PREDICTIVE FACTORS OF TIME TO DIE FROM COVID-19 IN INTENSIVE CARE UNITS

Gustavo Bergonzoli P, Felipe-José Tinoco Z, Carolina Jaramillo L, Cristhian Johan Rodríguez C

Hospital Departamental Tomás Uribe Uribe (HDTUU), Tuluá Valle del Cauca, Colombia

ABSTRACT

*To identify risk factors that increase or decrease the probability of dying from Covid-19 in Intensive Care Units (ICU) patients. This study is based on data collected retrospectively from the hospital records. The proportional model assumption was verified using the Kaplan–Meier method, and Cox Hazard Proportional Regression model to identify predictors' factors associated with time to death by Covid-19. Four factors were identified, two of them increase the probability of dying: age (Adjusted Hazard Ratio (HRa) = 1.032 (1.022–1.041), and breathing frequency HRa = 1.035 (1.016-1.054), and two decrease the probability: lymphocytes HRa = -0 815 (0.674–0.985), and diastolic pressure HRa = -0.992 (0.986–0.998). E*very five years of increase in age the probability of dying does the same by 13.5%; while with an increase of three breaths there is an increase in the probability of dying equal to 7.4%. *At the same time*, five ml increase in mercury pressure will decrease mortality probability by 1.6%, while a 1.5 increase in lymphocytes will decrease it by 7.9%. *Knowing these factors will undoubtedly be a useful tool to identify those patients who, due to their clinical condition, have a morbidity profile that classifies them as very high risk of dying, and therefore deserve personalized medical care.*

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Corresponding author
Gustavo Bergonzoli
✉
investigacion@hospitaltomasuribe.gov.co.
Hospital Departamental Tomás Uribe Uribe (HDTUU), Tuluá Valle del Cauca, Colombia

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INTRODUCTION

The SARS-CoV-2 pandemic, originating in the province of Wuhan, in China, became a great challenge for health systems in the world, mainly due to the most severe clinical form, characterized by a Syndrome of Acute respiratory failure, which usually leads quickly to death. According to the WHO, as of June 2022, more than 255 million cases have been registered, with more than 5 million deaths worldwide[1]. The Americas region had reported 165.428.595 million confirmed cases of Covid-19 with 2.769.969, for a case fatality rate of 1.7%. Almost a third, 30.6% of the cases and 10.6% of the deaths were reported between January

and March 2022. The North and South American subregions had the highest proportion of cumulative cases, 59% and 37%, respectively, and 49% and 47% of deaths, as of June 2022[2].

Colombia, on the same date, had reported 6.198.848 confirmed cases and 140.202 deaths, with a fatality rate of 2.3%. In the department of Valle del Cauca, as of June 2022, 551.933 cases and 15.119 deaths were registered, with a fatality rate of 2.7%[3]. Consequently, the scientific community has focused its interest on the identification of factors associated with the increase in the severity of the disease and death. Between 14% and 30% of hospitalized patients require Intensive Care Unit (ICU) care, and older age and male gender are factors reported to be associated with increased risk of ICU admission and high mortality[4-10].

A retrospective cohort study of critically ill patients in the ICU, in Lombardy, Italy, with laboratory-confirmed Covid-19, reported that the median length of ICU stay was 12 days, with a range from six to 21 days[11]. A Meta-Analysis study found that chronic comorbidities, such as acute kidney injury, COPD, diabetes, hypertension, cardiovascular disease, cancer, and increased D-dimer, and demographic variables such as male gender, older age, current smoking, and obesity are risk factors that increase the probability of a fatal outcome associated with the coronavirus in the ICU[12].

A retrospective cross-sectional study from a single center in Palmira, Colombia, reported risk factors that predict hospital mortality, due to Covid19, such as elevated levels of lactate dehydrogenase and high-sensitivity troponin I, acute renal failure, COPD and > 10 points in the MuLBSTA score; also need invasive mechanical ventilation in patients with SARS-CoV-2 pneumonia[13]. Great efforts have been made to identify the predictors of mortality from Covid-19 in critically ill patients hospitalized in the ICU, to implement early therapeutic protocols to reduce lethality. Although some factors have been reported in the scientific literature, these factors are still not well known in Colombia. This study aimed to identify some predictors of mortality from Covid-19 in patients hospitalized in Intensive Care Units (ICU) in a medium and high complexity hospital.

MATERIALS AND METHODS

A retrospective cohort study carried out with patients hospitalized for Covid-19, in the ICU of the Tomas Uribe Uribe departmental hospital of medium and high complexity in Tulua, Colombia. The number of patients hospitalized in the ICU with Covid-19 from April 1, 2020, to July 31, 2021, was 2.328, of which 1,468 were due to Covid-19, of which 895 were men. Among patients with Covid-19, 730 died from this cause, 456 men (62.5%), and 14 records were excluded for having incomplete data. Those patients over 15 years of age who had at least one record of a positive RT-PCR test for SARS-CoV-2 and sufficient data (>80%) on the variables of interest were included. The endpoint of interest was death from Covid-19.

Source of data. Data collected from the institutional information system were: heart and respiratory rate, diastolic and systolic pressure, D-dimer, hemoglobin, hematocrit, neutrophils, lymphocytes,

leukocytes, oxygen saturation, age, sex, weight, height, date of admission and discharge from the ICU, condition at discharge from the ICU (alive or dead). Numerical errors, such as multicollinearity, were reviewed to avoid inaccurate estimates; Collinearity was considered when the Pearson correlation coefficient was greater than 0.80, and none of the variables examined showed collinearity. The presence of complete separation and cells with zero observations were also checked. For the cell count, the logarithmic function was used, that is, they were included in the model in the form of a logarithm.

Statistical analysis. Data were collected and tabulated for statistical analysis in an Excel® spreadsheet. Quantitative data, continuous or not, were presented using mean and standard deviation (SD) and the age variable in tertiles because of its distribution was skewed towards older age groups. Categorical data were presented as number, and percentages. To evaluate the assumption of proportionality, perhaps the most important assumption when using the Cox proportional model, the Kaplan-Meier (KM) method[13-15] was applied to all the independent variables or predictors. Another way to test the proportionality assumption is to use the residuals[16].

Statistical significance was assessed using the Log-Rank statistical test, which gives equal weight to the variables throughout the series and, therefore, is very powerful in detecting differences that have a constant relative risk. Variables with a probability equal to or greater than 0.10 were excluded from the Cox proportional analysis. Cox Proportional Regression Model[13-15], was used, with the stepwise option, to identify the predictive factors that increase or decrease the probability of dying from Covid-19 in ICU, the statistical criteria for entering the model was alpha less than 0.15 and less than 0.10 to remain. Once in the model, all variables were a two-tailed test and the significance value was established if the alpha level < 0.05. The intervals were estimated at 95% confidence. The statistical procedures were done using the SAS[17] 9.4® software.

Ethical revision. The Committee for the Ethical and Scientific Evaluation of Research in human beings, or with a sample of human beings of the ESE Tomas Uribe Uribe Departmental Hospital of Tuluá-Empresa Social del Estado, approved the study as stated in the act number 03 of August of 2022. Data were collected from the hospital record system and informed consent was not necessary as the data were anonymized and no personal identifier was collected.

RESULTS

The study population is composed of elderly patients; hence, the mortality is higher in the group of 68 years and over. The mean stay was significantly shorter among the patients who died compared to those who survived. A statistically significant difference was observed between the biomarkers related to oxygen saturation, respiratory rate, D Dimer, lymphocyte count, neutrophils, and diastolic blood pressure. (Table 1).

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Table 1. Basic characteristics of the study population. Significant variables.

Variable	Survivors (%)	Deaths (%)	[a]Chi^2	[b]df	[c]p	[d]N	[e]$\bar{X}$	[f]SD	[g]t	[h]gl	[i]p
Age (Years)											
Young (15-54)	287(40.3)	173(24.0)	52.0	2	0.0001						
Adult (55-67)	242(33.9)	258(35.8)									
Old (68-95)	184(25.8)	289(40.2)									
Status											
Alive						715	57.6	13.1	8.12	1438	0,0000
Death						725	63.6	15.0			
Hospital stay											
Alive						711	12.6	11.8	3.37	1359.7	0.0008
Death						715	10.8	10.2			
O_2 Saturation											
Alive (>=95%)						681	79.2	32.1	2.55	1317	0.0008
Death (<95%)							638	74.7	31.6		
Respiratory Frequency											
Alive						681	20.4	8.5	-3.14	1239.6	0.0002
Death						638	22.1	10.2			
D Dimer											
Alive						575	1.8	2.9	-3.74	926.3	0.0002
Death						469	2.3	2.3			
Leukocytes											
Alive						617	11.1	6.0	-2.11	278.8	0,035
Death						254	12.8	17.1			
Lymphocytes											
Alive						609	24.8	14.0	3.38	860	0.0008
Death						253	21.2	15.5			
Neutrophils											
Alive						620	64.4	16.2	-3.40	870	0.0007
Death						252	68.8	17.2			
Diastolic Pressure											
Alive						1344	72.0	24.2	2.58	2185	0.01
Death						843	69.3	25.1			

Source: Own estimation. [a]Chi^2: Chi square, [b] DF: Degree of Freedom, [c] p: Likelihood.
[d] N: Number of study subjects, [e]$\bar{X}$: mean, [f] SD: Standard deviation, [g]: t of Student, [h] DF: Degree of freedom, [i]p: likelihood

There was no statistical difference, at baseline, between the following biomarkers: sex, BMI, heart rate, hematocrit, and systolic blood pressure. (Table 2).

Table 2. Basic characteristics of the study population. Non-significant variables.

Variable	Survivors (%)	Deaths (%)	[a]Chi^2	[b]df	[c]p	[d]N	[e]$\bar{X}$	[f]SD	[g]t	[h]gl	[i]p
Sex											
Men	430(59.6)	454(62.6)	1.43	1	0.23						
Women	292(40.4)	271(37.4)									
Body Mass Index (BMI)											
Low Weight	2(8.0)	4(1.6)									
Normal	54(23.7)	80(31.6)	4.7	3	0.19						
Overweight	90(39.5)	94(33.2)									
Obesity	82(36.0)	85(33.6)									
Heart frequency											
Alive						1344	81.9	37.9	-0.58	218	0.56
Death						843	82.8	38.9			
Hematocrit											
Alive						152	41.8	6.9	1.54	213	0,12
Death						63	40.3	6.5			
Hemoglobin											
Alive						617	13.7	2.5	1.91	869	0.056
Death						254	13.3	2.7			
Systolic pressure											
Alive						1344	115.3	42.8	1.40	2185	0.16
Death						843	112.7	44.1			

Source: Own estimation. [a]Chi^2: Chi square, [b] DF: Degree of Freedom, [c] p: Likelihood.
[d] N: Number of study subjects, [e]$\bar{X}$: mean, [f] SD: Standard deviation, [g]: t of Student, [h] DF: Degree of freedom, [i]p: likelihood

The Cox Proportional model showed two factors that increase the probability of dying, offending factors, age and respiratory rate. On the other hand, two factors were found that decreased this probability, protective factors, diastolic pressure and lymphocyte count. (Table3).

Table 3. Summary of the Cox Proportional Regression Model.

Variable	[a] DF	Coefficient	Standard Error	[b] Chi^2	[c] Likelihood	Hazard risk	Lower bound	Upper bound
							[d] 95%CI	
Age	1	0.03107	0.00467	44.27	<.0001	1.032	1.022	1.041
Lymphocytes	1	-0.20459	0.09686	4.46	0.0347	0.815	0.674	0.985
Diastolic	1	-0.00814	0.00308	6.99	0.0082	0.992	0.986	0.998
Breathing	1	0.03444	0.00924	13.91	0.0002	1.035	1.016	1.054

Source: Own estimation. [a] DF: degree of freedom, [b] Chi^2: Chi square, [c] p: Likelihood, [d] 95% confidence interval

DISCUSSION

This study identified four independent factors; two of them directly related to the increase in mortality probability: age and respiratory rate. The first, for every five years of increase in age the probability of dying does so by 13.5%; while the second factor, for an increase of three breaths, inhalation, and exhalation, there is an increase in the probability of dying equal to 7.4%.

There were two factors inversely related to mortality, which decrease the probability of dying, diastolic pressure, and lymphocytes, a five ml increase in mercury pressure will decrease mortality probability by 1.6%, while a 1.5 increase in lymphocytes will decrease it by 7.9%. A retrospective cohort study conducted between March 29 and December 19, 2020, with 456 patients with Covid-19 admitted to the Intensive Care Unit (ICU), in Bogotá, Colombia; reported that invasive mechanical ventilation (IMV) and age were associated with a higher risk of mortality[18]. This finding is similar to that found by our study regarding age factor.

In Egypt, a study carried out on 175 patients found that the increase in leukocytes did not discriminate between them; C - reactive protein and D-Dimer elevation were predictors of severity and death in the ICU[19]. The finding of the increased leukocyte count coincides with the finding of this study, although, in our case, the increase in lymphocytes has a protective effect.

A study carried out in Italy with 3,988 patients reported that increasing age, low oxygen saturation, and being male were factors that increased the probability of dying in the ICU[11]. The same finding in our study. Although there was no statistical difference between the sexes in our study. (Result non-shown). A multicenter study conducted in the United States[20] reported that increasing age, low oxygen saturation, and the presence of cardiovascular disease increased the risk of dying in the ICU. The same finding is in this study, except for that related to the presence of cardiovascular disease; we did not have enough data to evaluate its impact on mortality in patients with COVID-19 hospitalized in our ICU.

Another meta-analysis carried out with 42 studies and 423,117 patients found that being male, being a current smoker, being obese, having high D-dimer, and suffering from renal failure were independent factors that increased the probability of dying in the ICU[21]. This study only coincides, again, with the increase in age; in our case, the D-dimer did not reach statistical significance.

In China, a study reported that lymphocytes, D-dimer, and albumin were good predictors of mortality in ICU[22]. This is the first report that mentions lymphocytic action, although there is no mention of whether their relationship is direct or inverse.

A study carried out in Sweden reported that renal failure, diabetes, and obesity increased the risk of dying in the ICU, while hypertension and atrial fibrillation were not related to mortality[23]. In our study, mortality among overweight and obese patients was higher than in normal-weight and low-weight patients, but the difference was not statistically significant.

A study carried out that characterized monocytes and leukocytes in patients with Covid-19 within 72 hours of hospital admission, found that alteration of these cells was related to the severity of the infection[24]. By analogy, we could say that in our study lymphocytes were inversely related to mortality, leukocytes did not provide additional information.

In Iran, a study reported that age and male sex were independent risk factors for dying from Covid-19 in ICU[25], similar findings to those reported in our study. Some of the four predictors of death from Covid-19 in the ICU found in this study coincide with those reported in the scientific literature; however, it is difficult to obtain sufficient evidence on the contribution of each of these factors to mortality, mainly due to the diversity of methods used for their identification.

Among the main limitations of this study, we must highlight the fact that it is a work carried out with secondary data, collected for a purpose other than producing knowledge, which means that some variables of interest, reported by other researchers, are not available for comparison purposes. Another limitation is the lack of sufficient data, on some variables, which prevented their inclusion in the analytical process; this was the case for variables such as electrolytes, albumin, C-reactive protein, and others. There may be some selection bias, as patients were mainly old and more often male compared to the general population.

The findings of this study will contribute to the body of existing knowledge regarding the management of severe cases of Covid-19 in intensive care units. Knowing which factors increase or decrease the probability of dying will undoubtedly be a useful tool to identify those patients who, due to their clinical condition, have a morbidity profile that classifies them as very high risk of dying, and, therefore, deserve personalized attention.

CONCLUSION

The main findings of this study state that for every five years of increase in age the probability of dying does the same by 13.5%; while with an increase of three breaths there is an increase in the probability of dying equal to 7.4%. At the same time, five ml increase in mercury pressure will decrease mortality probability by 1.6%, while a 1.5 increase in lymphocytes will decrease it by 7.9%. The identification of this type of factors is basic knowledge for clinical management of patients, regarding to the prognosis of their survival status.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS CONSIDERATION

The study was approved by the Research Ethics Committee of the Tomas Uribe Uribe Hospital, as stated in the minutes # 02 of May 2023.

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AUTHOR CONTRIBUTION

All authors have contributed to all process in this research, and the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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