Predicting Mortality in Critically Ill COVID-19 Patients in A Low-Resources Setting

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Abstract

Background

Since its molecular isolation on January 7, 2020, the novel coronavirus SARS-CoV-2 has spread rapidly, taking governments worldwide off-guard. The virus arrived in low and middle-income countries violently, especially in Latin America. Ecuador received the worst outbreak in the world if we count excess mortality per capita. Although one study has reported the epidemiological impact of COVID-19 in Ecuador, there is no clinical course or outcome data among intensive care patients with COVID-19 in Ecuador. This study describes the clinical, epidemiological, and therapeutical features of 89 patients hospitalized in a secondary-level hospital in Quito, Ecuador.

Methods

We did a retrospective cohort study. We collected health records data from adult patients with severe COVID-19 admitted to the intensive care unit (ICU) in Quito, Ecuador, during the first five months of the SARS-CoV-2 outbreak in Ecuador. All patients had a confirmed SARS-CoV-2 RNA infection diagnostic, a positive real-time RT-PCR, and pulmonary imaging suggesting COVID-19. We used the Chi-square test or a Fisher's exact statistic to analyze risk and associations between survivors and non-survivors due to COVID-19. We used the ROC curve analysis to predict mortality, determining cut-off points for the parameters related to mechanical, analytical, and cytometry ventilation. At the multivariate level, we used the Wald test to evaluate model categorical predictors during the regression analysis.

Results

89 patients with COVID-19 were recruited during the study. The average age of the patients was 54.72 years. Man represented 68.54% (n = 61) and women 31,46% (n = 28). Significant differences were observed in terms of mortality (men 40.98% vs. women 17.76%). Serological parameters demonstrated that LDH and IL-6 at 24 hours were higher among non-survivors when compared with survivors. Persistent hypercapnia (> > 45 mmHg), a PaFiO2 ratio of less than 140 mmHg, and a positive end-expiratory pressure (PEEP) titration greater than nine mmHg were also associated with higher mortality.

Conclusions

Increased levels of LDH at 24 hours, IL-6, the lymphocyte and platelet count at 48 hours, the neutrophil count at 48 hours, and the INL are factors associated with higher motility, increased risk of failed extubation and reintubation

Introduction

On December 31, the Wuhan Municipal Health Committee informed the World Health Organization (WHO) that 27 people had been diagnosed with a type of pneumonia never described before [1]. On January 7, 2020, Chinese scientists had isolated and sequenced the etiological agent, a novel beta coronavirus later identified as SARS-CoV-2 (severe acute respiratory syndrome coronavirus type -two) [2]. The genome of this RNA virus was made available on January 12, 2020, allowing laboratories in different countries to produce specific primers for the infection diagnoses using real-time reverse transcription-polymerase chain reaction (RT-PCR) [2, 3]. On March 11, 2020, the WHO declares COVID-19 a pandemic after the virus arrived in several countries rapidly [4]. Up to October 5, 2020, more than 35 million people had been infected, causing more than 1 million deaths worldwide [3]

In Latin America, a region with high levels of social inequality, mortality rates, and attack rate due to COVID-19 are devastating, especially for those living in poverty [5]. Households in the lowest income group have reduced access to health services, molecular diagnosis, and treatment. Health systems with scarce economic resources and disrupted contact tracing capabilities are often incapable of controlling outbreaks at the community level, affecting mortality and hospital admission trends[6].

In mid-February, the disease reached Latin America and hit Ecuador abruptly. The first case in Ecuador was officially reported on February 27th, but the only scientific report available suggest that the virus has entered the country weeks earlier[7]. In March, the virus had spread massively within Ecuador's coastal provinces, causing thousands of deaths each day in Ecuador, highlighting Guayaquil as the first COVID-19 epicenter in Latin America and the worst-hit country in the world[8].

In Ecuador, there is only one report exploring the epidemiological trends of COVID-19 in Ecuador, including a brief description of the clinical presentation among asymptomatic and mildly ill patients; nevertheless, no data is available in terms of the clinical features and outcome among critically ill patients[7].

This study aims to present the outcome and clinical characteristics of COVID-19 patients admitted to the intensive care unit in a secondary level hospital in Quito, Ecuador, from April 1, 2020, to July 31, 2020.

Materials And Methods

Setting

The study was carried out in the Intensive Care Unit in the secondary level hospital Pablo Arturo Suárez Hospital, Quito, Ecuador. Quito is the capital of Ecuador and has a population of 2´781.641 million. The city is located in the province of Pichincha and has an elevation of 2,850 m above sea level, becoming the second-highest capital city in the world.

Study design

A retrospective cohort study of the clinical course and mortality due to COVID-19 among adult patients hospitalized and admitted to the ICU unit from April 1 to July 31, 2020

Population and sample size

Every patient admitted to the ICU unit with a suspected diagnosis of COVID-19 was included in the study. At the end of the study, we included 89 patients that fulfill the inclusion criteria while 12 were excluded from the study.

Inclusion criteria

Every patient admitted to the ICU unit with a positive molecular, serological, or clinical diagnosis of COVID-19 was included in the study. The clinical records (HC) of patients admitted with a confirmed result of COVID-19 by RT-PCR or suggestive tomographic pattern (CO-RADS 4 or 5) were included, and cases with a presumptive diagnosis of COVID-19 were excluded, with negative RT-PCR or tomographic pattern not compatible with COVID-19 (CO-RADS 0 to 3).

Exclusion criteria

Patients with a mild clinical presentation that were not admitted to the ICU or those with respiratory symptomatology that tested negative for SARS-CoV-2 infection through molecular testing (RT-PCR) did not have antibodies against SARS-CoV-2, and their clinical evolution dit not correspond to COVID-19.

Variables and measurements

Our team reviewed every patient's electronic records admitted to the ICU unit that fulfill the inclusion criteria. Information concerning epidemiological, clinical, serological, and cytometric data variables were collected. Every record was reviewed, and data retrieved from admission to discharge or death in the ICU during the data collection period.

Statistical analysis

We performed a complete descriptive statistical analysis, absolute and relative values of every qualitative variable. Mean, and standard deviation measures were used to describe differences and dispersion of the data set.

The assumption of normality of the quantitative variables was verified using the Shapiro test, where the t-test was used for parametric quantitative variables and the Mann Whitney test for those with non-parametric distributions.

We used the Chi-square test or Fisher's exact statistic to compare the proportion of survivors and non-survivors due to COVID-19. An odds ratio greater than one was used to indicate that the outcome was more likely to occur in one group.

We used the ROC curve analysis to predict mortality, determining cut-off points using the Younden index for the parameters related to mechanical ventilation and cytometric parameters. At the multivariate level, the Wald method forward logistic procedure regression was used, determining predictors of mortality for COVID-19. Statistical significance was established for p-value < 0.05.

Results

General results

During 121 days of follow-up, 89 patients with COVID-19 fulfilled the inclusion criteria. 68,54 % (n = 61) were men and 31,46% women (n = 28). The average length of stay (ALOS) in those who survived was not statistically significant among those who survived (9.31 days) versus those who died (10.29 days). The follow-up ended with 66.29% of patients (n = 59) discharged from the ICU unit, while 33.71% of them (n = 30) died due to COVID-19 (Table 1).

Age and sex differences

The average age of patients admitted to the hospital was 54.7 years, and survivors were 11 years younger (50.9) than non-survivors (62.2), and this difference was statistically significant (p-value: 0.001). In terms of sex, men were three times more likely to die due to COVID-19 when compared to women, representing 40.98% (n = 25) among men and 17.76% (n = 5) among women (p-value: 0.032).

Comorbidities and mortality risk

The most frequent comorbidity reported was hypertension (HT) in 20.22% (n = 18) followed by obesity 16.85% (n = 15) and diabetes mellitus (DM) 8.99% (n = 8). The mean body mass index (BMI) was 30.84, with significant differences being observed between survivors (31.99) and non-survivors (28.98), being these differences statistically significant (p-value: 0.026).

Assessment of mortality indicators

The sequential organ failure assessment (SOFA) score at 24, 48, and 72 hours after admission was found to be 7.91, 6.14, and 5.46, respectively. The differences were statistically significant at 48 hours in survivors (SOFA = 5.72) vs non-survivors (SOFA = 7) and at 72 hours (SOFA = 4.93) versus (SOFA = 6.62) with a p-value of 0.038 and 0.010 respectively.

The APACHE II indicator was found to be higher among non-survivors (19.37) versus those who survived (17.42), although the differences were not statistically significant (p-value: 0.197) (Table 1).

Treatment and mortality

Seventy-two patients (80.9%) received systemic corticosteroid, and among those, 25 patients (34.72%) did not survive while 47 (65.28%) survived within this group. Low molecular weight heparin (LMWH) was administered to 69 patients (78.41%), and from this group, 59.42% (n = 41) survived, and 40.58% died (n = 28).

Table 1
Relationship between mortality and clinical characteristics.

Clinical features	Total	Condition at discharge		p-vule	OR (IC95%)
		Decease	Survivor		
Age (mean (SD)) years [1/]	54,72 (11,51)	62,23 (9,76)	50,9 (10,45)	0,000*	-
Sex (n (%)) [2/]					
Male	61 (68,54)	25 (40,98)	36 (59,02)	0,032**	3,19*** (1,07–9,53)
Female	28 (31,46)	5 (17,86)	23 (82,14)		
DM (%)) [2/]					
Yes	8 (8,99)	2 (25,00)	6 (75,00)	0,712	-
No	81 (91,01)	28 (34,57)	53 (65,43)		
HTN (n (%)) [2/]					
Yes	18 (20,22)	8 (44,44)	10 (55,56)	0,281	-
No	71 (79,78)	22 (30,99)	49 (69,01)		
Obesity (n (%)) [2/]					
Yes	15 (16,85)	3 (20,00)	12 (80,00)	0,218	-
No	74 (83,15)	27 (36,49)	47 (63,51)		
BMI (mean (SD)) [3/]	30,84 (5,82)	28,98 (4,85)	31,99 (6,15)	0,026*	-
Apache II income (mean (SD)) [3/]	18,08 (5,84)	19,37 (6,08)	17,42 (5,65)	0,197	-
SOFA (mean (SD)) [3/]					
24 hours	7,91 (2,99)	8,33 (2,73)	7,69 (3,11)	0,251	-
48 hours	6,14 (2,54)	7 (2,61)	5,72 (2,41)	0,038*	-
72 hours	5,46 (2,84)	6,62 (2,76)	4,93 (2,74)	0,010*	-
Corticosteroid use (n (%)) [2/]	72 (80,90)	25 (34,72)	47 (65,28)	-	-
Heparin use Anticoagulation (n (%)) [2/]	69 (78,41)	28 (40,58)	41 (59,42)	-	-
Days of hospitalization (mean (SD)) [3/]	9,65 (5,44)	10,29 (5,66)	9,31 (5,34)	0,351	-
Note: SD = Standard Deviation; * significant differences in means, based on 1 / t test and 3 / Mann Whitney test; ** significant differences in the non-survivor condition, based on the Chi-square test or Fisher's exact statistic 2 /; *** OR = Odds Ratio significant, lower limit of the 95% confidence interval (95% CI) > 1					
Source: self-made					

Ventilatory and respiratorory parameters

To mitigate end-expiratory alveolar collapse, applied extrinsic PEEP values at 48 hours were significantly lower (7.89 cmH2O) among survivors versus non-survivors (9.26 cmH2O) and this difference was statistically significant (p-value: 0.015). The maximum PCO2 at 72 hours was higher among non-survivors (49.34 mmHg), versus survivors (41.37 mmHg), is this difference statistically significant (p-value: 0.026) (Table 2).

The PaO2/FiO2 ratio at 24 and 72 hours was always higher among survivors. For instance, Non-survivors reported a PaO2/FiO2 of 127.77 mmHg and 136.36 mmHg at 24 and 72 hours, respectively, while survivors had values of 152.97 mmHg and 181.09 mmHg at the same time interval, both differences statistically significant (p-value: 0.036 and 0.000).

Survivors remained intubated for seven days while non-survivors for ten days, difference statistically significant (p-value: 0.002).

Table 2
Relationship between mortality and mechanical ventilation parameters.

Mechanical ventilation parameters	Total	Condition at discharge		p-value
		Decease	Survivor	
Ventilatory mode of admission (n (%)) 2/				
Volume controlled	14 (15,73)	4 (28,57)	10 (71,43)	0,765
Pressure controlled	75 (84,27)	26 (34,67)	49 (65,33)	
Vt 24 hours (mean (SD))3/ ml/kg	403,15 (61,2)	398,33 (57,41)	405,59 (63,38)	0,761
Vt 48 hours (mean (SD)) 1/ ml/kg	417,69 (69,08)	411,9 (75,81)	420,63 (65,91)	0,582
Vt 72 hours (mean (SD)) 3/ ml/kg	424,41 (78,17)	434,21 (88,78)	418,57 (71,49)	0,222
PEEP 24 hours (mean (SD))3/ cmH20	9,46 (2,09)	9,83 (2,28)	9,27 (1,99)	0,329
PEEP 48 hours (mean (SD))3/ cmH20	8,35 (2,29)	9,29 (2,45)	7,89 (2,08)	0,015*
PEEP 72 hours (mean (SD))3/ cmH20	7,81 (2,26)	8,46 (2,81)	7,43 (1,79)	0,227
24-hour plateau pressure (mean (SD)) 1/ cmH20	23,19 (4,23)	23,73 (4,65)	22,92 (4,01)	0,391
48-hour plateau pressure (mean (SD)) 3/ cmH20	21,77 (3,83)	22,07 (4,54)	21,61 (3,44)	0,637
72-hour plateau pressure (mean (SD)) 3/ cmH20	21 (3,82)	22,11 (3,92)	20,35 (3,65)	0,074
Driving pressure 24 hours (mean (SD)) 3/ cmH20	13,62 (3,28)	13,53 (3,56)	13,66 (3,17)	0,776
Driving pressure 48 hours (mean (SD)) 3/ cmH20	13,33 (2,94)	13,07 (3,1)	13,47 (2,87)	0,252
Driving pressure 72 hours (mean (SD)) 3/ cmH20	13,42 (3,24)	14 (3,55)	13,07 (3,02)	0,250
$PCO_{2\ maximum}$ 24 hours (mean (SD)) 3/ mmHg	45,77 (13,55)	45,28 (10,92)	46,01 (14,79)	0,969
$PCO_{2\ maximum}$ 48 hours (mean (SD)) 3/ mmHg	45,23 (12,63)	46,53 (12,07)	44,6 (12,95)	0,492
$PCO_{2\ maximum}$ 72 hours (mean (SD)) 3/ mmHg	44,03 (12,86)	49,34 (17,92)	41,37 (8,4)	0,026*
$PaFiO_2$ 24 hours (mean (SD))3/ mmHg	144,47 (47,94)	127,77 (44,98)	152,97 (47,52)	0,036*
$PaFiO_2$ 48 hours (mean (SD))3/ mmHg	160,78 (47,77)	147,89 (35,14)	167 (51,93)	0,192
$PaFiO_2$ 72 hours (mean (SD)) 1/ mmHg	166,18 (54,96)	136,36 (41,04)	181,09 (55,25)	0,000*
Prone ventilation (n (%)) 2/	53 (59,55)	20 (37,74)	33 (62,26)	0,368
Days of pronation (mean (SD))3/	2,38 (1,42)	2,43 (1,36)	2,35 (1,48)	0,827
Use of relaxant (n (%)) 2/	55 (61,80)	17 (30,91)	38 (69,09)	0,477
Days with muscle relaxant (mean (SD))3/	2,22 (1,46)	2,38 (1,77)	2,14 (1,3)	0,769
Days in MV (mean (SD))3/	8,49 (5,67)	10,86 (5,26)	7,3 (5,54)	0,002*
Mechanical power 24 hours (mean (SD)) 3/ j/min	15,77 (4,59)	16,16 (4,26)	15,57 (4,77)	0,343
Mechanical power 48 hours (mean (SD)) 3/ j/min	14,92 (4,64)	14,64 (4,31)	15,07 (4,83)	0,961
Compliance 24 hours (mean (SD))3/ ml/cmH2O	26,49 (12,48)	26,17 (13,89)	26,66 (11,84)	0,742
Compliance 48 hours (mean (SD))3/ ml/cmH2O	27,42 (13,48)	29,61 (15,64)	26,2 (12,11)	0,428
Compliance 72 hours (mean (SD))3/ ml/cmH2O	34,32 (10,82)	34,45 (7,71)	34,24 (12,47)	0,575

Mechanical ventilation parameters	Total	Condition at discharge		p-value
		Decease	Survivor	
VT x Kg 24 hours (mean (SD))[3/]	6,97 (1,31)	6,91 (1,23)	7 (1,36)	0,888
VT x Kg 48 hours (mean (SD))[3/]	7,94 (7,04)	7,1 (1,29)	8,4 (8,68)	0,812
VT x Kg 72 hours (mean (SD))[3/]	8,53 (8,55)	7,71 (1,48)	9,05 (10,91)	0,353
Extubation (n (%)) [2/]				
Failed	20 (27,40)	14 (70,00)	6 (30,00)	0,000**
Successful	53 (72,60)	0 (0,00)	53 (76,81)	

Note: SD = Standard Deviation; * significant differences in means, based on 1 / t test and 3 / Mann Whitney test; ** significant differences in non-survivor condition, based on Chi-square test or Fisher's exact statistic 2 /

Source: self-made

Serological biomarkers

Lactate dehydrogenase levels (LDH) were higher among non-survivors (1025.47 U / L) versus survivors (891.10 U / L); Likewise, IL-6 presented was 137% higher among non-survivors (140.55 pg/ ml) versus survivors (59.3 pg. / ml) (p-value: < 0.05). D-dimer and ferritin at 24 and 48 hours did not show significant differences (Table 3).

Table 3
Relationship between mortality and analytical parameters.

Analytics parameters	Total	Condition at discharge		p-value
		Decease	Survivors	
D-dimer 24 hours (mean (SD)) ng / ml[2/]	3,237 (7,277)	4,947 (1,202)	2,382(2,581)	0,057
D-dimer 48 hours (mean (SD)) ng / ml[2/]	2,861 (2925)	3,594 (3,436)	2,478 (2,578)	0,185
Ferritin 24 hours (mean (SD)) ng / ml[2/]	1,085 (487)	1,223 (429,78)	1,015 (502)	0,094
Ferritin 48 hours (mean (SD)) ng / ml[2/]	1,086 (468)	1,158 (379,61)	1,051 (505)	0,388
LDH 24 hours (mean (SD)) U / L[2/]	936 (369)	1,025 (273,81)	891 (405)	**0,003***
LDH 48 hours (mean (SD)) U / L[1/]	814 (271)	842 (259,05)	799 (280)	0,540
IL-6 (mean (SD)) pg. / mL[2/]	86 (14,7)	140 (20)	59 (98)	**0,016***
Note: SD = Standard Deviation; * significant differences in means, based on 1 / t test and 2 / Mann Whitney test				
Source: self-made				

Flow cytometric analysis

Lymphocytes's count at 48 hours presented a mean of 753.79 x 103 / ml in survivors and 537.59 x 103 / ml in non-survivors (p-value 0.006). Neutrophilia was found to be significant among non-siurvuviors at 24 hours (11,741.63 x 103 / ml) in comparision with surviviros (9,282.54 x 103 / ml). For the neutrophil / lymphocyte index (INL) at 24, 48 and 72, non-survivors had significantly high INL than survivors (p-value: < 0.001) (Table 4).

Platelet's count at 48 hours shows that non-survivors had significantly lower platelent counts (320,103.45 x 103 / ml) than survivors (388,172.41 x 103 / ml).

Table 4
Relationship between mortality and cytometry parameters.

Cytometry parameters	Total	Condition at discharge		p-value
		Decease	Survivors	
Lymphocytes 24 hours (mean (SD))[2/]	849 (1383)	650(383)	950(1,673)	0,089
Lymphocytes 48 hours (mean (SD))[2/]	681 (381)	537 (300)	753 (398)	0,006*
Lymphocytes 72 hours (mean (SD))[2/]	771 (645)	594 (285)	856 (748)	0,079
Platelets 24 hours (mean (SD))[2/]	366,078 (135,037)	338, 266 (137,929)	380,220 (132,481)	0,164
Platelets 48 hours (mean (SD))[2/]	365,482 (139,212)	320,103(118,949)	388,172(143,9370	0,043*
Platelets 72 hours (mean (SD))[2/]	362,378(137,738)	324,107(120,235)	380,853(142,747)	0,055
Neutrophils 24 hours (mean (SD))[2/]	10,111(4,457)	11,741 (4,649)	9,282(4,154)	0,013*
Neutrophils 48 hours (mean (SD))[2/]	10,030 (4,585)	10,683 (4,059)	9,703(4,826)	0,322
Neutrophils 72 hours (mean (SD))[2/]	9,841(4,204)	11,064 (4,375)	9,250(4,025)	0,063
Eosinophilic edges 24 hours (mean (SD))[2/]	34,61(68,04)	27,8 (44,23)	38,07 (77,52)	0,922
Eosinophilic edges 48 hours (mean (SD)) [2/]	44,39 (87,52)	32,72 (56,89)	50,22 (99,32)	0,072
Eosinophilic edges 72hours (mean (SD)) [2/]	56,98 (104,83)	51,21 (86,85)	59,76 (113,1)	0,661
INL 24 hours (mean (SD))[2/]	18,54 (15,57)	23,8 (16,52)	15,87 (14,48)	0,002*
INL 48 hours (mean (SD))[2/]	18,96 (15,25)	26,01 (18,75)	15,44 (11,85)	0,000*
INL 72 hours (mean (SD))[2/]	18,68 (14,88)	22,64 (13,43)	16,77 (15,28)	0,004*
Note: SD = Standard Deviation; INL = neutrophil / lymphocyte ratio; * significant differences in means, based on 1 / t test and 2 / Mann Whitney test				
Source: self-made				

Predictive Factors For Mortality

PEEP analysis.

The area of the receiver operating characteristic (ROC) curve for PEEP at 48 hours was 0.661 (95% CI 0.535–0.787), maximum PCO2 at 72 hours 0.650 (95% CI 0.519–0.780), PaFiO2 at 24 hours 0.636 (95% CI 0.508–0.765), and PaFiO2 at 72 hours 0.747 (95% CI 0.638–0.857), these areas presented confidence intervals that do not include the value 0.5; therefore they are significant to predict mortality for COVID-19.

The cut-off points to predict mortality in the ROC curve using the Youden index of the mechanical ventilation parameters were positive for mortality if 48-hour PEEP ≥ 8.50 cmH20, where the sensitivity was 54% and specificity was 74% (Fig. 1). Positive for mortality if PCO2 maximum 72 hours ≥ 46.50 mmHg, where the sensitivity was 54% and specificity was 77%. Positive for mortality if 24-hour PaFiO2 ≤ 89 mmHg, where sensitivity was 30% and specificity was 97%. Positive for mortality if PaFiO2 72 hours ≤ 155.50 mmHg, the sensitivity was 82%, and specificity was 66%.

Biomarkers analysis.

The area of the ROC curve for IL-6 was 0.675 (IC95% 0.542–0.809), and for LDH at 24 hours 0.691 (IC95% 0.580–0.803), these areas presented confidence intervals that do not include the value 0.5; therefore, they are significant in predicting mortality for COVID-19.

The cut-off points to predict mortality in the ROC curve using the Youden index of the analytical parameters were positive for mortality if IL-6 ≥ 117 pg. / mL, where the sensitivity was 42%, and specificity was 91%. Positive for mortality if 24-hour LDH ≥ 783 U / L, where the sensitivity was 90% and specificity 43% (Fig. 2).

The area of the ROC curve for INL at 24 hours was 0.704 (95% CI 0.591–0.817), INL at 48 hours 0.743 (95% CI 0.634–0.851), INL at 72 hours 0.692 (95% CI 0.578–0.806), and platelets 48 hours 0.633 (95% CI 0.508–0.759), these areas presented confidence intervals that do not include the value 0.5; therefore they are significant to predict mortality for COVID-19 (Fig. 3).

The cut-off points for predicting mortality in the ROC curve using the Youden index of the cytometry parameters were the following: Positive for mortality if INL 24 hours ≥ 16.33, where sensitivity was 73% and specificity 64%. Positive for mortality if INL 48 hours ≥ 16.96, where the sensitivity was 76% and specificity was 67%. Positive for mortality if INL 72 hours ≥ 17.12, where the sensitivity was 64% and specificity 74%. Positive for mortality if Platelets ≤ 364,000 x 103 ml, where the sensitivity was 79% and specificity 50%.

SOFA mortality prediction analysis.

For the SOFA mortality predictors, the cut-off point for COVID-19 was determined, the ROC curves showed for SOFA at 48 hours an area of 0.637 (95% CI 0.511–0.763), and for 72 hours of 0.675 (95% CI 0.556–0.794), these areas were significant to predict mortality, the cut-off point established at 48 and 72 hours was positive for mortality if SOFA ≥ 6, at 48 hours, the sensitivity of 79% and specificity 48% were obtained, at 72 hours the sensitivity was 69% and specificity 57% (Fig. 4).

The results obtained showed that PaFiO2 72 hours ≤ 155.50 mmHg with p-value 0.009, IL-6 ≥ 117 pg. / mL with p-value 0.011, INL 24 hours ≥ 16.33 with p-value 0.013 and INL 72 hours ≥ 17.12 with p-value 0.005 are predictors of mortality for COVID-19; where values of PaFiO2 72 hours ≤ 155.50 mmHg, IL-6 ≥ 117 pg. / mL, INL 24 hours ≥ 16.33 and INL 72 hours ≥ 17.12 presented 9.24, 21.84, 6.13, and 13, 33 times more likely not to survive; the mechanical ventilation's cut-off points, analytical and cytometry parameters were determined (Table 5).

Table 5
Logistic regression to predict mortality for COVID-19, based on mechanical ventilation, analytical and cytometry parameters.

Variables	B	Wald	p-value	OR	95% CI-OR	
					Li	Ls
Inside the model						
$PaFiO_2$ 72 hours ≤ 155,50 mmHg	2,22	6,74	0,009*	9,24**	1,73	49,49
IL-6 ≥ 117 pg./mL	3,08	6,54	0,011*	21,84**	2,06	231,85
INL 24 hours ≥ 16,33	1,81	6,10	0,013*	6,13**	1,46	25,86
INL 72 hours ≥ 17,12	2,59	7,85	0,005*	13,33*	2,18	81,56
Constant	-4,39	17,38	0,000*			
Excluded from the model						
PEEP 48 hours ≥ 8,50 cmH20		0,30	0,587			
Maximum PCO2 72 hours ≥ 46.50 mmHg		1,55	0,213			
PaFiO2 24 hours ≤ 89 mmHg		2,63	0,105			
24-hour LDH ≥ 783 U / L		0,06	0,801			
INL 48 hours ≥ 16.96		0,78	0,378			
Platelets ≤ 364,000 10^3ml		0,82	0,366			
SOFA 48 hours ≥ 6		0,71	0,399			
SOFA 72 hours ≥ 6		0,06	0,805			
Note: INL = neutrophil / lymphocyte ratio; * significant variable p-value < 0.05, ** OR = significant odds ratio Li > 1; based on logistic regression forward procedure Wald method						

The results obtained showed that PaFiO2 72 hours ≤ 155.50 mmHg with p-value 0.009, IL-6 ≥ 117 pg. / mL with p-value 0.011, INL 24 hours ≥ 16.33 with p-value 0.013 and INL 72 hours ≥ 17.12 with p-value 0.005 are predictors of mortality for COVID-19; where values of PaFiO2 72 hours ≤ 155.50 mmHg, IL-6 ≥ 117 pg. / mL, INL 24 hours ≥ 16.33 and INL 72 hours ≥ 17.12 presented 9.24, 21.84, 6.13 and 13, 33 times more likely to not survive.

Discussion

This original research is the first report of the clinical characteristics of severely ill patients with COVID-19 who have been clinically managed in a secondary-level hospital ICU unit in Quito, Ecuador. The results showed that older age and sex is positively associated with mortality. These results are similar to several reports available [9, 10]. The average age of our admitted patients was 54 years, considerably younger populations than other countries. In China, two reports found that the mean age of patients admitted to the ICU was between 64 and 66 years, on average ten years older than our population [11, 12]. In other continents, the age of the admitted patients is also higher. For instance, in Italy and Spain, the available information reports an average age of 63 years, while in the USA, the average age is 79 years. [10, 13–16]. Mejia et al. 2020 published the only available study similar to ours in a cohort of Peruvian patients. They found that the median age of the admitted patients was 59 years [17]. Although there is no clear information on why older men are at higher risk of dying due to COVID-19, a higher proportion of comorbidities among men may play a significant role, and the presence of unhealthier lifestyles. It has also been hypothesized that men the angiotensin-converting enzyme-2 (ACE-2) receptor might play an important role. Previsluty published studies suggest that the ACE-2 receptor plays a role in other coronaviruses-related diseases such as Severe acute respiratory syndrome (SARS) or Middle East Respiratory Syndrome (MERS), finding higher concentrations of ACE-2 receptors among men [18, 19].

In terms of respiratory parameters, persisting hypercapnia for more than 72 hours, the $PaFiO_2$ ratio at 24 and 72 hours < 140 mmHg and PEEP greater than 9 cmH_2O were also associated with increased risk of mortality. External positive pressure ventilation increases intrathoracic pressure and does so more potently when the lungs are highly compliant[20]. Moderate PEEP levels are required to ventilate adequately and achieve normoxia. In our results, maintaining PEEP levels greater than 8 mmHg after 48 hours was associated with poorer prognosis. Although the impact of COVID-19 within the lungs is not quite the same as other diseases causing ARDS, the role of adequate ventilatory management is fundamental.

Gatinonni et al 2020 defined two phenotypic patterns in the clinical presentation of COVID-19, a Low (L) phenotype in which there is low elastacy, low shunt and poor recruitability with little response to PEEP and a High (H) phenotype, with high elastance, high shunt and favorable response to alveolar recruitment with PEEP[21, 22].

Regarding the presentation of the L and H phenotypes in ARDS due to COVID 19, we consider that their presentation was variable, if we take into account the relationship between compliance and PaO2 / fiO2 as reported by Panwar [23], patients with PaO2 / FiO2 lower, like those with low compliance died, however these variables can be very heterogeneous, because there could be H patterns with PaO2 / FiO2 greater than 150 and in other L phenotypes with PaO_2 /FiO_2 < 150mmHg. Both PaO_2 / FiO_2 as well as compliance have always been considered as a marker of severity, in our work, the patients who had lower values were the most serious and of them, those who died, had low compliance from admission as mentioned. in other studies, those whom improved PaO_2 / FiO_2 and improved their compliance pattern L, had better survival [22, 23].

In our study we also found that elevated levels of IL6, LDH at 24 hours, lymphopenia at 48 hours, neutrophilia at 24 hours, and high INL from admission to 72 hours were also associated with greater mortality. This has been evaluated in previous works which may indirectly indicate a reaction due to the massive inflammatory response or the cytokine storm constantly related with more severe clinical presentations[24, 25]. These results are similar to the others previously reported worldwide; however, it is interesting to note that ferritin and the D-dimer biomarker have not achieved enough statistical power to predict mortality[12, 26]. Furthermore, our findings support the use of cytometric analysis that are often affordable and available in low-resource settings.

Several laboratory data are identified as predictors of severity and mortality in COVID-19 such as: elevated D-dimer, lymphopenia, increased LDH, thrombocytopenia, increased C-reactive protein, elevated ferritin and interleukin 6, among others [27–34]. In our study, the factors associated with mortality were LDH values at 24 hours, IL-6, the lymphocyte and platelet count at 48 hours, the neutrophil count at 48 hours, and the INL in all its measurements; the latter, together with IL6, reached a predictive level. Results that are consistent with the existing evidence in the world. It was striking that D-dimer and ferritin at 24 and 48 hours did not present a significant association with mortality, which is far from the existing evidence at that time.

The most frequent comorbidities in our patients were: hypertension, obesity and diabetes mellitus (DM). For diabetes and hypertension there was no statistically significant difference in terms of risk of mortality, nevertheless, when evaluating body mass index, higher BMI was associated with greater risk of dying (Table 1) as described in other studies[26]. A clincal report from Wang, et.al 2020 showed statistically significant differences in terms of mortality among those with chronic hypertension[12]. On the other hand, other study found that hypertension was not an independent factor in terms of increasing mortality, opposing to hypercholesterolemia and DM[10].

In general terms, the overall mortality in our center seems to be adecuate when comparted to other countries. In Ecuador, we found that 33.7% of patients succumbed in the ICU unit due to COVID-19. A recently published report from China, including 517 patients reported a an overall mortality rate of 37.7% [12, 13]. These numbers seem to be lower than other reports coming from Europe. For instance, In Italy, Grasselli et al, 2020 included 1,715 patients and they found that the overall mortality was superior to 48% [10]. In Spain, a national cohort of 736 patients reported mortality rates greater than 42% [14]. On the other hand, information emerging from the USA shows that mortality was significantly lower in a cohort of 1,392 patients. They reported an overall mortality of 23.6% [13].

In latinamerica, reports are scarce. We found that in Peru, the overall mortality rate among severelly ill COVID-19 patients was 32.4% [35]. However, in this study, cut-off points for serological biomarkers and mechanical ventilation variables analysis were not determined, which might give a more in-depth insight into our results.

At the beginning of the pandemic, corticosteroids' use was controversial, and their use focused on quenching the so-called "cytokine storm" [27, 36–38]. During the first few months of the outbreak, very few scientific societies recommended using systemic corticosteroids to treat ARDS. Nevertheless, in our hospital, we adopted the SARS and MERS guidelines, and this could be associated with our mortality rates that relatively low when compared to other centers [22, 39–41].

Limitations

Our results came from an intensive care unit of 7 beds. Therefore, the time to collect a representative sample was more prolonged than in other centers. It is essential to point out that molecular analysis for COVID-19 using RT-PCR was not always available in situ; therefore, the diagnosis was based on radiological and clinical suspicion, and the confirmatory molecular or serological confirmation sometimes arrived days later.

Conclusions

The values of LDH at 24 hours, IL-6, the lymphocyte and platelet count at 48 hours, the neutrophil count at 48 hours, and the INL are factors associated with motility to these are added the failed extubation and the reintubation.

The clinical and physiopathological presentation of COVID-19 patients shares similarities with other respiratory diseases. These similarities allowed our secondary-level hospital to use corticosteroids as a therapeutic option from the beginning of the pandemic, although the WHO itself has contraindicated it, indeed inferring about the relatively low mortality rates that we have presented.

Although analytical markers such as IL 6 and LDH are acceptable and well-known parameters for managing critical patients, their use of predictive variables is a new finding. This strategy becomes a widely accessible and cost-effective way to establish the risk of mortality due to COVID-19 at a global level.

Declarations

Ethics approval and consent to participate

The present study was carried out in accordance with local and international guidelines and regulations including the declaration of Helsinki and the good clinical practices (GCP). The protocol was presented to the Hospital Pablo Arturo Suarez internal ethics board and received approval (MSP-CZ9-HPASGEHO-2020-2504-M). Informed consent prior ICU unit admission was obtained from all adult's subjects including in the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

JLV was entirely responsible for the conceptualization of the study and to direct the team when collecting information, obtaining ethical approval and the hospital's authorization. He drafted the first version of the manuscript and reviewed the final version of it. MPM, FEJ, SAM, WTM, LS, GJ, EI, EC, and CM were responsible for collecting information from the ICU unit and contributing equally to the data analysis. EVG as responsible for completing the dataset and completing the first draft of the manuscript. EOP was responsible for critically reviewing the first draft and completing the final version of the manuscript, and critically reviewing the entire analytical process around data collection.

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Figures

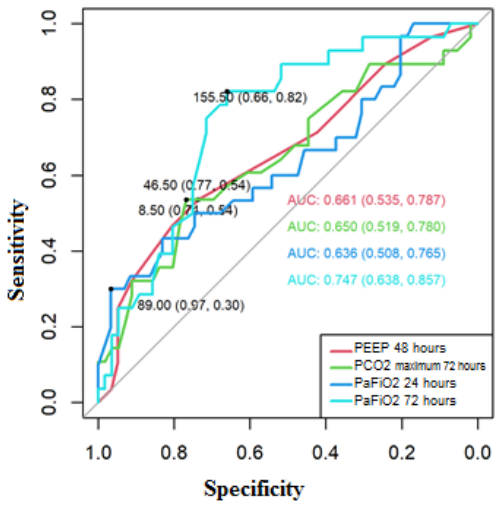

Figure 1

ROC curve to predict mortality for COVID-19, based on PEEP 48 hours, maximum PCO2 72 hours, PaFiO 2 24 and 72 hours.

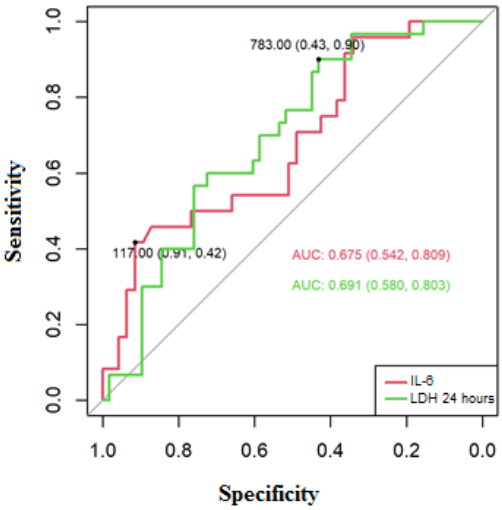

Figure 2

ROC curve to predict mortality for COVID-19, based on IL-6 and LDH at 24 hours.

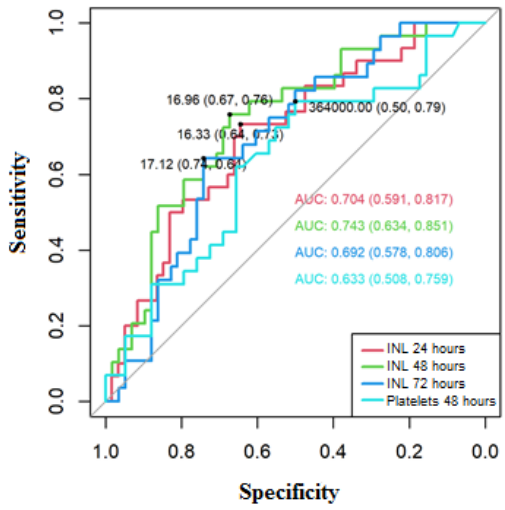

Figure 3

ROC curve to predict mortality for COVID-19, based on INL (24, 48 and 72 hours) and platelets 48 hours.

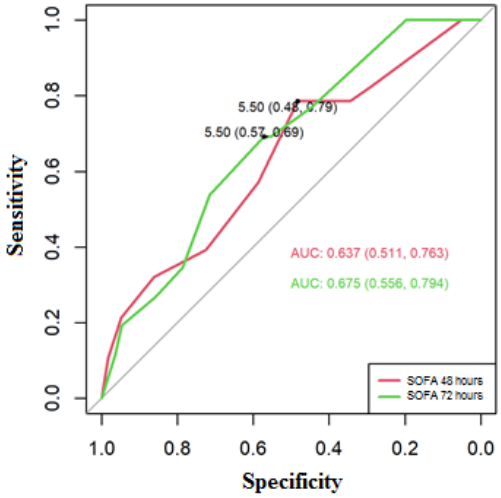

Figure 4

ROC curve to predict mortality for COVID-19, based on SOFA at 48 and 72 hours.