothesis that altitude could be a mitigating factor in the severity of cases or lethality due to COVID-19 [16]; in this sense, one aspect that could help explain these differences is related to the socioeconomic situation of the region. For example, the monetary poverty map prepared


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**Table 3.** Cox proportional hazards regression in patients hospitalized due to COVID-19. Simón Bolivar Hospital. Cajamarca. June-August 2020

| Variables | Univariate HR | | Multivariate HR | |
|---|---|---|---|---|
| | HR (95% CI) | p-value | HR (95% CI) | p-value |
| Age (years) | | | | |
| <60 | Ref. | | Ref. | |
| >=60 | 3.75 (2.35-5.98) | <0.001 | 2.87 (1.76-4.68) | <0.001 |
| Sex | | | | |
| Female | Ref. | | Not included | |
| Male | 1.02 (0.65-1.60) | 0.932 | | |
| Symptoms | | | | |
| 7 days or less | Ref. | | Not included | |
| More than 7 days | 0.90 (0.59-1.37) | 0.621 | | |
| Comorbidities | | | | |
| Doesn't have | Ref. | | Not included | |
| One comorbidity | 0.88 (0.55-1.42) | 0.605 | | |
| Two or more | 0.78 (0.44-1.36) | 0.375 | | |
| Arterial hypertension | | | | |
| No | Ref. | | Ref. | |
| Yes | 1.57 (1.02-2.43) | 0.041 | 1.22 (0.78-1.91) | 0.386 |
| Type 2 diabetes | | | | |
| No | Ref. | | Not included | |
| Yes | 0.82 (0.49-1.39) | 0.472 | | |
| Pre-hospitalization antibiotic use | | | | |
| No | Ref. | | Not included | |
| Yes | 1.05 (0.66-1.67) | 0.824 | | |
| Pre-hospitalization ivermectin use | | | | |
| No | Ref. | | Not included | |
| Yes | 0.88 (0.51-1.51) | 0.633 | | |
| Pre-hospitalization anticoagulant use | | | | |
| No | Ref. | | Not included | |
| Yes | 1.23 (0.49-3.04) | 0.657 | | |
| Pre-hospitalization corticoid use | | | | |
| No | Ref. | | Not included | |
| Yes | 1.07 (0.61-1.90) | 0.806 | | |
| Admission to ICU | | | | |
| No | Ref. | | Not included | |
| Yes | 1.30 (0.75-2.25) | 0.353 | | |
| Use of mechanical ventilator | | | | |
| No | Ref. | | Not included | |
| Yes | 1.34 (0.78-2.30) | 0.285 | | |
| Unattended ICU request | | | | |
| No | Ref. | | Ref. | |
| Yes | 5.60 (3.33-9.41) | >0.001 | 3.49 (2.02-6.05) | >0.001 |
| $O_2$ saturation at admission | | | | |
| >=90 | Ref. | | | |
| 85-89 | 1.92 (0.86-4.29) | 0.110 | 1.25 (0.55-2.86) | 0.591 |
| 80-84 | 1.60 (0.69-3.71) | 0.273 | 1.10 (0.47-2.57) | 0.823 |
| <80 | 4.40 (2.23-8.68) | >0.001 | 2.73 (1.35-5.53) | 0.005 |
| Antibiotic use | | | | |
| No | Ref. | | Not included | |
| Yes | 1.67 (0.41-6.80) | 0.472 | | |
| Ivermectin use | | | | |
| No | Ref. | | Ref. | |
| Yes | 1.73 (1.10-2.73) | 0.017 | 1.68 (1.06-2.68) | 0.028 |
| Corticoid use | | | | |
| No | Ref. | | Not included | |
| Yes | 2.45 (0.60-9.99) | 0.211 | | |
| Enoxaparin use | | | | |
| No | Ref. | | Not included | |
| Yes | 0.80 (0.39-1.66) | 0.553 | | |

HR: Hazard ratios. 95% CI: 95% confidence interval.

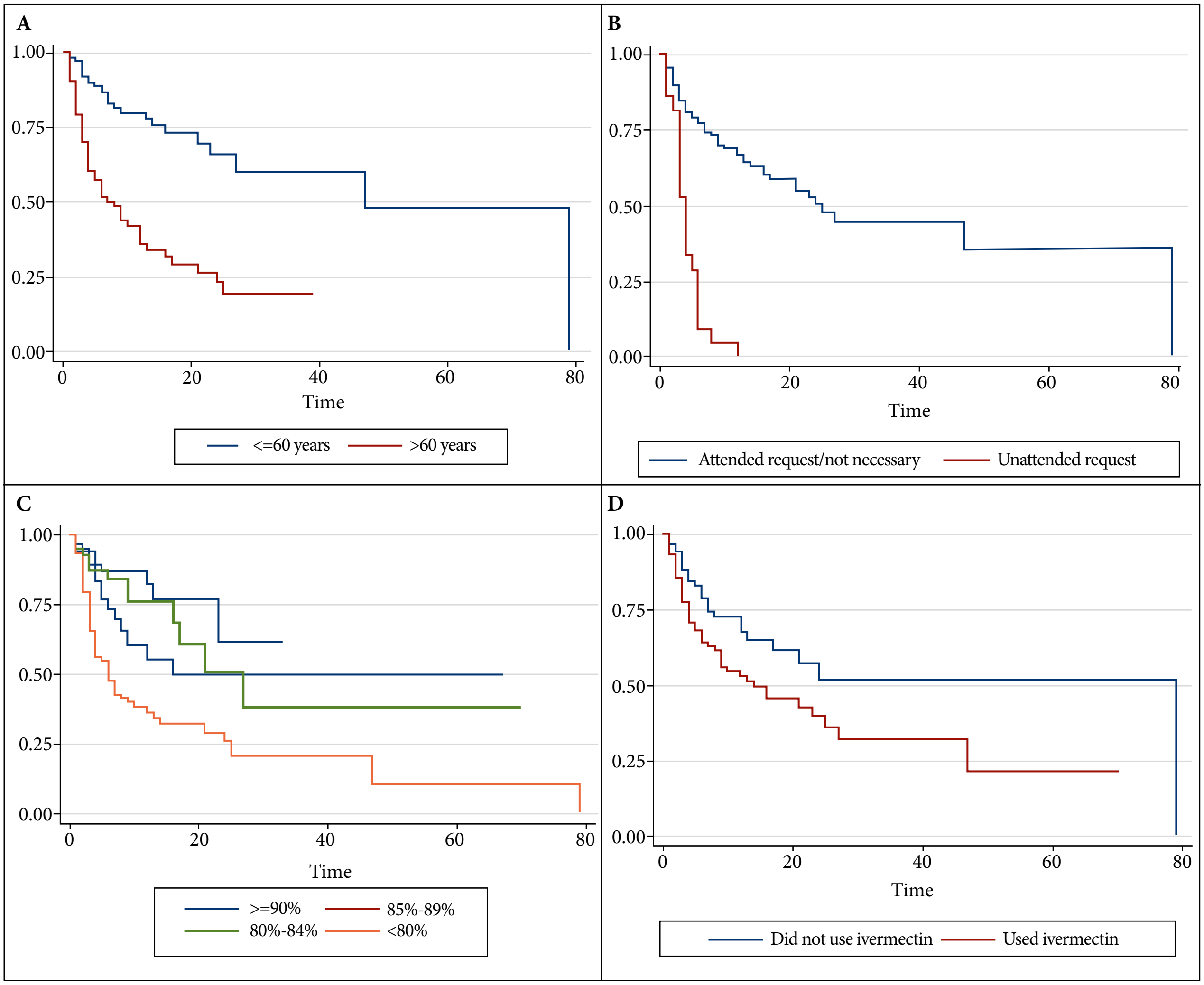


**Figure 1.** Survival curves for variables with statistically significant association in the Cox proportional hazards model adjusted analysis. a) Age; b) Unattended ICU request; c) $O_2$ saturation at admission and d) Ivermectin use at hospitalization.

by the National Institute of Statistics and Informatics (INEI) mentions that 16 of the 20 poorest districts in the country are located in the department of Cajamarca [17]. Previous studies have already suggested that poverty and social inequities are related to higher COVID-19 case fatality rates; however, they are still conservative in establishing causal relationships [18,19].

When studying the description of the deceased patients, we observed the presence of symptoms compatible with the clinical picture of COVID-19: dyspnea, cough, general malaise, fever and sore throat. A systematic review reports that symptoms such as cough or fever are very sensitive for the diagnosis of COVID-19, while symptoms such as anosmia or ageusia, rarely found in this study, are more specific [20]. On the other hand, 9.8% of those hospitalized were admitted to the ICU, and 10.2% required mechanical ventilation; findings similar to the 13.4% and 18.2% reported by Hueda-Zavaleta *et al.* (2021), in Tacna [9]. Another noteworthy result is the proportion of patients who self-medicated (34.7%), and among them, the high proportion of ivermectin consumption (18.7%) outside the hospital setting. In view of this, it should be noted that the World Health Organization does not recommend the use of this drug outside a clinical trial, due to its uncertain effects on the course of the disease, and the limited scientific evidence on the subject [21].

On the other hand, significant differences were found between hospitalization time and discharge condition, especially in the age group over 60 years. This finding is contrary to that reported by An *et al.* (2021), who found no significant differences between age groups, although the median times were mostly different [22]. In contrast, other publications agree that both age over 60 years and length


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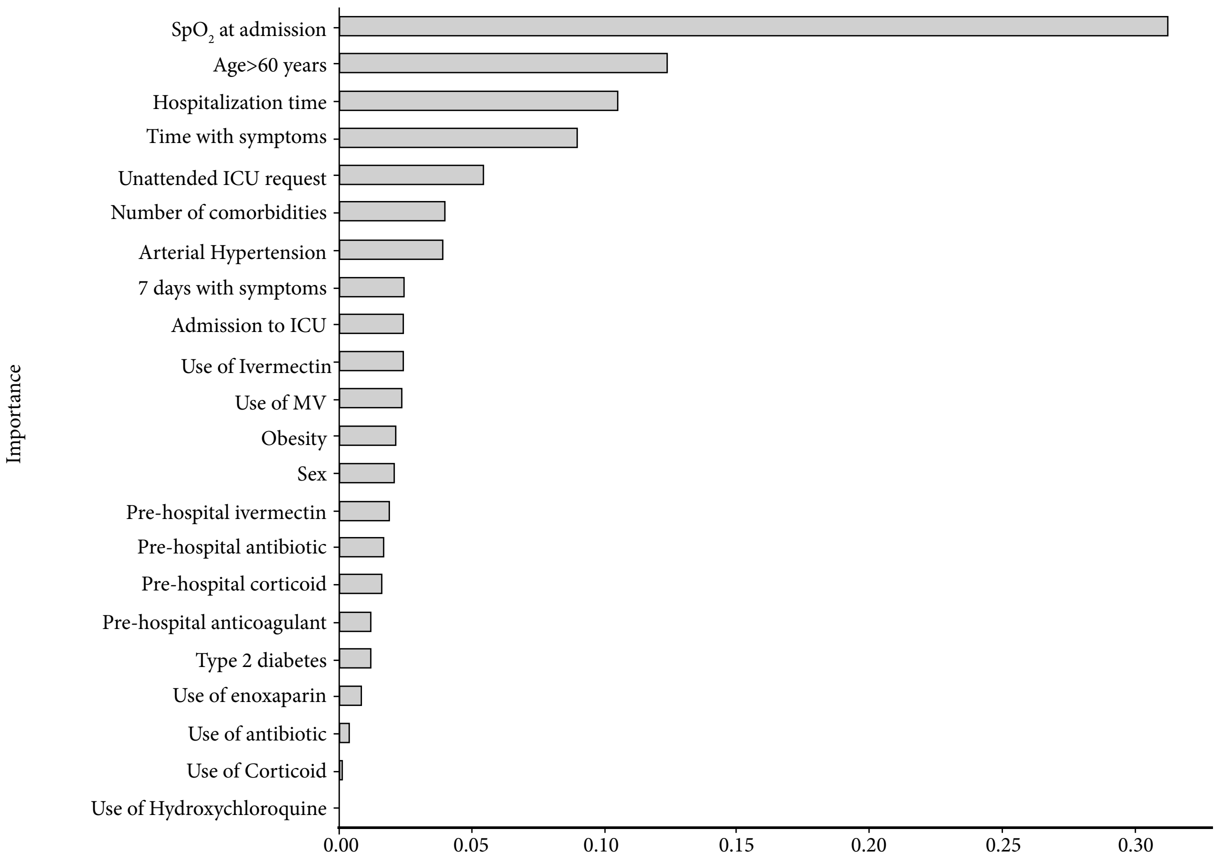


**Figure 2.** Importance of the attributes in the optimized classification model (Random Forest Classifier) for predicting COVID-19 lethality in the Hospital Simón Bolivar - Cajamarca Region.

of hospitalization can be considered factors associated with COVID-19 lethality [23,24].

The Cox proportional hazards model found previously reported conditions such as age over 60 years [25,26], arterial hypertension [25,27] and oxygen saturation less than 80% [9] to be associated with lethality. However, the presence of arterial hypertension (AHT) ceased to have a significant association when the adjusted model was evaluated. Therefore, it should be considered that the Cajamarca region is among those with lower AHT rate compared to the national average [28], which could affect the ability to report this comorbidity in the medical records.

Another associated factor was the use of ivermectin during hospitalization (HR: 1.79; 95% CI 1.12-2.88), which does represent a dissimilar finding with the study of Hueda-Zavaleta *et al*. Additionally, as mentioned, the evidence on the use of ivermectin for the treatment of COVID-19 is still uncertain [21]; however, this drug was included in the official therapeutic scheme by the Peruvian Ministry of Health [29]. Likewise, it should be considered that the use of this drug without appropriate caution, due to its adverse events, could be the cause of negative outcomes in some patients [30]. However, the level of evidence of this research does not allow us to consider the use of ivermectin as a risk factor for death due to COVID-19.

Another relevant aspect is the non-association between nutritional status and COVID-19 lethality ($p>0.05$). This finding is contradictory to results obtained by some studies, in which obesity is recognized as a risk factor [23], but consistent with those that found no significant association [9]. This finding could be explained by limitations in the selection of the sample, since nutritional status is related to socioeconomic factors that could be a barrier to healthcare, which could limit access to hospital care for certain patients. On the other hand, it should be noted that the use of medical records carries the possibility of information bias, and therefore some cases could not have been recorded correctly. Future studies, with better representativeness, should evaluate the true magnitude of the effect of this variable on the clinical outcomes of patients with COVID-19 in the Cajamarca region.

On the other hand, although no association was found between admission to the ICU and the possibility of death, a relationship was found between the unattended request for an ICU bed and this outcome (HR: 3.57; 95% CI: 2.06-6.17). This type of variables is not usually studied, and no previous studies were found that collected data on this subject. Considering the evident collapse of the Peruvian health system during the first wave of the COVID-19 pandemic, we suggest that future studies should explore this relationship.

A ML analysis was carried out, which found that the variables of oxygen saturation at admission, total hospitalization time, time of symptoms at admission, age over 60 years, and number of comorbidities were the most important factors for predicting the classification of the study outcome. A similar study, carried out with data from Korean population, found rather better performance in algorithms based on logistic regressions, such as LASSO, compared to RF [22]. Also, the most important factors were age, comorbidities such as hypertension, or the use of drugs related to the treatment of type 2 diabetes. Although this analysis could be considered preliminary, future studies with local data may help to develop algorithms that allow early detection of cases at high risk of death.

The limitations of this study include, as previously mentioned, the possibility of information bias due to the nature of the data source. Likewise, as it only represents what happened in a single facility, the conclusions of this study cannot be extrapolated to the entire Peruvian population, nor are they regionally representative. In addition, the design used (retrospective cohort), although it offers the possibility of adjusting the outcomes for the time factor, is not free of limitations regarding the quality of the registry and the collection of data on possible confounding variables. Consequently, our findings should be considered as the first evidence of possible risk factors that can be addressed by studies with other designs that consider the implementation of prospective follow-up of patient cohorts.

On the other hand, it should be noted that other technical criteria for death due to COVID-19 (e.g. radiological, clinical, epidemiological, etc.) have not been used in this research because the study population (hospitalized patients) has the particularity of having high compliance with serological or virological criteria. Likewise, this position helps the comparability of the results with similar studies in other countries, in which the classification of death due to COVID-19 is based solely on the history of the diagnosis and the clinical picture of the patient during hospitalization. However, future studies should determine the proportion of hospital deaths due to COVID-19 that did not meet serologic or virologic criteria and may not have been detected at an early stage by the healthcare systems.

Finally, we concluded that the factors associated with lethality due to COVID-19 in the Hospital Simón Bolívar (Cajamarca), between June-August 2020, were age over 60 years, arterial hypertension, oxygen saturation less than 80% on admission, the use of ivermectin in the hospital therapeutic plan, and the unattended request for an ICU bed.

**Author contributions:** WEAO, SVÑV, HCBC, ESC and VJZG were responsible for the conception, design, analysis and interpretation of the data in the manuscript. HCBC, ESC, and YAB collaborated in the design, analysis, and interpretation of data. WEAO and YAB drafted and reviewed the final version of the manuscript. All authors approved the final version of the manuscript and are responsible for ensuring the accuracy or completeness of any part of the study.

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## REFERENCES

1. Organización Mundial de la Salud. Información Oficial de la Enfermedad por Coronavirus [Internet]. Ginebra. 2020 [cited on May 22, 2021]. Available at: https://www.who.int/es/emergencies/diseases/novel-coronavirus-2019.
2. Organización Mundial de la Salud. La OMS caracteriza a COVID-19 como una pandemia [Internet]. 2020 [cited on May 22, 2021]. Available at: https://www.paho.org/es/noticias/11-3-2020-oms-caracteriza-covid-19-como-pandemia.
3. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. Int J Infect Dis. 2020;92 (2020):214–7. doi:10.1016/j.ijid.2020.01.050.
4. Rahman S, Montero MTV, Rowe K, Kirton R, Jr FK. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol. 2021;14(5):601–21. doi:10.1080/17512433.2021.1902303.
5. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course, and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020;395(10229):1054–62. doi:10.1016/S0140-6736(20)30566-3.
6. Taylor L. Covid-19: Why Peru suffers from one of the highest excess death rates in the world. BMJ. 2021;372:n611. doi:10.1136/bmj.n611
7. Ramírez-Soto MC, Arroyo-Hernández H, Ortega-Cáceres G. Sex differences in the incidence, mortality, and fatality of COVID-19 in Peru. PloS One. 2021;16(6):e0253193. doi:10.1371/journal.pone.0253193.
8. Munayco C, Chowell G, Tariq A, Undurraga EA, Mizumoto K. Risk of death by age and gender from CoVID-19 in Peru, March-May 2020. Aging. 2020;12(14):13869–81. doi:10.18632/aging.103687.

9. Hueda-Zavaleta M, Copaja-Corzo C, Bardales-Silva F, Flores-Palacios R, Barreto-Rocchetti L, Benites-Zapata VA. Factores asociados a la muerte por COVID-19 en pacientes admitidos en un hospital público en Tacna, Perú. Rev Peru Med Exp Salud Pública. 2021;38(2):214-23. doi:10.17843/rpmesp.2021.382.7158.
10. Burki T. COVID-19 in Latin America. Lancet Infect Dis. 2020;20(5):547–8. doi:10.1016/S1473-3099(20)30303-0.
11. La Contraloría General de la República. Operativo de control «Por una salud de calidad» [Internet]. Lima: LCGR; 2018 [cited on November 8, 2021]. 57 p. Available at: http://doc.contraloria.gob.pe/documentos/operativos/OPERATIVO_POR_UNA_SALUD_DE_CALIDAD.pdf.
12. Centro Nacional de Epidemiología, Prevención y Control de Enfermedades. Sala situacional COVID-19 [Internet]. Tableau Software. 2021 [cited on June 27, 2021]. Available at: https://public.tableau.com/views/SALASITUACIONALCOVID19/MODELOFINAL?:embed=y&:showVizHome=no&:host_url=https%3A%2F%2F-public.tableau.com%2F&:embed_code_version=3&:tabs=no&:tool-bar=yes&:animate_transition=yes&:display_static_image=no&:display_spinner=no&:display_overlay=yes&:display_count=yes&:language=es&:publish=yes&:loadOrderID=0.
13. Centro Nacional de Epidemiología, Prevención y Control de Enfermedades. Exceso de mortalidad [Internet]. CDC MINSA. 2021 [cited on November 8, 2021]. Available at: https://www.dge.gob.pe/portalnuevo/informacion-publica/reporte-de-exceso-de-mortalidad/
14. Benites-Goñi H, Vargas-Carrillo E, Peña-Monge E, Taype-Rondan A, Arróspide-Mormontoy D, Castillo-Córdova M, et al. Clinical characteristics, management and mortality of patients hospitalized with COVID-19 in a reference hospital in Lima, Peru. SciELO Pre-prints. 2020 [cited on May 22, 2021]. Available at: https://preprints.scielo.org/index.php/scielo/preprint/view/905.
15. Macedo A, Gonçalves N, Febra C. COVID-19 fatality rates in hospitalized patients: systematic review and meta-analysis. Ann Epidemiol. 2021;57(2021):14–21. doi:10.1016/j.annepidem.2021.02.012
16. Stephens KE, Chernyavskiy P, Bruns DR. Impact of altitude on COVID-19 infection and death in the United States: A modeling and observational study. PLOS ONE. 2021;16(1):e0245055. doi:10.1371/journal.pone.0245055.
17. Instituto Nacional de Estadística e Informática. Mapa de pobreza monetaria provincial y distrital 2018. [Internet]. Lima: INEI; 2020. 303 p. Available at: https://www.inei.gob.pe/media/MenuRecursivo/publicaciones_digitales/Est/Lib1718/Libro.pdf.
18. Mujica OJ, Pachas PE. Desigualdades sociales en la mortalidad durante la COVID-19 en Lima y Callao. Rev Peru Med Exp Salud Pública. 2021;38(1):183–4. doi:10.17843/rpmesp.2021.381.6740.
19. Cifuentes MP, Rodriguez-Villamizar LA, Rojas-Botero ML, Alvarez-Moreno CA, Fernández-Niño JA. Socioeconomic inequalities associated with mortality for COVID-19 in Colombia: a cohort nationwide study. J Epidemiol Community Health. 2021;75:610-15.
20. Struyf T, Deeks JJ, Dinnes J, Takwoingi Y, Davenport C, Leeflang MM, et al. Signs and symptoms to determine if a patient presenting in primary care or hospital outpatient settings has COVID-19. Cochrane Database Syst Rev. 2020;7(7):CD013665. doi:10.1002/14651858.CD013665.pub2.
21. Organización Mundial de la Salud. Ongoing living update of COVID-19 therapeutic option. Summary of Evidence [Internet]. Ginebra: OMS; 2021 [cited on June 26, 2021]. 275 p. Available at: https://iris.paho.org/bitstream/handle/10665.2/52719/PAHOIMSEIHCOVID-1921018_eng.pdf?sequence=45&isAllowed=y.
22. An C. Machine learning prediction for mortality of patients diagnosed with COVID-19: a nationwide Korean cohort study. Sci Rep. 2020;10(1):18716.
23. Muñoz-Rodríguez JR, Gómez-Romero FJ, Pérez-Ortiz JM, López-Juárez P, Santiago JL, Serrano-Oviedo L, et al. Characteristics and Risk Factors Associated With Mortality in a Multicenter Spanish Cohort of Patients With COVID-19 Pneumonia. Arch Bronconeumol. 2021;57(S2):34–41. doi:10.1016/j.arbres.2021.02.021.
24. Martins-Filho PR, Tavares CSS, Santos VS. Factors associated with mortality in patients with COVID-19. A quantitative evidence synthesis of clinical and laboratory data. Eur J Intern Med. 2020;76(2020):97–9. doi:10.1016/j.ejim.2020.04.043.
25. Wu Y, Li H, Zhang Z, Liang W, Zhang T, Tong Z, et al. Risk factors for mortality of coronavirus disease 2019 (COVID-19) patients during the early outbreak of COVID-19: a systematic review and meta-analysis. Ann Palliat Med. 2021;10(5):5069–83. doi:10.21037/apm-20-2557.
26. De Rosa FG, Palazzo A, Rosso T, Shbaklo N, Mussa M, Boglione L, et al. Risk Factors for Mortality in COVID-19 Hospitalized Patients in Piedmont, Italy: Results from the Multicenter, Regional, CORACLE Registry. J Clin Med. 2021;10(9):1951. doi:10.3390/jcm10091951
27. Izcovich A, Ragusa MA, Tortosa F, Lavena Marzio MA, Agnoletti C, Bengolea A, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. PloS One. 2020;15(11):e0241955. doi:10.1371/journal.pone.0241955.
28. Instituto Nacional de Estadística e Informática. Perú: Enfermedades no transmisibles y transmisibles, 2019. [Internet]. Lima: INEI; 2020 [cited on July 2, 2021]. 196 p. Available at: https://proyectos.inei.gob.pe/endes/2019/SALUD/ENFERMEDADES_ENDES_2019. pdf.
29. Ministerio de Salud. Documento Técnico: Prevención, Diagnóstico y Tratamiento de personas afectadas por COVID-19 en el Perú. Resolución Ministerial N° 193-2020-MINSA [Internet]. MINSA; 2020. Available at: https://www.gob.pe/institucion/minsa/normas-legales/473575-193-2020-minsa.
30. Zaheer T, Pal K, Abbas RZ, Torres MDPR. COVID-19 and Ivermectin: Potential threats associated with human use. J Mol Struct. 2021;1243(2021):130808. doi:10.1016/j.molstruc.2021.130808.