ORIGINAL ARTICLE

Mortality in patients treated for COVID-19 in the emergency department of a tertiary care hospital during the first phase of the pandemic: Derivation of a risk model for emergency departments

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Objective. To develop a risk model to predict 30-day mortality after emergency department treatment for COVID-19.

Methods. Observational retrospective cohort study including 2511 patients with COVID-19 who came to our emergency department between March 1 and April 30, 2020. We analyzed variables with Kaplan Meier survival and Cox regression analyses.

Results. All-cause mortality was 8% at 30 days. Independent variables associated with higher risk of mortality were age over 50 years, a Barthel index score less than 90, altered mental status, the ratio of arterial oxygen saturation to the fraction of inspired oxygen (SaO_2/FIO_2), abnormal lung sounds, platelet concentration less than 100 000/mm^3, a C-reactive protein concentration of 5 mg/dL or higher, and a glomerular filtration rate less than 45 mL/min. Each independent predictor was assigned 1 point in the score except age, which was assigned 2 points. Risk was distributed in 3 levels: low risk (score of 4 points or less), intermediate risk (5 to 6 points), and high risk (7 points or above). Thirty-day risk of mortality was 1.7% for patients who scored in the low-risk category, 28.2% for patients with an intermediate risk score, and 67.3% for those with a high risk score.

Conclusion. This mortality risk stratification tool for patients with COVID-19 could be useful for managing the course of disease and assigning health care resources in the emergency department.

Keywords: COVID-19. SARS-CoV-2 infection. Emergency department. Risk factors. Mortality.

Análisis de mortalidad de los pacientes atendidos por Covid-19 en el servicio de urgencias de un hospital de tercer nivel en la fase incial de la pandemia. Derivación de un modelo de riesgo para urgencias

Objetivo. Derivar un modelo de riesgo para estimar la probabilidad de mortalidad a los 30 días de la visita a urgencias de pacientes con COVID-19.

Método. Estudio observacional de cohortes retrospectivo de 2.511 pacientes con COVID-19 atendidos en el servicio de urgencias hospitalario (SUH) del 1 de marzo al 30 de abril de 2020. Se realizó análisis de supervivencia mediante Kaplan Meier y regresión de Cox.

Resultados. La mortalidad por cualquier causa a los 30 días fue de un 8%. Los factores asociados de forma independiente a mayor mortalidad fueron: edad ≥ 50 años, índice de Barthel < 90 puntos, alteración del nivel de consciencia, índice de SaO_2/FIO_2 < 400, auscultación respiratoria anómala, cifra de plaquetas < 100.000/mm^3, PCR ≥ 5 mg/dL y filtrado glomerular < 45 mL/min. A estos factores se les asignó una puntuación de 1, excepto a la edad, que se le asignó un valor de 2 puntos. Se dividió el modelo de riesgo en 3 categorías: riesgo bajo (menor o igual a 4 puntos), riesgo intermedio (5-6 puntos) y riesgo alto (igual o superior a 7 puntos). Para los pacientes clasificados como de bajo riesgo la probabilidad de mortalidad a los 30 días fue del 1,7%, en los casos de riesgo intermedio fue del 28,2% y para los de alto riesgo fue del 67,3%.

Conclusión. Disponer de una herramienta para estratificar el riesgo de mortalidad de los pacientes con COVID-19 que consultan a un SUH podría ser de utilidad para la gestión de los recursos sanitarios disponibles.

Palabras clave: COVID-19. Infección SARS-CoV-2. Urgencias. Indicador de mortalidad.

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Introduction

Since the health authorities in Wuhan, China, reported a cluster of cases of pneumonia of unknown origin in the city on December 31, 2019, the pandemic caused by SARS-CoV-2, the etiologic agent of COVID-19, has challenged health systems, even in countries with high rates of development[1-5]. The challenge of dealing with the pandemic has led to clinical trials being launched in record time to test the efficacy of new treatments or vaccines. While waiting for the results, patients with COVID-19 continue to arrive at healthcare centers and Europe is facing new waves of the pandemic[6,7].

The clinical spectrum of COVID-19 is very varied. About 80% of patients develop mild self-limited forms, 15% develop pneumonia requiring hospital admission and the remaining 5% develop critical illness, with respiratory distress, shock and multiorgan failure[8,9]. In the latter group, mortality reaches 50% despite intensive treatment[10].

The risk factors for severe disease have been described in multiple series, mostly in hospitalized patients[11,12]. However, patients treated in the emergency department for COVID-19 represent a broader spectrum of the disease and up to 39% of them can be discharged directly without requiring hospitalization[13]. Correctly identifying patients with a good prognosis is essential to avoid unnecessary hospital admissions, especially in a situation of high demand for resources.

The objectives of the present study were to identify factors related to mortality in a cohort of patients with a diagnosis of possible COVID-19 attended in a hospital emergency department (ED) and, secondly, to derive a risk model to estimate mortality 30 days after the ED visit.

Method

Observational retrospective cohort study of patients with COVID-19 treated in the ED from March 1 to April 30, 2020. The study was accepted by the Research Ethics Committee of Hospital Clínic de Barcelona (code no. 2020/0645) and was conducted in accordance with the general recommendations and, specifically, with regard to data confidentiality, as set out in the Helsinki Declaration on Biomedical Research.

The present study was carried out in the Emergency Department of the Hospital Clínic de Barcelona (HCB), a tertiary level university hospital and reference center for adult care in the Àrea Integral de Salut Barcelona Esquerra. According to 2020 data, this center provides healthcare coverage to a population of 523,725 people[14]. During the pandemic, the number of conventional hospitalization beds was 443, due to the fact that all rooms were converted into single rooms, and the number of critical or semi-critical beds was increased to 160. In addition, there was an integrated care service (home hospitalization) with a capacity to care for 250 patients and a medicalized hotel with 150 beds.

Patients over 18 years of age who were attended in the emergency department during a 2-month period and who were diagnosed with COVID-19 according to the World Health Organization (WHO) criteria for a confirmed or probable case were included[15]. The researchers retrospectively reviewed the electronic medical records of all patients identified in a database as "COVID-19" to confirm their inclusion in the study.

The clinical history of the ED episode of the patients was reviewed, after their selection, recording the following independent variables: 1) demographic: age and sex, socio-familial and functional situation according to the Barthel index; 2) pathological history: cardiovascular risk factors and diseases, respiratory disease, chronic kidney disease (glomerular filtration rate < 30 ml/min/1.73 m^2), venous thromboembolic disease, chronic liver disease, rheumatologic disease, dementia, neoplasm (solid or hematologic) and immunosuppression, as well as the degree of comorbidity according to the abbreviated Charlson index[16]; 3) symptoms at the time of ED consultation: fever, cough, odynophagia, dyspnea, chest pain, hemoptysis, syncope, lower extremity pain/volume increase, gastrointestinal, neurological; 4) physical examination in the ED: vital signs, SaO_2/FIO_2 index (O_2 saturation index/inspiratory O_2 fraction), respiratory auscultation (normal or pathological referring to any noise over-added to the vesicular murmur or absence or decrease of it), neurological examination (normal or altered level of consciousness, presence or absence of neurological focality); 5) laboratory parameters: blood count, biochemistry (creatinine and glomerular filtrate, liver tests, C-reactive protein, lactate dehydrogenase) and coagulation tests; 6) radiological findings (normal chest X-ray or altered if there was any type of pulmonary infiltrate, presence of pneumothorax or any other alteration of the lung parenchyma and its adjacent structures); 7) PCR (polymerase chain reaction) for the detection of SARS-CoV-2; 8) treatment administered in the emergency department: antivirals, antimicrobials, interleukin inhibitors, heparin, corticosteroids; 9) oxygen support required in the ED; 10) other supportive treatments; 11) final destination.

The primary outcome variable was 30-day all-cause mortality. Patient follow-up was completed as of June 30, 2020.

Continuous variables were presented as mean and standard deviation (SD) or median (according to their homogeneity) and categorical variables as absolute and relative frequencies. For variables with a proportion of 10% or more missing values, the multiple imputation of missing values command was executed.

The factors associated with mortality 30 days after the index visit were studied. To make the comparative analysis between groups of patients, according to the dependent variable, the Chi-square test was used to compare categorical variables and Student's t-test for continuous variables. Non-parametric tests were used for variables that did not meet the normality criteria. Significant continuous variables were dichotomized ac-

cording to the first value that was significant for mortality. To identify the independent variables related to mortality, conditional backward stepwise logistic regression was applied including the variables that were significant with a p value of less than 0.05 in the univariate analysis.

The variables found to be significant by logistic regression were included in the survival analysis using the Kaplan-Meier test (survival, log-rank). To determine the independent factors associated with the dependent variable mortality at the end of follow-up, the Cox regression test was applied (mortality, hazard ratio -HR-). Finally, with the poor prognostic factors identified by Cox regression, a prognostic index was calculated to identify patients at low, intermediate and high risk of poor outcome. The risk score for each patient was calculated by adding the points for each factor present.

Following the TRIPOD (Transparent Reporting of multivariable prediction model for Individual Prognosis or Diagnosis)[17] statement, the internal validity of the proposed indicator was analyzed. First, the indicator complied with the most common recommendation of including one predictor for every 10 events or non-events (the least frequent). Next, the performance of the indicator was evaluated by analyzing the area under the receiver operating characteristic (ROC) curve (AUC). In order to circumvent optimism bias, the AUC-ROC and its 95% confidence interval (95% CI) were estimated by resampling with replacement (n = 1,000), which in turn allowed us to quantify optimism bias. The calibration of the model was evaluated on the graph of the probability of the event estimated by the indicator versus the observed probability (calibration curve). The goodness of fit was measured with the Hosmer-Lemeshow test.

Analysis of results was performed with SPSS (version 20.0; SPSS, Inc., Chicago, USA) and Stata (version 14, College Station, TX, USA) statistical software.

Results

During the study period, 3,178 patients with suspected COVID-19 were seen, of whom 2,511 (79%) were diagnosed as confirmed or probable cases. Nasopharyngeal swab for detection of SARS-CoV-2 by PCR was performed in 1,077 patients (43%), being positive in 799 cases (32%). Table 1 shows the general characteristics of the series. The median age was 56 years (IQR: 43-71). Of the patients attended, 996 (40%) were discharged, 76 (3%) were admitted to the intensive care unit (ICU) and 39 (2%) died in the ED. The remaining patients were admitted to conventional wards, hospitalization at home or other authorized facilities (55%). At the end of follow-up, 210 patients died (9%), with a 30-day mortality probability of 8%.

Table 2 shows the results of the univariate and multivariate analysis of the independent factors related to mortality. These variables were the following: age equal to or greater than 50 years, Barthel index value less than 90 points, presence of altered level of consciousness, pathological respiratory auscultation, categorized SaO_2/FIO_2 index less than 400, lymphocyte count less than 1,000/mm^3, platelet count less than 100,000/mm^3, PCR equal to or greater than 5 mg/dL and glomerular filtration rate less than 45 mL/min.

The probability of 30-day mortality analyzed by the Kaplan Meier test and the factors independently associated with a higher risk of mortality at the end of follow-up obtained by Cox regression are shown in Table 3. These factors were: age equal to or older than 50 years (HR: 4.78; 95% CI: 1.90-12.06; $p < 0.001$), Barthel index less than 90 points (HR: 2.01; 95% CI: 1.32-3.08; $p < 0.001$), altered level of consciousness (HR: 2.12; 95% CI: 1.41-3.19; $p < 0.001$), SaO_2/FIO_2 index less than 400 (HR: 2.03; 95% CI: 1.45-2.85; $p < 0.001$), pathological respiratory auscultation (HR: 2.05; 95% CI: 1.25-3.37; $p = 0.005$), lymphocyte count less than 1. 000/mm3 (HR: 1.50; 95% CI: 1.04-2.17; $p = 0.03$), platelet count less than 100,000/mm^3 (HR: 2.58; 1.62-4.12; $p < 0.001$), PCR equal to or greater than 5 mg/dL (HR: 2.80; 95% CI: 1.82-4.30; $p < 0.001$) and glomerular filtration rate less than 45 mL/min (HR: 1.99; 95% CI: 1.33-2.86; $p < 0.001$).

All variables, with the exception of a lymphocyte count below 1,000/mm^3, were statistically significant with a HR $\geq$ 2 and a p value < 0.01. For this reason, it was agreed to select these factors (age equal to or greater than 50, Barthel index lower than 90 points, altered level of consciousness, SaO_2/FIO_2 index lower than 400, pathological respiratory auscultation, platelet count lower than 100,000/mm^3, PCR equal to or greater than 5 mg/dL and glomerular filtration rate lower than 45 mL/min) to define the risk model. As the HR value was similar in almost all the selected factors, these were assigned a score of 1, except for age, which was assigned a value of 2 points (Table 4). The sum of the score assigned to each of these variables (indicator value) could be calculated in 2,162 cases, the median value being 2 points (extremes from 0 to 9 points). Taking these results into account, the indicator was divided into 3 categories: low risk (less than or equal to 4 points), intermediate risk (5-6 points) and high risk (equal to or greater than 7 points). For patients with a low-risk indicator, the probability of 30-day mortality was 1.7%, for intermediate-risk cases it was 28.2% and for high-risk cases it was 67.3% (Table 5). Figure 1 shows the survival curve according to the indicator category.

The internal validity of the model was assessed by estimating its ability to predict actual 30-day mortality, after excluding from this analysis patients who had been censored before 30 days. First, the indicator complied with the recommendation to include one predictor for every 10 events. The AUC-ROC of the indicator in our series was 0.92, but decreased to 0.88 (95% CI: 0.85-0.92) when estimated by resampling, indicating an optimism factor equivalent to 0.03 area points. In the calibration curve, the average intercept and slope

Table 1. Clinical-epidemiological characteristics of patients attended in the emergency department with a diagnosis of probable or confirmed COVID-19 (results are expressed in absolute number and percentages if not otherwise specified)

	Valid N (%)	Lost N (%)	Total N = 2,511 N (% valid)
Men	2,511 (100)	0	1,278 (51)
Age in years [median (IQR)]	2,511 (100)	0	56 (43-71)
Socio-family situation	2,454 (98)	57 (2)	
Lives alone			216 (9)
Lives with family or caregiver			1,246 (51)
Lives in residence or SHC			204 (8)
Unknown			788 (32)
Triage level	2,475 (99)	36 (1)	
Level 1/2			225 (9)
Level 3			1,794 (73)
Level 4/5			456 (18)
Comorbidities			
Hypertension	2,459 (98)	52 (2)	808 (33)
Dyslipemia	2,455 (98)	56 (2)	516 (21)
Diabetes mellitus	2,444 (97)	67 (3)	318 (13)
Smoking	2,322 (92)	179 (7)	263 (11)
Neoplasia (solid/ hematologic)	2,446 (97)	65 (3)	204 (8)/42 (2)
Dementia	2,440 (97)	71 (3)	169 (7)
Obesity	2,210 (88)	301 (12)	146 (7)
COPD/Bronchial asthma	2,439 (97)	72(3)	155 (6)/143 (6)
Chronic renal failure	2,439 (97)	72(3)	142 (6)
Immunosuppression	2,444 (97)	67(3)	133 (5)
Ischemic heart disease	2,436 (97)	75(3)	121 (5)
Cerebrovascular disease	2,441 (97)	70(3)	113 (5)
Heart failure	2,441 (97)	70(3)	109 (4)
Abbreviated Charlson Index	2,417 (96)	94 (4)	
0-1 point			2,103 (87)
2-5 point			314 (13)
Barthel Scale	2,397 (95)	114 (5)	
91-100 points			2,148 (90)
90 points or less			249 (10)
Clinical manifestations			
Fever	2,496 (99)	15 (1)	1,937 (78)
Cough	2,475 (99)	36 (1)	1,729 (70)
Dyspnea	2,423 (96)	88 (3)	1,097 (45)
Diarrhea	2,371 (94)	140 (6)	474 (20)
Chest pain	2,343 (93)	168 (7)	281 (12)
Headache	2,339 (93)	179 (7)	278 (11)
Anosmia	2,227 (89)	284 (11)	221 (10)
Dysgeusia	2,223 (89)	288 (11)	225 (10)
Expectoration	2,408 (96)	103 (4)	231 (10)
Nausea/Vomiting	2,342 (93)	169 (7)	196 (8)
Odynophagia	2,342 (93)	169 (7)	214 (9)
Confusion/Alteration of level of consciousness	2,324 (93)	187 (7)	182 (8)
Vital signs [median (IQR)]			
Axillary temperature in ºC	2,307 (92)	204 (8)	36,7 (36,2-37,4)
SBP in mmHg	2,190 (87)	321 (13)	127 (114-142)
DBP in mmHg	2,190 (87)	321 (13)	77 (69-84)
Heart rate in beats per minute	1,952 (77)	555 (22)	86 (76-98)
Respiratory rate in breaths per minute	1,890 (75)	621(25)	18 (16-21)
SaO_2/FiO_2	2,485 (85)	26 (1)	
Less than or equal to 200			30 (2)
201-300			55 (2)
301-400			150 (6)
Greater than 400			2,250 (90)
Physical examination			
Altered respiratory auscultation	2,450 (98)	61 (2)	1,185 (48)
Neurological focus	2,292 (91)	219 (9)	22 (1)
Chest X-ray	2,498 (99)	13 (1)	
Not performed			133 (5)
Normal			830 (33)
Interstitial infiltrate			1,237 (50)
Alveolar infiltrate			241 (10)
Analytical results [median (IQR)]			
Leukocytes/mm^3	2,065 (82)	446 (18)	6,200 (4,595-8,140)
Lymphocytes/mm^3	2,062 (82)	449 (18)	1,000 (700-1,500)
Hemoglobin (g/L)	1,959 (78)	552 (22)	136 (124-147)
Platelets/mm^3	2,119 (84)	392 (16)	200,650 (150,120-255,023)
C-reactive protein (mg/dL)	2,081 (83)	430 (17)	4 (1,1-9,9)
Glomerular filtration rate (mL/min)	2,117 (84)	394 (16)	90 (70-90)
AST (U/L)	1,988 (79)	523 (21)	30 (22-46)
ALT (U/L)	2,024 (81)	487 (19)	25 (16-43)
Total bilirubin (mg/dL)	2,021 (80)	490 (20)	0,50 (0,4-0,7)
LDH (U/L)	1,902 (76)	602 (24)	253 (203-328)
Nasopharyngeal swab (SARS-CoV-2 CRP)	2,499 (99)	12 (< 1)	
Not realized			1,422 (57)
Positive			799 (32)
Negative			278 (11)
Treatment received in the emergency department			
Oxygen therapy	2,433 (97)	78 (3)	
No oxygen therapy			1,680 (67)
Goggles 2 liters per minute			362 (14)
Ventimask (24-60%)			344 (14)
High flow goggles			19 (1)
NIMV/IT + MV			27 (2)
Empirical antibiotic therapy	2,176 (87)	335 (13)	660 (26)
Prophylactic heparin/ anticoagulant	2,406 (96)	105 (4)	556 (22)
Steroids	2,421 (96)	90 (4)	174 (7)
Antivirals	2,431 (97)	80 (3)	1,327 (55)
Antinterleukins	2,374 (95)	137 (5)	47 (2)
Vasoactive drugs	2,411 (96)	100 (4)	14 (1)
Destination from the emergency department	2,496 (99)	15 (1)	
Discharge from the emergency department			996 (40)
Admission to the ward			953 (38)
Transfer to another hospital			291 (12)
Hotel Salud Admission			103 (4)
Admission to home hospitalization			38 (2)
Admission to ICU-intermediate			76 (3)
Deaths in the ED			39 (2)
Status at the end of the monitoring	2,408 (96)	103 (4)	
Alive			2,198 (91)
Dead			210 (9)

(It continues)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; PCC: primary care center; PCEC: primary care emergency center; SHC: social and healthcare center; COPD: chronic obstructive pulmonary disease; GCS: Glasgow Comes Scale; IT+MV: intubation and mechanical ventilation; LDH: lactate dehydrogenase; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR: interquartile range; SaO_2/FiO_2: ratio between peripheral oxygen saturation and inspired oxygen fraction: systolic blood pressure; CT: computed tomography; ICU: intensive care unit; NIMV: noninvasive mechanical ventilation.

Table 2. Univariate and multivariate analysis by logistic regression of factors related to mortality in the series of patients visited for COVID-19 (confirmed or probable) in the initial phase of the pandemic

	Alive N = 2,198 (% valid. column)	Dead N= 210 (% valid. column)	P	OR	IC 95%	p
Sex						
Female	1,098 (50)	80 (38)		1	Reference	
Male	1,100 (50)	130 (62)	< 0.001	0.75	0.50-1.14	0.200
Age						
Under 50 years old	894 (41)	6 (3)		1	Reference	
Age 50 or older	1,304 (59)	204 (97)	< 0.001	4.21	1.64-10.79	0.003
Abbreviated Charlson Index						
0-1 point	1,959 (89)	111 (53)		1	Reference	
2-5 points	239 (11)	99 (47)	< 0.001	1.50	0.94-2.38	0.100
Barthel Scale						
Greater than or equal to 90 points	1,971 (93)	91 (51)		1	Reference	
Less than 90 points	157 (7)	88 (49)	< 0.001	2.78	1.68-4.62	< 0.001
Altered level of consciousness*						
No	2,014 (96)	129 (68)		1	Reference	
Yes	84 (4)	61 (32)	< 0.001	3.17	1.82-5.53	< 0.001
Respiratory rate (breaths per minute)						
Less than 22	1,851 (84)	121 (58)		1	Reference	
Equal to or greater than 22	347 (16)	89 (42)	< 0.001	1.37	0.8-2.14	0.200
SaO_2/FIO_2					Reference	
Less than 200	18 (1)	18 (9)	< 0.001	15.81	8.04-31.13	< 0.001
200-300	40 (2)	19 (9)		7.51	4.23-13.34	
301-400	105 (5)	44 (21)		6.63	4.47-9.83	
Greater than 400	2,040 (93)	129 (61)		1		
Respiratory auscultation**						
Normal	1,240 (55)	35 (17)		1	Reference	
Altered	958 (45)	175 (83)	< 0.001	1.93	1.12-3.33	0.020
Chest X-ray***						
Normal	952 (43)	37 (18)		1	Reference	
Altered	1,246 (57)	173 (82)	< 0.001	1.06	0.60-1.89	0.800
Lymphocytes						
Equal or greater than 1,000/mm^3	1,471 (67)	60 (29)		1	Reference	
Less than 1,000/mm^3	727 (33)	150 (71)	< 0.001	1.70	1.10-2.63	0.020
Platelets						
Equal or greater 100,000/mm^3	2,126 (97)	177 (84)		1	Reference	
Less than 100,000/mm^3	72 (3)	33 (16)	< 0.001	3.66	1.89-7.09	< 0.001
C-reactive protein						
Less than 5 mg/dL	1,489 (68)	40 (19)		1	Reference	
Equal or greater 5 mg/dL	709 (32)	170 (81)	< 0.001	3.61	2.19-5.97	< 0.001
Total bilirubin						
Less than 2 mg/dL	2,176 (99)	203 (97)		1	Reference	
Equal to or greater than 2 mg/dL	22 (1)	7 (3)	0.01	0.57	0.13-2.59	0.500
Glomerular filtration rate						
Equal or greater than 45 mL/min	2,035 (97)	109 (52)		1	Reference	
Less than 45 mL/min	163 (3)	101 (48)	< 0.001	2.92	1.87-4.57	< 0.001
LDH						
Less than 300 U/L	1,695 (77)	96 (46)		1	Reference	
Equal or greater than 300 U/L	503 (23)	114 (54)	< 0.001	1.21	0.79-1.88	0.400

*Altered level of consciousness: refers to a Glasgow Come Scale score of 14 points or lower.
**Altered respiratory auscultation: refers to any noise in addition to the vesicular murmur or absence or decrease of it.
***Altered chest radiography: refers to any type of pulmonary infiltrate, presence of pneumothorax or any other alteration of the lung parenchyma and its adjacent structures.
SaO_2/FiO_2: ratio between peripheral oxygen saturation and inspired oxygen fraction; LDH: lactate dehydrogenase; OR: odds ratio; CI: confidence interval.

values were 0 and 0.97, respectively. The Hosmer-Lemeshow goodness-of-fit test presented a p value of 0.733. Finally, for the 4-point cut-off value, the sensitivity, specificity and positive and negative predictive values were 72%, 89%, 33% and 98%, respectively, for a prevalence of 6.1% (Figures 2 and 3).

Discussion

COVID-19 caused by SARS-CoV-2 has evolved from the detection of the first cases in December 2019 into a pandemic. EDs are a critical pillar in a health crisis of this scale[5]. Detection of those patients who can be safely dis-

Table 3. Survival analysis by Kaplan-Meier (probability of survival at 30 days) and Cox regression of the series of patients who consulted for COVID-19 (confirmed or probable) in the initial phase of the pandemic

	Events/n total	Probability of survival at 30 days	P	HR	95% CI	p
Age						
Less than 50 years old	6/905	99%		1	Reference	
50 years old or older	204/1,508	88%	0.001	4.78	1.90-12.06	< 0.001
Barthel Scale						
Greater than or equal to 90 points	91/2,066	96%		1	Reference	
Less than 90 points	88/245	67%	0.001	2.01	1.32-3.08	< 0.001
Altered level of consciousness						
No	129/2,145	95%		1	Reference	
Yes	61/145	62%	0.001	2.12	1.41-3.19	< 0.001
SaO_2/FIO_2						
Equal or greater than 400	129/2,169	95%		1	Reference	
Less than 400	81/244	70%	0.001	2.03	1.45-2.85	< 0.001
Respiratory auscultation						
Normal	32/1,224	98%		1	Reference	
Altered	175/1,133	86%	0.001	2.05	1.25-3.37	0.005
Lymphocytes						
Equal or greater than 1,000/mm^3	60/1,536	96%		1	Reference	
Less than 1.000/mm^3	150/877	85%	0.001	1.50	1.04-2.17	0.030
Platelets						
Equal or greater 100,000/mm^3	177/2,308	93%		1	Reference	
Less than 100,000/mm^3	33/105	75%	0.001	2.58	1.62-4.12	< 0.001
C-reactive protein						
Less than 5 mg/dL	39/1,527	98%	0.001	1	Reference	
Equal or greater 5 mg/dL	170/879	82%		2.80	1.82-4.30	< 0.001
Glomerular filtration rate						
Equal or greater than 45 mL/min	109/2,149	95%	0.001	1	Reference	
Less than 45 mL/min	101/264	65%		1.99	1.33-2.86	< 0.001

SaO_2/FiO_2: ratio of peripheral oxygen saturation to inspired oxygen fraction; CI: confidence interval; HR: Hazard ratio.

Table 4. Scores of the factors included in the mortality risk model of the series of patients attended by COVID-19 (confirmed or probable) in the initial phase of the pandemic

	Value
50 years of age or older	2 points
Barthel scale less than 90 points	1 point
Altered level of consciousness	1 point
SaO_2/FIO_2 less than 400	1 point
Altered respiratory auscultation	1 point
Platelets less than 100,000 /mm^3	1 point
C-reactive protein equal to or greater than 5 mg/dL	1 point
Glomerular filtration rate less than 45 mL/min	1 point

SaO_2/FiO_2: ratio of peripheral oxygen saturation to inspired oxygen fraction.

Tabla 5. Mortality risk categories of the series of patients attended by COVID-19 (confirmed or probable) in the initial phase of the pandemic

Category	Score	N	Events	Probability of mortality at 30 days
Low risk	0-4 points	1,824	35	1.7%
Intermediate risk	5-6 points	261	86	28.2%
High risk	> 6 points	55	39	67.3%

charged is a central aspect of hospital ED management. This study describes a prognostic model of clinical and analytical factors obtained in the first evaluation of the patient that allows stratification of patients into 3 risk categories according to their probability of death. This tool could be an aid in deciding the most appropriate emergency care resource for patients with COVID-19.

It is interesting to comment on some general aspects of the series. One of the most important is that the results and evolution of the first phase of the pandemic are presented. This cohort was characterized by several aspects: the scarce evidence available, the lack

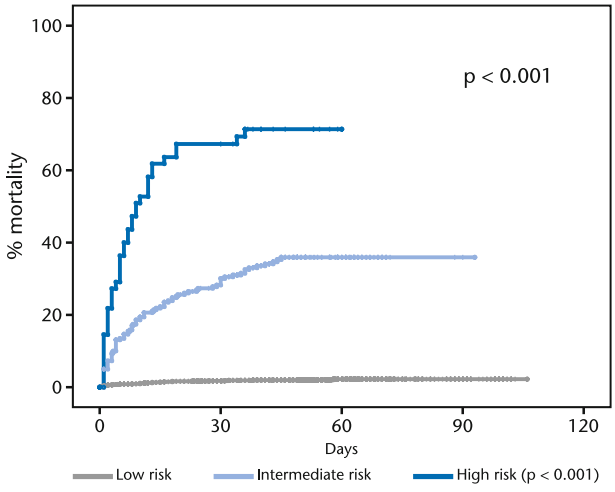

Figure 1. Probability of mortality by Kaplan Meier according to the risk categories of the indicator in 2,162 patients attended in the emergency department with a confirmed or probable diagnosis of COVID-19.

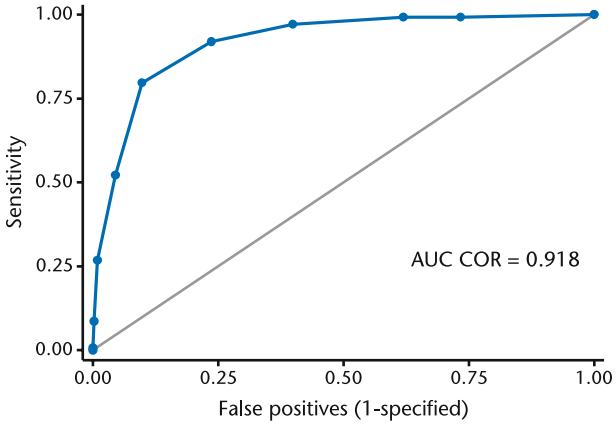

Figure 2. Receiver operating characteristic curve (ROC) of the indicator in the original series.
AUC: area under the curve.

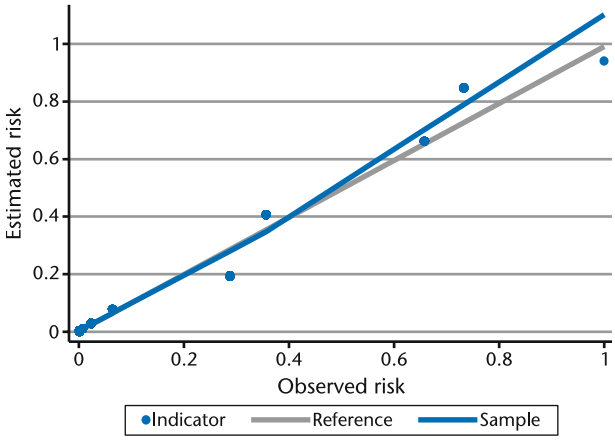

Figure 3. Model calibration curve.

of diagnostic means and effective therapeutic tools, as well as the successive changes in the action protocols. Despite these limitations, we believe that it is convenient to communicate the experience in the ED in order to help to better manage the future of this pandemic.

Variables that form part of the prognostic indicator have been described in previous studies as poor prognostic factors in patients with COVID-19. Age is one of the main risk factors for severe disease. In Spain, mortality due to SARS-CoV-2 ranges from 0.02% in patients under 50 years of age to 9.3% in patients 80 years of age or older, a pattern that is repeated in different series in other countries[10-12,18]. This fact can be explained by a greater vulnerability to infection in the elderly, due in part to the so-called "immunosenescence", but also to the pathophysiological changes in the respiratory system associated with age or the coexistence of comorbidities[19,20].

The main focus of SARS-CoV-2 is the respiratory system. Altered auscultation and the presence of respiratory failure, reflected in a $SaO_2/FIO_2 < 400$, indicate the existence of pulmonary involvement and, therefore, potential risk of clinical progression and severe complications[21]. Altered level of consciousness is a poor prognostic factor in patients with severe acute illness, and is attributed to multiorgan dysfunction and cytokine release. This parameter is part of different traditional risk scales such as NEWS-2 or qSOFA[22,23]. In patients with COVID-19, the altered level of consciousness can be explained by this reason, but also by the direct effect of the virus on the ascending reticular activating system or even occur in the context of meningoencephalitis[24].

Regarding analytical alterations, all the variables identified as risk factors have been associated with greater severity in previous studies of patients with COVID-19, but also in patients with severe disease such as sepsis[25]. Elevated CRP is an indicator of the activation of the systemic inflammatory response promoted by some proinflammatory cytokines, such as interleukin-6, which emerged as one of the main therapeutic targets in patients with severe forms of COVID-19[25,26]. Thrombocytopenia is an indicator of poor prognosis in patients with sepsis and may also be related to the development of thrombotic phenomena in patients with COVID-19, which are more frequent in severe disease. Renal failure is also a poor prognostic factor in patients with severe acute illness, including those with COVID-19[25]. Finally, a Barthel index < 90 points is also associated with increased mortality. The functional status of patients has prognostic implications in multiple clinical scenarios, including patients with COVID-19. At this point, it is important to note that, due to the saturation of health care resources in the initial phases of the pandemic, patients with a poorer functional status may have been limited in the application of certain treatments[27].

Various authors have developed other risk models according to their experience in recent months[28-32]. Most of the risk indicators, as in our model, were obtained retrospectively. Only the French BAS2IC score was obtained from a prospective cohort of patients, although its performance was modest[28]. Many of the variables included in these indicators coincide with ours. Age is a risk factor in all of them, as well as respiratory status[29,30], altered level of consciousness[32] and, among the analytical alterations, CRP[28-30], lymphocyte count[28,31], platelet count[29] and renal function[29,30]. All these indicators have been developed in cohorts of patients who required hospital admission. However, the present model has been derived from a large cohort of unselected patients seen in the emergency department for possible COVID-19. This offers several advantages. On the one hand, it encompasses a broader clinical spectrum of patients, which means that it can be easily applied, since its component variables are easy to obtain in the emergency department and are available in a short time. Finally, unlike other models where some variables were divided into several categories, in our model they were all dichotomized. This fact could reduce the discriminative capacity of a variable, although it facilitates its use in routine clinical practice because it is simplified.

The different categories of the indicator could help determine the most appropriate care resource for patients with probable or confirmed COVID-19 attended in the emergency department. Patients with a low-risk indicator have a 30-day survival rate of more than 98%. In

this group, direct discharge from the first ED visit could be considered, with continued clinical follow-up by the primary care team or, in some cases, by home care. Patients at intermediate risk would require hospital admission or, once clinical stability has been confirmed, admission to home hospitalization, since they probably require oxygen therapy and specific treatment[33,34]. Finally, early identification of high-risk patients would make it possible to establish which patients require admission to the ICU and in which subgroup the order for the adequacy of the therapeutic effort should be applied.

The main limitation of this study is that it is retrospective and this fact may have influenced the low prevalence of some clinical characteristics or the lack of recording of some variables such as respiratory frequency, which is of interest in a disease with mainly respiratory manifestations. Nor was the time of evolution of the symptoms systematically recorded, a fundamental aspect to know at what stage of the disease the patient is at, which allows us to put the results of the analytical parameters into context and to assess the probability of presenting clinical deterioration. In addition, we have few data related to the treatment received by the patients during hospital admission that could have influenced the course of the disease. On the other hand, the study was conducted in a single center, so the results may not be extrapolable to others. In addition, the lack of SARS-CoV-2 CRP testing and the presence of false negatives meant that in a high percentage of patients the diagnosis of COVID-19 was made according to clinical criteria, which was especially important in patients discharged from the emergency department. Nevertheless, 74% of the CRP performed in the overall series were positive, a figure similar to the sensitivity of the technique, which, together with the high incidence of the disease during the study period, leads us to believe that the majority were correctly diagnosed.

In conclusion, the availability of a tool for stratifying the risk of mortality in patients with COVID-19 makes it possible to identify those low-risk patients who could be discharged directly from the ED. This may facilitate the management of hospital resources in intermediate-high risk patients. Although the AUC-ROC values, calibration and goodness of fit of the indicator allow us to conclude that the risk model proposed here has been internally validated, this will need to be verified by a future prospective cohort.

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Addendum

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