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Factors associated with mortality in COVID-19 patients admitted to an intensive care unit in Medellín, Colombia. March-December 2020

Factores asociados a la mortalidad en pacientes con COVID-19 admitidos en una unidad de cuidados intensivos de Medellín, Colombia. Marzo-diciembre 2020

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Abstract

Introduction: COVID-19 is mild in 80% of cases; however, it progresses to severe disease in 5% of patients, thus requiring intensive care unit (ICU) admission.
Objective: To identify demographic, clinical, and treatment-related factors associated with mortality in patients with COVID-19 treated at the ICU of a quaternary care hospital in Medellín, Colombia.
Materials and methods: Retrospective cohort study. The medical records of 182 patients admitted to the ICU between March and December 2020 due to COVID-19 were analyzed. Bivariate analyses (chi-square, Fisher's exact, unpaired Student's t test, or Mann-Whitney U test) were performed to evaluate the association between demographic characteristics, presence of coexisting diseases, laboratory results, therapeutic interventions, ventilatory and hemodynamic support requirement, and mortality. In addition, a multivariate analysis was performed, in which simple and multiple binary logistic regressions were used, calculating crude and adjusted relative risks (RR). A significance level of $p<0.05$ was considered.
Results: Mortality was reported in 47.80% of patients. In the multivariate analysis model, the following factors were protective factors: age <60 years (aRR: 0.154, 95%CI: 0.059-0.401; $p=0.000$), use of vasopressors (aRR: 0.082, 95%CI: 0.021-0.319; $p<0.001$), and use of renal replacement therapy (aRR: 0.205 95%CI 0.059 - 0.716; $p=0.013$). On the other hand, not performing tracheostomy was an independent protective factor for mortality (aRR: 14.959, 95%CI: 4.865-45.998; $p<0.001$). A lower platelet count during the ICU stay had a neutral effect, although it was a significantly associated quantitative variable (aRR: 0.999, 95%CI: 0.990-0.999; $p=0.003$).
Conclusions: In the present study, age <60 years, the use of vasopressors, and renal replacement therapy were protective factors, while not performing tracheostomy was a risk factor for mortality. Furthermore, a lower platelet count during ICU stay was a significantly associated quantitative variable.

Resumen

Introducción. La COVID-19 se manifiesta en el 80% de los casos de forma leve; sin embargo, en el 5% progresa a enfermedad severa con necesidad de manejo en unidad de cuidados intensivos (UCI).
Objetivo. Identificar los factores demográficos, clínicos y de tratamiento asociados a la mortalidad en pacientes con COVID-19 atendidos en la UCI de un hospital de cuarto nivel de atención de Medellín, Colombia.
Materiales y métodos. Estudio de cohorte retrospectivo. Se analizaron las historias clínicas de 182 pacientes admitidos a UCI por COVID-19 entre marzo y diciembre de 2020. Se realizaron análisis bivariados (pruebas de chi-cuadrado, exacta de Fisher, t-Student no pareada o U de Mann-Whitney) para evaluar la asociación entre, por un lado, características demográficas, presencia de enfermedades coexistentes, resultados de laboratorio, intervenciones terapéuticas, requerimiento de soporte ventilatorio y hemodinámico, y, por otro, mortalidad. Además, se realizó un análisis multivariado en el que se construyeron regresiones logísticas binarias simples y múltiples, calculando riesgos relativos (RR) crudos y ajustados. Se consideró un nivel de significancia de $p<0.05$.
Resultados. La mortalidad fue de 47.80%. En el análisis multivariado, los siguientes factores se comportaron como protectores para mortalidad: edad <60 años (RRa: 0.154, IC95%: 0.059-0.401; $p=0.000$), uso de vasopresores (RRa 0.082, IC95%: 0.021-0.319; $p<0.001$) y uso de terapia de remplazo renal (RRa: 0.205, IC95%: 0.059-0.716; $p=0.013$). La realización de traqueostomía se comportó como un factor protector independiente para mortalidad (RRa: 0.073, IC95%: 0.012-0.827; $p<0.001$). El conteo más bajo de plaquetas registrado durante la estancia en UCI tuvo un efecto neutro, aunque fue una variable cuantitativa significativamente asociada (RRa: 0.999, IC95%: 0.990-0.999; $p=0.003$).
Conclusiones. En el presente estudio, la edad <60 años y el uso de vasopresores y de terapia de remplazo renal se comportaron como factores protectores, mientras que la no realización de traqueostomía se comportó como factor de riesgo para mortalidad. Además, el conteo más bajo de plaquetas registrado durante la estancia en UCI fue una variable cuantitativa significativamente asociada.

Introduction

The Coronavirus Disease 2019 (COVID-19), caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), emerged in 2019 in Wuhan, China,[1] and within a few months it became a pandemic, causing an estimated 5.9 million deaths worldwide by February 20, 2022.[2] SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 receptors in type II pneumocytes and generates a strong immune response, resulting in lung tissue damage and induction of a systemic inflammatory state. This may lead to cytokine storm, thrombotic complications, multiple organ system failure, and death.[3]

It is estimated that 80% of COVID-19 cases are mild; however, 5% progress to severe disease, requiring intensive care unit (ICU) admission.[4] Overall, mortality due to this disease is 2.3%, but it increases to 15-20% in hospitalized patients and to 40-49% in patients requiring ICU stay.[3-5] Mortality related to COVID-19 is associated with the presence of secondary complications such as acute respiratory distress syndrome (ARDS), acute liver failure, myocardial damage, coagulopathy, acute renal failure, and shock.[3] Likewise, it has been found that certain factors such as age >65 years and the presence of comorbidities tend to predispose to the development of a severe disease. Laboratory findings associated with poor prognosis have also been reported, such as increased levels of leukocytes, interleukin-6 (IL-6), D-dimer and ferritin, and the presence of organ dysfunction markers (elevated levels of bilirubin, or bilirubin or AST, urea nitrogen and creatinine; cardiac troponins; thrombocytopenia; etc.).[6-8]

In view of the above, the objective of the present study was to identify the demographic, clinical and treatment factors associated with mortality in patients with COVID-19 treated at the ICU of a quaternary care hospital in Medellín, Colombia.

Materials and methods

Design, study population, and sample

Retrospective cohort study. The study population consisted of adult patients (>18 years) with ARDS secondary to COVID-19 pneumonia treated in a 22-bed medical-surgical ICU at the Clínica CES between March and December 2020.

Patients with a diagnosis of COVID-19 confirmed using a positive nucleic acid amplification test (NAAT), regardless of clinical or epidemiological criteria,[9] and with ARDS as defined by the Berlin criteria (timing <1-week, bilateral opacities, absence of heart failure or fluid overload, and moderate to severe impaired gas exchange) were included.[10]

Patients on invasive mechanical ventilation for more than 24 hours on admission and those referred to another institution were excluded. Thus, during the study period, 194 patients were admitted to the ICU with a diagnosis of ARDS secondary to COVID-19 pneumonia, of which 2 were excluded due to admission with ventilatory support >24 hours and 10 because they were referred to another institution, resulting in a final sample of 182 patients.

Procedures

A review of the electronic medical records of the 182 patients was performed to collect data on their sociodemographic characteristics and coexisting diseases. Moreover, information was obtained regarding laboratory test findings on admission to the hospital and

the following clinical data related to their stay in the ICU: main diagnosis, ARDS etiology and classification, APACHE II (Acute Physiology and Chronic Health disease Classification System) score, days of ICU stay, and days on mechanical ventilation. Information was also obtained on the therapeutic interventions and support measures implemented, such as ventilatory parameters during ICU stay, type of ventilation, requirement of prone ventilation, need for intubation, fluid balance, use of steroids, use of neuromuscular blocking agents, measurement of transpulmonary pressure through esophageal catheter, performance of tracheostomy, and requirement of vasoactive support or renal replacement therapy.

Data were collected from admission to discharge from the ICU.

Statistical analysis

The outcome of interest was mortality during ICU stay during the observation period, i.e., until the occurrence of the event or hospital discharge (Y). As for independent variables (Xi), a univariate analysis that included measures of central tendency (means and medians), dispersion (standard deviation and interquartile range) and position (quartiles) was performed for quantitative variables, and their adjustment to normal distribution was verified using the Shapiro–Wilk test, with a significance level of $p<0.05$. Qualitative variables were analyzed using absolute frequencies and proportions. The cumulative incidence of death due to COVID-19 in the ICU was calculated.

Bivariate analyses were performed to evaluate the association between demographic characteristics, presence of coexisting diseases, laboratory results, therapeutic interventions, and requirement of ventilatory and hemodynamic support and mortality. For this purpose, chi-square test or Fisher's exact test were used to verify the difference in proportions, as well as the unpaired Student's t-test (independent samples) to identify the difference in means when the quantitative variables had normal distribution and equality of variances (Levene's test) or the Mann-Whitney U test for differences in medians for quantitative variables that did not meet the assumption of normality and homoscedasticity, taking into account a significance level of $p<0.05$ for significant associations. In order to evaluate the association with mortality, crude bivariate relative risks (RR) were calculated with their respective 95% confidence intervals (95%CI).

To identify the independent variables suitable for inclusion in the multivariate analysis, clinical and theoretical plausibility criteria were used, as well as the Hosmer-Lemeshow test value ($p<0.25$). Simple and multiple binary logistic regressions were constructed.

Variables were ranked from lowest to highest based on the Akaike information criterion (AIC) so that they could be entered into the multiple models, which were constructed using the manual "forward" method avoiding automated regression procedures. In the multivariate analysis, crude and regression-adjusted RR with their corresponding 95%CI were also calculated. The most parsimonious final model with the best coefficient of determination was identified (R^2). The model fit parameters were calculated: R^2, AIC, omnibus test, Hosmer-Lemeshow p-value, analysis of variance (ANOVA), and log likelihood ratio. The model assumptions were checked, and the variance inflation factor (VIF) made it possible to identify low collinearity (between 1 and 3). The final model chosen was fit and not predictive, so it was not validated. For all hypothesis tests, a significance level of $p<0.05$ was considered.

Ethical considerations

The present study took into account the ethical principles for research involving human subjects established in the Declaration of Helsinki,[11] as well as the provisions on health research contained in Resolution 8430 of 1993 of the Colombian Ministry of Health.[12] Likewise, it was approved by the Institutional Research Committee of the Clínica CES as per Minutes 013 of October 24, 2021. Due to its observational and retrospective nature, informed consent was not required.

This study was carried out based on the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[13]

Results

The median age of the participants was 62.5 years (IQR=25-75), 70.32% were male, and 47.80% died. Moreover, the mean length of ICU stay was 15 days (SD±10.7) and of mechanical ventilation requirement was 14 days (SD±10) (Table 1).

Table 1. Demographic characteristics and comorbidities of the study population (n=182).

Variable		Result
Age, median (IQR)		62.5 (25-75)
Sex, n (%)	Male	128 (70.32%)
	Female	54 (29.68%)
Body mass index, mean (SD)		28.75 (±4.84)
Comorbidities, n (%)	Arterial hypertension	99 (54.39%)
	Diabetes mellitus	79 (43.40%)
	Chronic kidney disease	17 (9.34%)
	Chronic obstructive pulmonary disease	25 (13.73%)
	Asthma	12 (6.59%)
	Human immunodeficiency virus	3 (1.64%)
	Oncologic disease	6 (3.29%)
	Autoimmune disease	3 (1.64%)
	Heart failure	14 (7.69%)
	History of smoking	52 (28.57%)
	Obstructive sleep apnea-hypopnea syndrome	6 (3.29%)

IQR: interquartile range; SD: standard deviation.
Source: Own elaboration.

High-flow nasal cannula was used in 22.53% of patients prior to mechanical ventilation and 54.39% received noninvasive mechanical ventilation prior to orotracheal intubation. In patients on mechanical ventilation, the median TV/PBW (tidal volume per kilogram predicted body weight) during ICU stay was 7 mL/kg (IQR=7-8), with median positive end-expiratory pressure of 17 cmH_2O (IQR=18-16) and median plateau pressure of 30 cmH_2O (IQR=32-27). Percutaneous tracheostomy was performed in 45.05% of patients, on average on the ninth day after intubation (SD±3).

The main complication was superinfection (72.53%), with enterobacteria isolates (30.30%) as the main causal agent. Furthermore, 68.68% of patients presented acute kidney injury and more than half of them (51.65%) required renal replacement therapy.

Within the specific treatments suggested for COVID-19, only dexamethasone was used consistently (92.86%) (Table 2).

Table 2. Clinical and treatment characteristics of the study population (n=182).

Variable		Results
APACHE II score, mean (SD)		11.97 (±5.72)
VT/PBW, median (IQR)		7 mL/kg (8-7)
Positive end-expiratory pressure, median (IQR)		17 cmH2O (18-16)
Plateau pressure, median (IQR)		30 cmH2O (32-27)
Severity of COVID-19 at ICU admission, n (%)	Mild	4 (2.19%)
	Moderate	17 (9.34%)
	Severe	161 (88.46%)
P/F ratio on admission, median (IQR)		123 (201-76.81)
Transpulmonary pressure measurement, n (%)		9 (4.94%)
Reintubation, n (%)		17 (9.34%)
Noninvasive mechanical ventilation prior to intubation, n (%)		99 (54.39%)
High-flow nasal cannula, n (%)		41 (22.53%)
Tracheostomy, n (%)		82 (45.05%)
Therapeutic interventions during ICU stay, n (%)	Neuromuscular blockade	152 (83.52%)
	Vasopressor support	132 (72.53%)
	Inotropic support	40 (21.98%)
	Renal replacement therapy	94 (51.65%)
	Prone ventilation	150 (82.42%)
	Antiarrhythmics	32 (17.58%)
	Use of corticosteroids (dexamethasone)	169 (92.86%)
Complications, n (%)	Acute kidney failure	125 (68.68%)
	Arrhythmia	34 (18.68%)
	Superinfection (total)	132 (72.53%)
	Superinfection (enterobacteria as main causative agent)	40 (30.30%)
	Superinfection (other germs as main causative agent)	92 (69.70%)
	Cerebrovascular disease	1 (0.55%)
	Thrombotic event	19 (10.44%)
	Myocarditis	9 (4.95%)
	Hyperglycemic crisis	18 (9.89%)
	Hyperglycemia without crisis	83 (45.60%)
	Acute myocardial infarction	4 (2.20%)
	Cytokine storm	18 (9.89%)

APACHE II: Acute Physiology and Chronic Health disease Classification System II; SD: standard deviation; TV/PBW: tidal volume per kilogram predicted body weight; IQR: interquartile range; ICU: intensive care unit; P/F ratio: partial pressure of oxygen in arterial blood to fraction of inspiratory oxygen concentration ratio (PaO_2/FiO_2).
Source: Own elaboration.

Table 3 summarizes the laboratory test results of parameters considered to be of poor prognosis in patients with COVID-19, both on admission to the ICU and the worst value during ICU stay.

Table 3. Laboratory test results of patients with COVID-19 in the intensive care unit during the study period.

Variable		Results
LDH (U/L), median (IQR)	On admission	449 (569-346)
	Higher level during ICU stay	489 (612-382)
D-dimer (ng/mL), median (IQR)	On admission	707 (1141-401)
	Higher level during ICU stay	1 075 (2 232-561)
Lymphocytes (10^3/uL), median (IQR)	On admission	883 (1248-598)
	Lower count during ICU stay	1 460 (2 098980)
Platelets (uL), mean (SD)	On admission	262 438 (±104 577)
	Lower count during ICU stay	182507 (±94 490)
Ferritin (ng/mL), median (IQR)	On admission	1 186 (1 854-707)
	Higher level during ICU stay	1 405 (2 282-849)

LDH: lactate dehydrogenase; IQR: interquartile range; SD: standard deviation.
Source: Own elaboration.

In the bivariate analysis, the following quantitative variables were found to be significantly associated with mortality: lactate dehydrogenase (LDH) on admission (p=0.03), higher LDH level during ICU stay (p=0.01), lymphocytes on admission (p=0.01), lower lymphocyte count during ICU stay (p=0.02), having a positive cumulative fluid balance (p=0.01), P/F (ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration, PaO_2/FiO_2) on admission (p=0.03), lower P/F value during ICU stay (p=0.00), total pronation time in days (p=0.04), lower platelet count during ICU stay (p=0.00), and APACHE-II score on admission (p=0.00). Similarly, during the ICU stay, the following ventilatory variables were associated with mortality: elevated driving pressure (p=0.008), high plateau pressure (p<0.001), peak pressure (p<0.001), higher tidal volumes (p=0.011), and lower pulmonary compliance value (p=0.00).

The association of mortality with the other qualitative and quantitative variables, without adjustment for confounding, is summarized in Table 4.

The bivariate analysis allowed identifying suitable candidates for inclusion in the multiple model (Hosmer-Lemeshow test and theoretical and clinical plausibility criteria). Subsequently, simple and multiple binary logistic regressions were run to adjust for confounding. The result of this multiple model adjustment can be seen in Table 5. Then, the variables that were not affected by confounding and that were significant in the multiple adjustment were entered into final logistic regression models, comparing parsimony and indicators of best performance among the run models. Table 6 shows the final model selected as the most parsimonious and with the best performance, showing the protective and risk variables that were significantly associated. It should be noted that since the overall incidence of the event in the cohort was high (>10%), and in order to avoid the overestimation that could be caused by ORs, they were converted to RRs.

Table 4. Factors associated with mortality in the study population without adjusting for confounding variables (n=182).

Qualitative variable	Dead		Alive		Crude RR	(95%)CI		*p*-value
	n	%	n	%				
Age >60 years	65	67.71	31	32.29	2.65	1.80	3.89	<0.0001 *
Sex (male)	59	46.09	69	53.91	0.89	0.65	1.22	0.477 *
Obesity (BMI>30 kg/m²)	27	39.13	42	60.87	0.74	0.52	1.04	0.067 *
Diabetes mellitus	43	54.43	36	45.57	1.27	0.94	1.72	0.117 *
Chronic kidney disease	7	41.18	10	58.82	0.85	0.47	1.53	0.566 †
Arterial hypertension	55	55.55	44	44.45	1.44	1.04	2	0.022 *
Chronic obstructive pulmonary disease	18	72.00	7	28.00	1.64	1.21	2.22	0.009 †
Bronchial asthma	5	41.67	7	58.33	0.86	0.43	1.72	0.660 †
Human immunodeficiency virus	1	33.33	2	66.67	0.69	0.14	3.46	1.000 †
Cancer	5	83.33	1	16.67	1.79	1.21	2.65	0.105 †
Autoimmune disease	3	100.00	0	0.00	2.13	1.82	2.49	0.107 †
Heart failure	6	42.86	8	57.14	0.89	0.48	1.66	0.700 †
Sleep apnea syndrome	4	66.67	2	33.33	1.41	0.79	2.54	0.428 †
Lymphocyte count >3 400 on admission ‡	0	0.00	3	100.00	1.95	1.69	2.24	0.247 †
Platelet count <150 000 during the ICU stay	44	66.67	22	33.33	1.80	1.34	2.41	<0.0001 *
Former smoker	35	67.31	17	32.69	1.68	1.27	2.23	0.001 *
Neuromuscular blockade	82	53.95	70	46.05	3.24	1.44	7.3	<0.0001 *
Vasopressor support	81	61.36	51	38.64	5.11	2.39	10.96	<0.0001 *
Inotropic support	31	77.50	9	22.50	1.97	1.51	2.56	<0.0001 *
Renal replacement therapy	65	69.15	29	30.85	2.77	1.88	4.07	<0.0001 *
Use of antiarrhythmics	22	68.75	10	31.35	1.59	1.18	2.14	0.009 *
Cytokine blood filtration	10	90.91	1	9.09	2.02	1.57	2.59	0.003 †
Severity of ARDS (mild)	2	50.00	2	50.00	1.05	0.39	2.82	1.000 †
Severity of ARDS (moderate)	3	17.65	14	82.35	0.35	0.12	0.98	0.010 †
Severity of ARDS (severe)	82	50.93	79	49.07	2.14	0.98	4.67	0.019 *
Non-invasive mechanical ventilation	43	43.43	56	56.57	0.82	0.61	1.11	0.198 *
Prone position	76	50.67	74	49.33	1.47	0.89	2.44	0.094 *
Reintubation	8	47.06	9	52.94	0.98	0.58	1.67	0.949 †
Transpulmonary pressure measurement	3	33.33	6	66.67	0.69	0.27	1,75	0.501 †
Tracheostomy	33	40.24	49	59.76	0.75	0.54	1.03	0.065 *
Acute renal failure	74	59.20	51	40.80	2.60	1.58	4.28	<0.0001 *
Cardiac arrhythmia	23	67.65	11	32.35	1.56	1.16	2.15	0.010 *
Hydroxychloroquine treatment	2	20.00	8	80.00	0.41	0.12	1.41	0.103 †
Azithromycin treatment	4	36.36	7	63.64	0.75	0.34	1.66	0.541 †
Lopinavir/ritonavir treatment	0	0.00	3	100.00	1.95	1.69	2.24	0.247 †
Treatment with convalescent plasma	1	14.25	6	85.75	0.29	0.05	1.80	0.120 †
Treatment with remdesivir	1	100.00	0	0.00	2.11	1.81	2.45	0.478 †
Treatment with ivermectin	2	100.00	0	0.00	2.12	1.82	2.47	0.227 †
Treatment with dexamethasone	81	47.93	88	52.07	1.04	0.57	1.91	0.902 *
Superinfection	66	50	66	50	1.19	0.82	1.72	0.335 *
Volume-controlled ventilation	84	47.2	94	52.8	0.63	0.35	1.13	0.271 *
Pressure-controlled ventilation	3	75.00	1	25.00	1.59	0.88	2.86	0.350 †
Complications associated with COVID-19	60	57.14	45	42.86	1.63	1.15	2.30	0.003 *

Table 4. Factors associated with mortality in the study population without adjusting for confounding variables (n=182). (Continued)

Quantitative variable	*p*-value
BMI (kg/m²)	0.59 **
Platelets on admission	1.00 **
Age	0.24 **
Weight in kg	0.30 **
D-dimer on admission	0.07 **
Higher D-dimer level during ICU stay	0.11 **
LDH on admission	0.03 **
Higher LDH level during ICU stay	0.01 **
Lymphocytes on admission	0.01 **
Higher lymphocyte count during ICU stay	0.02 **
Positive cumulative fluid balance	0.01 **
P/F on admission	0.03 **
Lower P/F value during ICU stay	0.00 **
Total pronation time in days	0.04 **
Lower platelet count during the ICU stay	0.00 **
Higher tidal volumes during ICU stay	0.01 **
APACHE-II score on admission	0.00 **
Elevated driving pressure	0.01 **
Elevated plateau pressure	0.00 **
Peak pressure	0.00 **
Lower pulmonary compliance value during invasive mechanical ventilation	0.00 **
Ferritin on admission	0.86 **
Higher ferritin level during ICU stay	0.93 **
Days of ICU stay	0.44 **
Days from admission to initiation of invasive mechanical ventilation	0.99 **
Total time in days of invasive mechanical ventilation	0.94 **
Total time in days of non-invasive mechanical ventilation	0.13 **
Total time in days of ventilation (invasive and noninvasive)	0,73 **
Time between the start of invasive mechanical ventilation and tracheostomy	0.99 **
Higher positive end-expiratory pressure value during invasive mechanical ventilation	0.07 **

RR: relative risks; BMI: body mass index; ARDS: acute respiratory distress syndrome; LDH: lactate dehydrogenase; P/F: ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2); ICU: intensive care unit; APACHE II: Acute Physiology and Chronic Health disease Classification System II.
* *p*-value obtained through the chi-square test for independence.
† *p*-value obtained using Fisher's exact test.
‡ Note: Since there is no evidence of a cutoff point in the literature, or at least a consistent cutoff point showing over what lymphocyte count or value there is an increased risk of death from COVID19, this data, although published in multiple previous studies, is not consistent. Therefore, it was decided to classify the value according to the median.
** *p*-value for Mann Whitney U-test.
Source: Own elaboration.

Table 5. Adjustment model for mortality (simple and multiple logistic regression) (n=182).

Variable	Crude RR	Adjusted RR	95%CI
Age *	1.01	1.02	0.96-1.08
D-dimer on admission *	1.00	1.00	1.00-1.00
Higher D-dimer level during ICU stay *	1.00	1.00	1.00-1.00
Total time in days of non-invasive mechanical ventilation *	0.94	0.86	0.63-1.19
Higher positive end-expiratory pressure value during invasive mechanical ventilation *	1.05	0.62	0.37-1.05
LDH on admission*	1.00	1.00	0.99-1.01
Higher LDH level during ICU stay*	1.00	1.00	0.99-1.00
Lymphocytes on admission *	1.00	1.00	1.00-1.00
Higher lymphocyte count during ICU stay *	1.00	1.00	1.00-1.00
Cumulative fluid balance *	1.00	1.00	1.00-1.00
P/F on admission *	1.00	1.00	0.99-1.01
Lower P/F value during ICU stay *	0.98	0.94	0.90-1.00
Total pronation time in days *	1.04	1.10	0.93-1.29
APACHE II score *	1.12	1.07	0.90-1.28
Higher driving pressure during ICU stay *	1.14	0.62	0.40-0.97
Higher plateau pressure during ICU stay *	1.21	1.22	0.79-1.86
Higher peak pressure during ICU stay *	1.16	1.34	0.97-1.84
Higher tidal volumes during the ICU stay *	1.00	0.99	0.98-1.00
Lower value of pulmonary compliance during ICU stay *	0.95	1.02	0.92-1.14
Age <60 years old †	0.16	0.06	0.01-0.43
Obesity (BMI >30 kg/m²) ‡	1.76	2.31	0.53-10.13
Diabetes mellitus ‡	0.62	2.96	0.44-19.79
Arterial hypertension (no)**	0.50	0.91	0.16-5.35
Chronic obstructive pulmonary disease (no) **	0.30	0.28	0.03-3.05
Cancer (no) **	0.17	0.04	0.00-10.41
Autoimmune disease ‡	0.00	2.13	1.82-2.49
Lymphocyte count >3 400 on admission ‡	1.95	1.95	1.69-2.24
Platelet count <150 000 (no) during ICU stay **	0.29	0.76	0.05-11.04
Former smoker (no) **	0.33	0.51	0.10-2.55
Cytokine filtration ‡	0.08	0.13	0.00-55.41
ARDS severity (moderate)‡	4.84	0.35	0.12-0.98
ARDS severity (severe) ‡	0.30	2.14	0.98-4.67
Inotropic support ‡	0.19	0.32	0.04-2.89
Prone position (no) **	0.51	8.05	0.60-108.51
Use of antiarrhythmics (no) **	0.35	1.59	1.18-2.14
Cardiac arrhythmia ‡	0.36	1.56	1.16-2.15
Hydroxychloroquine treatment ‡	3.91	1.49	0.03-63.78
Convalescent plasma therapy (no) **	5.80	14.10	0.47-422.82
Ivermectin treatment ‡	0.00	2.12	1.82-2.47

Table 5. Adjustment model for mortality (simple and multiple logistic regression) (n=182). (Continued)

Variable	Crude RR	Adjusted RR	95%CI
Complications associated with COVID-19 (no) **	0.41	0.64	0.13-3.15
Neuromuscular blockade ‡	0.17	0.03	0.00-0.72
Use of vasopressor support during ICU stay **	0.09	0.11	0.01-1.15
Tracheostomy (yes) ‡	0.26	0.00	0.00-0.90
Acute kidney injury ‡	0.20	1.86	0.18-18.76
Renal replacement therapy ‡	0.15	0.25	0.03-2.09
Lower platelet count during ICU stay *	1.00	1.00	1.00-1.00

LDH: lactate dehydrogenase; P/F: ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2); APACHE II: Acute Physiology and Chronic Health disease Classification System II; ARDS: acute respiratory distress syndrome.; ICU: intensive care unit; BMI: body mass index.
* Quantitative variable.
† Reference category: >60 years.
‡ Reference category: not having the condition.
** Reference category: having the condition.
Source: Own elaboration.

Table 6. Final explanatory mortality model (logistic regression) (n=182).

Variable	Regression coefficient (beta)	Standard error	Wald test statistic	*p*-value	Adjusted RR	95%CI
Intercept	7.894	1.922	4.107	0.000	-	-
Age <60 years[1]	-1.870	0.488	-3.832	0.000	0.154	0.059-0.401
Requirement for neuromuscular blockade (yes)[2]	-1.615	0.854	-1.892	0.058 *	0.199	0.037-1.060
Requirement for vasopressor support (yes)[2]	-2.505	0.694	-3.607	0.000	0.082	0.021-0.319
Requirement for tracheostomy (yes)[2]	-2.611	0.285	4.020	0.000	0.073	0.012-0.827
Acute kidney failure (yes)[2]	0.810	0.715	1.133	0.257 **	2.248	0.054-9.125
Requirement for renal replacement therapy (yes)[2]	-1.584	0.638	-2.485	0.013	0.205	0.059-0,716
Lower platelet count during ICU stay ***	-0.000	0.000	-2.996	0.003	0.999	0.990-0.999

Reference categories: 1. >60 years old, 2. No.
* Significant at 90% confidence; ** Variable not significant but needed in the model for fit and parsimony; *** Quantitative variable.
Overall AIC of the model: 147.87; LLR (likelihood) of the model: null deviance = 251.96 (181 gl), adjusted deviance = 129.87 (173 gl), p=0.000; p-value (H-L): 1.000; omnibus test: 0.041; VIF (collinearity): age <60 years = 1.184, neuromuscular blockade (yes) = 1.637, vasopressor support (yes) = 1.517, tracheostomy (yes) = 1.655, acute kidney failure (yes) = 2.164, renal replacement therapy (yes) = 2.06, lower platelet count during ICU stay = 1.301; coefficient of determination of the R^2 model: 75.20%; overall validity index of the model: 78.6%.
Source: Own elaboration.

Discussion

The present study, performed in 182 patients with COVID-19 admitted to the ICU, found an overall mortality of 48.70%. It was possible to establish that age <60 years, the use of vasopressor support, the performance of tracheostomy, and the use of renal replacement therapy were protective factors against mortality.

The prevalence of mortality found in the present study was considerably lower than the one reported at the beginning of the pandemic by Zhou *et al.*,[14] in a multicenter study conducted in Wuhan, China, in January 2020 with data from 191 patients hospitalized for COVID-19, who found a high mortality rate (97%) in the 32 patients who required invasive mechanical ventilation. However, due to the experience gained over time in the treatment of the disease, this figure has decreased worldwide, reaching values close to 50%[15-18] and similar to those reported in the present study.

Regarding the Colombian context, the mortality rate found in the present research was similar, although slightly higher, to the 38.4% reported by Henríquez *et al.*[19] in a multicenter study conducted with 229 adults admitted to the ICUs of 8 hospitals in Colombia due to COVID-19 between March and July 2020.

Concerning the scores used to predict mortality, the present work studied the applicability of the APACHE II score, obtaining a mean score of 11.97 (±5.72), with a predicted mortality of 15-25% for non-surgical patients and 7-12% for surgical patients. However, the observed mortality (48.70%) was almost twice as high as that predicted by the score, suggesting poor performance when extrapolated as a prognostic score for ICU mortality due to COVID-19. Thus, since no tools are available to adequately predict mortality in these patients at the time of the present study, it is necessary to study the predictive capacity of other scores or scales.

Mortality in patients with COVID-19 is also related to sociodemographic factors such as age.[5,8,14,19,20] In the present study, being younger than 60 years of age was found to be a protective factor (OR=0.154, 95%CI: 0.059-0.401; p<0.001), a finding that is consistent with what has been reported since the beginning of the pandemic, for example, by Henríquez *et al.*[19] who found that being aged ≥65 years was associated with increased mortality in the ICU (OR=11.9; 95%CI: 3.20-44.23). In turn, Petrilli *et al.*,[20] in a prospective cohort study conducted in New York, USA, including 5 279 patients with confirmed SARS-CoV-2 infection between March 1 and April 8, 2020, also found that being older than 75 years and between 65 and 74 years were associated with hospital admission and critical illness (OR=37.9, 95%CI: 26.10-56.03 and OR=8.7, 95%CI: 6.77-11.22, respectively, and p<0.001 for both). On the other hand, although comorbidities could be associated with more severe hypoxemia and a higher risk of developing multiple organ system dysfunction,[6,21] they acted as confounding factors and did not represent an independent risk of mortality in the present study.

Several authors have described predictors of poor prognosis based on mortality in patients upon hospital admission, which are explained as inflammatory, hematological, biochemical and immunological alterations that characterize severe SARS-CoV-2 infection.[7,8,22] In the present study, unlike the available evidence, the only variable with some impact on mortality demonstrated initially was a lower platelet count (<150 000) during ICU stay; however, when contrasted with the other variables, its independent influence as a protective factor was minimal (aRR=0.99, 95%CI: 0.900-0.999; p<0.003). Although a hypothesis for this may relate to the sample size, it is possible that it is caused by the heterogeneity of the initial symptoms of the disease and the difference in consultation times, since patients are admitted at different stages of severity of the disease and, therefore, paraclinical tests on hospital admission do not always show an alteration above the estimated ranges of poor prognosis.

The performance of tracheostomy was an independent protective factor for mortality in the present study (aRR=0.073, 95%CI: 0.012-0.827; p<0.001). The findings are consistent

with those reported by Abe *et al.*,[23] who in an international multicenter prospective cohort study involving 2 377 patients with ARDS receiving noninvasive and invasive mechanical ventilation therapy found that patients with tracheostomy had a lower 28-day mortality than patients who did not receive this therapy (23.4% vs. 38.1%, respectively). This may be explained by the fact that the weaning process was facilitated by reducing sedation, performing physical rehabilitation, and management of secretions.

Since the present study was conducted at the beginning of the pandemic, specific treatments for COVID-19 that had a promising behavior at that time were considered.[24-27] The most commonly used pharmacological therapy (92.86%) involved dexamethasone, a corticosteroid which, according to a study by the RECOVERY Collaborative Group[28] conducted in the United Kingdom in 6 245 patients hospitalized with COVID-19 (4 321 with standard care and 2 104 with standard care plus dexamethasone administration), resulted in lower 28-day mortality in patients receiving this drug (22.9% vs. 25.7%), with a statistically significant difference (age-adjusted rate ratio: 0.83; 95%CI: 0.75-0.93; $p<0.001$).

Despite the methodological limitations of the present study, the use of dexamethasone or any other drug was not clinically or statically associated with reduced mortality. This is consistent with the results of several studies that have shown no statistically significant impact on mortality reduction in patients hospitalized for COVID-19. One of these studies was carried out by Cao *et al.*,[24] who evaluated lopinavir/ritonavir in 199 patients in Wuhan and found that 28-day mortality was similar in the lopinavir/ritonavir group and in the standard care group (19.2% vs. 25.0%). In turn, Beigel *et al.*[25] conducted a double-blind, randomized, controlled trial in 1 062 adults hospitalized for COVID-19 in several countries, finding that mortality was 6.7% in the intervention group (intravenous remdesivir) and 11.9% in the placebo group. Finally, the study by Li *et al.*,[27] who conducted a randomized, multicenter, open-label clinical trial at 7 medical centers in Wuhan, China, evaluated the efficacy and adverse effects of convalescent plasma therapy in 103 patients with COVID-19 and found no significant difference in 28-day mortality (15.7% vs. 24.0%; OR=0.59, 95%CI: 0.22-1.59, $p=0.30$).

Notwithstanding the above, it should be pointed out that other studies have reported a significant association between the use of certain drugs and a reduction in mortality in these patients. This is described by the RECOVERY study for dexamethasone[28] and by Arribas *et al.*[29] in a study with 304 patients (intervention group: 226, placebo group: 78) for molnupiravir.

The use of vasopressor support (RR=5.11, 95%CI: 2.39-10.96; $p<0.001$), inotropics (RR=1.97, 95%CI: 1.51-2.56; $p<0.001$), and renal replacement therapy (RR=2.77, 95%CI: 1.88-4.07; $p<0.001$) was a risk factor for mortality. However, when adjusted in the multivariate model, the use of vasopressor support and renal replacement therapy had statistically significant associations, but as protective factors. This is similar to what was demonstrated in the meta-analysis performed by Belletti *et al.*[30] in 2015, in which they included 28 840 patients and where a reduction in mortality was observed in patients in whom vasopressors were used, although no overall association of vasopressor use with either decreased or increased mortality in the context of vasoplegia (complication resulting from septic shock arising from severe COVID-19 disease) was demonstrated.

Regarding renal replacement therapy, Burke *et al.*,[31] in a single-center prospective observational study conducted in 166 patients with COVID-19 admitted to the ICU, observed that patients who required this type of therapy had a more critical state of the disease and, therefore, higher mortality. Even so, the decrease in mortality demonstrated

in the present study may be related to the elimination of confounding variables, besides the fact that such therapy impacts blood pressure control and maintains negative fluid balance in patients.[30,32]

One limitation of the present study is that some missing data from laboratory tests and some clinical variables could not be corroborated in the main source of information, i.e., medical records. The biases inherent to research using secondary data sources and to the retrospective design of the study are also acknowledged. However, because the investigators work in the ICU where the patients were treated, they made every effort to reduce information bias associated with the reliability of the data obtained from the medical records to the greatest extent possible. The methodology and the statistical analysis that allowed adjusting the associations for confounding effects are highlighted as strengths. Furthermore, it should be noted that although this study was carried out in a single health care center and the findings cannot be extrapolated to other populations, the results are useful as a baseline for making decisions and adopting strategies in the institution, thus impacting service provision and allowing to obtain results that may be of interest to the unit, the clinic and the insurers, with an important relevance at the local level.

Conclusion

Mortality due to COVID-19 was similar to that reported in the international literature. Age <60 years and the use of vasopressors and renal replacement therapy were protective factors, while not having a tracheostomy was a risk factor for mortality. In addition, the lower platelet count recorded during ICU stay was a significantly associated quantitative variable.

Conflicts of interest

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