A Scoring System To Predict Mortality In Patients Admitted To Hospital With Covid-19

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Research article

Keywords: Mortality, COVID-19, cardiovascular disease, dyspnoea, pneumonia,

Posted Date: December 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-122946/v1

Abstract

Background: Mortality from COVID-19 has reached rates approaching 13,0%, and it is necessary to have tools to predict the course of the disease, risk of aggravation and probability of death. We propose a predictive mortality score in patients admitted with COVID-19.

Methods: We have collected and analysed more than 50 epidemiological, clinical, analytical and treatment variables in a referral cohort of 303 patients admitted for COVID-19. Those variables retained after multivariate analysis that compared survivors and non-survivors patients became the components of the risk of death score. To check the validity of the score, a validation cohort of patients admitted for COVID-19 was used.

Results: Mortality was 17% in the referral cohort. Candidate variables to predict risk of death were age ≥65 years, cardiovascular disease, dyspnoea, pneumonia, acute respiratory distress, non-invasive mechanical ventilation, abnormal prothrombin, elevated D-dimer, and abnormal lactate dehydrogenase. The proposed cut-off point in the scale was 7 (with 0-6 points representing a low risk of death and 7-17 a high risk). Application of the score in the validation cohort obtained a sensitivity of 100% and a specificity of 92%, with a positive predictive value of 71% and a negative predictive value of 100%.

Conclusions: Our study presents for the first time the development and validation of a risk-of-death scoring system for patients hospitalised with COVID-19 using clinical and laboratory parameters that can be retrieved from patients' admission records.

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, was initially reported in Wuhan, Hubei Province, China, in December 2019. The disease spread rapidly across China[1] and worldwide, with WHO characterising COVID-19 as a pandemic in March 2020.[2]

Most infected individuals are asymptomatic. Clinical manifestations, when present in otherwise healthy adults and children, usually consist of mild flu-like symptoms such as fever, cough, expectoration, headache, myalgia, and fatigue, but for vulnerable populations and those with underlying diseases, COVID-19 may be severe, resulting in multiple organ failure and death.[3]

However, not all patients with COVID-19 are at high risk of death. To date, several studies on complications and mortality in patients hospitalised with COVID-19 have been carried out locally[4,5,6] and also nationally in China and the United Kingdom. Most of these studies compare the clinical characteristics of survivors and non-survivors, but few analyse both clinical and laboratory variables alike.[7,8,9]

Mortality from COVID-19 has reached rates of 11,6%,[10] effective treatments are not yet available, and a vaccine is some time away. Therefore, we need tools based on our current knowledge to predict the

disease course and outcome.

The hypothesis of this study is that a risk profile for COVID-19 mortality can be defined based on epidemiological, clinical and laboratory parameters, its objective is to develop and validate a predictive clinical model to identify the risk factors associated with death from COVID-19, in order to identify which patients would benefit from invasive measures in the event of new outbreaks.

Methods

Study design and population

This study was conducted in Tenerife, Spain, at the Hospital Universitario de Canarias (HUC), a public 687-bed tertiary hospital serving 446,253 inhabitants in the northern area of the island and also La Palma island. During the study period, the HUC was the COVID-19 Reference Centre for the catchment area, where all SARS-CoV-2-positive patients with severe symptoms were admitted.

We carried out a follow-up study of patients diagnosed with COVID-19 admitted to the HUC. The referral cohort consisted of 303 patients admitted between 1 March and 31 May 2020 and the validation cohort consisted of 30 patients admitted between 1 June and 31 July 2020.

Case definitions

SARS-CoV-2 infection was confirmed at the Microbiology Service of the HUC using real-time reverse-transcription polymerase chain reaction (RT-PCR) testing of upper respiratory tract specimens (mainly nasopharyngeal swabs) from patients with suspected COVID-19. A COVID-19 diagnosis was confirmed in all patients with a positive RT-PCR test for SARS-CoV-2 and compatible symptoms. The clinical status of a patient was classified as discharged alive, currently hospitalised, or deceased. Deceased patients were defined as those who died in hospital, with a positive SARS-CoV-2 test, in whom the direct or indirect cause of death was COVID-19.

Clinical and Laboratory observed variables

From each patient in both cohorts, the following variables were collected from the medical records at the time of diagnosis: age, sex, admission origin (including admission from residential facilities), chronic diseases (chronic respiratory disease, diabetes mellitus, chronic kidney failure, hypertension, chronic cardiovascular disease, immunodeficiency, chronic liver disease, and obesity), and acute symptoms and factors (pneumonia and acute respiratory distress, smoking, and symptoms at the time of diagnosis: cough, fever [temperature > 37·6 °C], dyspnoea, myalgia, headache, nausea, abdominal pain, and diarrhoea). Data on intensive care unit (ICU) admission and the need for invasive or non-invasive mechanical ventilation were also collected. Laboratory parameters included leukocytes, neutrophils, lymphocytes, platelets, haemoglobin, activated partial thromboplastin time, prothrombin activity, prothrombin time, D-dimer, albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin,

serum creatinine, lactate dehydrogenase, troponin, procalcitonin, interleukin 6, erythrocyte sedimentation rate, and C-reactive protein.

Statistical analysis

The general characteristics of the patients in both cohorts were described, expressing qualitative variables as absolute and relative frequencies and quantitative variables as mean (standard deviation) or median (range), depending on whether they followed a normal distribution verified with the Kolmogorov-Smirnov test.

To carry out the predictive model, we first compared the collected variables, between the survivors and non-survivors in the referral cohort. Laboratory parameters were classified as normal (within the normal range) or abnormal (above or below the normal range). The cut-off value for age was 65 years. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test for small samples; variables with a non-normal distribution were compared with the Mann-Whitney U test.

The variables that achieved a statistical significance of $p \leq 0{\cdot}20$ were used as explanatory factors for death in univariate models, and applied later in multivariable binary logistic regression models with a full start strategy and backward stepwise elimination using the Wald criterion. Since 51 deaths occurred in the referral cohort, independent blocks of demographic, clinical and treatment, and laboratory factors with a maximum of four variables have been introduced to observe the Hosmer-Lemeshov criterion, eliminating factors without statistical significance ($p \leq 0{\cdot}05$) and combining the retained with the rest, until we obtained three nested models made up exclusively of significant factors at that level. The resulting factors were defined as the items in the risk-of-death score, calculating their estimated weight by rounding the value of their logistic regression coefficient to the nearest integer. The score obtained was assigned to each patient in the referral cohort and a ROC Type II curve analysis was performed to estimate the area under the scoring curve, and to obtain the sensitivity and specificity for each possible cut-off point of the scale that produces as output the "high" and "low" risk of death from COVID-19, choosing as the first option the point that meets the criteria of balance Sensitivity-Specificity of Yuden (Sensitivity + Specificity-1). The positive odds ratio of the scale was also calculated to estimate its performance. The predictive values of results were estimated taking as the population lethality that observed in the sample.

To check the validity of the score, it was used in the patients of the validation cohort, checking the maintenance of its metric properties.

For the data analysis, the SPSS 24.0™ of IBM Co® was used.

Ethical Aspects

The study was approved by the Institutional Ethic Review Board of the HUC, with code number CHUC_2020_82, and the need for consent was waived by the ethical review board, given its non-interventional and retrospective design.

Results

During the study period, 303 patients (referral cohort) were admitted to the HUC with a diagnosis of COVID-19, accounting for 33% of the total COVID-19 diagnoses made in our Reference Area.

The mean age of the patients was 68 years; however, 83% were over 50 years old, 16% were 30–49 years old and 1% were under 30 years old. The median stay was 13 days; 80% of the patients had some type of comorbidity; 9·9% required admission to the ICU; and 17% died. Table 1 shows the demographic, clinical, pharmacological, laboratory, and respiratory support characteristics of the patients studied.

Table 1
Demographic, clinical, pharmacological, laboratory, and respiratory support characteristics of patients with COVID-19 admitted from 5 March to 31 May 2020

Patient characteristics	Data available	Value
Sex (female)[1]	303	155 (51·2)
Age (years)[2]	303	68 (< 1–98)
Age over 65 years[1]	303	193 (63·7%)
Admission origin HUC[1]	303	214 (70·6)
Hospital length of stay (days)[2]	303	13 (2–40)
ICU admission[1]	303	30 (9·9)
ICU length of stay (days)[2]	30	21 (1–68)
Hospital-acquired infection[1]	303	35 (11·6)
Admitted from a residential facility[1]	303	62 (20·5)
Charlson comorbidity index[2]	303	2 (0–6)
Smoker[1]	303	29 (9·6)
Respiratory disease[1]	303	31 (10·2)
Diabetes mellitus[1]	303	99 (32·7)
Kidney disease[1]	303	31 (10·2)
Hypertension[1]	303	168 (55·4)
Cardiovascular disease[1]	303	81 (26·7)
Immunodeficiency[1]	303	38 (12·5)
Obesity[1]	303	56 (18·5)
Liver disease[1]	303	7 (2·3)
Pneumonia[1]	303	187 (61·7)
Acute respiratory distress syndrome[1]	303	21 (6·9)
Cough[1]	303	165 (54·5)

1, n (%); 2, median (range); 3, mean (SD).

Patient characteristics	Data available	Value
Fever (> 37·6ºC)[1]	303	171 (56·4)
Dyspnoea[1]	303	149 (49·2)
Myalgia[1]	303	91 (30)
Headache[1]	303	25 (8·3)
Nausea[1]	303	23 (7·6)
Abdominal pain[1]	303	13 (4·3)
Diarrhoea[1]	303	52 (17·2)
Antibiotic treatment[1]	303	303 (100)
Antiviral treatment with lopinavir and ritonavir [1]	303	184 (60·7)
Treatment with interferon[1]	303	78 (25·7)
Treatment with hydroxychloroquine[1]	303	215 (71·6)
Non-invasive mechanical ventilation[1]	303	32 (10·6)
Invasive mechanical ventilation[1]	303	15 (5·0)
Leukocytes (10^3/mm^3)[3]	296	7·7 (5·0)
Neutrophils (%)[3]	296	69·9 (14·1)
Lymphocytes (%)[3]	296	20·8 (13·6)
Platelet count (103/mm3)[3]	296	228·5 (109·0)
Haemoglobin (g /dL)[3]	295	12·8 (2·0)
Activated partial thromboplastin time (sec)[3]	44	33·6 (13·3)
Prothrombin activity (%)[3]	278	81·9 (22·7)
Prothrombin time (%)[2]	194	1·1 (0·8-289·0)
D-dimer (ng/mL) [2]	242	845 (161 – 55,220)
Albumin (g/dL)[3]	141	3·5(0·7)

1, n (%); 2, median (range); 3, mean (SD).

Patient characteristics	Data available	Value
Alanine aminotransferase (U/L)[2]	277	22 (2-307)
Aspartate aminotransferase (U/L)[2]	279	25 (7-298)
Total bilirubin (mg/dL)[3]	51	0·6 (0·5)
Serum creatinine (mg/dL)[3]	293	1·0 (0·6)
Lactate dehydrogenase (U/L)[3]	226	290·0 (124·6)
Troponin (ng/mL)[2]	24	39·1 (5·0-433·0)
Procalcitonin (ng/mL)[2]	175	0·06 (0·02–77·60)
Interleukin 6 (pg/mL)[2]	14	30·3 (1·7-379·0)
Erythrocyte sedimentation rate (mm/h)[2]	6	35 (5-112)
C-Reactive Protein (mg/L)[2]	280	38·7 (0·2-633·0)
1, n (%); 2, median (range); 3, mean (SD).		

In the comparisons between survivors and non-survivors, we observed significant differences among the non-survivors for the following variables: age, age over 65 years, hospital-acquired infection, admission from a residential facility, chronic respiratory disease, arterial hypertension, chronic cardiovascular disease, immunodeficiency, pneumonia, acute respiratory distress, dyspnoea, headache, and non-invasive mechanical ventilation (Table 2).

Table 2
Demographic, clinical, and respiratory support characteristics compared by outcome (survivors and non-survivors)

Patient characteristics	Data available	Outcome n (value with respect to the outcome)	
		Non-survivors (51)	Survivors (252))
Sex (female)[1]	303	29 (56·9)	126 (50·0)
Age (years)[2]	303	80 (34–98)	68 (< 1–98)
Age over 65 years[1]	303	43 (84·3)	150 (59·5)
ICU admission[1]	30	3 (5·9)	27 (10·7)
ICU length of stay (days)[2]	303	27 (5–68)	20 (1–65)
Hospital-acquired infection[1]	303	9 (17·6)	26 (10·3)
Admitted from a residential facility[1]	303	14 (27·4)	48 (19·0)
Smoker[1]	303	4 (7·8)	25 (9·9)
Respiratory disease[1]	303	8 (15·6)	23 (9·2)
Diabetes mellitus[1]	303	17 (33·3)	82 (32·5)
Kidney disease[1]	303	9 (17·6)	22 (8·7)
Hypertension[1]	303	34 (66·7)	134 (53·2)
Cardiovascular disease[1]	303	22 (43·1)	59 (23·4)
Immunodeficiency[1]	303	10 (19·6)	28 (11·1)
Obesity[1]	303	12 (23·5)	44 (17·4)
Liver disease[1]	303	1 (1·9)	6 (2·4)
Pneumonia[1]	303	38 (74·5)	149 (59·1)
Acute respiratory distress syndrome[1]	303	8 (15·6)	13 (5·2)

1 n(%) compared using Pearson's chi-square test or Fisher's exact test.

2 median (range) compared using Mann-Whitney U test.

Patient characteristics	Data available	Outcome n (value with respect to the outcome)	
		Non-survivors (51)	Survivors (252))
Cough[1]	303	24 (47·0)	141 (56·0)
Fever (> 37·6ºC)[1]	303	28 (55·0)	136 (54·0)
Dyspnoea[1]	303	36 (70·6)	113 (44·8)
Myalgia[1]	303	17 (33·3)	83 (32·9)
Headache[1]	303	1 (1·9)	24 (9·5)
Nausea[1]	303	4 (7·8)	19 (7·5)
Abdominal pain[1]	303	3 (5·9)	10 (3·9)
Diarrhoea[1]	303	8 (15·7)	44 (17·5)
Non-invasive mechanical ventilation[1]	303	12 (23·5)	20 (7·9)
Invasive mechanical ventilation[1]	303	4 (7·8)	11 (4·4)
1 n(%) compared using Pearson's chi-square test or Fisher's exact test. 2 median (range) compared using Mann-Whitney U test.			

Regarding the comparison of laboratory test results between survivors and non-survivors, by out-of-range frequency, we found statistically significant differences ($p < 0·05$) among deceased patients for the following variables: leukocytes, neutrophils, lymphocytes, platelets, haemoglobin, prothrombin activity, D-dimer, albumin, aspartate aminotransferase, creatinine serum, lactate dehydrogenase, procalcitonin, and C-reactive protein (Table 3).

Table 3
Laboratory test results on admission compared by outcome (survivors and non-survivors)

Parameter (Normal range)	Results available	Parameters out of range n (% of results available, by outcome)	
		Non-survivors (51)	Survivors (252))
Leukocytes ($4·50 - 11·0 \times 10^3/mm^3$)	296	26 (52·0)	65 (26·4)
Neutrophils (50·0–66·0%)	296	45 (90·0)	148 (60·2)
Lymphocytes (25·0–45·0%)	296	48 (96·0)	157 (63·8)
Platelet count ($150–400 \times 10^3/mm^3$)	296	19 (38·0)	66 (26·8)
Haemoglobin (12·0–16·0 g/dL)	295	24 (48·0)	87 (35·5)
Activated partial thromboplastin time (24·0–38·0 sec)	44	1 (16·7)	8 (21·1)
Prothrombin activity (70·0-100·0%)	278	20 (43·5)	37 (15·9)
Prothrombin time (11·0–13·5 sec)	194	32 (97·0)	161 (100·0)
D-dimer (< 500 ng/mL)	242	37 (94·9)	144 (70·9)
Albumin (3·8 – 5·4 g/dL)	141	18 (90·0)	68 (56·2)
Alanine aminotransferase (5–40 U/L)	277	12 (26·1)	54 (23·4)

* Relative frequencies compared using Pearson's chi-square test or Fisher's exact test.

Parameter (Normal range)	Results available	Parameters out of range n (% of results available, by outcome)	
		Non-survivors (51)	Survivors (252))
Aspartate aminotransferase (5–40 U/L)	279	16 (34·0)	55 (23·7)
Total bilirubin (0·10 – 1·10 mg/dL)	51	2 (20·0)	5 (12·2)
Serum creatinine (0·1–1·0 mg/dL)	293	23 (46·0)	56 (23·0)
Lactate dehydrogenase (135–225 U/L)	226	33 (94·3)	118 (61·8)
Troponin (< 5 pg/mL)	24	5 (100·0)	17 (89·5)
Procalcitonin (< 0·5 ng/mL)	175	12 (42·9)	15 (10·2)
Interleukin 6 (7 pg/mL)	14	5 (100·0)	7 (77·8)
Erythrocyte sedimentation rate (5–20 mm/h)	6	1 (33·3)	2 (66·7)
C-Reactive Protein (< 3 mg/L)	280	45 (95·7)	199 (85·4)
* Relative frequencies compared using Pearson's chi-square test or Fisher's exact test.			

The significant values reported in Tables 2 and 3 were candidate items for the risk-of-death scale for hospitalised patients with COVID-19.

The multivariate models showed that predictors of death retain were age, cardiovascular disease, pneumonia, acute respiratory distress, dyspnoea, non-invasive mechanical ventilation, and prothrombin, D-dimer, and lactate dehydrogenase activity levels. See Table 4 for the results of adjusting the univariate and by block multivariate binary logistic regression.

Table 4
Results of fitting the univariate and multivariate binary logistic regression models

Factor	Univariated model		Multivariated model**		
	OR (95% CI)	p-value	b_i	OR (95%CI)	p-Valor
Age over 65 years[1]	3·66 (1·65 – 8·10)	0·001	1·42	4·15 (1·21 – 8·23)	0,008
Hospital-acquired infection	1·86 (0·81 – 4·26)	0·140	0·48	1·62 (0·66 – 4·01)	0,293
Admitted from a residential facility	1·61 (0·81 – 3·21)	0·178	0·51	1·66 (0·78 – 3·51)	0,186
Respiratory diseases	1·85 (0·78 – 4·41)	0·164	0·6	1·81 (0·73 – 4·52)	0,201
Hypertension	1·76 (0·94 – 3·31)	0·079	0·28	1·33 (0·68 – 2·60)	0,405
Cardiovascular disease	2·48 (1·33 – 4·64)	0·004	0·78	2·19 (1·11 – 4·31)	0,024
Immunodeficiency	1·95 (0·88 – 4·32)	0·099	0·61	1·83 (0·79 – 4·27)	0,159
Pneumonia	2·02 (1·03–3·98)	0·04	0·88	2·41 (1·17 – 4·96)	0,017
Acute respiratory distress syndrome	3·42 (1·34 – 8·74)	0·010	2·64	14·09 (1·95 – 23·88)	0,009
Dyspnoea	2·95 (1·54 – 5·66)	0·001	0·98	2·68 (1·48 – 9·61)	0,013
Headache	0·19 (0·02 – 1·44)	0·108	-1·43	0·24 (0·03 – 1·86)	0,171
Non-invasive mechanical ventilation	3·57 (1·62 – 7·88)	0·002	2·09	8·11 (1·10– 14·51)	0,040
Leukocytes out of range	3·02 (1·62 – 5·62)	0·001	0·71	2·03 (0·67 – 6·16)	0,209
Neutrophils out of range	5·96 (2·28 – 15·5)	< 0·001	0·34	1·40 (0·24 – 5·26)	0,708
Lymphocytes out of range	13·6 (3·23 – 17·3)	< 0·001	1·74	5·71 (0·61 – 11·0)	0,125

** Multivariate models adjusted in maximum sequences of four factors.

b_i Regression coefficient

Factor	Univariated model		Multivariated model**		
	OR (95% CI)	p-value	b_i	OR (95%CI)	p-Valor
Platelet count out of range	1·67 (0·88 – 3·16)	0·114	0·62	1·86 (0·63 – 5·53)	0,262
Haemoglobin out of range	1·67 (0·91 – 3·10)	0·099	-0·07	0·93 (0·31 – 2·85)	0,905
Prothrombin activity out of range	4·05 (2·05–8·01)	< 0·001	1·61	4·99 (1·32 – 9·90)	0,018
D-Dimer out of range	7·58 (1·77 – 12·50)	0·006	2·03	7·62 (1·78 – 13·7)	0,006
Albumin out of range	7·01 (1·56 – 16·6)	0·011	1·42	4·13 (0·80 – 9·4)	0,090
Aspartate aminotransferase out of range	1·66 (0·85 – 3·26)	0·141	-0·77	0·46 (0·14 – 1·55)	0,213
Serum creatinine out of range	2·84 (1·51 – 5·35)	0·001	0·72	2·05 (0·67 – 6·26)	0,210
Lactate dehydrogenase out of range	10·21 (2·38 – 19·81)	0·002	0·55	1·74 (1·32 – 3·60)	0,042
Procalcitonin out of range	6·60 (2·63 – 16·55)	< 0·001	2·58	13·19 (3·27 – 21·29)	< 0,001
C- Reactive Protein out of range	3·84 (0·89 – 16·60)	0·071	1·14	3·13 (0·63 – 6·21)	0,109

** Multivariate models adjusted in maximum sequences of four factors.

b_i Regression coefficient

The subsample available for the risk-of-death score analysis derived from the multivariate regression consisted of 142 patients, of whom 19 died (see Table 5). With these data, we plotted the ROC Type II curve to identify the best cut-off point for high risk of death at 68 days of admission (Fig. 1). According to Youden's index (see bottom of Table 5), the most balanced cut-off point for the score was 7, such that patients scoring 0–6 points were at low risk of death and those scoring 7–17 were at high risk of death. The ROC curve for the derived scale showed an area under the curve of 0·872 ($p < 0·001$). For the cut-off point of 7, sensitivity was 79% and specificity was 81%. Considering the COVID-19 hospital mortality rate of 17% observed in the study sample, the cut-off point of 7 showed a positive predictive value of 39%, a negative predictive value of 96%, and positive odds ratio 4·16 (see bottom of Fig. 1).

Table 5
Construction of the risk-of-death score for patients hospitalised with COVID-19 derived from the multivariate logistic regression coefficients that attain statistical significance $p \leq 0{\cdot}05$

Prognostic factor	b_i	Condition	Points	Condition	Points
Age over 65 years	1·42	Age under 65 years	0	65 years or over	1
Cardiovascular disease	0·68	No history	0	Yes	1
Pneumonia	0·88	Absent	0	Present	1
Acute respiratory distress syndrome	2·64	Absent	0	Present	3
Dyspnoea	0·98	Absent	0	Present	1
Non-invasive mechanical ventilation	2·09	Not applied	0	Applied	2
Prothrombin activity	1·61	70–100%	0	< 70 or > 100%	2
D-Dimer	2·03	< 500 ng/ml	0	≥ 500 ng/mL	2
Lactate dehydrogenase	0·55	135–225 U/L	0	< 135 or > 225 U/L	1
Procalcitonin	2·58	< 0·5 ng/mL	0	≥ 0·5 ng/mL	3
Total score	—	(minimum)	0	(maximum)	17
Assessment of the risk of death according to Yuden's criteria: 0–6 low, 7–17 high.					

The validation cohort consisted of 31 patients who had all the necessary data to calculate the COVID-19 risk-of-death score. In this sample, 81% were older than 65 years, 55% were male, none was admitted to the ICU, 32% had chronic cardiovascular disease, 42% developed dyspnoea, 55% pneumonia, 3% acute respiratory distress syndrome, 3% required non-invasive mechanical ventilation and 16% (5 patients) died. When we applied the cut-off point of 7 for patients who scored 7–17 points (high risk-of-death category), we obtained a sensitivity and specificity of 100% and 92%, respectively, a positive predictive value of 71% and a negative predictive value of 100%.

The sensitivity, specificity, and positive and negative predictive values for each possible cut-off point in the score are provided in a table in order to select the most appropriate value in different use cases (see bottom of Fig. 1).

Discussion

Through this study, we have developed and validated a scoring system to predict the risk of death in patients hospitalised with COVID-19, based on ten clinical and laboratory variables. To date, many studies have been published on mortality risk factors in COVID-19 patients,[11,12,13,14,15,16] but as far as we

know, none of them proposes a score to assess the probability of death at the time of admission. Zhang et al proposed a disease severity predictive score based on five parameters to guide treatment strategies at early stages of the disease.[17].Our proposed score is based on a combination of clinical and laboratory variables to help identify patients in whom we should focus therapeutic and support efforts to try to prevent death.

In our study, 33% of patients with COVID-19 required hospital admission and of these, 10% needed ICU admission. These results corroborate the findings of Guan[7] and Colaneri,[18] which confirms the representativeness of our referral cohort.

Of the ten items in our predictive model, the greatest weight was attributed to respiratory distress, the use of non-invasive mechanical ventilation, and laboratory values of procalcitonin, D-dimer, and prothrombin activity.

The development of acute respiratory distress as a complication of COVID-19 infection constitutes a predictor of death in the study by Zhou et al[15] with a prevalence that doubles the prevalence found in our cohort.

The use of mechanical ventilation as adjunctive treatment for severe respiratory failure derived from COVID-19 infection was found to be a predictor of mortality in studies by Zhou et al, Peng et al and Rong Hui et al,[15,19,20] with a prevalence of 44%, 42% and 47·6% respectively in the non-survival groups, however it was not retained as a factor in their risk-of-death scales in the multivariate analyses. In our cohort, the use of mechanical ventilation was a predictor of mortality and had a prevalence of 23·5% among the non-survivors.

Increasing procalcitonin levels is indicative of the involvement of secondary bacterial infections. In the study by Zhou et al,[15] elevated procalcitonin was detected in 25% of non-survivors compared to 1% of survivors, although this laboratory value was not retained as a factor in their risk-of-severity scale in their multivariate analysis. In a study by Chen et al,[21] procalcitonin was also an independent risk factor associated with death from COVID-19, while in a study by Hui et al,[20] no difference was found between survivors and non-survivors. In our study, abnormally high levels of procalcitonin were observed in about half of the non-survivors.

Many studies have found elevated D-dimer to also be an independent risk factor associated with death from COVID-19,[5,15,20,21,22,23] and, indeed, we found abnormally high levels in 95% of non-survivors.

The score that we have derived presents acceptable metric characteristics with a proposed cut-off point with well-balanced sensitivity and specificity, and the possibility of other cut-off points that can be used to increase specificity for screening.

The main limitation of our study is the missing laboratory results for some patients on admission in the referral cohort. The results of all laboratory tests performed during the hospital stay were collected during

the follow-up process, but for the purpose of obtaining the risk-of-death score, only those available at the time of admission were used. The low frequency of indication of laboratory determinations that could not be used in the analyzes due to their scarcity points to the appreciation of their low usefulness in the assessment of the status of patients with COVID-19 by the doctors who attended the cases, which that could justify his absence.

Another limitation that affects our results is the small number of non-survivors in the referral cohort which prevented us from using a single-stage multivariate regression model. As a result, we may have missed interactions between candidate score factors that could be important predictors of mortality. The strategy of using blocks by type of variable with the maximum number of factors allowed to avoid over-saturation of the models and their subsequent combination, although it does not allow the identification of interactions between factors, does not leave out any of the scores with predictive power independent on mortality.

We also identified as a limitation of the score that the risk of dying with respect to age should be more graduated for this component of the score because we know that it is higher with each year of age in older people. The decision to estimate the risk for people over 65 years of age in the score instead of estimating it for each year after that age, or groups of 5 more years after that age, for example, is based on obtaining a score with maximum simplicity of use, an objective that would have been hampered if its exit score depended on the age of the patient.

In conclusion, we believe this risk-of-death scoring system for patients hospitalized with COVID-19 may offer clinicians a simple and reproducible tool to classify those subsidiary patients of respiratory support with high flow or mechanical ventilation and the use of certain treatments indicated in patients with moderate - severe disease, thereby guiding early treatment, prioritizing therapeutic efforts, and optimizing health resources[24] both in intensive care and on the ward.

More studies are needed to contrast the efficacy of the scoring system with larger patient cohorts.

References

Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. N Engl J Med. 2020;382:1199–207.

Internet WHO.WHO characterizes COVID-19 as a pandemic. Published at March 13. 2020.https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen.

Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China*Lancet*. 2020;395(10223):497–506.

Deng Y, Liu W, Liu K, et al. Clinical characteristics of fatal and recovered cases of coronavirus disease 2019 in Wuhan, China: a retrospective study. Chin Med J (Engl). 2020;133(11):1261–7.

Chen T, Wu D, Chen H, Yan W, Yang D, Chen G. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020. 368.

Wang Y, Lu X, Li Y, et al. Clinical Course and Outcomes of 344 Intensive Care Patients with COVID-19. Am J Respir Crit Care Med. 2020;201(11):1430–4.

Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

Liang WH, Guan WJ, Li CC, et al. Clinical characteristics and outcomes of hospitalised patients with COVID-19 treated in Hubei (epicentre) and outside Hubei (non-epicentre): a nationwide analysis of China. Eur Respir J. 2020;55(6):2000562.

Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985.

Internet. Actualización Nº216, Enfermedad por COVID-19. Publicado el 28 de Septiembre de 2020. https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_216_COVID-19.pdf.

Gong J, Ou J, Qiu X, et al. A Tool for Early Prediction of Severe Coronavirus Disease 2019 (COVID-19): A Multicenter Study Using the Risk Nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020;71(15):833–40.

Liu J, Liu Y, Xiang P, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18(1):206.

Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China [published online ahead of print, 2020 Feb 7]. JAMA. 2020;323(11):1061–9.

Yang AP, Liu JP, Tao WQ, Li HM. The diagnostic and predictive role of NLR, d-NLR and PLR in COVID-19 patients. Int Immunopharmacol. 2020;84:106504.

Zhou F, Yu T, Du R, 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(10229):1054–62.

Berenguer J, Ryan P, Rodríguez-Baño J, et al. Characteristics and predictors of death among 4·035 consecutively hospitalized patients with COVID-19 in Spain. *Clin Microbiol Infect*. 2020;S1198-743 × (20)30431-6.

Zhang C, Qin L, Li K, et al. A Novel Scoring System for Prediction of Disease Severity in COVID-19. Front Cell Infect Microbiol. 2020;10:318.

Colaneri M, Sacchi P, Zuccaro V, et al. Clinical characteristics of coronavirus disease (COVID-19) early findings from a teaching hospital in Pavia, North Italy, 21 to 28 February 2020. Euro Surveill. 2020;25(16).

Xu PP, Tian RH, Luo S, et al. Risk factors for adverse clinical outcomes with COVID-19 in China: a multicenter, retrospective, observational study. Theranostics. 2020;10(14):6372–83.

Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5):2000524.

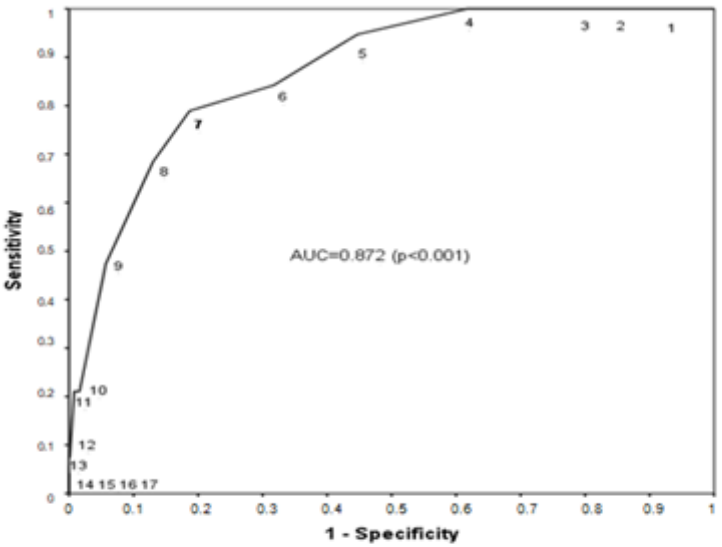
Chen R, Liang W, Jiang M, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. Chest. 2020;158(1):97–105.

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.2020.2648.

Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and Antiphospholipid Antibodies in Patients with COVID-19. N Engl J Med. 2020;382(17):e38.

Laure Wynants B, Van Calster GS, Collins RD, Riley G, Heinze E, Schuit, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal.BMJ. 2020; 369.

Figures



* The best cut-off point according to Youden's criteria is a score of 7.

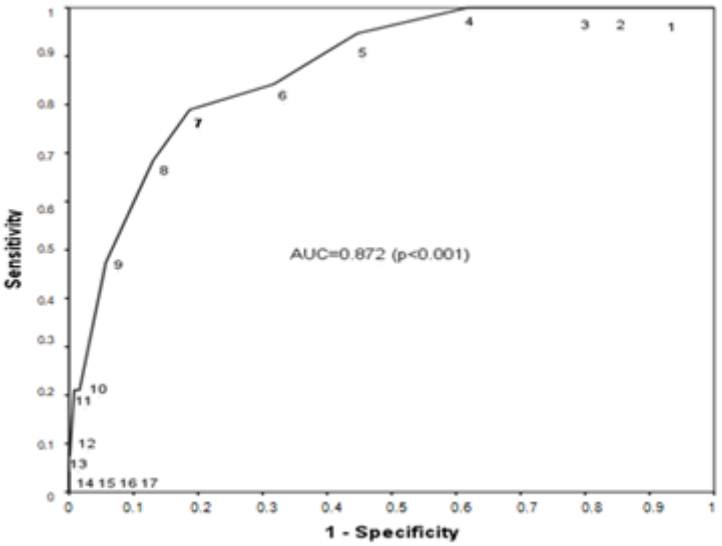
Metric properties of the risk-of-death score at different cut-off points

Cut-off point equal to or greater than	Sensitivity (%)	Specificity (%)	Positive predictive value (%)*	Negative predictive value (%)*
0	100	0	---	---
1	100	2·4	13·7	100
2	100	7·3	14·3	100
3	100	15·4	15·4	100
4	100	38·2	20·0	100
5	94·7	55·3	24·7	98·6
6	84·2	68·3	29·1	96·6
7	78·9	81·3	39·5	96·2
8	68·4	87·0	44·8	94·7
9	47·4	94·3	56·3	92·1
10	21·1	98·4	66·7	89·0
11	21·1	99·2	80·0	87·7
12	5·3	99·5	88·9	87·2
13	2·1	99·8	96·3	86·6
14	0·0	100	100	0·0
15	0·0	100	100	0·0
16	0·0	100	100	0·0
17	0·0	100	100	0·0

*Estimated with the 17% mortality rate observed in the referral cohort.

Figure 1

ROC type II curve of the risk-of-death score of patients hospitalised with COVID-19 at 68 days of admission *



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