ORIGINAL

Validation of the mortality risk model in a prospective cohort of patients from the sixth epidemic wave of COVID-19 in a hospital emergency department.

Leticia Fresco, Gina Osorio, Daniel N. Marco, Lourdes Artajona, Dora Sempertegui, Daniela Piñango, Natalija Demidenoka, Julia García-Gozalbes, Míriam Carbó, Milagrosa Perea*, Mª del Mar Ortega Romero* representing the COVID-19 Working Group on Emergency Care (COVID19-URG)

Objective. Validation of a mortality indicator derived during the first months of the COVID-19 pandemic in patients with COVID-19 seen during the sixth epidemic wave in a hospital emergency department (ED).

Method. Prospective non-interventional observational study. Patients > 18 years diagnosed with confirmed cases of COVID-19 (1 December 2021-28 February 2022) were included. The indicator was calculated for each patient: age $ 50 years (2 points), Barthel index < 90 points (1 point), impaired consciousness (1 point), SaO /FIO_{22} < 400 (1 point), pathological respiratory auscultation (1 point), platelets < 100 x $^{109/L}$ (1 point), C-reactive protein $ 5 mg/dL (1 point) and glomerular filtration rate < 45 mL/min (1 point). The performance of the indicator was assessed by analysis of the area under the receiver operating characteristic curve (ABC-COR).

Results. Of the 1,156 patients included in the study, 790 (68%) had received at least one dose of vaccine. The 30-day survival probability of the series was 96%. The risk indicator could be calculated in 609 patients. Four hundred and seventeen patients were classified as low risk, 182 as intermediate risk and 10 as high risk. The probability of 30-day mortality was 1%, 13% and 50%, respectively. Sensitivity, specificity and positive and negative predictive values for a cut-off point less than or equal to 3 points were 88%, 72%, 19%, 99%, respectively. The ABC-COR for the indicator was 0.87.

Conclusion. A low-risk indicator value allows safe discharge of patients with COVID-19 seen in an ED of a tertiary care centre.

Keywords: COVID-19. Mortality. Risk factors. Emergency medicine. Survival analysis. Vaccination.

*Both authors have contributed equally to this work.

Authors' affiliation:
Emergency Department, Hospital Clínic de Barcelona, Spain.

Authors' contribution: All authors have confirmed their authorship of the document. author's liability, publication agreement and transfer of rights to EMERGENCIAS.

Corresponding author: Mª del Mar Ortega Romero
Emergency Department
Hospital Clínic de Barcelona.
C/ Villarroel, 170
08036 Barcelona, Spain

E-mail:
mortega@clinic.cat

Article information:
Received: 5-9-2022
Accepted: 20-10-2022
Online: 24-11-2022

Responsible editor:
Agustín Julián-Jiménez

Mortality risk model validation in a prospective cohort of patients from the sixth wave of the COVID-19 pandemic in a hospital emergency department

Objective. To validate risk factors for mortality in patients treated for COVID-19 in a hospital emergency department during the sixth wave of the pandemic.

Method. Prospective observational noninterventional study. We included patients over the age of 18 years with a confirmed diagnosis of COVID-19 between December 1, 2021, and February 28, 2022. For each patient we calculated a risk score based on age 50 years or older (2 points) plus 1 point each for the presence of the following predictors: Barthel index less than 90 points, altered level of consciousness, ratio of arterial oxygen saturation to fraction of inspired oxygen less than 400, abnormal breath sounds, platelet concentration less than 100 × $^{109/L}$, C-reactive protein level of 5 mg/dL or more, and glomerular filtration rate less than 45 mL/min. The model was assessed with the area under the receiver operating characteristic curve (AUC).

Results. Of the 1156 patients included, 790 (68%) had received at least 2 vaccine doses. The probability of 30-day survival was 96%. A risk score was calculated for 609 patients. Four hundred seventeen patients were at low risk of death, 180 were at intermediate risk, and 10 were at high risk. The probability of death within 30 days was 1%, 13%, and 50% for patients in the 3 risk groups, respectively. The sensitivity, specificity, and positive and negative predictive values of a risk score of 3 points or less were 88%, 72%, 19%, 99%, respectively.The AUC for the model was 0.87.

Conclusion. The risk model identified low risk of mortality and allowed us to safely discharge patients treated for COVID-19 in our tertiary-care hospital emergency department.

Keywords: COVID-19. Mortality. Risk factors. Emergency medicine. Survival analysis. Vaccination.

Introduction

The World Health Organisation (WHO) declared a SARS-CoV-2 pandemic on 11 March 2009. 2020. Since then, the new coronavirus has spread worldwide, infecting more than 440 million people and causing more than 6 million deaths (data as of March 2022). The emergence of the

The emergence of this new disease, as well as its rapid spread and the exponential increase in severe cases that have had to be dealt with in several epidemic waves, has overloaded health systems to unthinkable levels and has challenged health systems globally even in countries with high rates of development[1-5]. Despite the effectiveness of vaccines developed in record time, the uneven progress of vaccination across countries and the emergence of new variants of the virus mean that COVID-19 continues to pose a challenge to health services globally[6,7].

The clinical spectrum of COVID-19 is very varied and therefore early risk stratification is one of the priorities of the emergency physician[8-10]. Since the beginning of the pandemic, studies have been published describing variables related to increased mortality and risk stratification models have been developed which were useful but had some limitations[11-15]. In order to explore this aspect further, our working group described a COVID-19 mortality model for the ED in the early phase of the pandemic[16]. Although the referral cohort was retrospective, the fact that the variables included were easily identifiable at the ED visit together with the results of the internal validity analysis allowed us to conclude that the model could be useful in risk stratifying patients with COVID-19 in the ED. Subsequently, a temporal validation was performed with the cohort of confirmed COVID-19 patients seen in the ED from 1 December 2020 to 28 February 2021. This study, which demonstrated the usefulness of the model for stratifying mortality risk in patients seen in the ED, allowed the indicator to be categorised into three categories: low risk (0-3 points), intermediate risk (4-6 points) and high risk (equal to or greater than 7 points)[17].

The COVID-19 pandemic continues to progress and we are now well into the sixth epidemic wave[18]. Some aspects have changed compared to March 2020. The majority of the adult population in Spain has now received at least one dose of vaccine and there has been a change in the course of the disease with a decrease in severe cases. Health services face the challenge of adapting to this new situation. Therefore, the aim of this study is to validate the mortality indicator in the prospective cohort of patients with SARS-CoV-2 infection seen during the sixth epidemic wave in a hospital emergency department (ED) of a tertiary care centre.

Method

Scope of the study

The present study was carried out in the Emergency Department of the Hospital Clínic de Barcelona, a single hospital in Barcelona.

The hospital is a tertiary level hospital and a reference centre for adult care in the *Barcelona Esquerra Integrated Health Area*, which provides healthcare coverage for a population of 523,725 people, according to data from 202019. During the study period, the hospital had 482 conventional hospitalisation beds and 118 critical or semi-critical hospitalisation beds. On average, 57 conventional and 23 critical or semi-critical beds were dedicated to COVID-19 care. In addition, the hospital also had 70 beds for integrated care (home hospitalisation).

Type of study, inclusion and exclusion criteria

Prospective non-interventional observational study. Patients aged $ 18 years who consulted the ED during a 3-month period (1 December 2021 to 28 February 2022) and who were diagnosed with COVID-19 according to WHO criteria[20] were included.

Patients presenting to the emergency department with clinical manifestations compatible with SARS-CoV-2 infection were considered candidates for the study. All patients underwent a standardised microbiological test for diagnosis. Finally, patients who were diagnosed with COVID-19 were included in the study. Pregnant patients and patients in police custody were considered non-candidates for the study. The research team followed up the included cases prospectively using the electronic medical record without intervening in their direct health care.

Independent variables, outcome variable and follow-up

The following independent variables were recorded: 1) demographic: age and sex, socio-familial and functional situation according to the Barthel index; 2) pathological antecedents: cardiovascular risk factors and diseases, respiratory pathology, chronic kidney disease (glomerular filtration rate < 30 ml/min/1.73 m^2), venous thromboembolic disease, chronic liver disease, rheumatological disease, diabetes, neoplasia (solid or haematological) and immunosu- pressures, as well as the degree of comorbidity according to the abbreviated Charlson index[21], 3) vaccination status against SARS-CoV-2 (number of doses and type of vaccine);
4) symptoms at the time of ED visit: fever, cough, odynophagia, dyspnoea, chest pain, haemoptysis, syncope, pain/volume increase in lower extremities, gastrointestinal, neurological; 5) physical examination in the ED: vital signs, SaFI index (O saturation index$_2$ /inspiratory O fraction$_2$, SaO /FIO$_{22}$), respiratory auscultation (normal or altered, the latter referring to any noise in addition to the vesicular murmur or the absence or decrease of this), neurological examination (normal or altered level of consciousness); 6) laboratory parameters: complete blood count, biochemistry (creatinine and filtrate

glomerular filtration rate, liver tests, C-reactive protein, lactate dehydrogenase) and coagulation tests; 7) radiological findings (normal chest X-ray or pa- thorax defined as presence of pulmonary infiltrate, pneumothorax or any other alteration of the lung parenchyma and its adjacent structures);
8) microbiological tests: polymerase chain reaction (PCR) or rapid antigen test (TRA) for SARS-CoV-2 detection; 9) treatment administered in the emergency department: antivirals, antimicrobials, interleukin inhibitors, heparin, corticosteroids; 10) type of oxygen therapy required; 11) other supportive care; and 12) final destination.

The primary outcome variable was 30-day all-cause mortality.

Patients were followed up to 30 days from the ED visit.

Calculation of the mortality indicator

The mortality indicator was calculated based on the previously described risk model for emergencies16. This indicator includes the following variables: age $ 50 years (2 points), Barthel index < 90 points (1 point), altered level of consciousness (1 point), SaFI index < 400 (1 point), pathological respiratory auscultation (1 point), platelet count (1 point), blood platelet count (1 point) and blood pressure (1 point).
< 100 x 109/L (1 point), C-reactive protein $ 5 mg/ dL (1 point) and glomerular filtration rate < 45 mL/min (1 point). The sum of the score assigned to each of these variables was the value of the indicator as a continuous variable.

Back-calculation of sample size

The *post hoc* estimation of the sample size required to detect a minimum area under the receiver operating characteristic curve (ABC-COR) analysis of 80% with a probability of 0.8, an alpha risk of 0.05 and the ratio of deaths to survivors obtained in the study showed that a minimum of 144 observations (8 deaths and 136 survivors) would be required. Medcalc software version 20 (www.me- dcalc.org) was used for the retrospective sample size calculation.

Statistical analysis

The statistical analysis was carried out in two phases as described below.

Univariate analysis: mortality analysis of the cohort of patients in whom 30-day follow-up was completed; analysis of the clinical and epidemiological characteristics of patients who had received at least one dose of vaccine versus patients who had not received any dose of vaccine; and analysis of factors related to mortality in vaccinated patients in whom 30-day follow-up was completed. The chi-square test was used to analyse between groups of patients.

to compare categorical variables and Student's t-test for continuous variables. Non-parametric tests were applied for variables that did not meet the normality criteria.

Main analysis: the most relevant outcome of the study was the observed 30-day mortality, its comparison with that expected from the application of the prognostic model to this new cohort of patients and the calibration of the model. Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as percentages. Survival curves were plotted by the Kaplan and Meier method and compared with each other using *log-rank* and chi-square statistics for trend. The performance of the indicator was assessed with the ABC-COR analysis and its 95% confidence interval (95% CI). The ABC-CORs for the indicator and the three risk categories of the indicator were compared with each other. Sensitivity, specificity and predictive values were estimated for various decision points, as well as positive and negative likelihood ratios.

The analysis of results was performed with the statistical programmes SPSS (version 21.0; SPSS, Inc., Chicago, USA) and Stata (version 14, StataCorp. LLC, College Station, Texas, USA). The comparison between the ABC- CORs was performed using the *roccomp* module integrated in Stata. The *pmcalplot* module running in Stata22 was used to calibrate the model. A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

The study was accepted by the Clinical Research Ethics Committee of the Hospital Clínic de Barcelona (code number HCB/2022/0020) and complies with the Declaration of Helsinki on biomedical research. Patients gave their consent to include their data in an anonymised database.

Results

During the study period, 1,156 patients diagnosed with a confirmed case of COVID-19 (female 53%, mean age 52 years, SD: 20) were included. Fifty-eight percent were diagnosed by a positive ART. Of the patients included, 790 (68%) had received at least one dose of any of the vaccines accepted by the National Health System. After initial assessment, 804 patients (70%) were discharged from the emergency department. Follow-up at 30 days was completed in 1,091 patients of whom 53 (5%) failed. Figure 1 shows the patient flow diagram of the study and table 1 shows the univariate analysis of factors related to 30-day mortality.

Table 2 shows the clinical-epidemiological characteristics of the patients included in the study with known vaccination status: 790 received at least one dose of vaccine versus 251 who did not.

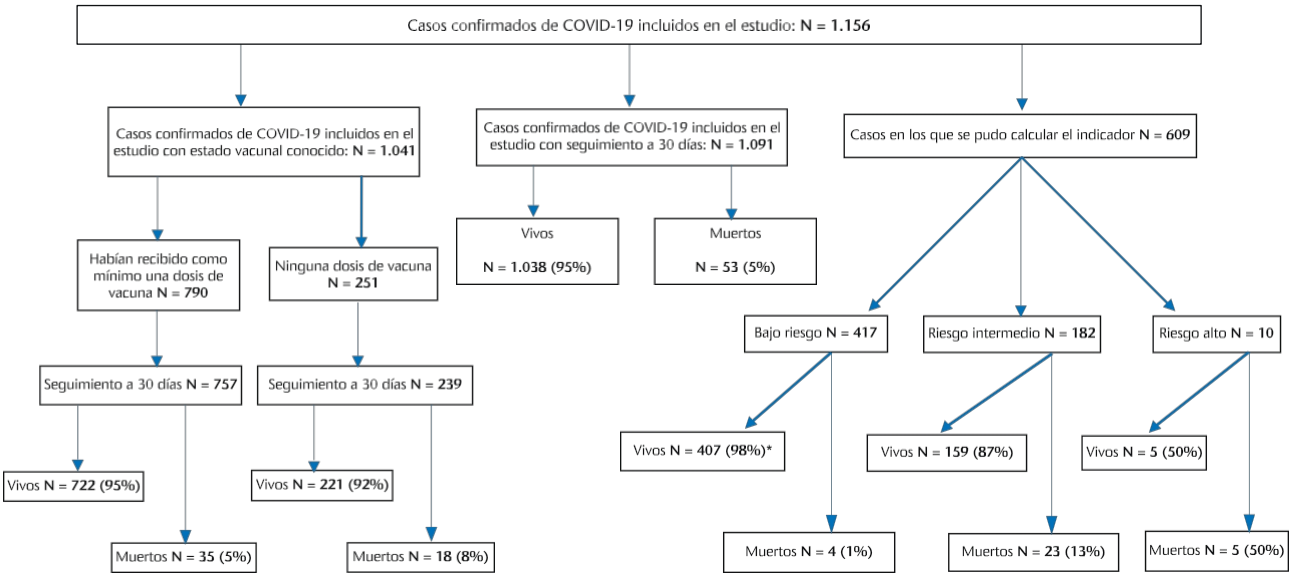

Figure 1. Flow diagram of the patients included in the study. *6 low-risk patients were lost from control at 30 days.

no doses. Although there were no differences in sex or age, unvaccinated patients had lower comorbidity and lower dependency. On the other hand, unvaccinated patients had a more severe disease with a higher frequency of respiratory involvement, required more oxygen support and a higher percentage were admitted to the intensive care unit (ICU). Mortality at 30 days could be established in a total of 757 patients who had received at least one dose of vaccine and in 239 unvaccinated patients, which was 4% versus 8%, respectively (p = 0.06).

Univariate analysis of mortality-related factors in the group of patients who had received at least one dose of vaccine is shown in table 3. Of the 757 patients who completed follow-up, 35 died. Age 50 years or older, Charlson index of 2 points or more, Barthel scale of less than 90 points, altered level of consciousness, SaFI (SaO /FIO_{22}) of less than 400, pathological respiratory auscultation, lymphocyte count of less than $1.^{000/mm3}$, platelet count less than $100,^{000/mm3}$, C-reactive protein value equal to or greater than 5 mg/ dL, glomerular filtration rate less than 45 mL/min, ICU stay and the presence of respiratory or thrombo- embolic complications were significantly associated with higher mortality.

The 30-day survival probability of the total series was 96% (96% of vaccinated patients vs. 94% of unvaccinated patients, p= 0.2). The mortality risk indicator could be calculated for 609 patients. With respect to the indicator categories, 417 patients were classified as low risk with a score of 3 points or less, 182 patients as intermediate risk with a score of 4-6 points and 10 patients as high risk with a score of 3 points or less, 182 patients as intermediate risk with a score of 4-6 points and 10 patients as high risk with a score of 4-6 points and 10 patients as high risk with a score of 3 points or less.

a score equal to or greater than 7 points. All patients for whom the indicator could be calculated were followed up for at least 30 days after the ED visit, except for 6 patients in the low-risk group who were lost to follow-up. The probability of death at 30 days in the established low, intermediate and high risk groups was 1%, 13% and 50% respectively (Figure 2). Table 4 summarises the validity parameters of the indicator for a cut-off point greater than or equal to 3 points. As can be seen, the negative predictive value (NPV) or, in other words, the estimated probability of survival for patients with an indicator value below or equal to 3 points is 98.8% (95% CI 97.1-99.6). Figure 3 shows the curves for the COR of the indicator and the risk categories derived from it, as well as the statistical comparison between the two. It is clear that categorisation of the indicator into three risk groups is accompanied by a significant decrease in ABC. Figure 4 shows the calibration of the indicator in this new cohort and the comparison of the observed frequencies with those expected from applying the prognostic model evaluated. It can be seen that the observed mortality is lower than that estimated by the model the higher the value of the indicator. The table embedded in Figure 4 confirms that the deviation between observed and expected values is minimal for the low and intermediate risk groups while in the high risk group the observed mortality is substantially lower than expected (50% and 65%, respectively).

Discussion

Since the WHO declared the SARS-CoV-2 pandemic, it has progressed in the form of several waves of epidemics.

Table 1. Univariate analysis of risk factors related to 30-day mortality in patients included in the study and followed up at 30 days.

	Number of patients with available data N = 1,091	Vivo N = 1.038 n (%)	Dead N = 53 n (%)	p
Female sex	1.091	546 (53)	23 (43)	0,1
Age in years [mean (SD)] **Age in years** [mean (SD)] **Age in years** [mean (SD)] **Age in years [**mean (SD)	1.091	52 (19)	80 (13)	**0,001**
Under 50 years old		502 (48)	2 (4)	
Equal to or older than 50 years of age		536 (52)	51 (96)	
Vaccination status	996			0,06
No dose		221 (23)	18 (34)	
At least one dose		722 (77)	35 (66)	
Abbreviated Charlson Index	1.091			**0,001**
0-1 point		874 (84)	24 (45)	
2-5 points		164 (16)	29 (55)	
Barthel Scale	1.064			**0,001**
91-100 points		968 (95)	25 (54)	
90 points or less		50 (5)	21 (46)	
Altered level of consciousness	1.051			**0,001**
No		999 (99)	41 (87)	
Yes		5 (1)	6 (13)	
SaO /FiO_{22}	994			**0,001**
Equal to or greater than 400		875 (93)	27 (52)	
Less than 400		67 (7)	25 (48)	
Respiratory auscultation	1.067			**0,001**
Normal		718 (71)	13 (25)	
Altered		296 (29)	40 (75)	
Chest radiological pattern	805			**0,001**
Normal		497 (66)	12 (25)	
Altered		261 (34)	35 (75)	
Platelets	707			**0,001**
Equal to or greater than 100,$^{000/mm3}$		622 (95)	39 (78)	
Less than 100,$^{000/mm3}$		35 (5)	11 (22)	
C-reactive protein	684			**0,001**
Less than 5 mg/dL		430 (68)	14 (28)	
Equal to or greater than 5 mg/dL		204 (32)	36 (72)	
Glomerular filtration	706			**0,001**
Equal to or greater than 45 mL/min		564 (86)	27 (54)	
Less than 45 mL/min		92 (14)	23 (46)	
ICU admission	830			**0,001**
No		744 (95)	35 (70)	
Yes		36 (5)	15 (30)	
Complications during admission	832			**0,001**
No		696 (89)	9 (18)	
Respiratory progression/thromboembolic disease		47 (6)	23 (43)	
Indicator risk categories	609			**0,001**
Low risk		412 (72)	5 (12)	
Intermediate risk		151(27)	31 (76)	
High risk		5 (1)	5 (12)	

SD: standard deviation; SaO /FiO_{22} : ratio of peripheral oxygen saturation to inspired oxygen fraction; ICU: intensive care unit.
Bolded values denote statistical significance ($p < 0.05$).

Despite efforts to contain infections in the form of restrictive measures and the development of national vaccination programmes, the number of cases and mortality from infection has been increasing exponentially. Our research group described an easy-to-use tool to decide the most appropriate recourse for patients at times of peak care pressure in the ED. In the present work we confirm by means of a prospective cohort of mostly elderly patients that this tool is still useful in the

The current situation in deciding quickly and safely on the discharge of patients with COVID-19 after initial care in the emergency department.

It is interesting to comment on some general aspects of the current series. Compared to our group's previous studies, the cohort we present has 68% of patients who had received at least one dose of vaccine. Compared to these, the unvaccinated patients had a higher percentage of respiratory complications, required more frequent admission to the ICU and, finally, had a higher incidence of respiratory complications.

Table 2. Clinical-epidemiological characteristics of patients who had received at least one dose of vaccine (n = 790) versus non-vaccinated patients (n = 251) included in the study.

	Number of patients with available data N = 1,041	Unvaccinated N = 251 n (%)	Vaccinated* N = 790 n (%)	p
Female sex	1.041	132 (53)	419 (53)	0,5
Age in years [mean (SD)] **Age in years** [mean (SD)] **Age in years** [mean (SD)] **Age in years [**mean (SD)	1.041	52 (19)	54 (20)	0,2
Under 50 years old		116 (46)	358 (45)	
Equal to or older than 50 years of age		135 (54)	432 (55)	0,4
Abbreviated Charlson Index	1.041			**0,001**
0-1 point		232 (92)	626 (79)	
2-5 points		19 (8)	164 (21)	
Barthel Scale	1.007			**0,03**
90 points or more		238 (96)	701 (92)	
Less than 90 points		10 (4)	58 (8)	
Altered level of consciousness	990			**0,5**
No		239 (99)	740 (99)	
Yes		2 (< 1)	9 (1)	
SaO /FiO_{22}	970			**0,003**
Equal to or greater than 400		201 (85)	676 (92)	
Less than 400		34 (15)	59 (8)	
Respiratory auscultation	1.007			**0,03**
Normal		154 (63)	532 (70)	
Altered		91 (36)	230 (30)	
Chest radiological pattern	759			**0,001**
Normal		101 (50)	371 (66)	
Altered		99 (50)	188 (34)	
Platelets	674			**0,2**
Equal to or greater than 100,$^{000/mm3}$		159 (92)	472 (94)	
Less than 100,$^{000/mm3}$		14 (8)	29 (6)	
C-reactive protein	652			**0,08**
Less than 5 mg/dL		101 (59)	315 (65)	
Equal to or greater than 5 mg/dL		70 (41)	166 (35)	
Glomerular filtration	673			**0,003**
Equal to or greater than 45 mL/min		156 (90)	405 (81)	
Less than 45 mL/min		17 (10)	95 (19)	
ICU admission	837			**0,001**
No		173 (89)	614 (96)	
Yes		22 (11)	28 (4)	
Complications during admission	839			**0,002**
No		153 (78)	559 (87)	
Respiratory progression/thromboembolic disease		28 (14)	42 (7)	
Indicator risk categories	579			0,4
Low risk		104 (67)	287 (68)	
Intermediate risk		50 (32)	128 (30)	
High risk		1 (1)	9 (2)	
Vital status at 30 days	996			0,06
Vivo		221 (92)	722 (96)	
Dead		18 (8)	35 (4)	

SD: standard deviation; SaO /FiO_{22} : ratio of peripheral oxygen saturation to inspired oxygen fraction; ICU: intensive care unit; *vaccinated: patients who have received at least one dose of vaccine.
Bolded values denote statistical significance (p < 0.05).

higher mortality. This has been observed in the series of other groups coinciding with the vaccination of the population, although in our case the differences were not statistically significant, probably due to the size of the cohort[23-25].

According to our results, the model described above is useful for identifying patients with a higher risk of poor outcome and thus deciding on the most appropriate health care resource in situations of care overcrowding, even when the percentage of vaccinated patients is high. As in previous work, the method used in the

The inclusion of patients was consecutive, the setting was the ED of a tertiary level hospital and the variables necessary to clearly describe the characteristics of the patients and the course of the disease were collected. In addition, for greater clarity, the analysis excluded patients in whom the indicator could not be calculated due to a missing value, almost always analytical, and those in whom follow-up was not 30 days and therefore their status at that time was unknown. In addition, 30-day mortality was used as the dependent variable because, although there are many

Univariate analysis of risk factors associated with 30-day mortality in patients who had received at least one dose of vaccine.

	Number of patients with available data N = 757	Alive N = 722 n (%)	Killed N = 35 n (%)	p
Female sex	757	380 (53)	16 (46)	0,3
Age in years [mean (SD)] **Age in years** [mean (SD)] **Age in years** [mean (SD)] **Age in years [**mean (SD)	757	53 (20)	81 (13)	**0,001**
Under 50 years old		333 (46)	2 (6)	
Equal to or older than 50 years of age		389 (54)	33 (94)	
Abbreviated Charlson Index	757			**0,001**
0-1 point		590 (82)	8 (23%)	
2-5 points		132 (18)	27 (77)	
Barthel Scale	733			**0,001**
90 points or more		661 (94)	14 (47)	
Less than 90 points		42 (6)	16 (53)	
Altered level of consciousness	728			**0,001**
No		693 (99)	26 (84)	
Yes		4 (1)	5 (16)	
SaO /FiO_{22}	711			**0,001**
Equal to or greater than 400		633 (94)	20 (59)	
Less than 400		44 (6)	14 (41)	
Respiratory auscultation	740			**0,001**
Normal		502 (71)	11 (31)	
Altered		203 (29)	24 (69)	
Chest radiological pattern	542			**0,001**
Normal		344 (67)	10 (33)	
Altered		168 (33)	20 (67)	
Platelets	491			**0,001**
Equal to or greater than 100,$^{000/mm3}$		437 (95)	25 (78)	
Less than 100,$^{000/mm3}$		22 (5)	7 (22)	
C-reactive protein	471			**0,001**
Less than 5 mg/dL		297 (68)	10 (31)	
Equal to or greater than 5 mg/dL		142 (32)	22 (69)	
Glomerular filtration	490			**0,001**
Equal to or greater than 45 mL/min		381 (83)	16 (50)	
Less than 45 mL/min		77 (17)	16 (50)	
ICU admission	621			**0,001**
No		569 (97)	24 (75)	
Yes		20 (3)	8 (25)	
Complications during admission	623			**0,001**
Respiratory progression/thromboembolic disease		28 (5)	14 (42)	
Indicator risk categories	417			**0,001**
Low risk		275 (70)	5 (19)	
Intermediate risk		111 (28)	17 (65)	
High risk		5 (1)	4 (15)	

Patients with 30-day follow-up are included, n = 757.
SD: standard deviation; SaO /FiO_{22} : ratio of peripheral oxygen saturation to inspired oxygen fraction; ICU: intensive care unit.
Bolded values denote statistical significance ($p < 0.05$).

In the emergency department, there are several factors that influence the late survival of patients with COVID-19, and an indicator is needed to identify cases with a high risk of early mortality. On this occasion, the number of patients in which the indicator could be calculated was lower because, after the initial assessment, the care team decided to discharge or admit the patient directly according to their clinical condition without waiting for the results of the complementary [examinations26].

Compared to the 2021 cohort, the ABC-COR of the indicator in the current cohort was slightly higher (0.86 vs. 0.81)[17]. Sensitivity values, especially for the current cohort, were slightly higher (0.86 vs. 0.81)17.

The positive predictive value (PPV) is low because the event (death # 30 days) is very infrequent and the NPV for a cut-off point of 3 points allows us to state that the indicator is a safe tool for discharging patients after initial assessment in the ED. The positive predictive value (PPV) is low because the event (death # 30 days) is very low. Therefore, most of those scoring > 3 points do not die and are false positives. Sensitivity is not affected by the frequency of the event and therefore has a higher value. In this case the indicator rating curve is below the diagonal (slope < 1). For example, a model-estimated risk of 0.4 corresponds to an actual risk, observed in the current series, slightly above 0.3. These ci-

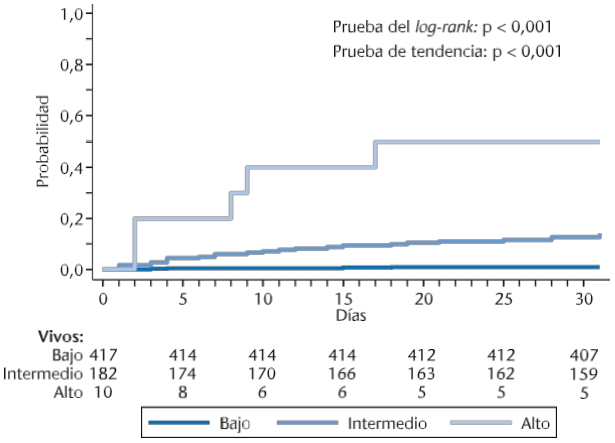

Figure 2. Mortality by risk group. Follow-up of survivors is censored at 30 days except for 6 patients in the low-risk group who were lost to follow-up.

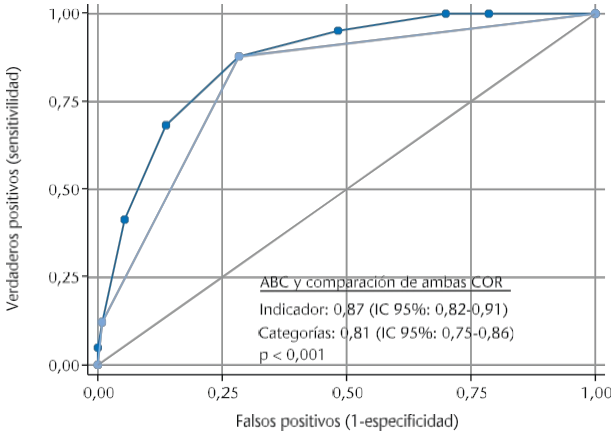

Figure 3. Curves of the CORs corresponding to the value of the indicator (blue) and the three risk categories (grey), and comparison of the ABCs corresponding to both CORs.
ABC: area under the curve; COR: receiver operating characteristic; 95% CI: 95% confidence interval.

fras correspond to the 30-day probability of death. This means that the indicator tends to overestimate the risk observed in the current series or, in other words, that the indicator was constructed with more severe patients than the current ones. These patients with the same indicator value were more likely to die within 30 days. This explanation seems reasonable, as the indicator was constructed with data from patients in the first phase of the pandemic in which mortality in the published series, including ours, was 10%16[27,28]. As expected, the categorisation of the indicator into three risk groups significantly reduced the ABC- ROC from 0.87 to 0.81. We believe this is the price of the greater clinical utility of using three risk categories rather than a numerical indicator with 9 different values.

Since the beginning of the pandemic, the identification of risk factors for poor outcome has been a priority objective of interest for different research groups. The most developed indicator is the '4C Mortality Score' which is periodically reviewed and has external validity studies29[30]. However, it has not been validated for the ED setting. The indicator we propose is composed of clinical and analytical variables obtained in the initial assessment of the patient. In the ED setting, it is of interest to detect patients who have

The low risk group was the most numerous and had the lowest mortality. According to our series, the low-risk group was the largest and had the lowest mortality. Four patients with a low-risk indicator died during admission due to complications.

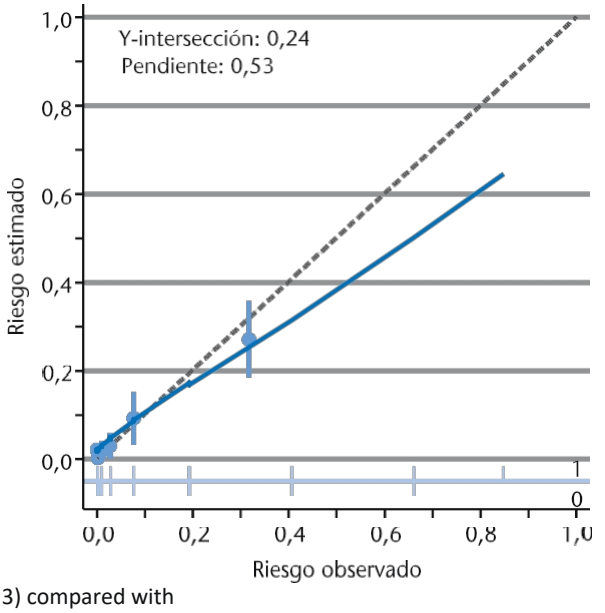

Table 4. Sensitivity, specificity and predictive values for 30-day mortality for intermediate and high risk categories (indicator > 3) compared with the low risk category (indicator #3)

	Central value (95% CI)
Sensitivity87	.8% (73.8-95.9)
Specificity71	.6% (67.7-73.3)
Positive likelihood ratio3	.1 (2.6-3.7)
Negative likelihood ratio0	.2 (0.1-0.4)
Positive predictive value	18.7%(13.4-24.9)
Negative predictive value98	.8% (97.1-99.6)

95% CI: 95% confidence interval.

Table 4. Sensitivity, specificity and predictive values for 30-day mortality for intermediate and high risk categories (indicator > 3) compared with intermediate and high risk categories (indicator > 3)

		Frecuencia observada		Frecuencia esperada	
Categoría de riesgo	Nº pacientes	Eventos	Porcentaje	Eventos	Porcentaje
Bajo (0-3 puntos)	417	4	1%	3	0,6%
Intermedio (46 puntos)	182	23	13%	29	16%
Alto (≥ 7 puntos)	10	5	50%	7	65%

Figure 4. Calibration curve of the indicator and comparison between observed and expected frequencies. The solid line corresponds to the smoothed logistic function connecting the average irrigation estimates (grey dots, with their 95% CI). The dashed diagonal line represents the ideal calibration.
95% CI: 95% confidence interval; No.: number.

cations related to previous comorbidity. Of the patients with an indicator value of less than or equal to 3 points discharged, none required subsequent admission. Associated comorbidity has always been considered a poor prognostic factor in studies on COVID-19 mortality. In our study it is also associated with poor prognosis. In the current phase of the pandemic, with a decrease in severe cases mainly because a significant percentage of the population is vaccinated, associated comorbidity must be considered in clinical decisions. In other words, the value of the indicator indicates the risk of mortality due to COVID-19. If the patient is vaccinated and has a low-risk indicator, it is safe to discharge him/her if he/she does not have comorbidities that could become complicated in a short period of time.

The study we present has a number of limitations. The main limitation is that it is a cohort from a single hospital, so the results may not be extrapolable to other hospitals, although we think it could be useful in centres similar to ours. In other words, external validation of the indicator would be desirable. On the other hand, although the series is prospective, some variables still show missing values. Most of them are analytical determinations, which can be explained by the fact that the decision to request them was made at the discretion of the professional responsible for the direct care of the patient. Finally, our results reflect a particular context of the pandemic. In any case, given the ease with which the virus mutates, it is not surprising that COVID-19 cases will continue to be seen in the ED and having an indicator of severity will be useful in the near future.

In conclusion, the SARS-CoV-2 pandemic is evolving and we are now facing another epidemiological phase: mass vaccination of the population has modified the course of the disease. However, given the ease with which the virus mutates, cases of infection are on the increase. In this context, the mortality risk indicator continues to be useful at times of peak care to organise specific COVID-19 care circuits within the ED based on risk category. Specifically, if at the ED visit a patient with a diagnosis of SARS-CoV-2 infection is classified as low risk and also has no comorbidity that could lead to severe decompensation, he/she can be discharged safely directly from the ED.

Conflict of interest: The authors declare that there is no conflict of interest in relation to this study.

Funding: The authors declare that they have no funding in relation to this article.

Ethical responsibilities: All authors have confirmed the maintenance of confidentiality and respect for the rights of patients in the author's responsibilities document, publication agreement and assignment of rights to EMERGENCIAS. The study was approved by the Clinical Research Ethics Committee of the Hospital Clínic de Barcelona (protocol code no. HCB/2022/0020).

Article not commissioned by the Editorial Board and peer-reviewed.

Acknowledgements: To all the professionals who have participated in the care of patients with COVID-19. To the patients and their families, for their understanding during this health crisis and for facilitating our work all these days. Finally, we would like to thank Dr Arturo Pereira for his invaluable and disinterested help without which it would have been impossible to complete this work.

Addendum

Collaborators belonging to the COVID19-URG group: Sira Aguiló, Francesc Xavier Alemany, José Ramón Alonso, Ane Altuna, Jesús Alfredo Álvarez, Francisco Aya, Ana Belén Azuaga, Giovanna Benedetti, Alex Bata- ller, Ernest Bragulat, Adriá Carpio, Daniel Armando Cazar, Alicia Caprini, Pedro Cepas, María Blanca Coll-Vinent, Pierre Comice, Irina Ileana Cotir- ta, Sandra Cuerpo, David Curtelín, Filippo de Caneva, Adrián Díaz, Sara Isabel Dos Santos, María Rosa Escoda, Ona Escoda, José Alberto Evange- lista, D. Fajardo, Álvaro José Fernández, Andrea Fernández, Andreu Fer- nández, Sandra Fernández, Vanesa Paola Flores, Beatriz Frade, Miguel Ángel Galicia, Ana García, Víctor Gil, Elisenda Gómez, María Isabel Gon- zález, Elena Guillén, Evelyn Hermida, Thomas Hock, Sonia Jiménez, Bea- triz López, Nuria López, Gemma Martínez, Liliana Martínez, Jaume Mes- tre, Natalia Miota, Òscar Miró, Concepción Moll, Laia Montañola, Ilhame Msabri, Adriana Pané, Sandra Paredes, Silvia Pere, Verónica Pereira, Rodri- go Perlá, Catalina Piqueras, Arrate Placer, Daniel Repullo, Martha Rivas, Andrea Rivero, Juan José Rodríguez, Emilio José Salgado, Miquel Sánchez, Carolina Sánchez, Marc Santos, Laia Sentis, Adrián Tomé, Juan B Valencia, Sara Vázquez, Carolina Xipell, Marc Xipell.

Bibliography

1 World Health Organization: Coronavirus disease (COVID-19) (Accessed 15 August 2022). Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
2 Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579:270-3.
3 Boserup B, McKenney M, Elkbuli A. The impact of the COVID-19 pandemic on emergency department visits and patient safety in the United States. Am J Emerg Med. 2020;38:1732-6.
4 Li R, Rivers C, Tan Q, Murray MB, Toner E, Lipsitch M. Estimated demand for US hospital inpatient and intensive care unit beds for patients with COVID-19 based on comparisons with Wuhan and Guangzhou, China. JAMA Netw Open. 2020;3:e208297.
5 Vollmer MAC, Radhakrishnan S, Kont MD, Flaxman S, Bhatt S, Costelloe C, et al. The impact of the COVID-19 pandemic on patterns of attendance at emergency departments in two large London hospitals: an observational study. BMC Health Serv Res. 2021;21:1008.
6 Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384:403-16.
7 Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383:2603-15.
8 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323:1239-42.
9 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395:1054-62.
10 Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ. 2020; 369:m1966.
11 Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339.
12 Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ. 2020;369:m1328.
13 Gupta RK, Harrison EM, Ho A, Docherty AB, Knight SR, van Smeden M, et al. Development and validation of the ISARIC 4C Deterioration model for adults hospitalized with COVID-19: a prospective cohort study. Lancet Resp Med. 2021;9:349-59.
14 Update to living systematic review on prediction models for diagno- sis and prognosis of covid-19. Available at: https://www.covprecise.org/living-review/

15 González del Castillo J. Keys to the interpretation of prognostic models in patients with COVID-19. Emergencias. 2021;33:251-3.
16 García-Martínez A, López-Barbeito B, Coll-Vinent B, Placer A, Font C, Rosa Vargas C, et al. 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. Emergencias. 2021;33:273-81.
17 Fresco L, Osorio G, Carbó M, Marco DN, García-Gozalbes J, Artajona L, et al. Risk score for mortality due to COVID-19: a prospective temporal validation cohort study in the emergency department of a tertiary care hospital. Emergencias. 2022;34:196-203.
18 Ministry of Health and Consumer Affairs (Accessed 15 August 2022). Available at: https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Actualizacion_621_ COVID-19.pdf
19 Salut integral Barcelona (Accessed 15 August 2022). Available at: http://salutintegralbcn.gencat.cat/ca/inici
20 World Health Organization: W H O case definitions for COVID-19. Updated in the document entitled "Public Health Surveillance for COVID-19" published on 16 December 2020. (Accessed 15 September 2021). Available at: https://www.who.int/es/emergencies/diseases/novel-coronavi- rus-2019/technical-guidance
21 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-83.
22 Ensor J, Snell KI, Martin EC. PMCALPLOT: Stata Module to Produce Calibration Plot of Prediction Model Performance. Statistical Software Components. 2018. (Accessed 30 June 2022). Available at: ht- tps://ideas.repec.org/c/boc/bocode/s458486.html.
23 Tenforde MW, Self WH, Adams K, Gaglani M, Ginde AA, McNeal T, et al. Association between mRNA vaccination and COVID-19 hospitalization and disease severity. JAMA. 2021;326:2043-54.
24 Haas EJ, Angulo FJ, McLaughlin JM, Anis E, Singer SR, Khan F, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021;397:1819-29.
25 Accorsi EK, Britton A, Fleming-Dutra KE, Smith ZR, Shang N, Derado G, et al. Association between 3 doses of mRNA COVID-19 vaccine and symptomatic infection caused by the SARS-CoV-2 Omicron and Delta variants. JAMA. 2022;327:639-51.
26 Albert A, Llorens P, Aguirre A, Martín-Sánchez FJ, Minguez S, Moreno O, et al. Revisit after discharge from the emergency department in a cohort of patients with COVID-19 pneumonia and analysis based on the healthcare resource used for follow-up. RESALSEVID study. J Healthc Qual Res. 2022 (in press). doi: 10.1016/j.jhqr.2022.05.007.
27 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395:497-506.
28 Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8:475-81.
29 de Jong VMT, Rousset RZ, Antonio-Villa EN, Buenen AG, Van Calster B, Bello-Chavolla OY, et al. Clinical prediction models for mortality in patients with covid-19: external validation and individual participant data meta-analysis. BMJ. 2022;378:e069881
30 Hassan S, Ramspek CL, Ferrari B, van Diepen M, Rossio R, Knevel R, et al. External validation of risk scores to predict in-hospital mortality in patients hospitalized due to coronavirus disease 2019. Eur J Intern Med. 2022;102:63-71.