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Clinical characteristics and mortality in mechanically ventilated COVID-19 patients: prospective cohort study

Características clínicas y mortalidad en pacientes COVID-19 ventilados mecánicamente: estudio de cohorte prospectivo

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What do we know about this problem?

Research describing populations affected by severe COVID-19 infection in Latin America is scant.

There is a paucity of studies dedicated to investigating the critically ill population under intensive care, particularly in Colombia.

What does this study contribute?

Advanced age, male sex, immunosuppression, thrombocytopenia, increased driving pressure and the use of renal replacement therapy were associated with the risk of mortality in patients diagnosed with severe SARS-CoV-2 infection.

These results in 273 patients with COVID-19 who required mechanical ventilation in a tertiary care hospital in southwestern Colombia in 2020 provide an overview of the local behavior of the disease and identify risk factors in severe cases, allowing improved coordination and implementation of direct strategies for the management of this condition.

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Abstract

Introduction: Factors associated with mortality among mechanically ventilated COVID-19 patients have been scarcely studied in Latin America.

Objective: To identify factors associated with mortality in mechanically ventilated COVID-19 patients.

Methods: This prospective study was undertaken in a single center between April and October 2020, recruiting COVID-19 patients managed with mechanical ventilation. We excluded patients who died within the first 24 hours after endotracheal intubation. Clinical characteristics, laboratory results, ventilation interventions, and outcomes were collected and compared between the deceased and surviving groups. The association between these factors and hospital death was examined, and relevant covariates were included in a multivariate logistic regression model.

Results: A total of 273 patients were included (72.5% male), the mortality rate was 37% (95% CI 31% - 43%), and the median age was 63 years (IQR 52-72). The most frequent comorbidity was hypertension (45%). Factors associated with mortality were: older age (OR 1.08; 95% CI 1.05-1.11), male gender (OR 2.79; 95% CI 1.30-6.01), immunosuppression (OR 3.98; 95% CI 1.57-10.06), thrombocytopenia (OR 3.84; CI 95% 1.47-10.01), driving pressure (OR 1.20; 95% CI 1.07-1.34) and the use of dialysis (OR 4.94; 95% CI 2.56-9.51). Chronic hypertension (OR 0.35; 95% CI 0.17-0.71) and fever on admission (OR 0.51; 95% CI 0.27-0.98) were found to have a protective effect.

Conclusions: Older age, male sex, immunosuppression, thrombocytopenia, increased driving pressure, use of dialysis, absence of fever, or arterial hypertension were associated with an increased risk of mortality among mechanically ventilated COVID-19 patients.

Keywords: Coronavirus infections; Artificial respiration; Respiratory failure; Risk factors; Intensive care; Mortality.

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Resumen

Introducción: Es poco lo que se han estudiado en América Latina los factores asociados con mortalidad en pacientes con COVID-19 ventilados mecánicamente.

Objetivo: Identificar los factores asociados con mortalidad en pacientes con COVID-19 manejados con ventilación mecánica.

Métodos: Este estudio prospectivo se adelantó en un solo centro entre los meses de abril y octubre de 2020 e incluyó pacientes con COVID-19 manejados con ventilación mecánica. Se excluyeron pacientes que fallecieron en las primeras 24 horas después de la intubación orotraqueal. Se recopilaron datos de las características clínicas, resultados de laboratorio, intervenciones ventilatorias y desenlaces, y se hizo una comparación entre el grupo de pacientes fallecidos y el grupo de sobrevivientes. Se examinó la asociación entre estos factores y la muerte intrahospitalaria, y las covariables relevantes se incluyeron en un modelo multivariable de regresión logística.

Resultados: Se incluyó un total de 273 pacientes (72.5% hombres), la tasa de mortalidad fue del 37% (IC 95% 31% - 43%), la mediana de edad fue de 36 años (RIC 52-72) y la comorbilidad más frecuente fue la hipertensión (45%). Los factores asociados con mortalidad fueron: edad avanzada (OR 1.08; IC 95% 1.05-1.11), género masculino (OR 2.79; IC 95% 1.30-6.01), inmunosupresión (OR 3.98; IC 95% 1.57-10.06), trombocitopenia (OR 3.84; CI 95% 1.47-10.01), presión de distensión (OR 1.20; IC 95% 1.07-1.34) y el uso de diálisis (OR 4.94; IC 95% 2.56-9.51). La presencia de hipertensión (OR 0.35; IC 95% 0.17-0.71) y de fiebre (OR 0.51; IC 95% 0.27-0.98) al momento de la hospitalización demostraron tener un efecto protector.

Conclusiones: Se encontró asociación entre la edad avanzada, el sexo masculino, la inmunosupresión, la trombocitopenia, una presión de distensión elevada, el uso de diálisis, la ausencia de fiebre o de hipertensión y un mayor riesgo de mortalidad en pacientes con COVID-19 ventilados mecánicamente.

Palabras clave: Infecciones por coronavirus; Respiración artificial; Insuficiencia respiratoria; Factores de riesgo; Cuidado intensivo; Mortalidad.

INTRODUCTION

In late 2019, an outbreak of pneumonia cases began in Wuhan, China. Subsequently, its cause was identified to be a novel coronavirus, and in March 2020, due to the number of cases and countries affected, the outbreak was declared a pandemic (1), becoming the most significant infectious disease of recent times. As of June 2022, more than 535 million cases have been recorded, with more than 6.3 million deaths worldwide. In Colombia, there have been approximately 6.1 million cases and approximately 140,000 deaths (2).

The pathophysiology of severe COVID-19 involves impaired gas exchange that may require the use of invasive mechanical ventilation. The need for invasive ventilation varies from 29 to 89% across different published cohorts (3,4). This wide variation may be due to the lack of standardized management criteria, the urgency of the disease, and the differences in access to resources and infrastructure across the regions of the world. These factors also influence the mortality rate of patients requiring mechanical ventilation, with the rate at the beginning of the pandemic ranging between 65 and 88% (3), and dropping to 43-33% in more recent publications (4, 5, 6).

Primary healthcare systems and epidemiological surveillance are widely examined among health systems in developing countries, many in Latin America (7).

Few epidemiological studies have examined the application of mechanical ventilation in the Latin American population or the management strategies used in patients diagnosed with COVID-19 (8, 9). However, multicenter studies have been conducted by specialized research groups in other areas of the world (10-14).

The current study describes the clinical and paraclinical characteristics, ventilatory parameters, complications and mortality of COVID-19 patients who require mechanical ventilation, with the aim of identifying factors associated with hospital mortality.

METHODS

Design and participants

This is a prospective, observational, analytical cohort study. The dataset was derived from the "Mechanical Ventilation Registry," referred to as REVEMECA (acronym in Spanish for "Registro de Ventilación Mecánica"), which included a total of 892 ventilated patients. The primary aim of the registry was to delineate the baseline characteristics, strategies, outcomes, and complications of adult patients requiring mechanical ventilation over a six-month period. The study protocol was approved by the Biomedical Research Ethics Committee of the institution (Record # 1308). In light of its classification as a non-interventional observational study, the requirement for informed consent was waived for data collection, in accordance with the decision made by the Institutional Review Board. This study included all patients who were at least 18 years old, diagnosed with COVID-19 via polymerase chain reaction (PCR) in accordance with the WHO criteria (15), and required invasive ventilatory support in the intensive care unit (ICU), regardless of the initial severity and comorbidities, between April 15, 2020, and October 16, 2020. Patients under 18 years of age and those who died within 24 hours after intubation were excluded from the registry. Follow-up was performed until

hospital discharge or death, with the latter defined as mortality occurring during the same hospitalization in which mechanical ventilation was required.

The criteria for initiating invasive mechanical ventilation during the study period included hypoxemic respiratory failure, hemodynamic instability, multiple organ failure, or altered mental state. Participants with mild respiratory impairment underwent a high-flow nasal cannula or a non-rebreather mask trial, limited to a maximum duration of 2 hours. The decision to proceed with endotracheal intubation was determined based on observable signs of respiratory distress, hypoxemia, overall clinical status, response to oxygenation strategies and arterial blood gas analysis results during this 2-hour period.

For the purposes of this registry, immunosuppression status was defined as individuals undergoing cancer treatment, transplant recipients, those with primary or acquired immunodeficiencies or those with a history of chronic use of steroids or other immunosuppressive medications. Thrombocytopenia was considered to be present when platelet counts were below 150000/microliter, while lymphopenia, was defined as a lymphocyte count lower than 1500/microliter.

The strategies employed for managing hypoxemic respiratory failure in the ICU included intravenous corticosteroid therapy; lung-protective ventilation with a tidal volume between 6 and 8 ml/kg of predicted weight; prone positioning in individuals with persistent hypoxemia despite sedation optimization and the level of end-expiratory pressure (positive end-expiratory pressure - PEEP); individualized use of neuromuscular blocking agents and/or alveolar recruitment maneuvers, fluid restriction tactics, and the consideration of extracorporeal membrane oxygenation (16-19).

Data collection

Data were collected using the REDCap software. The main sources of information were electronic clinical records and hard copy records of the intensive care unit. Some admission characteristics were drawn from an institutional COVID-19 registry. Information included clinical characteristics, initial symptoms, paraclinical results, chest X-ray findings and severity indices. Information pertaining to interventions in ICU patients as well as mechanical ventilation settings and strategies was also collected.

Plateau pressures in patients ventilated in pressure-controlled mode were measured by generating a manual inspiratory pause of 3 seconds during a state of comfort and equilibrium between sedation and agitation.

Complications such as the necessity for tracheostomy and ventilator-associated pneumonia (VAP) were documented in the study. Criteria for tracheostomy as a complication in this research included persistence of an altered state of consciousness, unresolved underlying pathology, or sustained respiratory compromise. VAP was recorded based on criteria established by the Centers for Disease Control and Prevention (CDC) (20). These criteria included positive radiological finding consisting of new or progressive and persistent infiltrate, and at least one of the following: fever or hypothermia, leukopenia or leukocytosis, worsening of oxygenation or ventilation, where culture of tracheal secretion 48 hours after the start of mechanical ventilation confirmed the acquired superinfection in the hospital.

Daily monitoring of each patient was performed. Data with the highest deviations (i.e., data further from physiological normality) were selected for paraclinical results. Respiratory monitoring variables and cumulative fluid balance represent the first 7 days of mechanical ventilation and interventions and outcomes during the ICU stay.

The duration of mechanical ventilation was defined as the time (in days) between the time of intubation and the first successful extubation, the tracheostomy or the day of death if the patients died before weaning from invasive ventilation.

Statistical analysis

An assessment of factors associated with mortality was carried out, given the exploratory nature of this study. A total sample size of 190 patients was determined considering clinical variables such as fever and dyspnea — reported in 71% and 74% of cases, respectively — along with comorbidities like chronic arterial hypertension, observed in 63% in one of the robustly documented cohorts (11). The sample consisted of 95 patients in the case group and 95 patients in the control group, factoring in a confidence level of 95% and a statistical power of 80%.

Data were reviewed and verified using source documents in cases of missing or irregular data. Continuous variables are described using measures of central tendency and dispersion. Normally distributed data are described as mean and standard deviation (SD), and non-normally distributed data are described as median and interquartile range (IQR). Nominal variables are described as absolute and relative frequencies.

Baseline characteristics and treatments were compared between survivors and patients who died in order to identify risk factors. The Chi2 test or the Fisher test were used to compare categorical variables, and Student's t test or the Mann–Whitney test were used to compare continuous variables. The normality of continuous variables was examined using the Shapiro–Wilk test.

A multivariate logistic regression analysis was used to identify factors associated with mortality. Variables with $p < 0.2$ or variables that were relevant according to the opinion of the authors were subsequently included in a model for multivariate logistic regression analysis in accordance with the purposeful variable selection method proposed by Hosmer and Lemeshow (21). In specific cases in which no laboratory data were documented, multiple imputation was used to compute data (specifically in the laboratory entry results: C-reactive protein 91.9% complete information; dehydrogenase and lactic

acid 90.8% complete information; ferritin 71.1% complete information; and D-dimer 85.7% complete information). Variables with missing data did not show differences in the multivariate analysis. The frequency of outcomes of interest and the measures of association are reported with 95% confidence intervals (95% CI).

RESULTS

Of 892 patients initially included in the 'Mechanical Ventilation Registry,' 273 individuals required invasive ventilatory support due to a COVID-19 diagnosis during the follow-up period. Table 1 describes the basic demographic, clinical and physiological characteristics. There was a higher proportion of male patients (72%), and the median age of the included population was 63 years (IQR 52-72). The most common comorbidity was hypertension (45%), followed by obesity and diabetes (39% and 27%, respectively). Dyspnea was the most common initial consultation symptom (80%), followed by fever (62.3%) and cough (60.1%).

Lymphopenia was common in this cohort (median for lymphocytes 0.96 x1000/µL); the lymphocyte count was lower among non-survivors than among survivors (median of 0.80x1000/µL vs. 1.0x1000/µL, respectively). A similar result was found for thrombocytopenia, with 4 survivors and 24 non-survivors having thrombocytopenia, respectively, The D-dimer test also revealed an important difference between the two groups (median of 1.0 µg/dL vs. 1.8 µg/dL). In the majority of patients (54%), global interstitial infiltrates were the radiological finding, followed by multifocal alveolar infiltrate in more than a quarter of the patients (28%).

There was no significant difference between the groups studied in terms of the NEWS score (National Early Warning Score) on admission (8.48 ± 3.23 versus 8.49 ± 3.86). The median SOFA (Sepsis Organ Failure Assessment) score on admission was 9 points (IQR 7-11). Among survivors and

Table 1. Demographic, clinical and physiological characteristics of COVID-19 patients on mechanical ventilation.

Variable	Total Patients	Survivors	Non-survivors	P	n
Total, n (%)	273	172 (63)	101 (37)		
Sex, n (%)					
Female	75 (27.5)	53 (30.8)	22 (21.8)	0.107	
Male	198 (72.53)	119 (69.2)	79 (78.2)		
Age (years), median (IQR)	63 (52-72)	58 (48.5-68)	68 (58-77)	<0.001	
Comorbidities, n (%)					
Chronic pulmonary disease	29 (10.6)	20 (11.6)	9 (8.9)	0.482	
Immunosuppression	36 (13.2)	15 (8.7)	21 (20.8)	0.008	
Chronic kidney disease	32 (11.7)	12 (6.9)	20 (19.8)	0.003	
Cardiac failure	7 (2.5)	4 (2.3)	3 (2.9)	0.514	
Hypertension	124 (45.4)	78 (45.4)	46 (45.5)	0.975	
Obesity	109 (39.9)	78 (45.4)	31 (30.7)	0.024	
Diabetes	75 (27.5)	44 (25.6)	31 (30.7)	0.361	
Symptoms on admission, n (%)					
Fever	170 (62.3)	116 (67.4)	54 (53.5)	0.021	
Cough	164 (60.1)	105 (61.1)	59 (58.4)	0.668	
Dyspnea	221 (80.9)	146 (84.9)	75 (74.3)	0.031	
Odynophagia	35 (12.8)	21 (12.2)	14 (13.9)	0.693	
Fatigue	122 (44.7)	70 (40.7)	52 (51.5)	0.083	
Rhinorrhea	44 (16.1)	25 (14.5)	19 (18.8)	0.353	
Headache	42 (15.4)	30 (17.4)	12 (11.9)	0.219	
Myalgia	54 (19.8)	33 (19.2)	21 (20.8)	0.748	
Arthralgias	38 (13.9)	26 (15.1)	12 (11.9)	0.456	
Loss of smell	11 (4)	11 (6.4)	0	0.05	
Loss of taste	13 (4.8)	10 (5.8)	3 (2.9)	0.224	
Diarrhea	52 (19.1)	34 (19.8)	18 (17.8)	0.693	
Time from onset of symptoms to admission (Days), median (IQR)	7 (4-8)	7 (4-8)	7 (3-8)	0.418	
Previous vital signs, median (IQR)					
Oxygen saturation (%)	82 (70-90)	82 (70-89)	80 (66-91)	0.959	
Pa O2/FIO2 ratio	103 (78-152)	100 (76-138)	106 (78-162)	0.429	
Initial laboratory results, median (IQR)					
Neutrophils (x1000/UL)	8.8 (6.4-13.2)	8.9 (6.6-13.4)	8.8 (6-12.9)	0.562	
Lymphocytes (x1000/UL)	0.96 (0.63-1.3)	1.02 (0.69-1.5)	0.8 (0.5-1.2)	0.010	
Lymphopenia = <1000					
(Dichotomous variable)		82 (47.7)	61 (60.4)	0.057	
Neutrophil-lymphocyte ratio	9.5 (5.3-16.3)	9.2 (5.3-14.9)	9.8 (5.3-18.6)	0.379	
Platelets (x1000/UL)	247 (180-315)	258 (205-315)	219 (152-319)	0.003	
Thrombocytopenia = <150 (dichotomous variable)		8 (4.7)	24 (23.8)	<0.001	
Lactate dehydrogenase (LDH) (U/L)	476 (384-658)	450 (382.5-619.5)	533 (387-752)	0.05	
C-Reactive Protein (mg/L)	17.9 (9.9-28.4)	18.4 (9.7-28.1)	17.3 (10.1-30.4)	0.883	251
Ferritin (ng/ml)	1328 (809-2404)	1289 (854-1836)	1564 (788-3016)	0.312	194
D-dimer (µg/DL)		1.06 [0.59. 2.03]	1.84 [1.14. 6.84]	<0.001	233
- D-dimer >2		40 (25.8)	36 (45.6)	0.004	233
- D-dimer >4		26 (16.8)	29 (36.7)	0.001	233
Chest X-ray findings, n (%)					
None	15 (5.5)	10 (5.8)	5 (4.9)	0.498	
Focal interstitial	10 (3.7)	4 (2.3)	6 (5.9)	0.116	
Global interstitial	150 (54.9)	93 (54.1)	57 (56.4)	0.704	
Focal alveolar	8 (2.9)	6 (3.5)	2 (1.9)	0.379	
Multifocal alveolar	77 (28.2)	50 (20.1)	27 (26.7)	0.679	
Mixed alveolar opacities	5 (1.8)	4 (2.3)	1 (0.9)	0.389	
Ground-glass opacity	8 (2.9)	5 (2.9)	3 (2.9)	0.621	
Severity scores					
NEWS score, mean (SD)	8.48 ± 3.47	8.48 ± 3.23	8.49 ± 3.86	0.977	
Initial SOFA score, median (IQR)	9 (7-11)	8 (7-10)	10 (8-12)	<0.001	
APACHE II score, mean (SD)	23.83 ± 6.41	22.82 ± 5.86	25.56 ± 6.95	<0.001	

IQR= Interquartile range, SD= Standard Deviation.
Source: Authors.

non-survivors, median scores were 8 (IQR 7-10) and 10 points (IQR 8-12), respectively. On the other hand, the average score on the APACHE II (Acute Physiology and Chronic Health disease) scale was 23.8 (SD ± 6.41) upon admission to the emergency room and 22.8 (SD ± 5.86) vs. 25.56 (SD ± 6.95) among survivors and non-survivors, respectively.

ICU stay

Twelve percent of patients did not receive any type of oxygen support prior to intubation. A total of 42% received support with a high-flow nasal cannula; the same proportion received a conventional nasal cannula. The median time between consultation and the start of mechanical ventilation was 9 hours (IQR 1-49). Tracheostomy was necessary in 24% of participants.

Regarding ventilatory parameters, volume-controlled mode was initially used in 91% of the patients. The median FiO2 was 0.5 (IQR 0.4-0-6), and the average PEEP in the first 24 hours was 12.3 cmH2O (SD ± 2.6). The average tidal volume was adjusted to the predicted weight of 7.4 ml/kg (SD ± 1.13).

Mean peak pressure, mean pressure and plateau pressure were 28, 15 and 23 cmH2O, respectively (SD ± 4, 3 and 3). On the other hand, the median (IQR) driving pressure was 12 (10-13) cmH2O, and the dynamic respiratory compliance was 31 ml/cm H2O (IQR 26-39). Airway pressures were consistently higher among non-survivors (Table 2).

Table 2. Management of COVID-19 patients in the ICU.

Variable	Total de pacientes	Pacientes vivos	Pacientes fallecidos	p
Total, n (%)	273	172 (63)	101 (37)	
Ventilatory support prior to intubation, n (%)				
No support	33	21 (64.6)	12 (36.4)	0.936
Non-rebreather mask	116	69 (59.5)	47 (40.5)	0.3
High flow cannula	115	75 (65.2)	40 (34.8)	0.518
Other supports	9	7 (77.8)	2 (22.2)	0.289
Time to IMV (hours), median (IQR)	9 (1-49)	12.5 (1-43.5)	5 (1-62)	0.224
Mechanical ventilation mode, n (%)				
Volume control	225	144 (64)	81 (36)	0.460
Pressure control	6	4 (66.7)	2 (33.3)	0.607
Assisted/Controlled by volume	26	14 (53.8)	12 (46.2)	0.309
Assisted/Controlled by pressure	16	10 (62.5)	6 (37.5)	0.966
Ventilatory parameters				
FiO2, median (IQR)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.5 (0.4-0.6)	0.102
PEEP (cm H2O), mean (DS)	12.3 ± 2.6	12.3 ± 2.5	12.3 ± 2.8	0.804
Tidal volume (mL), mean (SD)	469 ± 75	473 ± 70	463 ± 83	0.287
Peak pressure (cmH2O), mean (SD)	28 ± 4	27 ± 4	29 ± 5	0.008
Mean pressure (cmH2O), mean (SD)	15 ± 3	15 ± 3	16 ± 3	0.032
Plateau pressure (cmH2O), mean (SD)	23 ± 3	23 ± 3	24 ± 4	0.002
Driving pressure (cmH2O), median (IQR)	12 (10-13)	12 (10-13)	12 (11-13)	0.039
Dynamic compliance, median (IQR)	31 (26-39)	32 (27-42)	30 (24-36)	0.025
Static compliance, median (IQR)	43 (35-51)	43 (36-52)	42 (34-49)	0.085
AutoPEEP, median (IQR)	0 (0-0)	0 (0-1)	0 (0-0)	0.724
Ventilatory complications, n (%)				
Ventilator-associated Pneumonia	131	80 (61.1)	51 (38.9)	0.525
Self-extubation	24	20 (83.3)	4 (16.7)	0.022
Time from MV to first extubation (days), median (IQR)	9 (6-13)	8 (6-13)	13 (8-17)	0.004
Fluid balance, median (IQR)	144(-129-457)	78.5 (-220-342)	290 (21-691)	<0.001
Need for vasoactive (%)	223	128 (57.4)	95 (42.6)	<0.001
ICU interventions, n (%)				
Need for tracheostomy, n (%)	66	40 (60.6)	26 (39.4)	0.643
Renal replacement therapy	99	38 (38.4)	61 (61.6)	<0.001
Neuromuscular blocker	205	126 (61.5)	79 (38.5)	0.360
Corticosteroids	264	169 (64)	95 (36)	0.066
Prone position	124	73 (58.9)	51 (41.1)	0.197
Need for nitric oxide (NO2)	10	5 (50)	5 (50)	0.116
Length of ICU stay (days), median (IQR)	14 (9-22)	14 (9-21)	15 (8-22)	0.714
Length of hospital stay (days), median (IQR)	20 (12-32)	23 (15-41.5)	15 (8-24)	<0.001

IQR= Interquartile range, SD= Standard deviation.
Source: Authors.

Cumulative water balance and complications

The median cumulative fluid balance during the first 7 days of mechanical ventilation was 144 ml (IQR 129-457), with 78.5 ml being the median (IQR-220-342) in the patients who survived, and 290 ml (IQR 21-691) in non-survivors.

The use of vasoactive medications was necessary in 82% of the population (74% among survivors and 94% among non-survivors), with an average of 5 days (SD ± 5.59) of use during their stay.

Forty-eight percent of patients met the criteria for ventilator-associated pneumonia. The proportion was similar between those who lived and those who died.

The most common microorganism was Pseudomonas aeruginosa (44 reports), followed by Klebsiella pneumoniae (33 reports) and Staphylococcus aureus (32 reports). The microbiological isolates derived from orotracheal secretion

cultures conducted by the laboratory are shown in the table included in the annex. No differentiation is made between commensal agents and microorganisms responsible for ventilator-associated pneumonia. (See Complementary material)

Intervention strategies in the intensive care unit

The requirement of renal replacement therapy (RRT) was 36%. Neuromuscular relaxation was applied in 75% of all patients, and 97% received corticosteroids. Prone positioning was needed in 45% of patients (42% among survivors and 50% among non-survivors).

Hospital mortality was 37% (95% CI 31% - 43%), and occurred after a median of 13 days (IQR 8-17) after the start of invasive mechanical ventilation. For the survivors, the median length of stay in the ICU was 14 days (IQR 9-21). Table 3 shows the risk factors associated with death and the differences in the characteristics and treatments received during the ICU stay between these two comparison groups. The SOFA and APACHE II severity indices on admission were consistently higher among non-survivors.

Multivariate analysis

Age stands out among the characteristics that were independently associated with mortality, such that a one-year increase in age is associated with an 8% increase in the risk of mortality (OR 1.08; 95% CI 1.05-1.11). On the other hand, the risk of dying was approximately three times higher among men than among women (OR 2.79; 95% CI 1.30-6.01) (Table 3).

Regarding comorbidities and admission characteristics, hypertensive patients and those who presented with fever had a lower risk of dying (OR 0.35; 95% CI 0.17-0.71 and OR 0.51; 95% CI 0.27-0.98), respectively. In contrast, patients who were immunosuppressed or those

Table 3. Factors associated with death in the ICU in mechanically ventilated COVID-19 patients.

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	p	OR	95% CI	p
Age, years	1.05	1.03-1.07	<0.001	1.08	1.05–1.11	<0.001
Sex (male)	1.60	0.90-2.84	0.108	2.79	1.30–6.01	0.009
Hypertension, mm Hg	1.01	0.62-1.65	0.975	0.35	0.17–0.71	0.004
Obesity	0.53	0.32-0.89	0.018			
Asthma	0.21	0.03-1.66	0.138			
Immunosuppression	2.75	1.34-5.62	0.006	3.98	1.57–10.06	0.002
Chronic kidney disease	3.29	1.53-7.07	0.002			
Fever on admission	0.55	0.33-0.92	0.022	0.51	0.27–0.98	0.048
Dyspnea	0.51	0.28-0.95	0.033			
Fatigue	1.55	0.94-2.54	0.084			
Lymphopenia	1.67	1.02-2.76	0.043			
Thrombocytopenia	6.39	2.75-14.87	<0.001	3.84	1.47–10.01	0.005
D-dimer µg/dL	1.02	1.00-1.04	0.025			
LDH U/L	1.00	1.00-1.00	0.041			
Ferritin ng/mL	1.00	0.99-1.00	0.209			
PaO2: FiO2 ratio on admission	1.00	0.99-1.00	0.323			
Time from admission to intubation	1.00	1.00-1.00	0.037			
SOFA on day 2	1.29	1.16–1.43	<0.001			
APACHE II	1.07	1.03–1.12	0.001			
FiO2 on the first day	1.02	0.99–1.03	0.007			
Plateau pressure, cmH2O	1.13	1.04–1.23	0.003			
Peak inspiratory pressure,cmH2O	1.08	1.02–1.15	0.009			
Mean airway pressure, cmH2O	1.10	1.01–1.21	0.034			
Driving pressure, cmH2O	1.16	1.05–1.29	0.005	1.20	1.07–1.34	0.004
Static compliance, mL/cm H2O	0.98	0.96–1.00	0.064			
Dynamic compliance, mL/cmH2O	0.98	0.95–0.99	0.041			
Systemic corticosteroids	0.28	0.07–1.15	0.077			
Prone ventilation	1.38	0.84–2.27	0.198			
Use of nitric oxide	2.65	0.73–9.64	0.138			
Bacterial pneumonia	1.33	0.65–2.72	0.443			
Use of renal replacement therapy	5.38	3.14–9.20	<0.001	4.94	2.56–9.51	<0.001
Self-extubation	0.31	0.10–0-94	0.039			

Source: Authors.

with thrombocytopenia had a higher risk of dying (OR 3.98; 95% CI 1.57-10.06 and OR 3.84; 95% CI 1.47-10.01, respectively).

A 1 cmH2O increase in driving pressure was associated with a 20% increase in the odds of dying (OR 1.20 95% CI 1.07-1.34). Similarly, the use of renal replacement therapy in the ICU was associated with an increase in mortality (OR 4.94; 95% CI 2.56-9.51).

DISCUSSION

This study described factors associated with mortality among 273 patients who required invasive mechanical ventilation, a cornerstone therapy for the management of severe cases of COVID-19 infection.

The majority of subjects in our cohort were men with a median age greater than 60 years. The demographic profile is similar to that reported in previous studies (10-14). Age has been shown to be a risk factor for increased mortality (22, 23); this finding was replicated in the current study, where a one-year increase in age led to a gradual increase in the risk of mortality.

The greater risk among men has been attributed to the differences in the immune response linked to the X chromosome, the level of estrogen, the greater production of antibodies and the differences in the release of cytokines between men and women (24). The association between advanced age and mortality has been explained by the decrease in immune function that occurs as part of the natural aging process, which affects both innate and acquired immunity and even leads to a proinflammatory and procoagulant state (25), resulting in worse prognosis among older patients.

The most frequent comorbidities were hypertension, obesity and diabetes, which are the three most common chronic diseases in most of the available descriptive cohorts (10, 12, 14, 26). In our population, regardless of age and the presence of comorbidities, the risk of mortality was higher among immunosuppressed individuals; this relationship has been established by the different degrees of deterioration of the immune system among people receiving cancer treatment, smokers, transplant patients, those with immunodeficiencies, and prolonged use of corticosteroids or immunosuppressive drugs (27).

In the literature, there are associations between arterial hypertension and severe disease or mortality due to SARS-CoV-2. Therefore, arterial hypertension has been recognized as a risk factor, independent of age and smoking (28), because of the action of angiotensin-converting enzyme 2 as an entry receptor to the cell (29). However, Patel et al. (30) found that arterial hypertension was prevalent but not associated with mortality in a large age-adjusted cohort of hospitalized patients. On the other hand, Meng et al. (31) analyzed a small sample of patients and suggested that hypertensive patients treated with angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists are less likely to experience severe disease due to the attenuation of the inflammatory response by inhibition of IL-6, which decreases the Th1/Th2 ratio. This is consistent with the finding that the presence of hypertension had a protective effect against mortality in our population of ventilated patients, independent of the effect of other variables.

In our experience, although fever was one of the most frequent clinical manifestations, those subjects who presented with fever at the beginning of hospitalization had a reduced risk of dying. This finding is consistent with the results of a meta-analysis by Zheng et al. who reported that fever was associated with a decrease in disease severity and a lower risk of death (32). Other reviews consider fever to be unrelated to the risk of mortality and thus do not examine its predictive value (33, 34, 35).

Regarding alterations in laboratory parameters among the infected patients, this study determined that thrombocytopenia was independently associated with a higher relative risk of death. A probable explanation is the decrease in platelet synthesis by direct viral infection in the bone marrow, destruction by the immune system and increased consumption by platelet aggregation in the lung (36). This pattern is similar to that reflected in international cohorts where lymphopenia, thrombocytopenia, elevated liver enzymes, lactic dehydrogenase, C-reactive protein, D-dimer and proinflammatory markers, among others, have been recognized to be associated with severe disease and increased risk of death (10, 37, 38).

The bivariate analysis highlighted the difference in cumulative fluid balance between patients who survived and those who died, such that a higher cumulative volume was significantly associated with higher mortality. This has been the subject of research in acute respiratory distress syndrome (ARDS) due to the association between pulmonary edema and increased vascular permeability, which exacerbates the increase in hydrostatic pressure over oncotic pressure and radically deteriorates gas exchange, thereby worsening clinical stability and prognosis (39-41). For SARS-CoV-2 positive patients, the conservative fluid strategy is recommended instead of the liberal strategy in multiple management guidelines (16-19).

In our cohort, interventions such as tracheostomy and pronation to manage prolonged mechanical ventilation and refractory hypoxemia, respectively, showed no association with the risk of death. However, RRT, which was necessary in more than one-third of patients, was shown to be an independent risk factor for mortality, consistent with previous findings by Fominskiy et al., who reported that patients with COVID-19 who were on invasive mechanical ventilation had a mortality rate exceeding 50% (42).

In the current study population, patients who died presented consistently and significantly higher airway pressures (peak, mean, plateau and driving pressure). In addition, driving pressure was an independent factor associated with a higher risk of dying. These findings, added to

lower lung compliance, confirm a frequent alteration in respiratory mechanics that was not evident in all individuals and is explained by the varied pathophysiology of the novel coronavirus, where the existence of several phenotypes correspond to different phases of the disease (43, 44).

Limitations and strengths of the study

This was a single-center study. The characteristics of a group of patients in a tertiary care university hospital were analyzed, and the information was collected in the initial phase of the pandemic, when knowledge about the disease was more limited. In a few cases, paraclinical information was lacking due to logistic issues.

The collection of electronic clinical records and physical records of the intensive care unit was performed prospectively, allowing verification of the information in the source documents or in the patient in real time, thus ensuring the quality of the collected data. The small sample size may be a limitation when it comes to the interpretation of our results.

CONCLUSION

We found a lower mortality rate than that reported in other studies around the world. Age, male sex, absence of arterial hypertension on admission, absence of fever on admission, immunosuppression, thrombocytopenia, high driving pressure and the requirement of renal replacement therapy were documented as associated factors for mortality among patients with COVID-19 who required invasive mechanical ventilation.

ETHICAL DISCLOSURES

Ethics committee approval

The study protocol was approved by the Biomedical Research Ethics Committee of the institution (Record # 1308).

Protection of human and animal subjects

The authors declare that no experiments were performed on humans or animals for this study. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics commit-tee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data

The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent

The authors declare that no patient data appear in this article.

In light of its classification as a non-interventional observational study, the requirement for informed consent was waived for data collection, in accordance with the decision made by the Institutional Review Board.

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Author's contributions

All authors participated in the design and implementation of the research project as well as in the literature review, statistical analysis and interpretation of the results, discussion, preparation and revision of the manuscript.

JDGM: Data collection.

AFGM, MPVO, AGR and JCY: Study planning, interpretation of the results, and writing of the manuscript.

JDGM: Study planning, data collection, interpretation of the results, and initial writing of the manuscript.

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Conflict of interest

The authors declare no conflicts of interest.

Presentations

None declared.

Appreciations

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COMPLEMENTARY MATERIAL

Complementary material 1. Microbiological isolates.

Isolated microorganism	Records
Acinetobacter baumannii	3 (2.2%)
Acinetobacter calcoaceticus	1 (0.7%)
Acinetobacter johnsonii	1 (0.7%)
Acinetobacter junii	1 (0.7%)
Acinetobacter pitti	1 (0.7%)
Burkholderia cepacia	1 (0.7%)
Burkholderia lata	1 (0.7%)
Candida albicans	8 (6.1%)
Candida glabrata	1 (0.7%)
Candida tropicalis	1 (0.7%)
Citrobacter koseri	2 (1.5%)
Elizabethkingia anophelis	1 (0.7%)
Enterobacter cloacae complex	2 (1.5%)
Enterococcus faecalis	1 (0.7%)
Escherichia coli	4 (3.0%)
Haemophilus influenzae	3 (2.2%)
Klebsiella oxytoca	1 (0.7%)
Klebsiella aerogenes	1 (0.7%)
Klebsiella pneumoniae	32 (24.4%)
Morganelle morganii	1 (0.7%)
Ochrobactrum anthropi	1 (0.7%)
Proteus hauseri	1 (0.7%)
Proteus mirabilis	3 (2.2%)
Providencia rettgeri	1 (0.7%)
Pseudomonas mosselii	1 (0.7%)
Pseudomonas aeruginosa	44 (33.5%)
Pseudomonas putida	3 (2.2%)
Rothia mucilaginosa	1 (0.7%)
Serratia marcescens	9 (6.8%)
Staphylococcus aureus	33 (25.1%)
Stenotrophomonas maltophilia	18 (13.7%)
Streptococcus pneumoniae	1 (0.7%)
Streptococcus agalactiae	2 (1.5%)
Trichosporon asahii	1 (0.7%)
1 microorganism identified	88 (67.2%)
>1 microorganism identified	43 (32.8%)
Total cases of pneumonia associated with mechanical ventilation	131 (47.9%)

Source: Authors.