ASSOCIATED FACTORS WITH MORTALITY DUE TO COVID-19 IN A HIGH COMPLEXITY CENTER IN BOGOTÁ, COLOMBIA

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This thesis makes part of the project: “FACTORES DE RIESGO ASOCIADOS A MORTALIDAD EN COVID-19: UN ESTUDIO DE COHORTE HISTÓRICA” by Juan-Manuel Anaya, Manuel Eduardo Rojas Quintana, Yhojan Rodríguez Velandia, and Elizabeth Zapata Gómez and is approved by the CREA and the ethics committee of Clínica del Occidente.

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ABSTRACT

BACKGROUND

COVID-19 has generated an unprecedented impact. Patients in critical states present a reported mortality of up to 61%, and aggressive treatment does not seem to be enough. Different studies have described associated factors to mortality; however, in Latin America, the information is scarce. Thus, we aimed to determine the associated factors with mortality due to COVID-19 in a high-complexity hospital in Bogotá, Colombia.

METHODS

This case-control study included 282 individuals who died due to COVID-19, compared with 282 individuals who survived. Individuals were matched by age, sex, and month of admission to determine if there were associated variables with the primary outcome. Multiple imputations by chained equation (MICE) were implemented to account for missing variables. Classification and regression trees (CART) were estimated to evaluate the interaction of factors on admission and their role in predicting mortality during hospitalization.

RESULTS

Most of the patients included were males in the seventh decade. Recovered patients reported heterogeneous symptomatology, whereas deceased patients were most likely to present respiratory distress, dyspnea, and seizures on admission. In addition, the latter group exhibited a higher burden of comorbidities and alterations in laboratory biomarkers. After the imputation of datasets, CART analysis estimated 14 clinical profiles. The accuracy model for prediction was 85.6% ($P < 0.0001$).

CONCLUSION

Multivariate analysis yielded a reliable model to predict mortality in COVID-19. This analysis revealed new interactions between clinical and paraclinical features. Furthermore, this predictive model could offer new clues for the personalized management of this condition in clinical settings.

KEYWORDS

COVID-19; SARS-CoV-2; Mortality; Risk Factor; Protective Factor

RESUMEN

ANTECEDENTES

El COVID-19 ha generado un impacto sin precedentes. Los pacientes en estado crítico presentan una mortalidad hasta del 61%, y el tratamiento agresivo no parece ser suficiente. Diferentes estudios han descrito factores asociados a la mortalidad, sin embargo, en Latinoamérica la información es escasa. Nuestro objetivo fue determinar los factores asociados con la mortalidad por COVID-19 en un hospital de alta complejidad en Bogotá, Colombia.

MÉTODOS

Este estudio de casos y controles incluyó a 282 personas que fallecieron a causa de COVID-19 y 282 que sobrevivieron. Los individuos fueron emparejados por edad, sexo y mes de ingreso, para determinar las variables asociadas con la mortalidad. Se implementaron imputaciones múltiples por ecuación encadenada (MICE) para las variables con datos faltantes. Se estimaron árboles de clasificación y regresión (CART) para evaluar la interacción de los factores y su papel en la predicción de la mortalidad durante la hospitalización.

RESULTADOS

La mayoría de los pacientes eran varones en la séptima década. Aquellos que se recuperaron reportaron sintomatología heterogénea, mientras que los pacientes fallecidos presentaron dificultad respiratoria, disnea y convulsiones al ingreso. Además, este último grupo presentó una mayor carga de comorbilidades y alteraciones en los biomarcadores de laboratorio. Después de la imputación de conjuntos de datos,

el análisis CART estimó 14 perfiles clínicos. La precisión del modelo fue del 85,6 % (P < 0,0001).

CONCLUSIÓN

El análisis multivariante arrojó un modelo confiable para predecir la mortalidad en COVID-19. Este análisis reveló nuevas interacciones entre las características clínicas y paraclínicas. Además, este modelo predictivo podría ofrecer nuevas pistas para el manejo personalizado de esta condición en entornos clínicos.

PALABRAS CLAVE

COVID-19; SARS-CoV-2; Mortalidad; Factor de riesgo; Factor protector

1. PROBLEM FORMULATION

1.1 PROBLEM STATEMENT

COVID-19, caused by the SARS-CoV-2 virus, has generated an unprecedented impact. As of today, this disease is responsible for approximately 760,000,000 confirmed cases and 6,900,000 deaths spread around the world (1). The main transmission route is by droplets and aerosol particles produced by the respiratory tract (1–3). It is worth noting that the virus has an affinity for a wide range of organs, such as the heart, lungs, blood vessels, and kidneys, among others that have high expression of the receptor for angiotensin-converting enzyme-2 (ACE-2) (3–6).

Although most patients present with mild symptoms (81%), a smaller proportion develop severe disease (14%) that usually begins seven days after the clinical onset (1,7,8). When the patient progresses to a critical stage, the reported mortality reaches 61%, and aggressive treatment using mechanical ventilation and a broad array of drugs seems insufficient (7,9). The leading cause behind this clinical deterioration is the respiratory distress syndrome characterized by impaired gas exchange (3,5). Additionally, a hypercoagulability state responsible for the increase in thrombotic events, the multiorgan failure, and the superinfection of other pathogens contribute to the mortality of this disease (3,4,6).

Different studies have demonstrated that the severity of the disease and the fatality rate increases when individuals have pre-existing comorbidities, such as diabetes, hypertension, chronic obstructive pulmonary disease (COPD), and obesity. In addition, sociodemographic factors like sex and age, and biological markers such as D-dimer, C-reactive protein, and lactate dehydrogenase have been reported to play an important role (9–17). However, in Latin America, there is scarce information on this field. Therefore, there is a need to determine those individuals at higher risk of an adverse

outcome and thus respond appropriately in a timely and effective manner considering the particular characteristics of the population.

1.2. JUSTIFICATION

Studying the associated factors with mortality due to COVID-19 for the Colombian population is fundamental. As reported by the World Health Organization, the Americas region has contributed to about 40% of the total deaths from this disease (1). As for Colombia, this infection has affected 6,400,000 individuals and caused approximately 142,000 deaths (18,19).

Despite the volume of current evidence around the world, there are still doubts about the disease behavior and its impact on middle and low-income countries in which research is limited, and many sociodemographic, political, and economic factors play a decisive role in the health of the community (15). Knowing the risk factors that affect the region can benefit professionals who face the challenge of taking care of these patients to make an opportune diagnosis, implement effective and safe measurements, and allocate resources wisely.

Additionally, since a specific treatment against the virus has yet to be approved, the investigation of new clinical biomarkers is essential. It may allow a better predictive characterization of SARS-CoV-2 infection, presenting new pharmacological targets for its control. Therefore, this case-control study aims to evaluate the association between the different variables and the mortality due to COVID-19. Also, a supervised machine learning algorithm was implemented to assess the interactions between variables and their potential usefulness to predict mortality on admission.

1.3. RESEARCH QUESTION

What are the clinical and paraclinical factors associated with mortality due to COVID-19 in a high-complexity center in Bogotá, Colombia?

2. THEORETICAL FRAMEWORK

2.1 EPIDEMIOLOGY OF COVID-19

In December 2019, the first reports of new viral pneumonia were presented in Wuhan, China, characterized by severe respiratory symptoms (6,9,20). At first, the responsible microorganism was unknown. However, by January 2020, SARS-CoV-2 was identified. As time went by, the virus spread through Asia and Europe and then massively through the rest of the world. Given its clinical characteristics and the number of cases detected, the COVID-19 pandemic was declared on March 11, 2020 (20,21).

To date, nearly 760,000,000 confirmed cases have been documented worldwide which 6,9000,000 correspond to deceased individuals. Heading the list of affected countries, the United States (U.S.) has the highest reported confirmed cases, with almost 92,000,000 and 1,030,000 deaths, followed by Brazil and India, with 685,000 and 530,000 deaths, respectively (1,22). The case lethality rate, defined as the ratio between the cases of mortality and the confirmed cases of the disease at the beginning of the pandemic, was around 3.7%, decreasing up to 1.09%, nowadays (22).

As for the Americas region, according to the Pan American Health Organization (PAHO), 175,000,000 cases have been reported in 54 countries, from which 2.8 million individuals have died (23). This implies that 40% of the deaths worldwide have occurred in this territory (1,23). As mentioned before, the U.S. and Brazil have presented the most cases. Regarding the confirmed deaths per million people, which evaluates the country's mortality related to its population, Peru has the highest rate worldwide, with 6484.4 cases per million people (22,23).

In Colombia, there have been approximately 6,500,000 cases and 142,000 deaths due to this disease. The case fatality rate to date is 2.5%, which means that of every 1000

infected individuals, 25 died. The departments whew most of the cases have taken place are Bogotá, D.C., with 1,850,000 confirmed cases; Antioquia, with 942,000 patients; and Valle del Cauca, with 563,000 positive cases. According to the mortality per million people by departments, the highest rate reported is in Barranquilla, with 4815 cases per million population. On the other hand, the departments with the lowest mortality rate are Guaviare and Bolivar, with 86 and 423 cases per million inhabitants, respectively. Some data may be affected by under registration of information (19).

Specifically facing the situation of Bogotá, as mentioned before, 1,850,000 confirmed cases have been reported, from which 45,7% are men and 54,3% are women. Also, it is worth noting that most cases (60,3%) are between 20 and 49 years old. As for the death attributed to this disease, 29,800 individuals have died with a lethality rate of 1.6%. Comparing Bogotá with other big cities in Latin America, it occupies the eighth position with 3846 deaths per million population (24).

2.2 PATHOGENESIS

The SARS-CoV-2 is a positive single-stranded RNA, enveloped virus that belongs to the beta coronavirus family. They are spherical virions with a central core and a surface that looks like a crown as it has projections of surface proteins, hence their name (4,25). It is worth noting that it has a genomic configuration almost 96% similar to a strain of coronavirus found in Chinese bats; therefore, it was initially classified as a zoonosis (4). Also, in the pangolins, a strain of coronavirus was identified to have a receptor-binding domain that closely resembled that of SARS-CoV-2 (26). Despite those mentioned above, the source and the mechanism by which it started infecting humans are not clear (4,25).

This pathogen has four main structural proteins: the spike protein (S), the envelope protein (E), the membrane protein (M), and the nucleocapsid protein (N) (2,27). Each

one of them fulfills different but essential functions. The S protein is responsible for the interaction between the virus and the ACE-2 receptor of the host cell (4,28). This receptor has been found in different tissues such as oral and nasal epithelium, large and small intestine, kidneys, liver, alveolar epithelium, and vascular endothelium, which can explain the multiorgan alteration of the disease (29). The M protein is the most abundant protein, which constitutes the viral envelope, and simultaneously interacts with other structural glycoproteins that allow the stabilization of the nucleocapsid. Protein E works as a transmembrane protein that allows ion exchange. Likewise, it plays a vital role in the viral assembly and its maturity by allowing membrane curvature, which prevents the aggregation of the M protein. Finally, the N protein is tightly bound to genomic RNA, allowing viral assembly and budding (4,28).

The main transmission route is by droplets and aerosol particles produced by the respiratory tract (2,28). Once the virus enters the body, it binds to the epithelium of the oral and nasal cavities and can travel up to the small respiratory airways (4). After the attachment to the host cells, it releases the RNA into the cytoplasm and begins replication due to the viral machinery. Finally, the new virion is packed and fuses with the plasma membrane emerging the cell via exocytosis (27).

As the virus enters the systemic circulation, it triggers the innate and adaptive immune response. Macrophages and dendritic cells present the viral antigen via the main histocompatibility complexes I and II (3,28). Then, the T lymphocytes will recognize the antigen and cause the release of cytokines (4). However, an increase in the levels of these proteins generates a potential risk causing systemic effects and collateral damage to vital organs(5). In the SARS-CoV-2 infection, as in other viral processes like influenza, the immune cells might be hyperactivated with the overexpression of cytokines, known as a “cytokine storm” (3,5). Among the proteins observed in this type of response, the IL-1 beta, IL-6, IP-10, TNF, type I interferon (INF-I), and the alpha and beta macrophage inflammatory protein (MIP) have been widely described (5).

Additionally, it has been observed that the activation of the immune system correlates with the viral load levels and that, in the context of comorbidities such as hypertension, diabetes, and obesity, it has been associated with severe presentation, development of complications, and organic dysfunction, which can lead to death (3,5).

2.3 CLINICAL PRESENTATION

COVID-19 has a wide range of clinical manifestations that vary from asymptomatic disease to individuals who develop acute respiratory failure (3,4,8). The infection incubation period is about five days, and most patients (approximately 98%) will present symptoms after 11 days (30). Cough, fever, and dyspnea are the most common symptoms referred by about 50 to 70% of the patients (4,27). Odynophagia, malaise, headache, gastrointestinal symptoms such as diarrhea and vomiting, anosmia, dysgeusia, and headache are also frequently mentioned (3,4,8,27).

According to the severity of the signs and symptoms presented by the patients, the National Institutes of Health (NIH) classified individuals into five main categories. The first includes those individuals who, despite not showing symptoms compatible with SARS-CoV-2 infection, have a positive antigen or PCR test. The second group would coincide with the mild disease, in which the patients manifest the typical symptoms previously described, but are not associated with dyspnea or alterations in the radiological images of the chest. Moderate disease constitutes the third category, characterized by symptoms and radiological signs compatible with the lower respiratory tract infection and normal oxygen saturation on room air (31). The 81% of patients diagnosed with COVID-19 belong to the previously mentioned categories (7).

The severe disease, which usually begins seven days after the symptom onset in 14% of the patients, is defined by the presence of dyspnea accompanied by tachycardia (heart rate >100) and tachypnea (respiratory rate> 30). Regarding the clinical signs,

abnormal oxygen saturation on room air, PaO2/FiO2 less than 300 mmHg, and pulmonary infiltrates that affect more than 50% of the lungs are observed (3,7,32). Finally, the most severe manifestation is a critical illness which presents in 5% of the individuals with acute respiratory failure, multiorgan failure, or septic (7,31).

2.4 ASSOCIATED COMPLICATIONS

Secondary complications due to SARS-CoV-2 infection are usually seen in critically ill patients who require admission to the intensive care unit and are the leading causes of mortality in these individuals (4). Three main underlying processes have been described that could explain the development of most of these phenomena. First, as mentioned earlier, the cytokine storm is defined as a potentially fatal systemic inflammatory syndrome in which the hyperactivity of immune cells and the presence of high levels of cytokines are observed (5). Also, molecular mimicry between the virus and body proteins and the direct damage by the microorganism to tissues with high expression of the ACE-2 receptor, such as lungs, liver, blood vessels, and the brain, among others, are mentioned as culprits of the adverse outcomes (3,4,6).

The main complication of COVID-19 is acute respiratory distress syndrome (ARDS), which is present in up to 30% of patients. It is characterized by developing respiratory failure de novo or worsening existing respiratory symptoms (4,31). Thanks to the hyperinflammatory state seen in this disease, there will be a leak in the alveolar capillaries with subsequent formation of edema and hyaline membranes. All these changes result in alveolar damage and collapse, which hinders gas exchange (3,4,6). The Berlin definition divides this disorder into mild (PaO2/FiO2 between 200 and 300), moderate (PaO2/FiO2 between 100 and 200), and severe (PaO2/FiO2 less than 100) respiratory distress (33).

Other frequently reported complications are septic shock (20%) associated with superinfection by other pathogens favored by the use of mechanical ventilation and invasive monitoring, cardiac disorders (17%), and coagulopathies (19%) (4,6,11,12,27). As for cardiac complications, the development of arrhythmias, myocardial injury, heart failure, and coronary syndromes have been described (4,11,12). About coagulopathies, thrombotic events are commonly seen, which include venous events such as deep vein thrombosis and pulmonary thromboembolism and arterial events such as myocardial infarction, critical ischemia, and ischemic stroke. The hypercoagulability state observed in this infection can be explained by the alteration of the endothelial cells, the exaggerated proinflammatory state, and the increase in blood viscosity secondary to hypoxia (4,6,10–12).

Hematological alterations also play an essential role in this disease, especially lymphopenia and thrombocytopenia (18,27,34). It has been proposed that the increase in proinflammatory cytokines such as IL-6 could decrease their production in the bone marrow and cause a process of apoptosis in the systemic circulation (18,34). It has also been observed that there could be a high expression of the ACE-2 receptor in lymphocytes, favoring the direct damage by the microorganism (18).

Finally, renal complications have been described to a lesser extent secondary to multifactorial etiology: low output phenomena such as hypovolemia, the use of nephrotoxic drugs, and direct damage from the pathogen. Furthermore, neurological alterations such as seizure disorders, strokes, and multifactorial encephalopathies have been found in these patients (4,6,11,12,27).

2.5. TREATMENT

Dealing with the treatment of this disease was initially a challenge since, despite recognizing the responsible virus, the systemic implications led to decision-making

based on solving acute problems and responding to the needs of patients. As the pandemic evolved, therapeutic measures changed because new knowledge was available. Some of the most employed drugs include immunomodulators such as corticosteroids, chloroquine, hydroxychloroquine, and biological therapy (32,35,36). Also, antivirals played a vital role in the containment of the disease and were initially used to interfere with the replicative activity of the virus. Lopinavir/ritonavir, remdesivir, and darunavir/cobicistat were the most crucial antivirals tested against SARS-CoV-2 (4,32,36). Finally, other therapies described to control specific symptoms and complications including antibiotics, angiotensin-converting enzyme blockers, nonsteroidal anti-inflammatory drugs, anticoagulation, and bronchodilators (32,36).

Seeking to establish an adequate therapeutic plan, patients are stratified by the severity of their clinical characteristics as proposed by the National Institute of Health (NIH) (36). Symptomatic management is encouraged for patients with asymptomatic or mild disease who do not require hospitalization or supplemental oxygen. As for moderate, severe, and critical illness, in-hospital management and oxygen supplementation are needed. According to the progression rate and severity, immunomodulatory therapy, such as dexamethasone and tocilizumab, is recommended, as well as remdesivir. Transversely, anticoagulant therapy at a prophylactic dose is endorsed in all patients who do not have a high risk of bleeding (36).

2.6. ASSOCIATED FACTORS WITH MORTALITY DUE TO COVID-19.

Associated factors are characteristics that increase or decrease the probability of developing a pathology if present in an individual. The sociodemographic features, clinical symptoms, and biomarkers that increase the likelihood of dying from COVID-19 are described below.

2.6.1. SOCIODEMOGRAPHIC FACTORS

Age

One of the risk factors that is frequently associated with mortality due to COVID-19 is age. It has been described that elderly patients are more likely to die from acute infection compared to younger individuals. However, there is no consensus about the age at which death would increase significantly since the cut-off point varies between articles (11–18). In a study including 10,000 patients who died from this disease in England, individuals over 80 years were 20 times more likely to die than individuals between 50 and 59 years old (13). Similarly, a systematic review in South Africa reported that older patients present 2.6 times the probability of dying compared to younger individuals (16). To explain this phenomenon, it has been proposed that these patients display an inadequate innate and adaptive immune response, which allows the persistence of viral replication and a prolonged proinflammatory response, which makes them more susceptible to ARDS (11,14,15,18). It should also be considered that older individuals often have more comorbidities that, as discussed later, are also related to higher mortality (11–18).

Sex

Another sociodemographic factor of great importance is sex (13–18,37,38). It has been reported that men have between 45% and 72% higher risk of dying than women (15,16). This may be secondary to cellular and humoral immune system differences (14,15,17). Men have lower numbers of T and B lymphocytes compared to women, which would limit their response to infection (15,16,18). Moreover, women have higher expression of TLR7, which could be advantageous, due to the location on the X chromosome of some regulatory genes (15). On the other hand, the variation in the levels of circulating sex hormones would modulate the immune system favoring a lower

mortality rate in women (17). Finally, it should be considered that men have a higher prevalence of comorbidities and smoking, crucial factors associated with death by COVID-19 (14).

2.6.2. CLINICAL FACTORS

Clinical features and in-hospital management

As mentioned above, those patients with severe disease are more likely to die from this infection (7). Therefore, factors such as the requirement of mechanical ventilation, vasoactive supports, use of multiple drugs, and hospitalization in the ICU are associated with higher mortality rates (39). Regarding clinical features presented on admission, dyspnea, tachycardia, tachypnea, and hypoxemia increase the probability of dying from this disease between 1.2 and 5 times (16). It should be noted that no significant association with mortality has been described with other common signs and symptoms (16).

Past medical history

Smoking

Smoking, a modifiable risk factor, has been frequently related to fatal outcomes. Smoking history and active smoking are significantly associated with higher mortality from COVID-19 (12,13,15,16,38). This is presumably due to the higher prevalence of lung disease associated with cigarette smoking that impairs basal lung function. Also, it produces a proinflammatory state that can promote an inadequate immune response (12,13,15). It has been described that, in those patients who smoke, there might be a greater expression of ACE-2 receptors that would favor direct damage to the lung parenchyma (18).

Type II diabetes mellitus

Regarding the comorbidities in patients who died from COVID-19, a history of diabetes mellitus significantly increases the risk of dying. An added risk has also been seen in those patients without adequate glycemic control (18). Diabetes favors a proinflammatory state that, together with the cytokine storm described in this disease, could explain the high prevalence of respiratory distress syndrome developed in these individuals (37). It should also be emphasized that patients with diabetes present a state of immunosuppression due to an inadequate innate immune response that limits the response to the virus (14).

Arterial hypertension

A history of arterial hypertension is also significantly associated with the probability of death (13–18,37,38). Both in a cross-sectional study carried out in Malaysia and a systematic review from Argentina, patients with this disease have 2 to 3 times the probability of dying compared to patients without this condition (14,16). It has been reported that in these individuals, the expression of the ACE-2 receptor is increased, which favors the direct damage of the microorganism in the tissues (14,37).

COPD and other lung diseases

Considering the significant compromise of the lungs due to SARS-CoV-2 infection, those patients with a history of COPD and other pneumopathies, such as severe asthma, have a higher risk of mortality from COVID-19. It has been described that there is an increased risk of dying between 2 and 3 times higher in those patients with COPD compared to their counterparts without this disease (16,17). Since patients with these

comorbidities have a baseline hypoxic state and previous damage in the lung parenchymal, they are more susceptible when an infection presents (13,16,17,38).

Other comorbidities

Other comorbidities associated with increased mortality from COVID-19 are obesity, kidney disease, cardiovascular disease, and cancer (13,15–17). Regarding obesity, an increase in the risk mortality of 34 to 92% has been seen in obese patients compared to patients with normal BMI. A person with excess weight can present multiple associated comorbidities and a chronic proinflammatory state related to worse outcomes. In addition, acute and chronic kidney injuries are significantly associated with increased mortality. If a cytokine storm occurs in a patient with prior kidney involvement, it may have less responsiveness, leading to decreased function. In addition, nephrotoxic drugs and low cardiac output contribute to additional damage (13,15–17).

Regarding the history of cardiac disorders, in a systematic review from Argentina, patients with coronary heart disease and a history of heart failure have twice the risk of dying from COVID-19 compared to individuals without these characteristics. This same study showed that the risk of mortality also increased if the patient had a history of arrhythmia (16). Finally, concerning cancer, most studies reviewed, do not distinguish which type of tumor specifically presents this positive association with mortality. Nevertheless, cancer patients are more susceptible to infection due to the state of immunosuppression caused by the malignancy and the treatments used to control it, such as chemotherapy (13,15–17).

2.6.3 BIOMARKERS

A *biomarker* is defined as “a specific characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or response to an exposure or intervention,” according to the FDA BEST group (40). There are different types of biomarkers. In this case, those related to the susceptibility to present a fatal outcome or poor prognosis will be mentioned.

Complete blood count

Regarding hematological alterations, lymphopenia and thrombocytopenia can be frequently observed. These confer five times higher risk of developing severe disease and dying from COVID-19 (5,16,18,34).

Inflammatory markers

Inflammatory protein elevation results from the cytokine storm seen in COVID-19 (5,11,12,16,38). Among those frequently described in the literature, C-reactive protein (CRP), ferritin, and inflammatory cytokines, especially IL-6, are the most relevant (5,16,34). CRP is a plasmatic protein synthesized in the liver that increases in response to inflammatory events (41). This protein is elevated in many conditions; however, in SARS-CoV-2 infection, it is a predictor of disease prognosis (42). Finally, it is necessary to highlight the role of INF-I, since its deficiency is related to persistent viral replication and worse outcomes (5,18,43).

D-dimer

D-dimer, a product of fibrin degradation, is present in the blood after clot degradation by fibrinolysis and is associated with a higher mortality risk (44). In the study presented

by Gallo et al., it was found that elevated levels of D-dimer are indicative of extensive fibrinolysis and increased thrombin formation, which could be associated with prothrombotic states, specifically pulmonary thromboembolism, thus increasing the risk of ventilation and perfusion uncoupling (42). On the other hand, the proinflammatory environment promotes hypercoagulability, which generates an increased risk of mortality from 2 to 20 times compared to patients without this condition (11,12,17,34).

International Normalized Ratio (INR)

INR is a standardized measure of prothrombin time, which indicates the time it takes for plasma to coagulate using the tissue factor (45). This marker relates to the prothrombotic states of patients, and its elevation relates to complications in patients with COVID-19 (46).

Troponin

Troponin is a protein in the sarcoplasm of striated muscle composed of three polypeptide subunits: Troponin C, Troponin I, and Troponin T. These are released into the bloodstream when a cardiac injury is present. This is how in patients diagnosed with COVID-19 with cardiac dysfunction, the elevation of troponins became an indicator of prognosis and mortality, with a more remarkable presentation in patients older than 60 years (47).

Lactic dehydrogenase (LDH)

LDH is an enzyme that participates in the generation of cellular energy. Its elevation has been used to predict respiratory failure in acute respiratory distress syndrome patients with COVID-19 as it relates to cell injury and death (16,18,34,38).

Renal function

In patients with SARS-CoV-2 infection, multifactorial renal dysfunction has been documented (42). In the study by Cheng et al., it was reported that the elevation of creatinine and BUN above normal values and a decrease in the glomerular filtration rate below 60 ml/min were associated with complications that could lead to mortality (48).

Liver function

In patients with liver disorders secondary to COVID-19 infection, there is an insidious onset elevation of the aspartate aminotransferase (ASAT), the alanine aminotransferase (ALAT) and the total bilirubin. In a study reported by Piano et al., it was described that liver injury was associated with complications and mortality. Patients who presented alterations in liver function and had COVID-19 infection died in 21% of the cases versus 11% in those patients who did not have laboratory anomalies (49).

3. HYPOTHESIS

3.1. NULL HYPOTHESIS

The distribution of sociodemographic, clinical, and laboratory findings are the same in the patients who died from SARS-CoV-2 infection than those who survived.

3.2. ALTERNATIVE HYPOTHESIS

The distribution of sociodemographic, clinical, and laboratory findings are different in the patients who died from SARS-CoV-2 infection than those who survived.

4. OBJECTIVES

4.1. GENERAL OBJECTIVE

To determine the associated factors with mortality due to COVID-19 in a high-complexity hospital in Bogotá, Colombia, between March 22, 2020, and January 30, 2021.

4.2. SPECIFIC OBJECTIVES

4.2.1. To describe the epidemiological and clinical features of the patients from the studied sample.

4.2.2. To determine the sociodemographic, clinical, and laboratory factors associated with mortality due to COVID-19.

4.2.3. To analyze the association of sociodemographic, clinical, and laboratory factors with mortality in the studied sample.

4.2.4 To evaluate the interactions among variables and their potential to predict mortality on admission.

5. METHODS

5.1. METHODOLOGICAL APPROACH

This study has a quantitative approach as it seeks to identify the association of different sociodemographic, clinical, and laboratory factors and evaluate the association with mortality outcome due to COVID-19.

5.2. STUDY TYPE AND DESIGN

This is a quantitative observational analytical case-control study in which individuals who died due to COVID-19 were compared to those who did not to determine if independent variables were associated with the primary outcome of interest in a sample of a historical cohort treated at the participating center.

5.3. POPULATION

- Target population: Patients with SARS-CoV-2 infection confirmed by a positive PCR test.
- Eligible population: Patients with SARS-CoV-2 infection confirmed by a positive PCR test in Bogotá, Colombia.
- Accessible population: Patients with SARS-CoV-2 infection confirmed by a positive PCR test in Bogotá, Colombia, who consulted the high complexity health center.
- Sample: Patients with SARS-CoV-2 infection confirmed by a positive PCR test in Bogotá, Colombia, who consulted the high complexity health center between March 22, 2020, and January 30, 2021.

5.4. SAMPLE DESIGN

The total number of patients that constituted the available sample of the primary study was approximately 4163 individuals, which were used to calculate the sample size. A non-probabilistic convenience sampling was conducted to select the cases, including all subjects who died from COVID-19 at the health center during the established period (n=282). As for the controls, stratified random sampling was conducted by age group, sex, and month of consultation, considering the patients diagnosed with COVID-19 who attended the emergency room at the institution but did not die because of it (n=282), maintaining a 1:1 ratio between cases and controls.

5.5. SELECTION CRITERIA

5.5.1 CASES

5.5.1.1 INCLUSION CRITERIA

- >18 years
- Consultation at the emergency department of the high-complexity hospital between March 22, 2020, and January 30, 2021.
- Diagnosis of COVID-19 confirmed by positive PCR test verified at SISMUESTRAS.
- Death registered in death certificate adequately filled out by a doctor of the high complexity hospital.

5.5.1.2 EXCLUSION CRITERIA

- Incomplete medical history

5.5.2 CONTROLS

5.5.2.1 INCLUSION CRITERIA

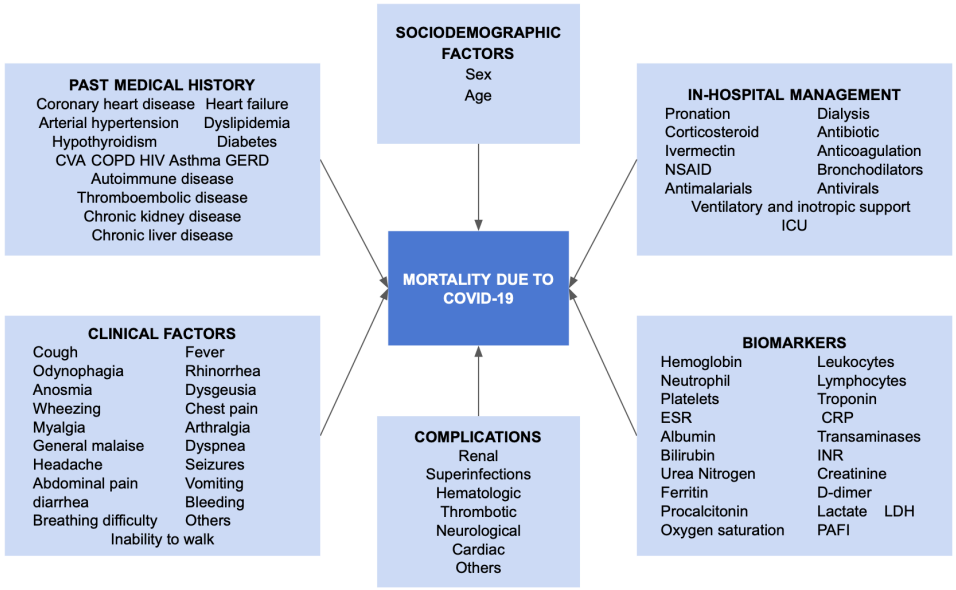
- >18 years
- Consultation at the emergency department of the high-complexity hospital between March 22, 2020, and January 30, 2021.
- Diagnosis of COVID-19 confirmed by positive PCR test verified at SISMUESTRAS.

5.5.2.2 EXCLUSION CRITERIA

- Medical referral to another health center
- Incomplete medical history

5.6. VARIABLE DESCRIPTION

5.6.1. DIAGRAM OF THE RESEARCH VARIABLES



5.6.2. TABLE OF VARIABLES

Table 1. Variables

Variable name	Definition	Type	Scale of measurement	Value
Dependent variable				
Mortality due to COVID-19	Patient diagnosed with SARS-CoV-2 infection who died during the hospital stay.	Qualitative	Nominal	0 - No 1 - Yes
Independent variable				
		Sociodemographic		
Identification	Identification number	Quantitative	-	Id number
Sex	Sex at birth	Qualitative	Nominal	1 - Woman 2 - Man
Age	Age at the time of consultation	Quantitative	Ratio	Number of years
		Clinical		
Date of onset of symptoms	Date of onset of symptoms	Qualitative	Nominal	Date
Days of symptoms	Time elapsed since the beginning of the symptoms	Quantitative	Ratio	Number of days
Fever	Fever prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Cough with sputum	Cough with sputum prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Hemoptysis	Hemoptysis prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Dry cough	Dry cough prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Odynophagia	Odynophagia prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Anosmia	Anosmia prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Dysgeusia	Dysgeusia prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Rhinorrhea	Rhinorrhea prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Wheezing	Wheezing prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Chest pain	Chest pain prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Myalgias	Myalgias prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Arthralgias	Arthralgias prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
General discomfort	General discomfort prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Dyspnea	Dyspnea prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Inability to walk	Inability to walk prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Respiratory distress	Respiratory distress prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Headache	Headache prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Seizure	Seizures prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Abdominal pain	Abdominal pain prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Nausea/ Vomiting	Nausea or vomiting prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Diarrhea	Diarrhea prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Bleeding	Bleeding prior to the time of consultation	Qualitative	Nominal	0 - No 1 - Yes
Other symptoms	Other symptoms prior to the time of consultation	Qualitative	Nominal	Symptom name
		Past medical history		
Coronary heart disease	History of coronary heart disease	Qualitative	Nominal	0 - No 1 - Yes
Heart failure	History of heart failure	Qualitative	Nominal	0 - No 1 - Yes
Hypertension	History of hypertension	Qualitative	Nominal	0 - No 1 - Yes
Thrombo-embolic disease	History of thromboembolic disease	Qualitative	Nominal	0 - No 1 - Yes
Dyslipidemia	History of dyslipidemia	Qualitative	Nominal	0 - No 1 - Yes
Chronic obstructive pulmonary disease (COPD)	History of chronic obstructive pulmonary disease	Qualitative	Nominal	0 - No 1 - Yes
Asthma	History of asthma	Qualitative	Nominal	0 - No 1 - Yes
Chronic kidney disease	History of chronic kidney disease	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Chronic liver disease	History of chronic liver disease	Qualitative	Nominal	0 - No 1 - Yes
Cerebrovascular accident (CVA)	History of cerebrovascular accident	Qualitative	Nominal	0 - No 1 - Yes
Gastroesophageal reflux disease	History of gastroesophageal reflux disease	Qualitative	Nominal	0 - No 1 - Yes
Hepatitis C	History of hepatitis C	Qualitative	Nominal	0 - No 1 - Yes
Hepatitis B	History of hepatitis B	Qualitative	Nominal	0 - No 1 - Yes
Human immunodeficiency virus (HIV)	History of human immunodeficiency virus	Qualitative	Nominal	0 - No 1 - Yes
Tuberculosis (TBC)	History of mycobacterium tuberculosis infection	Qualitative	Nominal	0 - No 1 - Yes
Type II diabetes mellitus	History of type II diabetes mellitus	Qualitative	Nominal	0 - No 1 - Yes
Cancer	History of cancer	Qualitative	Nominal	0 - No 1 - Yes
Obesity	History of obesity (BMI>30)	Qualitative	Nominal	0 - No 1 - Yes
Hypothyroidism	History of hypothyroidism	Qualitative	Nominal	0 - No 1 - Yes
Autoimmune disease	History of autoimmune disease	Qualitative	Nominal	0 - No 1 - Yes
Type of autoimmune disease	Autoimmune disease diagnosed	Qualitative	Nominal	Name of the disease
Other	History of other diseases	Qualitative	Nominal	0 - No 1 - Yes
Never smoke	Have never smoke cigarette before	Qualitative	Nominal	0 - No 1 - Yes
Active smoking	Active smoking at the time of hospitalization	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Former smoker	History of smoking cigarette	Qualitative	Nominal	0 - No 1 - Yes
In-hospital management				
Date of admission to the hospital	Date in which the patient was admitted to the hospital	Qualitative	Nominal	Date
Hospital departure date	Date in which the patient departure from the hospital	Qualitative	Nominal	Date
Days of hospitalization	Time elapsed between the hospital admission and departure	Quantitative	Ratio	Number of days
Pronation therapy	Need for pronation therapy	Qualitative	Nominal	0 - No 1 - Yes
Nasal cannula	Need for supplemental oxygen by nasal cannula	Qualitative	Nominal	0 - No 1 - Yes
Non-rebreather mask	Need for supplemental oxygen by non-rebreather mask	Qualitative	Nominal	0 - No 1 - Yes
High flow cannula	Need for supplemental oxygen by high flow cannula	Qualitative	Nominal	0 - No 1 - Yes
Orotracheal intubation	Need for orotracheal intubation	Qualitative	Nominal	0 - No 1 - Yes
Orotracheal intubation time	Duration of orotracheal intubation	Quantitative	Ratio	Number of days
Corticosteroids	Administration of corticosteroids on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Azithromycin	Administration of azithromycin on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Antibiotics	Administration of antibiotics on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Ivermectin	Administration of ivermectin on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Non-steroidal antiinflammatory drugs (NSAIDs)	Administration of NSAIDs on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Angiotensin II receptor blocker (ARBs)	Administration of ARBs on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Bronchodilators	Administration of bronchodilators on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Anticoagulation	Administration of anticoagulation on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Antimalarials	Administration of antimalarials on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Antivirals drugs	Administration of antiviral drugs on the first day of hospitalization	Qualitative	Nominal	0 - No 1 - Yes
Dialysis	Need for dialysis	Qualitative	Nominal	0 - No 1 - Yes
Intensive care unit (ICU)	Admission to the intensive care unit	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Days of intensive care unit (ICU)	Number of days admitted at the intensive care unit	Quantitative	Ratio	Number of days
Inotrope or vasopressors support	Need for inotrope or vasopressors support	Qualitative	Nominal	0 - No 1 - Yes
Time of inotropes or vasopressors support	Time elapsed between the symptom onset to start of vasopressor or inotropic support	Quantitative	Ratio	Number of days
Complications				
Date of death	Date in which the patient died	Qualitative	Nominal	Date
Cause of death	Cause of death according to the death certificate	Qualitative	Nominal	Name of cause
Renal	Development of renal alteration	Qualitative	Nominal	0 - No 1 - Yes
Renal type	Type of renal alteration	Qualitative	Nominal	Name of alteration
Co-infection	Development of co-infection by another pathogen different from SARS-CoV-2	Qualitative	Nominal	0 - No 1 - Yes
Type of co-infection	Type of co-infection developed	Qualitative	Nominal	Name of infection
Time of co-infection	Time elapsed between hospital admission and the diagnosis of co-infection	Quantitative	Ratio	Number of days
Hematological	Development of hematological alteration	Qualitative	Nominal	0 - No 1 - Yes

Variable name	Definition	Type	Scale of measurement	Value
Hematological type	Type of hematological alteration	Qualitative	Nominal	Name of alteration
Hematological time	Time elapsed between hospital admission and the diagnosis of hematological alteration	Quantitative	Ratio	Number of days
Thrombotic	Development of thrombotic event	Qualitative	Nominal	0 - No 1 - Yes
Thrombotic type	Type of thrombotic event	Qualitative	Nominal	Name of alteration
Thrombotic time	Time elapsed between hospital admission and the diagnosis of thrombotic event	Quantitative	Ratio	Number of days
Neurological	Development of neurological alteration	Qualitative	Nominal	0 - No 1 - Yes
Neurological type	Type of neurological alteration	Qualitative	Nominal	Name of alteration
Neurological time	Time elapsed between hospital admission and the diagnosis of neurological alteration	Quantitative	Ratio	Number of days
Cardiac	Development of cardiac alteration	Qualitative	Nominal	0 - No 1 - Yes
Cardiac type	Type of cardiac alteration	Qualitative	Nominal	Name of alteration
Cardiac time	Time elapsed between hospital admission and the diagnosis of cardiac alteration	Quantitative	Ratio	Number of days
Other outcomes	Development of other outcomes	Qualitative	Nominal	Name of outcome

Variable name	Definition	Type	Scale of measurement	Value
		Biomarkers		
Hemoglobin	Hemoglobin level at admission	Quantitative	Ratio	G/dl
Platelets	Platelet count at admission	Quantitative	Ratio	Cell/ul
Leukocytes	Leukocyte count at admission	Quantitative	Ratio	Cell/ul
Lymphocytes	Lymphocyte count at admission	Quantitative	Ratio	Cell/µl
Neutrophils	Neutrophil count at admission	Quantitative	Ratio	Cell/µl
C-reactive protein (CRP)	CRP level at admission Reference: <5.0	Quantitative	Ratio	Mg/l
Erythrocyte sedimentation rate (ESR)	ESR value at admission Reference: 0-20	Quantitative	Ratio	Mm/hr
International normalized ratio (INR)	INR value at admission	Quantitative	Ratio	INR value
Aspartate aminotransfera-se (ASAT)	ASAT value at admission Reference: 0-40	Quantitative	Ratio	U/l
Alanine aminotransfera-se (ALAT)	Alat value at admission Reference: 0-41	Quantitative	Ratio	U/l
Albumin	Albumin level at admission Reference: 3.97-4.94	Quantitative	Ratio	Gr/dl
Total bilirubin	Total bilirubin value at admission reference: 0-1.2	Quantitative	Ratio	Mg/dl
Blood urea nitrogen (BUN)	Bun level at admission Reference: 6-23	Quantitative	Ratio	Mg/dl

Variable name	Definition	Type	Scale of measurement	Value
Creatinine	Creatinine level at admission Reference: 0.67-1.17	Quantitative	Ratio	Mg/dl
Creatine kinase (CK)	CK level at admission Reference: 20-200	Quantitative	Ratio	U/l
D-dimer	D-dimer value at admission Reference: <0.55	Quantitative	Ratio	Mg/l
Ferritin	Ferritin level at admission Reference: M: 30-400 W:13-150	Quantitative	Ratio	Ng/ml
Lactic acid	Lactic acid level at admission Reference: 0.5-2.2	Quantitative	Ratio	Mmol/l
Lactate dehydrogenase (LDH)	LDH level at the admission Reference: M: 135-225 W: 35-214	Quantitative	Ratio	U/l
Procalcitonin	Procalcitonin level at admission Reference: 0.5-2	Quantitative	Ratio	Ng/ml
Troponin	Troponin level at admission Reference:<0.014	Quantitative	Ratio	Ng/ml
Pao2 fio2	Pa/fi value according to the arterial gasses at admission	Quantitative	Ratio	Mmhg
Oxygen saturation	Oxygen saturation level according to arterial gasses at admission	Quantitative	Ratio	%

5.7 DATA COLLECTION TECHNIQUE

5.7.1. SOURCE OF INFORMATION

For this study, only secondary sources of information were used. Data was taken from the primary study database collected from the medical records of patients admitted to the high-complexity institution diagnosed with SARS-CoV-2 in Bogotá until January 2021.

5.7.2 INSTRUMENT FOR THE COLLECTION OF INFORMATION

The instrument for the recollection of the information corresponds to the same database as for the primary study from which a group of patients was selected. The record of the other individuals that were not included was erased.

5.7.3. PROCESS FOR OBTAINING THE INFORMATION

The information from the medical records was consulted through an access to the server assigned by the hospital. Researchers were able to review the data without altering or downloading it. Information considered relevant for this investigation was extracted, including sociodemographic variables, clinical features, past medical history, in-hospital management (that is, need for ventilatory support, ICU requirement, use of vasopressor support, and medications administered on admission), organic outcomes during hospitalization and their respective dates. Research participants always remained anonymous.

5.8. PILOT STUDY

Considering that all the information was contained in the database of the primary study, a pilot study was not performed. No new variables were added or modified.

5.9. ERROR AND BIAS CONTROL

- Confusion: During the period studied, massive vaccination against COVID-19 was implemented worldwide, which could have affected the clinical outcome and the laboratory findings of the patients. Since the vaccination in Colombia started in February 2021, no patients included received the vial, thus controlling this confounding factor.

- Information: Considering that the study's primary outcome was in-hospital mortality due to COVID-19, to deal with the errors in the classification of the controls, only patients with confirmed SARS-CoV-2 infection by PCR test were included. Also, those referred to another health center were excluded because of the interruption in their follow-up.

5.10. DATA ANALYSIS

Univariate descriptive statistics were performed. Categorical variables were analyzed using frequencies, and continuous quantitative variables were expressed as the median and interquartile range (IQR). The Mann–Whitney U-test or Fisher exact tests were used based on the results. None of the included parameters were subjected to statistical transformation or normalization.

The missing data rates for each variable in the study were evaluated. Most of the missingness was secondary to the lack of standardization during the pandemic for

laboratory values required in the follow-up and management of the patients. Multiple imputations by chained equation (MICE) were used to create and analyze five multiply imputed datasets for variables with less than 80% of data missingness. Multiple imputations are considered cutting-edge by methodologists since they enhance accuracy and statistical power when compared to other missing data strategies. Incomplete variables were imputed under wholly conditional specification, using the default settings of the mice 3.14 package (50).

Then, classification and regression trees (CART) were built to evaluate the relationship between clinical variables and mortality in each imputed dataset on admission. This strategy aimed to identify, at each partitioning step, the best predictive variable and corresponding splitting value while optimizing a statistical criterion. Variables with a p-value ≤ 0.25 in the bivariate analysis were included in the model 2. Each model's confusion matrix was built to determine MICE's best predictive model from the five imputed datasets and was reported accordingly. The significance level of the study was set to 0.05. Statistical analyses were done using R software version 4.1.2.

6. ETHICAL CONSIDERATIONS

Based on resolution 8430 of 1993, which determines the scientific and administrative standards for health research, this is a risk-free research in which no intervention was performed on the participants, and data was obtained retrospectively by reviewing medical records. There was no extraction of sensitive information that could put at risk the integrity and confidentiality of the individual (51). In addition, it complies with the established in the declaration of Helsinki, and the ethics of beneficence, non-maleficence, justice, and autonomy are respected. There are no conflicts of interest on the part of the authors in this study.

The researchers carried out the study under the regulations and guidelines indicated during the medical practice, following the country's ethics and in accordance with the approval of the Ethics Committee of the Universidad del Rosario.

7. RESULTS

7.1 SOCIODEMOGRAPHIC AND CLINICAL CHARACTERISTICS AT ADMISSION

A total of 564 patients, 282 recovered and 282 deceased individuals, were included for analysis. The general characteristics are summarized in Table 2. As patients were paired by age, sex, and month of admission to the hospital, these variables were very similar between both groups, with no significant difference among them. Most patients were men (62%, n=344), with a median age of 68 for the control group and 69 for the cases. Almost a third of the patients were admitted between July and August 2020, corresponding to Colombia's first SARS-CoV-2 pandemic peak.

As for the past medical history of the subjects, hypertension was the most reported pathology, especially in deceased patients (57.4%). Type II diabetes, obesity, chronic kidney disease, and coronary heart disease were also frequently mentioned. Regarding the clinical characteristics at admission, dry cough (62,8%), fever (59.2%), myalgias (24.8%), headache (23.4%), odynophagia (23.4 %), diarrhea (16%), dysgeusia (12.1%), anosmia (11.3%), and arthralgias (11%), were often reported in recovered patients. On the other hand, dyspnea (80.5%), general discomfort (80.1%), respiratory distress (52,8%), and seizures (1.8%) were most common in deceased patients.

Table 2. General characteristics of patients diagnosed with COVID-19.

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Sociodemographics (%)				
Sex			1.0000	0 (0)
Female	110 (39.0)	110 (39.0)		
Male	172 (61)	172 (61)		
Age (Median - IQR)	68 (60 - 77)	69 (60 - 78)	0.4843	0 (0)
The month of admission (2020-2021)			1.0000	0 (0)
April	4 (1.4)	4 (1.4)		
May	8 (2.8)	8 (2.8)		
June	17 (6.0)	17 (6.0)		
July	77 (27.3)	77 (27.3)		
August	49 (17.4)	49 (17.4)		
September	20 (7.1)	20 (7.1)		
October	16 (5.7)	16 (5.7)		
November	9 (3.2)	9 (3.2)		
December	37 (13.1)	37 (13.1)		
January	45 (16.0)	45 (16.0)		
Clinical characteristics on admission (%)				
Fever	167 (59.2)	138 (48.9)	0.0179	0 (0)
Cough with sputum	41 (14.5)	45 (16.0)	0.7255	0 (0)

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Hemoptysis	1 (0.4)	1 (0.4)	1.0000	0 (0)
Dry cough	177 (62.8)	162 (57.4)	0.2286	0 (0)
Odynophagia	66 (23.4)	35 (12.4)	0.0009	0 (0)
Anosmia	32 (11.3)	7 (2.5)	< 1e-04	0 (0)
Dysgeusia	34 (12.1)	7 (2.5)	< 1e-04	0 (0)
Rhinorrhea	27 (9.6)	18 (6.4)	0.2134	0 (0)
Wheezing	4 (1.4)	4 (1.4)	1.0000	0 (0)
Chest Pain	55 (19.5)	35 (12.4)	0.0285	0 (0)
Myalgias	70 (24.8)	40 (14.2)	0.0020	0 (0)
Arthralgias	31 (11.0)	14 (5.0)	0.0122	0 (0)
General discomfort	165 (58.5)	226 (80.1)	< 1e-04	0 (0)
Dyspnea	137 (48.6)	227 (80.5)	< 1e-04	0 (0)
Inability to walk	1 (0.4)	0 (0.0)	1.0000	0 (0)
Respiratory distress	22 (7.8)	149 (52.8)	< 1e-04	0 (0)
Headache	66 (23.4)	29 (10.3)	< 1e-04	0 (0)
Seizure	0 (0.0)	5 (1.8)	0.0614	0 (0)
Abdominal pain	21 (7.4)	21 (7.4)	1.0000	0 (0)
Nausea/ Vomiting	27 (9.6)	15 (5.3)	0.0766	0 (0)

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Diarrhea	45 (16.0)	22 (7.8)	0.0039	0 (0)
Bleeding	8 (2.8)	7 (2.5)	1.0000	0 (0)
Comorbidities (%)				
Coronary heart disease	22 (7.8)	25 (8.9)	0.7609	0 (0)
Heart failure	9 (3.2)	21 (7.4)	0.0374	0 (0)
Hypertension	131 (46.5)	162 (57.4)	0.0114	0 (0)
Thromboem bolic disease	9 (3.2)	10 (3.5)	1.0000	0 (0)
Dyslipidemia	17 (6.0)	23 (8.2)	0.4124	0 (0)
COPD	43 (15.2)	38 (13.5)	0.6312	0 (0)
Asthma	3 (1.1)	2 (0.7)	1.0000	0 (0)
Chronic kidney disease	39 (13.8)	51 (18.1)	0.2058	0 (0)
Chronic liver disease	2 (0.7)	4 (1.4)	0.6858	0 (0)
Stroke	5 (1.8)	13 (4.6)	0.0910	0 (0)
Gastroesopha geal reflux disease	17 (6.0)	6 (2.1)	0.0311	0 (0)
Hepatitis C	1 (0.4)	0 (0.0)	1.0000	0 (0)
Hepatitis B	0 (0.0)	0 (0.0)	-	0 (0)
HIV	1 (0.4)	2 (0.7)	1.0000	0 (0)
TBC	2 (0.7)	1 (0.4)	1.0000	0 (0)

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Type II diabetes	63 (22.3)	89 (31.6)	0.0175	0 (0)
Cancer	14 (5.0)	23 (8.2)	0.1729	0 (0)
Obesity	16 (5.7)	58 (20.6)	< 1e-04	0 (0)
Hypo thyroidism	47 (16.7)	51 (18.1)	0.7390	0 (0)
Autoimmune disease	10 (3.5)	11 (3.9)	1.0000	0 (0)
Former smoking	32 (11.3)	36 (12.8)	0.6983	0 (0)
Active smoking	3 (1.1)	12 (4.3)	0.0328	0 (0)
In-hospital management on admission (%)				
Corticosteroids	130 (46.1)	163 (57.8)	0.0069	0 (0)
Azithromycin	2 (0.7)	5 (1.8)	0.4502	0 (0)
Antibiotics	124 (44.0)	186 (66.0)	< 1e-04	0 (0)
Ivermectin	0 (0.0)	0 (0.0)	-	0 (0)
NSAIDs	112 (39.7)	35 (12.4)	< 1e-04	0 (0)
ARBs	56 (19.9)	26 (9.2)	0.0005	0 (0)
Bronchodilator	86 (30.5)	88 (31.2)	0.9274	0 (0)
Anti-coagulation	30 (10.6)	33 (11.7)	0.7894	0 (0)
Antimalarials	1 (0.4)	4 (1.4)	0.3728	0 (0)
Antiviral drugs	1 (0.4)	0 (0.0)	1.0000	0 (0)
In-hospital management follow-up (%)				

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Pronation therapy	26 (9.2)	121 (42.9)	< 1e-04	0 (0)
Nasal cannula	154 (54.6)	127 (45.0)	0.0285	0 (0)
Non-rebreather mask	42 (14.9)	208 (73.8)	< 1e-04	0 (0)
High flow cannula	9 (3.2)	38 (13.5)	< 1e-04	0 (0)
Orotracheal intubation	14 (5.0)	169 (59.9)	< 1e-04	0 (0)
Dialysis	9 (3.2)	51 (18.1)	< 1e-04	0 (0)
ICU admission	20 (7.1)	126 (44.7)	< 1e-04	0 (0)
Inotropic or vasopressor support	14 (5.0)	141 (50.0)	< 1e-04	0 (0)
Clinical outcomes (%)				
Renal alterations	37 (13.1)	130 (46.1)	< 1e-04	0 (0)
Co-infection	20 (7.1)	57 (20.2)	< 1e-04	0 (0)
Hematological alterations	146 (51.8)	242 (85.8)	< 1e-04	0 (0)
Thrombotic events	6 (2.1)	18 (6.4)	0.0199	0 (0)
Neurological alterations	22 (7.8)	31 (11.0)	0.2481	0 (0)
Cardiac alterations	18 (6.4)	95 (33.7)	< 1e-04	0 (0)
Paraclinics on admission (Median - IQR)				
Hemoglobin (g/dL)	14.8 (13.5-16.2)	14.4 (12.4-15.8)	0.0086	106 (18.79)

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
Platelets (Cells/µL)	206,000 (170,000 - 268,000)	217,000 (157,000 - 274,000)	0.8015	106 (18.79)
Leukocytes (Cells/µL)	7,860 (5,620 - 10,285)	10,670 (6,730 - 14,720)	< 1e-04	106 (18.79)
Lymphocytes (Cells/µL)	1,130 (740 - 1,650)	860 (585-1200)	< 1e-04	106 (18.79)
Neutrophils (Cells/µL)	5,700 (3,630 - 8,196)	8,915 (5,267 - 13,112)	< 1e-04	107 (18.97)
C-reactive protein (mg/L)	102.3 (40.2 - 171.2)	174.7 (85.8 - 267.5)	< 1e-04	247 (43.79)
Erythrocyte sedimentation rate (mm/hr)	22 (22 - 22)	18 (12 - 20)	0.3798	558 (98,94)
International normalized ratio	1.06 (1 - 1.17)	1.07 (0.99 - 1.2)	0.9196	453 (80.32)
Aspartate aminotransferase (U/L)	37 (27 - 59)	64.5 (41.8 - 97.5)	0.0002	474 (84.04)
Alanine aminotransferase (U/L)	30 (21.5 – 54.5)	46 (30 - 93.3)	0.0268	473 (83.87)
Albumin (gr/dL)	3.32 (2.97 - 3.48)	3.21 (2.43 - 3.43)	0.3918	543 (96.28)
Total bilirubin (mg/dL)	0.64 (0.45 - 0.87)	0.68 (0.49 - 1.09)	0.4640	422 (74.82)
Blood urea nitrogen (mg/dL)	18.4 (13.8 - 28.8)	26.3 (18.4 - 43.2)	< 1e-04	166 (29.43)
Creatinine(mg/dL)	0.99 (0.78 - 1.24)	1.16 (0.9 - 1.85)	< 1e-04	138 (24.47)
Creatine kinase (U/L)	6.18 (6.18 - 6.18)	105 (78 - 135)	0.1432	558 (98.94)

Variable	Recovered patients (n=282)	Deceased patients (n=282)	P-value[a]	Misssingness (n=564)
D-dimer (mg/dL)	0.775 (0.41 - 1.74)	1.52 (0.67 - 4.08)	< 1e-04	186 (32.98)
Ferritin (ng/mL)	878.6 (495.1 - 1,501)	1,378 (731.2 - 2,475.5)	< 1e-04	211 (37.41)
Lactic acid (mmol/L)	1.44 (1.14 - 1.99)	2.11 (1.5 – 3.37)	0.0180	443 (78.55)
Lactate dehydrogenase (U/L)	298 (225.5 - 377.5)	466 (335.5 - 652)	< 1e-04	190 (33.69)
Procalcitonin (ng/mL)	0.778 (0.55 - 1)	0.14 (0.09 – 0.19)	0.0641	558 (89.94)
PaO_2/FiO_2 (mmHg)	252.6 (211 - 297.80	115 (71.5 - 222.15)	< 1e-04	155 (27.48)
Oxygen saturation (%)	92.9 (89.15 - 95.85)	90.2 (86 - 93,78)	0.0002	131 (23.23)

[a] p-values for categorical variables obtained by Fisher's exact test. Quantitative variables were analyzed by Mann–Whitney U-test. Abbreviations: NSAIDs: Non-steroidal anti-inflammatory drugs; IQR: Interquartile range; ARBs: Angiotensin II receptor blockers; HIV: Human immunodeficiency virus; TBC: Tuberculosis; ICU: Intensive care unit; PaO_2/FiO_2: partial pressure of oxygen (PaO2) to inspired (FiO2) partial pressure of oxygen ratio.

7.2 IN HOSPITAL MANAGEMENT

A wide range of pharmacological and nonpharmacological therapies were used on admission and in follow-up management. Deceased patients were more likely to receive corticosteroids (57.8 % vs. 46.1%, p=0.006) and antibiotics (66% vs. 44%, p < 1e-04) upon admission (Table 2). Otherwise, recovered patients were given more NSAIDs and ARBs. Few patients received antimalarials or antivirals.

During the follow-up, in-hospital management, critically ill and deceased patients frequently required oxygenation therapy administered by non-rebreather mask, high

flow cannula, and orotracheal intubation ($p < 1e-04$). ICU admission, pronation therapy, inotropic or vasopressor support, and dialysis requirement were also significantly associated with a negative outcome.

7.3 ADVERSE CLINICAL OUTCOMES

As expected, higher rates of systemic and organic compromise during the hospitalization were associated with mortality due to COVID-19. The most common complications were hematological alterations such as anemia, leucopenia, and thrombocytopenia, observed in 85.5% of deceased patients ($p < 1e-04$). Renal and cardiac alterations were also remarkably high, diagnosed in 46.1% and 33.7% of the deceased patients, respectively ($p < 1e-04$). Finally, it is worth highlighting the significant prevalence of thrombotic complications presented as SARS-COV-2 promotes a hypercoagulable state.

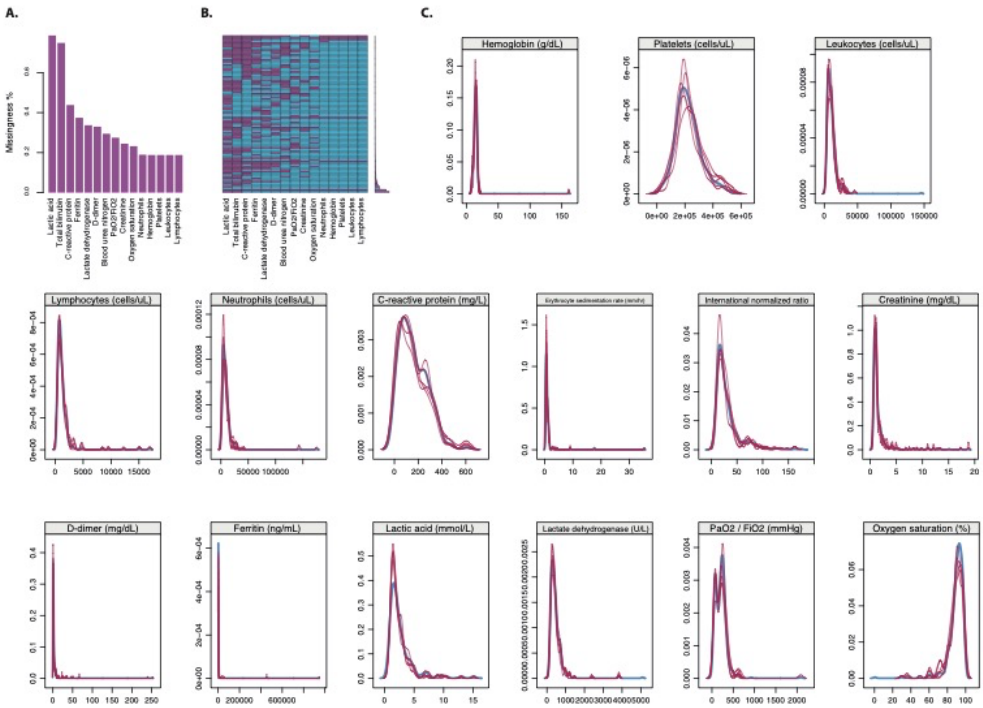
7.4 BIOMARKERS AT ADMISSION

Biomarkers varied markedly at admission between recovered and decease patients due to COVID-19. Critical patients exhibited paraclinical alterations in inflammatory markers related to hematological, hepatic, renal, and pulmonary function (Table 2). Leukocytosis, leucopenia, and neutropenia were the most prevalent findings ($p < 1e-04$). A mild decrease in kidney function as well as elevations of CRP and ferritin, were significantly associated with mortality as well. As for the respiratory parameters, a median PaO2/FiO2 of 115 was observed in the deceased patient's group, associated with lower oxygen saturation values and the elevation of LDH, which correlates with acute respiratory distress.

7.5 MISSING DATA IMPUTATION

The missing values across the variables range between 18.79% and 98.94%. The high missingness rate was related to laboratory variables, mainly albumin, creatine kinase, procalcitonin, and the erythrocyte sedimentation rate (Table 2 and Figure 1 A-C). However, clinical characteristics, in-hospital admission management, and comorbidities did not have missed values. Since this study aimed to evaluate the interaction between clinical and paraclinical factors on admission in predicting mortality, a MICE imputation strategy was conducted to include all the cases in multivariate models.

Figure 1. Missing data and imputation.



A. Histogram of frequency of missing variables in the total of patients included (n: 584). **B.** Heatmap for the distribution of missing data**. C.** Distribution of imputated variables by MICE. Red lines correspond to the five imputed datasets, whereas the blue line corresponds to the original dataset. MICE: multiple imputations by chained equation.

Five multiply imputed datasets were created and analyzed for variables with less than 80% of data missingness (Figure 1C). The sensitivity analysis yielded no significant differences between the primary and the five imputed datasets (Table 3). This confirmed that the distribution of imputed data was similar to the original dataset and confirmed the imputation models' stability.

Table 3. P-values from sensitivity analysis between main dataset and imputed dataset.

Variable	Main Vs. Imputed Dataset 1	Main Vs. Imputed Dataset 2	Main Vs. Imputed Dataset 3	Main Vs. Imputed Dataset 4	Main Vs. Imputed Dataset 5
Paraclinics on admission					
Hemoglobin (g/dL)	0.4503	0.8956	0.7301	0.8204	0.7955
Platelets (Cells/μL)	0.9705	0.7900	0.4258	0.5854	0.8971
Leukocytes (Cells/μL)	0.9079	0.7048	0.5637	0.4226	0.8877
Lymphocytes (Cells/μL)	0.9808	0.7245	0.8874	0.9945	0.8053
Neutrophils (Cells/μL)	0.8364	0.4069	0.6002	0.2971	0.6169
C-reactive protein (mg/L)	0.7267	0.9855	0.6387	0.8920	0.4734
Total bilirubin (mg/dL)	0.1539	0.4270	0.7628	0.8548	0.7584
Blood urea nitrogen (mg/dL)	0.9875	0.5288	0.6392	0.3416	0.9320
Creatinine (mg/dL)	0.8553	0.7842	0.9174	0.6214	0.7608
D-dimer (mg/dL)	0.9702	0.9092	0.6611	0.9079	0.7723
Ferritin (ng/mL)	0.7442	0.5230	0.1959	0.8348	0.4637

Variable	Main Vs. Imputed Dataset 1	Main Vs. Imputed Dataset 2	Main Vs. Imputed Dataset 3	Main Vs. Imputed Dataset 4	Main Vs. Imputed Dataset 5
Lactic acid (mmol/L)	0.2466	0.2657	0.3806	0.4587	0.2240
Lactate dehydrogenase (U/L)	0.7523	0.4675	0.9154	0.7937	0.5737
PaO2/FiO2 (mmHg)	0.9339	0.9456	0.6239	0.7643	0.5535
Oxygen saturation (%)	0.6625	0.9327	0.4655	0.6727	0.8556

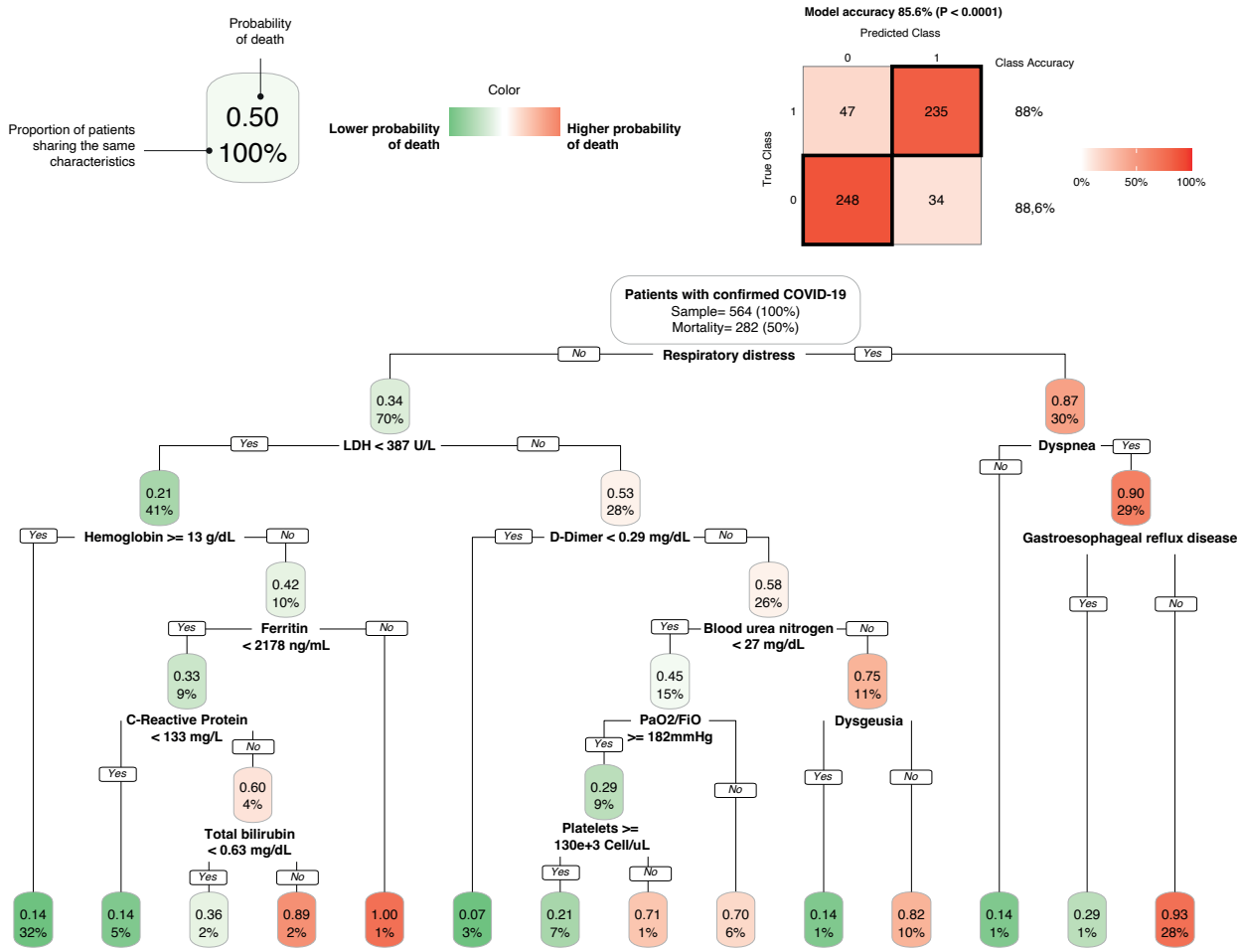
[a] p-values for quantitative variables were analyzed by Mann–Whitney U-test. PaO2/FiO2: partial pressure of oxygen (PaO2) to inspired (FiO2) partial pressure of oxygen ratio.

7.6 A MULTIVARIATE ANALYSIS AND PREDICTIVE MODEL FOR MORTALITY

After imputation, we aimed to evaluate the interaction of multiple variables in predicting mortality on admission. We estimated CART models using the variables with p-values ≤ 0.25 from the bivariate analysis for each imputed dataset. For each CART model, we constructed confusion matrix to estimate the best-fitted model to the data. After this analysis, we selected the best model based on estimated accuracy (Figure 2).

The analysis revealed that multiple variables interacted in the prediction of mortality. Respiratory distress on admission was the first splitting variable from the tree. Then, the second node was determined by LDH and dyspnea. The former interacted with hemoglobin, D-dimer, ferritin, BUN, CRP, PaO2/FiO, dysgeusia, total bilirubin, and platelets. The latter interacted with gastroesophageal reflux disease (Figure 2). The accuracy model for prediction was 85.6% ($P < 0.0001$).

Figure 2. Classification and regression tree (CART).



This strategy estimated a predictive model and 14 clinical profiles, including respiratory distress, LDH, dyspnea, hemoglobin, D-dimer, ferritin, blood urea nitrogen, C-reactive protein, PaO2/FiO, dysgeusia, total bilirubin, platelets, and gastroesophageal reflux disease.

8. DISCUSSION

As for today, a few papers have previously characterized the risk factors associated with COVID-19 mortality in Latin American patients (52,53). Therefore, the present study highlights multiple variables, including laboratory abnormalities and clinical features associated with COVID-19 mortality different from age and sex. The main findings in our study were the significant associations between total bilirubin levels (TBIL), ferritin, D-dimer levels, dyspnea, and increased risk of mortality in COVID-19 patients compared to the healthy controls. In contrast, dysgeusia and gastroesophageal reflux disease (GERD) were associated with a better prognosis. Other trends were found between BUN, respiratory distress, platelet count, PaO2/FiO2, and C-reactive protein.

The role of increased TBIL in poor COVID-19 outcomes shown in this work is consistent with previous findings (54). It has been suggested that an elevation in the bilirubin level can correlate with severe hepatic injury seen in critically ill COVID-19 patients. Some plausible explanations for this alteration are the direct cytopathic effect, immune-mediated effects, hypoxia-induced changes, and microvascular thrombosis (55,56). Considering this, it is not surprising that other authors have recognized the importance of ordering a TIBL test at hospital admission to evaluate patients' disease progression (55).

Regarding serum ferritin, it has been cited as one of the mortality indicators in COVID-19 patients due to its capability to assess intracellular iron status (57,58). Iron metabolism participates in different pathogenic mechanisms, including infections and multiple hematological and immunological disorders (59). Current literature shows that iron profiles can withstand essential changes that can be employed in predicting patient mortality, as shown in the present work. Previous studies suggest that numerous pro-inflammatory cytokines, such IL-1, IL-6, interferon γ, and tumor necrosis factor-α

(TNFα), have been involved in inducing the transcription of the H chain of ferritin in different cell types (60–64). Additionally, some cytokines also regulate ferritin synthesis pos-transcriptionally (65). These processes are commonly seen in the pathogenesis of the cytokine storm and other inflammatory phenomena in SARS-CoV-2 infection, corroborating the hypothesis of a hyperinflammatory state as an underlying mechanism of the complications seen in COVID-19. Therefore, ferritin has been postulated as a reliable biomarker to identify the progression and mortality risk due to this disease (58).

On the other hand, D-dimer is a product of the fibrin degradation seen in coagulation alterations present in various infections (66,67). Previous studies have found extremely high D-dimer levels in COVID-19 patients, which can correlate to clotting disorders and peripheral microthrombi formation seen in these individuals (68). In the present paper, higher D-dimer levels at admission were associated with an increased mortality risk. Other studies have consistently suggested its use as a prognostic factor in estimating mortality in COVID-19 cases due to various mechanisms. Viral infection triggers a pro-inflammatory response followed by insufficient anti-inflammatory activity (69). Also, endothelial dysfunction may result from these events, resulting in excessive thrombin secretion (68). Finally, hypoxia in severe COVID-19 patients may increase blood viscosity and activate pathways that rely on hypoxia-induced transcription factors (70).

Likewise, dyspnea has been elicited by previous studies as a significant clinical variable for predicting mortality among COVID-19 patients (71). This might be explained due to a viral invasion of the alveolar epithelium and pulmonary parenchyma with a subsequent inflammatory response that limits the gas exchange. Furthermore, it stimulates multiple receptors, such as pulmonary mechano-chemoreceptors, that starts a signal pathway to the brainstem contributing to the central mechanism of COVID-19-induced hypoxia and, therefore, increasing risk of mortality (72)(73). In the present study, more than 80% of the patients that presented a negative outcome referred to this symptom at admission highlighting its importance as a prognosis factor.

Related to the previously mentioned, the presence of respiratory distress and the PaO2/FiO2 ratio has been widely used to diagnose and assess the severity of patients with ARDS present in critically ill COVID-19 patients (33,74). They might be partially consequence of the mechanism involving the lung and the central nervous system exhibited before. The present study found that a decreased PaO2/FiO2 ratio increases the risk of mortality in infected individuals. Additionally, previous studies have considered this ratio at admission as an independent predictor for death (75).

As for LDH, it has been identified as a systematic inflammation biomarker that plays a key role in the anaerobic glycolysis pathway and increases in the bloodstream under conditions of membrane instability (76). In most studies, authors have concluded that LDH is a highly accurate prognostic biomarker for predicting in-hospital mortality in critically ill patients with COVID-19 (77,78). Our results reveal a positive trend between higher LDH levels and an increment in the risk of COVID-19 mortality. Severe infections such as COVID-19 may cause cytokine-mediated tissue damage and consequent LDH release. Additionally, the severe form of interstitial pneumonia that often evolves into acute respiratory distress syndrome may contribute to more significant amounts of LDH in the circulation of COVID-19 patients (79).

Other paraclinical factors such as BUN, platelets, and CRP have been highlighted in association with COVID-19 mortality. Multiple studies have suggested that higher levels of CRP on admission are linked to disease progression and death (80–82). Likewise, a significant association was found between BUN and the risk of mortality among COVID-19 patients related to kidney injury (83). Lastly, thrombocytopenia is considered a potential risk factor for mortality in this group of patients (84,85). This can be explained by the virus' direct infection of bone marrow cells and inhibition of platelet synthesis, platelet destruction by the immune system, and platelet aggregation in the lungs, resulting in microthrombi and platelet consumption (86).

Finally, in our study, dysgeusia and GERD were significantly associated with patients who recovered from COVID-19. Regarding dysgeusia, these patients can display a different inflammatory profile with a better local immune response, which could limit the spread of the virus in the body, resulting in minor systemic disease. Nevertheless, a strong local inflammatory response is observed, affecting mainly the taste receptors. However, when researching about this topic in the literature, there is still a lack of information regarding dysgeusia, perhaps because of the heterogeneity in how it has been assessed and defined (87). Concerning GERD association with COVID-19, it appears to be protective against ARDS and mortality. This is possibly due to a conversely increased acidic environment that suppresses COVID-19 viral load at the gastrointestinal point of entry, favoring a milder disease course as previously described (88).

As far as we know, a viable model for predicting death in COVID-19 patients using multivariate analysis based on Latin-American populations, such as the one proposed in this paper, has not been previously described. It can be a valuable tool to implement in these cases, not only offering a predicting system for patients with worst outcomes but because it compounds common clinical and paraclinical factors, which will provide a helpful and easily reproducible instrument to apply at the hospital admission.

9. CONCLUSIONS

COVID-19 affected the world's population in an unparalleled way. Although pharmacological advances have rapidly evolved, critically ill patients continue to have a high mortality rate, and aggressive treatment is not enough. Herein, a viable model for predicting death in SARS-CoV-2 infection using multivariate analysis is presented. In addition to age and sex, this research identified additional interactions between clinical and paraclinical parameters. This predictive approach may also provide fresh insights into the tailored management of this illness in several clinical settings. Knowing these factors can also help the health workers facing the challenge of caring for these patients daily. However, further research is needed to elucidate unknown genetic and physiological factors in order to understand COVID-19 disease better.

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