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

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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 and worldwide, with WHO characterising COVID-19 as a pandemic in March 2020.

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.

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 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.

Mortality from COVID-19 has reached rates of 11.6%, 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 \( p \leq 0.20 \) 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 \( (p \leq 0.05) \) 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 (> 37.6°C)                                            | 303            | 171 (56.4)     |
| Dyspnoea                                                    | 303            | 149 (49.2)     |
| Myalgia                                                     | 303            | 91 (30)        |
| Headache                                                    | 303            | 25 (8.3)       |
| Nausea                                                      | 303            | 23 (7.6)       |
| Abdominal pain                                              | 303            | 13 (4.3)       |
| Diarrhoea                                                   | 303            | 52 (17.2)      |
| Antibiotic treatment                                        | 303            | 303 (100)      |
| Antiviral treatment with lopinavir and ritonavir            | 303            | 184 (60.7)     |
| Treatment with interferon                                   | 303            | 78 (25.7)      |
| Treatment with hydroxychloroquine                           | 303            | 215 (71.6)     |
| Non-invasive mechanical ventilation                         | 303            | 32 (10.6)      |
| Invasive mechanical ventilation                             | 303            | 15 (5.0)       |
| Leukocytes (10^3/mm^3)^3                                     | 296            | 7.7 (5.0)      |
| Neutrophils (%)                                             | 296            | 69.9 (14.1)    |
| Lymphocytes (%)                                             | 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).
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).
| Patient characteristics                                      | Data available | Outcome n (value with respect to the outcome) | Non-survivors (51) | Survivors (252) |
|---------------------------------------------------------------|----------------|-----------------------------------------------|--------------------|-----------------|
| Sex (female)                                                  | 303            |                                               | 29 (56·9)          | 126 (50·0)      |
| Age (years)                                                  | 303            |                                               | 80 (34–98)         | 68 (< 1–98)     |
| Age over 65 years                                             | 303            |                                               | 43 (84·3)          | 150 (59·5)      |
| ICU admission                                                 | 30             |                                               | 3 (5·9)            | 27 (10·7)       |
| ICU length of stay (days)                                     | 303            |                                               | 27 (5–68)          | 20 (1–65)       |
| Hospital-acquired infection                                   | 303            |                                               | 9 (17·6)           | 26 (10·3)       |
| Admitted from a residential facility                          | 303            |                                               | 14 (27·4)          | 48 (19·0)       |
| Smoker                                                        | 303            |                                               | 4 (7·8)            | 25 (9·9)        |
| Respiratory disease                                           | 303            |                                               | 8 (15·6)           | 23 (9·2)        |
| Diabetes mellitus                                             | 303            |                                               | 17 (33·3)          | 82 (32·5)       |
| Kidney disease                                                | 303            |                                               | 9 (17·6)           | 22 (8·7)        |
| Hypertension                                                  | 303            |                                               | 34 (66·7)          | 134 (53·2)      |
| Cardiovascular disease                                        | 303            |                                               | 22 (43·1)          | 59 (23·4)       |
| Immunodeficiency                                              | 303            |                                               | 10 (19·6)          | 28 (11·1)       |
| Obesity                                                       | 303            |                                               | 12 (23·5)          | 44 (17·4)       |
| Liver disease                                                 | 303            |                                               | 1 (1·9)            | 6 (2·4)         |
| Pneumonia                                                     | 303            |                                               | 38 (74·5)          | 149 (59·1)      |
| Acute respiratory distress syndrome                           | 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<sup>1</sup>                            | 303            | 24 (47·0)                                    | 141 (56·0)         |
| Fever (&gt; 37·6°C)<sup>1</sup>              | 303            | 28 (55·0)                                    | 136 (54·0)         |
| Dyspnoea<sup>1</sup>                         | 303            | 36 (70·6)                                    | 113 (44·8)         |
| Myalgia<sup>1</sup>                          | 303            | 17 (33·3)                                    | 83 (32·9)          |
| Headache<sup>1</sup>                         | 303            | 1 (1·9)                                      | 24 (9·5)           |
| Nausea<sup>1</sup>                           | 303            | 4 (7·8)                                      | 19 (7·5)           |
| Abdominal pain<sup>1</sup>                   | 303            | 3 (5·9)                                      | 10 (3·9)           |
| Diarrhoea<sup>1</sup>                        | 303            | 8 (15·7)                                     | 44 (17·5)          |
| Non-invasive mechanical ventilation<sup>1</sup> | 303              | 12 (23·5)                                    | 20 (7·9)           |
| Invasive mechanical ventilation<sup>1</sup>  | 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                              | Results available | Parameters out of range n (% of results available, by outcome) |
|----------------------------------------|-------------------|---------------------------------------------------------------|
| (Normal range)                         |                   | Non-survivors (51) Survivors (252))                          |
| Leukocytes (4·50 – 11·0 × 10³/mm³)     | 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 × 10³/mm³)    | 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  | 44                | 1 (16·7) 8 (21·1)                                           |
| (24·0–38·0 sec)                        |                   |                                                               |
| 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) |
|--------------------------|-------------------|-------------------------------------------------------------|
| Aspartate aminotransferase (5–40 U/L) | 279 | 16 (34·0) Non-survivors (51) 55 (23·7) Survivors (252) |
| Total bilirubin (0·10 – 1·10 mg/dL) | 51 | 2 (20·0) |
| Serum creatinine (0·1–1·0 mg/dL) | 293 | 23 (46·0) Non-survivors (51) 56 (23·0) Survivors (252) |
| Lactate dehydrogenase (135–225 U/L) | 226 | 33 (94·3) Non-survivors (51) 118 (61·8) Survivors (252) |
| Troponin (< 5 pg/mL) | 24 | 5 (100·0) Non-survivors (51) 17 (89·5) Survivors (252) |
| Procalcitonin (< 0·5 ng/mL) | 175 | 12 (42·9) Non-survivors (51) 15 (10·2) Survivors (252) |
| Interleukin 6 (7 pg/mL) | 14 | 5 (100·0) Non-survivors (51) 7 (77·8) Survivors (252) |
| Erythrocyte sedimentation rate (5–20 mm/h) | 6 | 1 (33·3) Non-survivors (51) 2 (66·7) Survivors (252) |
| C-Reactive Protein (< 3 mg/L) | 280 | 45 (95·7) Non-survivors (51) 199 (85·4) Survivors (252) |

* 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<sub>i</sub> | OR (95% CI) | p-value |
| Age over 65 years<sup>1</sup>               | 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<sub>i</sub>, Regression coefficient
| Factor                              | Univariated model          | Multivariated model** |
|------------------------------------|---------------------------|-----------------------|
|                                    | OR (95% CI)               | *p*-value | *b*   | OR (95% CI) | *p*-value |
| 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  | 1.66 (0.85 – 3.26)        | 0.141       | -0.77 | 0.46 (0.14 – 1.55) | 0.213 |
| range                              |                           |            |       |              |          |
| 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* 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 \( p \leq 0.05 \)

| 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      | \( \geq 500 \text{ ng/mL} \)     | 2      |
| Lactate dehydrogenase                    | 0.55      | 135–225 U/L                      | 0      | < 135 or > 225 U/L               | 1      |
| Procalcitonin                            | 2.58      | < 0.5 ng/mL                       | 0      | \( \geq 0.5 \text{ ng/mL} \)     | 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,\textsuperscript{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.\textsuperscript{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\textsuperscript{7} and Colaneri,\textsuperscript{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\textsuperscript{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,\textsuperscript{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,\textsuperscript{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,\textsuperscript{21} procalcitonin was also an independent risk factor associated with death from COVID-19, while in a study by Hui et al,\textsuperscript{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,\textsuperscript{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\textsuperscript{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.

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**Figures**
Figure 1

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

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            | 68.7                          | 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.