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Identification of Factors and Development of a Clinical Risk Score to Predict Mortality in Critically Ill Patients with COVID-19

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ABSTRACT

OBJECTIVES: To identify factors influencing the mortality risk in critically ill patients with COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit (ICU).

DESIGN: A multicenter cohort study

SETTING AND PARTICIPANTS: 1542 patients with COVID-19 admitted to ICUs in public hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.

MAIN OUTCOMES AND MEASURES: The primary outcome was time from ICU admission until death. We used competing risk regression models and Least Absolute Shrinkage and Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the score was assessed by the area under the receiver operating characteristic curve (AUC), and the Brier score using 500 bootstraps replications.

RESULTS: Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged, and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95% confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven factors associated with mortality, and included in the risk score: age (adjusted hazard ratio [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31), lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI, 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95% CI, 0.63–0.78), and oxygen saturation (SpO_2) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed a freely available web-based risk calculator (https://icumortalityrisk.shinyapps.io/ICUrisk/).

CONCLUSION: In critically ill patients with COVID-19, we identified factors associated with mortality, and developed a risk prediction tool that showed high predictive ability. This tool may

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have utility in clinical settings to guide decision-making, and may facilitate the identification of supportive therapies to improve outcomes.

Key words: COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical care

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Strengths and limitations of this study

- Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of mortality, and to the best of our knowledge, no study has yet reported the prediction of mortality among these patients.
- The risk prediction score includes clinical features which are readily available at ICU admission, thus amplifying its clinical applicability.
- A major limitation is the generalizability of risk prediction score in other settings, and external validation of our risk prediction score in other populations is the next step in the model development.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 79 million patients, and more than 1.7 million have died, as of November 1st, 2020[1]. A wide spectrum of clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure leading to hospital admission and death[2 3].

The preventive and treatment challenge of COVID-19 is very high because of the complexity of its transmission, substantial heterogeneity in the progression of disease, and lack of proven treatment[4 5]. Several studies have attempted to address this by predicting clinical outcomes using statistical association analyses or prediction model development methods in order to guide the management and prognostication of patients with COVID-19[6-11]. Based on patient characteristics at the time of hospital admission, Liang et al.[7] proposed a risk score to predict critical illness defined as a composite of intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, various demographics, clinical and hospital level risk factors have been reported to be associated with death in patients admitted to ICU[8].

Earlier studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases ranging between 2% and 81%[12-14], and high mortality prevalence among ICU patients ranging between 5% and 83%[3 14 15]. A meta-analysis of twenty-five studies with 24,677 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence among patients admitted to ICU with a severe form of COVID-19[14].

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To the best of our knowledge, no study has yet reported the prediction of death in patients admitted to ICU with confirmed COVID-19. Therefore, the aim of the present study is to identify the risk factors and the set of clinical markers that increase the risk of death among ICU admitted COVID-19 patients, and develop a risk prediction score that may facilitate the identification of supportive therapies to improve outcomes.

METHODS

Study design and Data sources

This is a multicenter cohort study in which data of all laboratory confirmed COVID-19 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical records. We considered patients who were admitted to a regular ICU room or to a high-dependency unit (HDU) or if they were consistently receiving any form of oxygen therapy during their hospital stay in a make-shift ICU. Patients with available data on important clinical characteristics at the date of ICU admission such as laboratory findings and vitals, in addition to demographics and medical history were included. The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Patient and Public Involvement:

Due to unprecedented scenario of COVID-19 pandemic, it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

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Outcomes

The primary outcome of this study is the survival time defined as the duration of time, from the date of ICU admission, until the date of death. Patients still hospitalized at the date of data extraction were considered as right censored and those discharged alive from the hospital were considered as competing events to death due to COVID-19.

Statistical Analyses

Baseline characteristics were summarized using descriptive statistics including mean and standard deviation for continuous measures, and frequencies tables for categorical variables. We compared categorical variables using the chi-square or Fisher's exact test, and continuous variables using the unpaired t-test or its non-parametric equivalent (Wilcoxon rank sum test) in case the normality assumption is violated.

We used the competing risk regression model to investigate the association between death due to COVID-19 and all potential risk factors. We have chosen to use this model, instead of the standard Cox proportional hazard model, because discharge alive or recovery is clearly a competing event to death due to COVID-19[16 17]. Ignoring this property will lead to biased estimates of the hazard ratios and the survival curves. We estimated and plotted the survival curves using the cumulative incidence function taking into account competing risks. Cumulative incidence curves of different groups were compared using the Gray's test[18] for sub-distribution hazards, an equivalent of the log-rank test in the case of competing events. We used the Fine & Gray proportional hazards regression models[19] to investigate the association between potential risk factors and the primary outcome, and also to derive the risk prediction score. All statistical analysis and

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data management carried out in this paper were done using the R software version 3.6.3 and *P*-values <0.05 were considered as statistically significant.

Potential predictive variables

We considered 36 patient's characteristics at the time of ICU admission as potential predictors based on demographics, clinical signs and symptoms, medical history and laboratory findings. Demographic variables included age and sex. Clinical signs and symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate, Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen saturation (SpO2). Medical history included status of coexisting conditions: diabetes, hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer, and liver disease. Laboratory findings included white blood cells, monocytes count, monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count, lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate dehydrogenase (LDH), ferritin, hemoglobin, hematocrit, sodium, potassium, chloride, bicarbonates, creatinine and red blood cell distribution width (RDW).

Variables selection method and derivation of the risk prediction score

We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes Information criterion (BIC) for variables selection[20 21]. This method uses a shrinking parameter to penalize non-significant coefficients of the Fine and Gray competing risk regression model. Larger shrinking parameters make the coefficients of non-significant risk factors to shrink towards zero, so that only the strongest predictors remain in the survival model. Unlike the standard selection methods, such as stepwise forward or

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backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36 potential predictors were scaled using the z-score transformation, and were entered in the selection process. The most predictive covariates were selected by choosing the shrinking parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were statistically significant were retained to construct the risk prediction score.

Validation of the risk prediction score

We derived the risk of death using the estimates obtained from the Fine & Gray competing risk regression model. The predictive ability of this proposed risk prediction score was assessed using discrimination and calibration. Discrimination refers to how well the predictive model is capable of discriminating between individuals who died and those who were discharged alive, whereas calibration refers to the agreement between observed and predicted number of deaths. Discrimination was assessed via the time-dependent area under the receiver-operator characteristic curve (AUC). Calibration was assessed via the time-dependent Brier score, and visually by plotting expected versus observed deaths. To reduce overfitting and optimism bias, we carried out internal validation of the risk prediction score by estimating the AUC and Brier score using 500 bootstraps replications. This method allows all of the original data to be used in the model development while providing insight into the extent to which the original model is overfitting or too optimistic.

We also developed an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator also provides stratification of patients into high and low risk

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categories based on an estimated cutoff risk corresponding to optimal performance measures of sensitivity and specificity.

RESULTS

Among the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%) were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the date of data extraction). Taking into account right-censored observations, the cumulative incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI, 83.54–87.26) (Figure 1).

The demographic and clinical characteristics of the patients are presented in Table 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168 (12.7%) died. Compared with patients who were discharged alive, those who died were older and had higher prevalence of diabetes, hypertension, chronic kidney disease, cardiovascular disease, and liver disease; lower diastolic blood pressure, higher respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO_2 and a higher percentage of patients requiring oxygen therapy.

The laboratory findings of these patients are presented in Table 2. Compared with patients who were discharged alive, those who died had unfavorable laboratory profile on almost all variables including levels of C-reactive protein, creatinine, LDH, red blood cell distribution width, white blood cell count, potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count, hemoglobin, hematocrit, and serum bicarbonates.

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The results of the univariate competing risk model for each of the 36 potential predictors measured at ICU admission are presented in the supplement (eTable 1). Of these 36 variables, seven statistically significant predictors of mortality were retained by the LASSO selection procedure in the multivariable competing risk regression model (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals of these significant variables are presented in Table 3. The significant predictors increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–2.31]; *P*<0.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<0.001), higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<0.001), higher respiratory rate (HR, 1.31 [95% CI, 1.15–1.49]; *P*<0.001), and high levels of creatinine (HR, 1.19 [95% CI, 1.11– 1.28]; *P*<0.001). The significant predictors lowering the risk of death included higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<0.001) and higher SpO_2 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<0.001).

The cumulative incidence function of these 7 predictors retained by LASSO in the multivariable model is shown in the supplement (eFigure 2). In case of continuous risk factors, we created a binary variable based on the median split.

Validation of the risk prediction score

The results of the internal validation using 500 bootstrap samples are shown in Figure 2. The predictive ability of the derived risk prediction score was quite promising. Indeed, regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2 also shows the calibration plot for the risk prediction score, in which the predicted frequencies of deaths were plotted against the observed ones.

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From Figure 2, it is evident that the predicted frequencies of death were very close to the observed ones suggesting a very good calibration. The risk prediction score provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%. The online risk calculator derived from the risk prediction score for the calculation of mortality in patients admitted to ICU with COVID-19 is freely available at (https://icumortalityrisk.shinyapps.io/ICUrisk/).

DISCUSSION

We developed and validated a clinical risk prediction score and a web-based risk calculator to predict the risk of death in adult patients with confirmed COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms or discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect similarity between predicted and expected deaths. We identified seven readily available clinical features at ICU admission to be used for risk prediction of mortality namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings, neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these variables in an easy-to use web-based risk calculator has the potential to accurately classify ICU admitted patients as likely to be discharged alive or die.

A major strength of this study is the relatively large number of laboratory confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk prediction score includes clinical features that are readily available at ICU admission that increases its clinical applicability. An obvious limitation of this study is the generalizability of risk prediction score in other settings, and we acknowledge that

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external validation of our risk prediction score in other populations is the next step in model development.

To the best of our knowledge, our study is the first one to provide a risk prediction score of mortality for COVID-19 patients admitted to ICU. Previous studies have reported risk prediction scores of mortality based on the clinical features at the time of hospital admission, not ICU admission, including patients with mild, moderate or severe forms of disease[6 7 9 10] Meanwhile, other statistical association analyses have been published to investigate the factors affecting mortality due to COVID-19 in patients admitted to ICU[11]. For instance, a multicenter cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted to ICU in the US identified 9 risk factors independently associated with the 28-days mortality. These risk factors included age, sex, body mass index, coronary artery disease, active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the number of hospital ICU beds[8]. The difference in the number and types of independent clinical features associated with ICU mortality between our study and others may be explained by the differences in the baseline characteristics of the population or the choice of the statistical analyses. Indeed, we have chosen to use the competing risk regression model instead of the standard Cox proportional hazard model or the logistic regression model because recovery is clearly a competing event to death due to COVID-19[16 17]. Ignoring this property will definitely lead to biased effect estimates.

A recent meta-analysis showed that more than one-fourth of patients with COVID-19 were admitted to ICU globally, and the prevalence of mortality among these patients was very high (31%)[14]. The relative high number of deaths in the ICU presents

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an enormous challenge to the prognostication and management of patients with COVID-19. We believe that the results of our study and the stratification of ICU admitted patients into high and low risk categories throughout the patient's encounter may facilitate the clinical and ICU teams to identify and promptly focus on the medications and supportive therapies to prevent deaths.

Conclusion

We developed and validated a risk tool for predicting death among COVID-19 patients admitted to ICU, which shows high predictive accuracy. This tool may have utility in clinical settings to guide decision-making, and may facilitate the identification of medications and supportive therapies to improve outcomes. To the best of our knowledge, this is the first mortality prediction model for patients admitted to ICU due to COVID-19. The parameters selected are easily available at the time of ICU admission. The freely available web-based calculator may facilitate the early identification of patients at high risk of death, and may be used as a guidance in busy ICU units to stratify patients according to their risk in order to deliver the best available supportive care.

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Author Contributions: All authors contributed to the development of the research question and study design. AO led the development of advanced statistical aspects. SA, AA, MA, RG, II, MAA and AO were involved in data specification, curation, and collection. AO did data management and statistical analyses, which were checked by SA, AA, MA, and JN. AO developed the software for the web calculator. All authors contributed to the interpretation of the results. SA, AA, JN and AO wrote the first draft of the paper. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. AO is the guarantor.
The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Data availability statement: To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the data is according to the information and rules and regulations of Abu Dhabi Health Services - SEHA and Cerner.

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Figure legends

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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Table 1. Demographics and Clinical Characteristics among Critically Ill Patients with COVID-19.

Characteristics	Total	Died	Alive	*P*-value[†]
No. (%)	1542 (100)	196 (13)	1346 (87)	
Female sex, n (%)	221 (14.3)	28 (14.3)	193 (14.3)	
Age, mean (SD), years	49.9 (12.7)	56.7 (13.3)	47.8 (12.1)	0.000
Race/ethnicity, n (%)				
Arab	373 (24.2)	55 (28.1)	318 (23.6)	
Asian	1130 (73.3)	136 (69.4)	994 (73.9)	
Other	27 (1.8)	4 (2.0)	23 (1.7)	0.376
Systolic blood pressure, mean (SD), mmHg	126.2 (17.4)	125.5 (21.1)	126.3 (16.8)	0.286
Diastolic blood pressure, mean (SD), mmHg	75.5 (12.1)	72.2 (12.5)	76.0 (12.0)	0.000
Respiratory rate, mean (SD), breaths/min	23.3 (6.7)	27.1 (7.4)	22.7 (6.4)	0.000
Oxygen saturation (SpO_2), n (%)				
<90	487 (31.6)	138 (70.4)	349 (25.9)	
90-94	569 (36.9)	39 (19.9)	530 (39.4)	
≥95	486 (31.5)	19 (9.7)	467 (34.7)	
Oxygen therapy, n (%)				
Hypoxic respiratory failure requiring supplemental oxygen	736 (47.7)	18 (9.2)	718 (53.3)	
Hypoxic respiratory failure requiring none-invasive mechanical ventilation	76 (4.9)	11 (5.6)	65 (4.8)	
Hypoxic respiratory failure requiring invasive mechanical ventilation	519 (33.7)	167 (85.2)	352 (26.2)	0.000
Coexisting conditions, n (%)	0.29 (±0.45)	0.38 (±0.49)	0.27 (±0.45)	0.006
0	498 (32.3)	39 (19.9)	459 (34.1)	
1	403 (26.1)	45 (23.0)	358 (26.6)	
≥2	641 (41.6)	112 (57.1)	529 (39.3)	0.000
Diabetes, n (%)				
No	874 (56.7)	86 (43.9)	788 (58.5)	
Yes	668 (43.3)	110 (56.1)	558 (41.5)	0.000
Hypertension, n (%)				
No	854 (55.4)	82 (41.8)	772 (57.4)	

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Characteristics	Total	Died	Alive	*P*-value[†]
Yes	688 (44.6)	114 (58.2)	574 (42.6)	0.000
Respiratory disease, n (%)				
No	1,361 (88.3)	166 (84.7)	1,195 (88.8)	
Yes	81 (11.7)	30 (15.3)	151 (11.2)	0.123
Cardiovascular Disease, n (%)				
No	1,053 (68.3)	100 (51.0)	953 (70.8)	
Yes	489 (31.7)	96 (49.0)	393 (29.2)	0.000
Chronic Kidney Disease, n (%)				
No	1,397 (90.6)	159 (81.1)	1,238 (92.0)	
Yes	145 (9.4)	37 (18.9)	108 (8.0)	0.000
Cancer, n (%)				
No	1,479 (95.9)	183 (93.4)	1,296 (96.3)	
Yes	63 (4.1)	13 (6.6)	50 (3.7)	0.083
Liver disease, n (%)				
No	1,437 (93.2)	174 (88.8)	1,263 (93.8)	
Yes	105 (6.8)	22 (11.2)	83 (6.2)	0.013
Glasgow Coma Scale, mean (SD)	13.83 (±3.42)	11.94 (±5.07)	14.28 (±2.71)	0.000
Mild, n (%)	1,391 (90.2)	121 (61.7)	1,270 (94.4)	
Moderate, n (%)	21 (1.4)	7 (3.6)	14 (1.0)	
Severe, n (%)	130 (8.4)	68 (34.7)	62 (4.6)	0.000

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.
[†]Continuous variables were compared using the t-test or Wilcoxon-rank-sum test, while categorical variables were compared using the Chi-square or Fisher's exact test.
Glasgow Coma Scale: Mild (14-15), Moderate (9-13) or Severe (3-8).

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Table 2. Laboratory Findings among Critically Ill Patients with COVID-19.

Variable	Total	Died	Alive	*P*-value
Number. (%)	1542 (100)	196 (13)	1346 (87)	
White blood cells, mean (SD), $^{x}10^{9}$/L	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	0.000
Lymphocyte count, mean (SD), $^{x}10^{9}$/L	1.28 (0.71)	0.93 (0.57)	1.33 (0.72)	0.000
Lymphocyte percent, mean (SD), %	18.76 (10.74)	10.86 (6.93)	19.92 (10.72)	0.000
Neutrophil count, mean (SD), $^{x}10^{9}$/L	6.00 (3.77)	8.85 (5.65)	5.58 (3.21)	0.000
Neutrophil percent, mean (SD), %	73.04 (13.28)	83.29 (9.96)	71.55 (13.05)	0.000
Neutrophil-lymphocyte count ratio	6.81 (9.39)	13.66 (18.16)	5.82 (6.73)	0.000
Neutrophil-lymphocyte percent ratio	6.82 (9.46)	13.69 (18.33)	5.82 (6.77)	0.000
Monocytes count, mean (SD), $^{x}10^{9}$/L	0.51 (0.36)	0.50 (0.72)	0.51 (0.28)	0.769
Monocytes percent, mean (SD), %	6.93 (3.67)	4.94 (4.99)	7.22 (3.34)	0.000
Platelet count, mean (SD), $^{x}10^{9}$/L	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $^{x}10^{12}$/L	4.75 (0.71)	4.56 (0.80)	4.78 (0.70)	0.000
Red blood cell distribution width, %	13.49 (1.60)	13.97 (1.76)	13.42 (1.56)	0.000
Hemoglobin level, mean (SD), g/L	131.90 (18.24)	126.18 (19.59)	132.73 (17.89)	0.000
Hematocrit, mean (SD), L/L	0.39 (0.05)	0.38 (0.06)	0.40 (0.05)	0.000
Creatinine level, mean (SD), µmol/L	97.76 (111.80)	149.97 (188.91)	90.15 (93.23)	0.000
C-reactive protein level, mean (SD), mg/L	102.13 (94.00)	173.05 (112.06)	91.80 (86.39)	0.000
Lactate dehydrogenase, mean (SD), IU/L	409.32 (223.16)	605.80 (291.22)	380.71 (195.74)	0.000
Serum Chloride, mean (SD), mmol/L	99.25 (4.50)	99.05 (5.97)	99.28 (4.25)	0.600
Serum bicarbonate, mean (SD), mmol/L	22.80 (3.28)	21.02 (4.23)	23.06 (3.04)	0.000
Potassium, mean (SD), mmol/L	4.05 (0.55)	4.21 (0.76)	4.03 (0.50)	0.002
Sodium, mean (SD), mmol/L	136.98 (4.36)	136.97 (5.80)	136.98 (4.11)	0.984
Ferritin, mean (SD), ng/mL	1209.37 (1374.60)	1779.63 (1930.98)	1126.33 (1252.99)	0.000

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.

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Table 3. Multivariable Adjusted Competing Risk Regression Model for Mortality.

Variables	HR (95% CI)	P-value
Age, years	1.98 (1.71 to 2.31)	<.001
Neutrophils $^{x}10^{9}$/L, percentage	1.71 (1.27 to 2.31)	<.001
Lactate dehydrogenase, IU/L	1.31 (1.15 to 1.49)	<.001
Respiratory rate, breaths/min	1.31 (1.15 to 1.49)	<.001
Glasgow Coma Scale	0.70 (0.63 to 0.78)	<.001
Oxygen saturation (SpO_2)	0.82 (0.74 to 0.91)	<.001
Creatinine, μmol/L	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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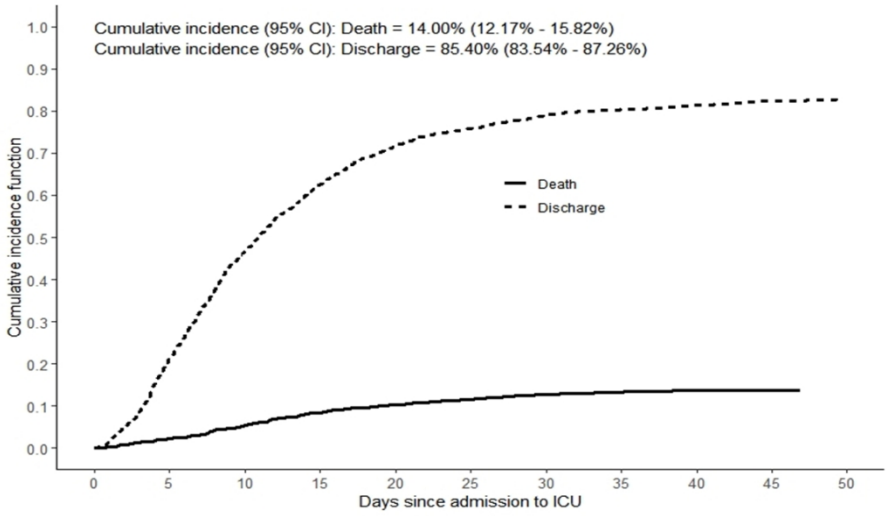

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

338x190mm (96 x 96 DPI)

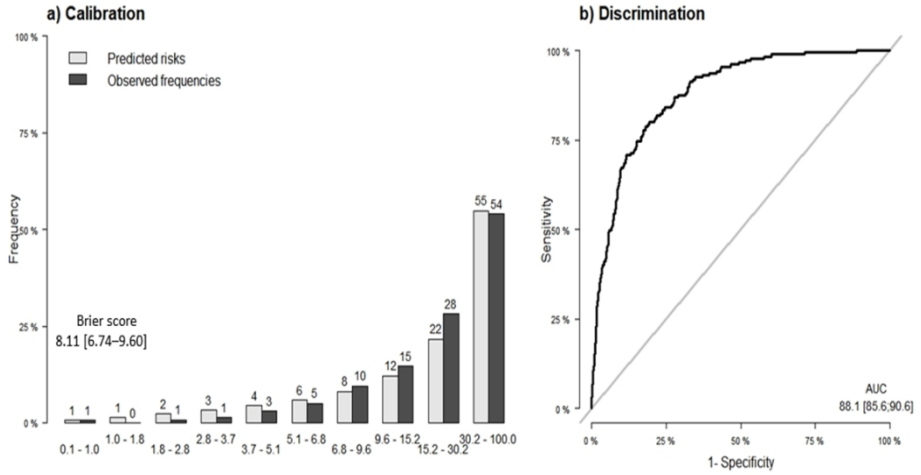

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

338x190mm (96 x 96 DPI)

Online-Only Material

Salem AlKaabi et al. Identification of Factors and Development of a Clinical Risk Score to Predict Mortality in Critically Ill Patients with COVID-19.

eTable 1. Univariate competing risk models on candidate predictors.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.

eFigure 2. Mortality curves according to risk factors retained in LASSO.

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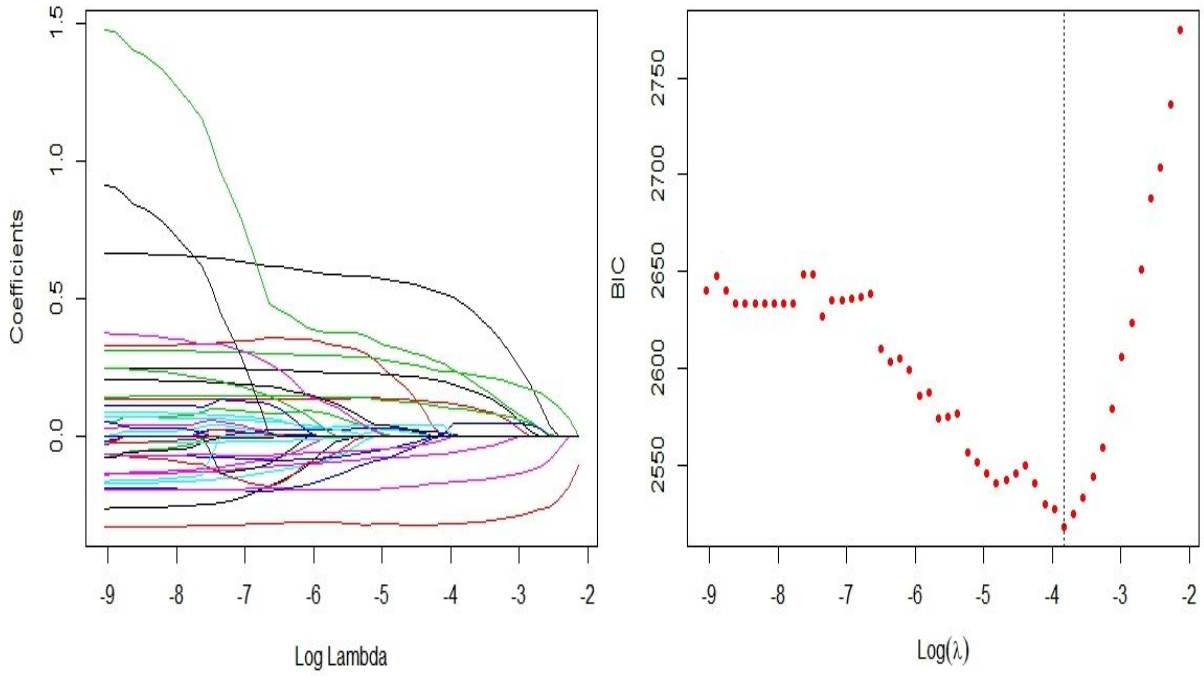
eTable 1. Univariate competing risk models on candidate predictors.

Variable	HR (95% CI)	P-value	AUC (95% CI)
Age	1.83 (1.61, 2.09)	<0.001	67.22 (63.11, 71.33)
Male sex	1.02 (0.68, 1.53)	0.92	49.95 (47.20, 52.71)
Diabetes	1.69 (1.28, 2.24)	<0.001	56.86 (52.91, 60.80)
Hypertension	1.70 (1.28, 2.26)	<0.001	56.31 (52.37, 60.24)
Respiratory disease	1.32 (0.90, 1.94)	0.16	50.82 (48.10, 53.54)
Cardiovascular disease	2.10 (1.58, 2.77)	<0.001	58.02 (54.09, 61.95)
Chronic kidney disease	2.36 (1.65, 3.37)	<0.001	54.85 (51.87, 57.82)
Cancer	1.72 (0.97, 3.05)	0.062	51.45 (49.51, 53.39)
Liver disease	1.65 (1.07, 2.55)	0.023	51.40 (49.06, 53.73)
Chloride	0.94 (0.78, 1.14)	0.55	52.46 (47.39, 57.52)
Bicarbonate	0.63 (0.55, 0.72)	<0.001	67.62 (62.91, 72.33)
Hemoglobin	0.74 (0.65, 0.83)	<0.001	59.28 (54.81, 63.76)
Monocytes percentage	0.42 (0.29, 0.61)	<0.001	73.55 (69.54, 77.56)
Neutrophil percentage	3.31 (2.57, 4.25)	<0.001	76.94 (73.36, 80.51)
Platelets	0.77 (0.65, 0.93)	0.0052	56.86 (52.15, 61.58)
Potassium	1.34 (1.15, 1.57)	<0.001	54.51 (49.45, 59.58)
Red blood cell width	1.25 (1.14, 1.38)	<0.001	60.02 (55.74, 64.30)
White blood cell	1.55 (1.44, 1.66)	<0.001	66.32 (61.80, 70.84)
Creatinine	1.21 (1.12, 1.32)	<0.001	61.37 (56.39, 66.34)
Lactate dehydrogenase	1.34 (1.18, 1.51)	<0.001	79.00 (75.62, 82.38)
Ferritin	1.26 (1.16, 1.37)	<0.001	65.05 (60.92, 69.18)
Systolic blood pressure	0.95 (0.79, 1.13)	0.53	53.33 (48.28, 58.39)
Diastolic blood pressure	0.73 (0.62, 0.85)	<0.001	58.82 (53.97, 63.67)
Respiratory rate	1.49 (1.35, 1.64)	<0.001	69.45 (65.44, 73.47)
Glasgow coma scale	0.57 (0.52, 0.62)	<0.001	67.89 (64.10, 71.68)
C-reactive protein	1.74 (1.55, 1.96)	<0.001	71.21 (67.13, 75.30)
Neutrophil-lymphocyte ratio	1.31 (1.25, 1.38)	<0.001	75.67 (72.06, 79.27)
Neutrophil-lymphocyte percentage ratio	1.31 (1.25, 1.38)	<0.001	75.67 (72.07, 79.28)
Minimum SpO2	0.68 (0.63, 0.74)	<0.001	75.82 (71.75, 79.89)
Sodium	1.00 (0.82, 1.22)	0.99	46.84 (41.81, 51.88)
Hematocrit	0.77 (0.67, 0.88)	<0.001	57.83 (53.24, 62.43)
Red blood cell	0.76 (0.65, 0.88)	<0.001	58.08 (53.38, 62.78)
Lymphocytes count	0.44 (0.33, 0.57)	<0.001	68.28 (64.11, 72.44)
Neutrophils count	1.61 (1.49, 1.73)	<0.001	70.90 (66.79, 75.02)
Monocytes count	0.94 (0.58, 1.51)	0.79	60.74 (55.92, 65.57)
Lymphocytes percentage	0.29 (0.23, 0.38)	<0.001	75.40 (71.78, 79.01)

Abbreviations: HR, hazard ratios; CI, confidence interval; AUC, area under the receiver operating characteristics curve; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.



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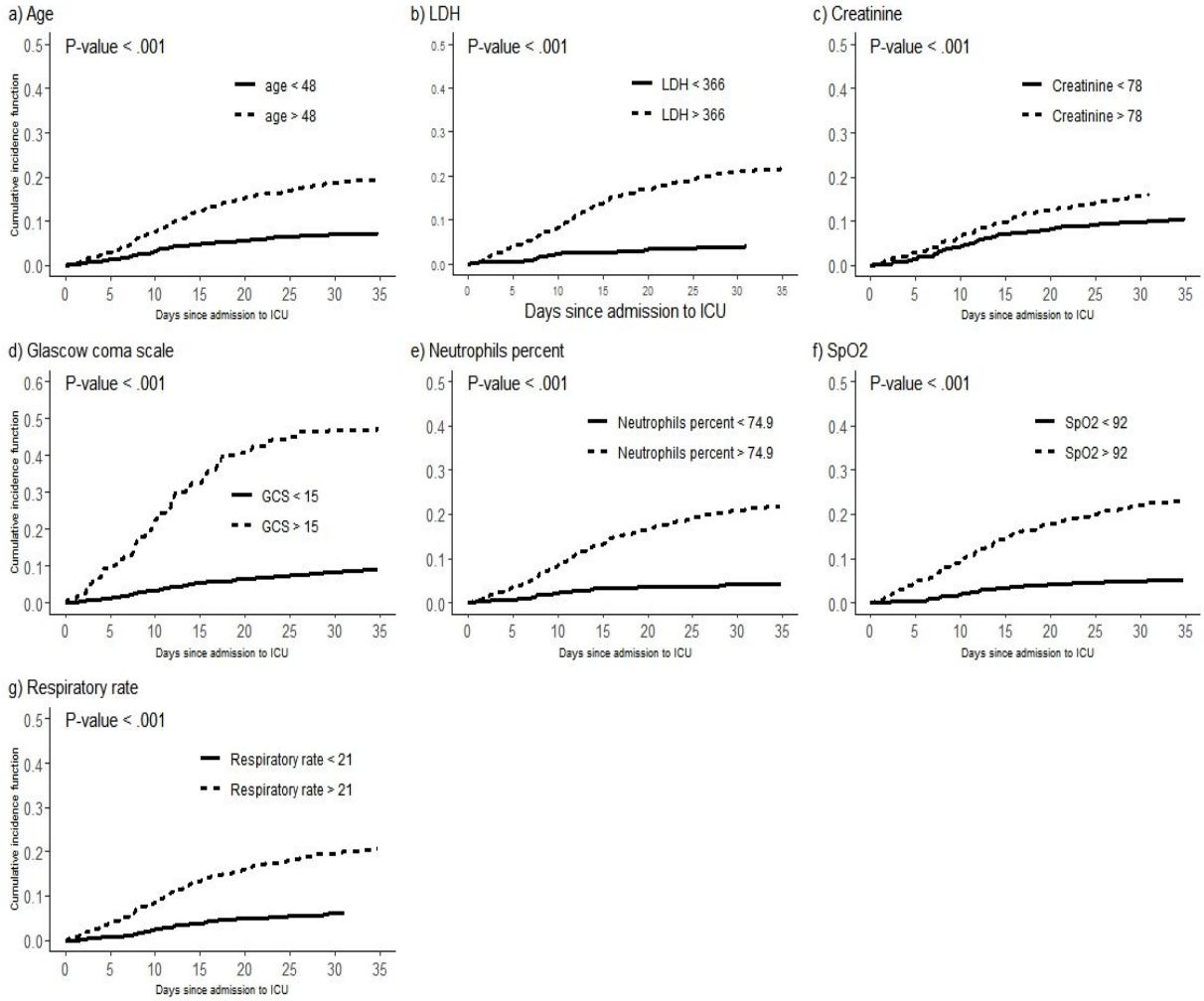
eFigure 2. Mortality curves according to risk factors retained in LASSO



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STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	9, 15
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	6
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	

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Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10, 11
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12, 13
		(*b*) Report category boundaries when continuous variables were categorized	13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15,16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

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Manuscript Word Count: 3148

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ABSTRACT

OBJECTIVES: To identify factors influencing the mortality risk in critically ill patients with COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit (ICU).

DESIGN: A multicentre cohort study

SETTING AND PARTICIPANTS: 1542 patients with COVID-19 admitted to ICUs in public hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.

MAIN OUTCOMES AND MEASURES: The primary outcome was time from ICU admission until death. We used competing risk regression models and Least Absolute Shrinkage and Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the score was assessed by the area under the receiver operating characteristic curve (AUC), and the Brier score using 500 bootstraps replications.

RESULTS: Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged, and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95% confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven factors associated with mortality, and included in the risk score: age (adjusted hazard ratio [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31), lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI, 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95% CI, 0.63–0.78), and oxygen saturation (SpO_2) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed a freely available web-based risk calculator (https://icumortalityrisk.shinyapps.io/ICUrisk/).

CONCLUSION: In critically ill patients with COVID-19, we identified factors associated with mortality, and developed a risk prediction tool that showed high predictive ability. This tool may

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have utility in clinical settings to guide decision-making, and may facilitate the identification of supportive therapies to improve outcomes.

Key words: COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical care

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Strengths and limitations of this study

- Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of in-hospital mortality, however, limited data is available regarding the risk prediction scores in this population.
- Our clinical risk score includes clinical features which are readily available at ICU admission, thus amplifying its clinical applicability.
- The score showed high predictive ability for in-hospital mortality.
- A major limitation is the generalizability of risk prediction score to other settings, and external validation should be the next step.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million patients, and more than 3.1 million have died, as of May 04, 2021[1]. A wide spectrum of clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure leading to hospital admission and death[2 3].

The preventive and treatment challenge of COVID-19 is very high because of the complexity of its transmission, substantial heterogeneity in the progression of disease, and lack of proven treatment[4 5]. Several studies have attempted to address this by predicting clinical outcomes using statistical association analyses or prediction model development methods in order to guide the management and prognostication of patients with COVID-19[6-15]. Based on patient characteristics at the time of hospital admission, Liang et al.[7] proposed a risk score to predict critical illness defined as a composite of intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19 patients which consisted of six parameters assessed at the time of hospital admission[12].

A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU admission has also shown higher mortality in COVID-19 patients with high nutritional risk compared with those with low nutritional risk[14]. Further, a prognostic score using machine learning methods has been shown to predict death in ICU patients with COVID-19[15]. Additionally, various demographics, clinical and hospital level risk factors have been reported to be associated with death in patients admitted to ICU[8].

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A recent meta-analysis showed that more than one-fourth of patients with COVID-19 were admitted to ICU globally, and the prevalence of mortality among these patients was very high (31%)[16]. However, limited data is available related to prognostic risk score of in-hospital mortality in critically ill patients with COVID-19 who were admitted to ICU. Therefore, the aim of the present study was to identify the risk factors and the set of clinical markers that increase the risk of death among ICU admitted COVID-19 patients, and to develop a risk prediction score that may facilitate the identification of supportive therapies to improve outcomes. We also aim to develop an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator will provide stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity.

METHODS

Study design and Data sources

This is a multicentre cohort study in which data of all laboratory confirmed COVID-19 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE) between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical records. The data was collected from four major hospitals as well as newly developed field hospitals operating with some ICU bed capacity. The estimated bed capacity for ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We included patients who were admitted to a regular ICU room or to a HDU or if they were consistently receiving any form of oxygen therapy during their hospital stay in a make-

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shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Outcomes

The primary outcome of this study is the survival time defined as the duration of time, from the date of ICU admission, until the date of death. Patients still hospitalized at the date of data extraction were considered as right censored and those discharged alive from the hospital were considered as competing events to death due to COVID-19.

Statistical Analyses

Baseline characteristics were summarized using descriptive statistics including mean and standard deviation for continuous measures, and frequencies tables for categorical variables. We compared categorical variables using the chi-square or Fisher's exact test, and continuous variables using the unpaired t-test or its non-parametric equivalent (Wilcoxon rank sum test) in case the normality assumption is violated.

Potential predictive variables

We considered 36 patient's characteristics assessed at the time of ICU admission as potential predictors based on demographics, clinical signs and symptoms, medical history and laboratory findings. Demographic variables included age and sex. Clinical signs and symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate, Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen saturation (SpO_2). Medical history included status of coexisting conditions: diabetes, hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer, and liver disease. Laboratory findings included white blood cells, monocytes count,

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monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count, lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride, bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with available data on these characteristics were included in the final analysis.

The statistical model

We used the competing risk regression model to investigate the association between death due to COVID-19 and all potential risk factors. We have chosen to use this model, instead of the standard Cox proportional hazard model, because discharge alive or recovery is clearly a competing event to death due to COVID-19[17 18]. Ignoring this property will lead to biased estimates of the hazard ratios and the survival curves. We estimated and plotted the survival curves using the cumulative incidence function taking into account competing risks. Cumulative incidence curves of different groups were compared using the Gray's test[19] for sub-distribution hazards, an equivalent of the log-rank test in the case of competing events. We used the Fine & Gray proportional hazards regression models[20] to investigate the association between potential risk factors and the primary outcome, and also to derive the risk prediction score. All statistical analysis and data management carried out in this paper were done using the R software version 3.6.3 and *P*-values <0.05 were considered as statistically significant.

Variables selection method and derivation of the risk prediction score

We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes Information criterion (BIC) for variables selection[21 22]. This method uses a shrinking

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parameter to penalize non-significant coefficients of the Fine and Gray competing risk regression model. Larger shrinking parameters make the coefficients of non-significant risk factors to shrink towards zero, so that only the strongest predictors remain in the survival model. Unlike the standard selection methods, such as stepwise forward or backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36 potential predictors were scaled using the z-score transformation, and were entered in the selection process. The most predictive covariates were selected by choosing the shrinking parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were statistically significant were retained to construct the risk prediction score. We also investigated all statistical interactions between pairs of the retained predictors.

Validation of the risk prediction score

We derived the 28-day risk of in-hospital death using the estimates obtained from the Fine & Gray competing risk regression model. The predictive ability of this proposed risk prediction score was assessed using discrimination and calibration. Discrimination refers to how well the predictive model is capable of discriminating between individuals who died and those who were discharged alive, whereas calibration refers to the agreement between observed and predicted number of deaths. Discrimination was assessed via the time-dependent area under the receiver-operator characteristic curve (AUC). Calibration was assessed via the time-dependent Brier score, and visually by plotting expected versus observed deaths. To reduce overfitting and optimism bias, we carried out internal validation of the risk prediction score by estimating the AUC and Brier score using 500 bootstraps replications. This method allows all of the original data to be used in the

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model development while providing insight into the extent to which the original model is overfitting or too optimistic.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Among the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%) were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the date of data extraction). Taking into account right-censored observations, the cumulative incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI, 83.54–87.26) (Figure 1).

The demographic and clinical characteristics of the patients are presented in Table 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168 (12.7%) died. Compared with patients who were discharged alive, those who died were older and had higher prevalence of diabetes, hypertension, chronic kidney disease, cardiovascular disease, and liver disease; lower diastolic blood pressure, higher respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO_2 and a higher percentage of patients requiring oxygen therapy.

The laboratory findings of the patients included in our study are presented in Table 2. Compared with patients who were discharged alive, those who died had unfavourable laboratory profile on almost all variables including levels of C-reactive

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protein, creatinine, LDH, red blood cell distribution width, white blood cell count, potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count, haemoglobin, haematocrit, and serum bicarbonates.

The results of the univariate competing risk model for each of the 36 potential predictors measured at ICU admission are presented in the supplement (eTable 1). Of these 36 variables, seven statistically significant predictors of mortality were retained by the LASSO selection procedure in the multivariable competing risk regression model (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals of these significant variables are presented in Table 3. The significant predictors increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–2.31]; *P*<.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<.001), higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), higher respiratory rate (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), and high levels of creatinine (HR, 1.19 [95% CI, 1.11– 1.28]; *P*<.001). The significant predictors lowering the risk of death included higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<.001) and higher SpO_2 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<.001). We found no statistically significant interaction terms between pairs of the retained predictors.

The cumulative incidence function of these 7 predictors retained by LASSO in the multivariable model is shown in the supplement (eFigure 2). For graphical presentation, we created a binary variable based on the median split in case of continuous risk factors.

Validation of the risk prediction score

The results of the internal validation using 500 bootstrap samples are shown in Figure 2. The predictive ability of the derived risk prediction score was quite promising. Indeed,

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regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2 also shows the calibration plot for the risk prediction score, in which the predicted frequencies of deaths were plotted against the observed ones.

From Figure 2, it is evident that the predicted frequencies of death were very close to the observed ones suggesting a very good calibration. The risk prediction score provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.

We also developed an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator also provides stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity. The online risk calculator is freely available at (https://icumortalityrisk.shinyapps.io/ICUrisk/).

DISCUSSION

We developed and validated a clinical risk prediction score and a web-based risk calculator to predict the risk of in-hospital death in adult patients with confirmed COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect similarity between predicted and expected deaths. We identified seven readily available clinical features at ICU admission to be used for risk prediction of in-hospital mortality namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings, neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these

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variables in an easy-to use web-based risk calculator has the potential to accurately classify ICU admitted patients as likely to be discharged alive or die.

A major strength of this study is the relatively large number of laboratory confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk prediction score includes clinical features that are readily available at ICU admission that increases its clinical applicability. An obvious limitation of this study is the generalizability of risk prediction score in other settings, and we acknowledge that external validation of our risk prediction score in other populations is the next step in model development. Further, the participants included in this study were younger compared with other studies using the data at the time of ICU admission[8 12-15], which may in turn limit the generalizability in older patients.

Previous studies have reported risk prediction scores of mortality based on the clinical features at the time of hospital or ICU admission, including patients with mild, moderate or severe forms of disease[6 7 9 10 12-15]. For instance, using data of 4711 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was developed and validated, and consisted of six variables (age, oxygen saturation, mean arterial pressure, blood urea nitrogen, C-Reactive protein, and the international normalized ratio) assessed at the time of hospital admission[12]. Moreover, 10 variables (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct bilirubin) were found to be independent predictive factors, and were included in the risk score to predict the occurrence of critical illness in hospitalized patients with COVID-

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19[7]. The International Severe Respiratory and emerging Infections Consortium (ISARIC) developed and validated a mortality score consisting of eight variables (age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein) that were available at the initial hospital assessment[9]. In line with this, methods using machine learning have identified 8 important risk factors to predict mortality in ICU admitted patients with COVID-19[15]. Interestingly, nutritional status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time of ICU admission predicted twice the probability of death in patients with high nutritional risk than low risk patients[14]. The difference in the number and types of independent clinical features associated with mortality between our study and others may be explained by the differences in the baseline characteristics of the population or the choice of the statistical analyses. Indeed, we have chosen to use the competing risk regression model instead of the standard Cox proportional hazard model or the logistic regression model because recovery is clearly a competing event to in-hospital death due to COVID-19[17 18]. Ignoring this property will definitely lead to biased effect estimates. Another plausible reason for this difference in the results is the younger age of the participants in our study compared to other studies[12-15], which could likely influence the clinical features to be included in the risk prediction score.

Other statistical association analyses have been published to investigate the factors affecting mortality due to COVID-19 in patients admitted to ICU[8 11]. For instance, a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted to ICU in the US identified 9 risk factors independently associated with the 28-days mortality. These risk factors included age, sex, body mass index, coronary artery disease,

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active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the number of hospital ICU beds[8]. In our risk score, none of the comorbid conditions achieved statistical significance for in-hospital mortality, however, other significant laboratory findings such as increased LDH and increased creatinine levels may represent underlying diseases such as liver disease, lung disease or kidney dysfunction.

Interestingly, a non COVID-19 prediction score named Waterlow score has shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly patients[23]. The Waterlow score is a multidimensional pressure ulcer risk assessment tool and includes age, nutritional status, weight, mobility, gender, smoking status, comorbidities, use of medication and continence[23]. One of the significant predictors of mortality included in our risk score is Glasgow Coma Scale which is an objective and reliable way of recording the initial and subsequent level of consciousness, and could be used as a proxy to continence. Although, the association between Waterlow score and mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac and stroke conditions, its application in patients with confirmed COVID-19 warrants further investigations.

The recent COVID-19 epidemiological update from WHO, as of May 04, 2021, reported over 5.7 million new weekly cases worldwide which is at the highest level since the beginning of the pandemic[1]. The WHO European and American regions accounted for 20% and 23% of new weekly cases, respectively. The largest increase accounting for 47% of new weekly cases was noted in South East Asia region particularly in India which accounted for over 90% of both cases and deaths in the region. The Eastern Mediterranean region that includes UAE accounted for 6% of new weekly cases[1]. Earlier

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studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases ranging between 2% and 81%[16 24 25], and high mortality prevalence among ICU patients ranging between 5% and 83%[3 16 26]. A meta-analysis of twenty-five studies with 24,677 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence among patients admitted to ICU with a severe form of COVID-19[16]. The relative high number of deaths in the ICU presents an enormous challenge to the prognostication and management of patients with COVID-19. We believe that the risk tool provided in this study may have utility in clinical settings to guide decision-making, and may facilitate the early identification of patients at high risk of death, and may be used as a guidance in busy ICU units to stratify patients according to their risk in order to deliver the best available supportive care. The parameters selected are easily available at the time of ICU admission.

Conclusion

We developed and validated a risk tool for predicting in-hospital death among COVID-19 patients admitted to ICU, which shows high predictive accuracy. This tool can assist in early identification of patients during ICU admission who are at high risks of death, and consequently can facilitate optimal delivery of supportive care for these patients.

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Author Contributions: SA, AA, MAH, MAA, RG, II, JN and AO contributed to the development of the research question and study design. AO led the development of advanced statistical aspects. SA, AA, MAH, MAA, RG, II and AO were involved in data specification, curation, and collection. AO did data management and statistical analyses, which were checked by SA, AA, MAH, and JN. SA, AA, MAH, MAA, RG, II, JN and AO contributed to the interpretation of the results. SA, AA, JN and AO wrote the first draft of the paper. SA, AA, MAH, MAA, RG, II, JN and AO contributed to the critical revision of the manuscript for important intellectual content and approved the final version of the manuscript. AO developed the software for the web calculator. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. AO is the guarantor.
The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Data availability statement: To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the data is according to the information and rules and regulations of Abu Dhabi Health Services - SEHA and Cerner.

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Competing interest statement: All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Figure legends

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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Table 1. Demographics and Clinical Characteristics among Critically Ill Patients with COVID-19.

Characteristics	Total	Died	Alive	*P*-value†
No. (%)	1542 (100)	196 (13)	1346 (87)	
Female sex, n (%)	221 (14.3)	28 (14.3)	193 (14.3)	
Age, mean (SD), years	49.9 (12.7)	56.7 (13.3)	47.8 (12.1)	<.001
Race/ethnicity*, n (%)				
Arab	373 (24.2)	55 (28.1)	318 (23.6)	
Asian	1130 (73.3)	136 (69.4)	994 (73.9)	
Other	27 (1.8)	4 (2.0)	23 (1.7)	0.376
Systolic blood pressure, mean (SD), mmHg	126.2 (17.4)	125.5 (21.1)	126.3 (16.8)	0.286
Diastolic blood pressure, mean (SD), mmHg	75.5 (12.1)	72.2 (12.5)	76.0 (12.0)	<.001
Respiratory rate, mean (SD), breaths/min	23.3 (6.7)	27.1 (7.4)	22.7 (6.4)	<.001
Oxygen saturation (SpO_2), n (%)				
<90	487 (31.6)	138 (70.4)	349 (25.9)	
90-94	569 (36.9)	39 (19.9)	530 (39.4)	
≥95	486 (31.5)	19 (9.7)	467 (34.7)	
Oxygen therapy**, n (%)				
Hypoxic respiratory failure requiring supplemental oxygen	736 (47.7)	18 (9.2)	718 (53.3)	
Hypoxic respiratory failure requiring none-invasive mechanical ventilation	76 (4.9)	11 (5.6)	65 (4.8)	
Hypoxic respiratory failure requiring invasive mechanical ventilation	519 (33.7)	167 (85.2)	352 (26.2)	<.001
Coexisting conditions, n (%)				
0	498 (32.3)	39 (19.9)	459 (34.1)	
1	403 (26.1)	45 (23.0)	358 (26.6)	
≥2	641 (41.6)	112 (57.1)	529 (39.3)	<.001
Diabetes, n (%)				
No	874 (56.7)	86 (43.9)	788 (58.5)	
Yes	668 (43.3)	110 (56.1)	558 (41.5)	<.001
Hypertension, n (%)				
No	854 (55.4)	82 (41.8)	772 (57.4)	

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Characteristics	Total	Died	Alive	*P*-value†
Yes	688 (44.6)	114 (58.2)	574 (42.6)	<.001
Respiratory disease, n (%)				
No	1,361 (88.3)	166 (84.7)	1,195 (88.8)	
Yes	181 (11.7)	30 (15.3)	151 (11.2)	0.123
Cardiovascular Disease, n (%)				
No	1,053 (68.3)	100 (51.0)	953 (70.8)	
Yes	489 (31.7)	96 (49.0)	393 (29.2)	<.001
Chronic Kidney Disease, n (%)				
No	1,397 (90.6)	159 (81.1)	1,238 (92.0)	
Yes	145 (9.4)	37 (18.9)	108 (8.0)	<.001
Cancer, n (%)				
No	1,479 (95.9)	183 (93.4)	1,296 (96.3)	
Yes	63 (4.1)	13 (6.6)	50 (3.7)	0.083
Liver disease, n (%)				
No	1,437 (93.2)	174 (88.8)	1,263 (93.8)	
Yes	105 (6.8)	22 (11.2)	83 (6.2)	0.013
Glasgow Coma Scale, mean (SD)	13.83 (±3.42)	11.94 (±5.07)	14.28 (±2.71)	<.001
Mild, n (%)	1,391 (90.2)	121 (61.7)	1,270 (94.4)	
Moderate, n (%)	21 (1.4)	7 (3.6)	14 (1.0)	
Severe, n (%)	130 (8.4)	68 (34.7)	62 (4.6)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.
†Continuous variables were compared using the t-test or Wilcoxon-rank-sum test, while categorical variables were compared using the Chi-square or Fisher's exact test.
Glasgow Coma Scale: Mild (14-15), Moderate (9-13) or Severe (3-8).
*The percentages do not sum up to 100% because of the missing data.
** The percentages do not sum up to 100% because there are patients not requiring any form of oxygen therapy.

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Table 2. Laboratory Findings among Critically Ill Patients with COVID-19.

Variable	Total	Died	Alive	*P*-value
Number. (%)	1542 (100)	196 (13)	1346 (87)	
White blood cells, mean (SD), $^{x}10^{9}$/L	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $^{x}10^{9}$/L	1.28 (0.71)	0.93 (0.57)	1.33 (0.72)	<.001
Lymphocyte percent, mean (SD), %	18.76 (10.74)	10.86 (6.93)	19.92 (10.72)	<.001
Neutrophil count, mean (SD), $^{x}10^{9}$/L	6.00 (3.77)	8.85 (5.65)	5.58 (3.21)	<.001
Neutrophil percent, mean (SD), %	73.04 (13.28)	83.29 (9.96)	71.55 (13.05)	<.001
Neutrophil-lymphocyte count ratio	6.81 (9.39)	13.66 (18.16)	5.82 (6.73)	<.001
Neutrophil-lymphocyte percent ratio	6.82 (9.46)	13.69 (18.33)	5.82 (6.77)	<.001
Monocytes count, mean (SD), $^{x}10^{9}$/L	0.51 (0.36)	0.50 (0.72)	0.51 (0.28)	0.769
Monocytes percent, mean (SD), %	6.93 (3.67)	4.94 (4.99)	7.22 (3.34)	<.001
Platelet count, mean (SD), $^{x}10^{9}$/L	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $^{x}10^{12}$/L	4.75 (0.71)	4.56 (0.80)	4.78 (0.70)	<.001
Red blood cell distribution width, %	13.49 (1.60)	13.97 (1.76)	13.42 (1.56)	<.001
Haemoglobin level, mean (SD), g/L	131.90 (18.24)	126.18 (19.59)	132.73 (17.89)	<.001
Haematocrit, mean (SD), L/L	0.39 (0.05)	0.38 (0.06)	0.40 (0.05)	<.001
Creatinine level, mean (SD), µmol/L	97.76 (111.80)	149.97 (188.91)	90.15 (93.23)	<.001
C-reactive protein level, mean (SD), mg/L	102.13 (94.00)	173.05 (112.06)	91.80 (86.39)	<.001
Lactate dehydrogenase, mean (SD), IU/L	409.32 (223.16)	605.80 (291.22)	380.71 (195.74)	<.001
Serum Chloride, mean (SD), mmol/L	99.25 (4.50)	99.05 (5.97)	99.28 (4.25)	0.600
Serum bicarbonate, mean (SD), mmol/L	22.80 (3.28)	21.02 (4.23)	23.06 (3.04)	<.001
Potassium, mean (SD), mmol/L	4.05 (0.55)	4.21 (0.76)	4.03 (0.50)	0.002
Sodium, mean (SD), mmol/L	136.98 (4.36)	136.97 (5.80)	136.98 (4.11)	0.984
Ferritin, mean (SD), ng/mL	1209.37 (1374.60)	1779.63 (1930.98)	1126.33 (1252.99)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.

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Table 3. Multivariable Adjusted Competing Risk Regression Model for Mortality.

Variables	HR (95% CI)	P-value
Age, years	1.98 (1.71 to 2.31)	<.001
Neutrophils $^{x}10^{9}$/L, percentage	1.71 (1.27 to 2.31)	<.001
Lactate dehydrogenase, IU/L	1.31 (1.15 to 1.49)	<.001
Respiratory rate, breaths/min	1.31 (1.15 to 1.49)	<.001
Glasgow Coma Scale	0.70 (0.63 to 0.78)	<.001
Oxygen saturation (SpO_2)	0.82 (0.74 to 0.91)	<.001
Creatinine, μmol/L	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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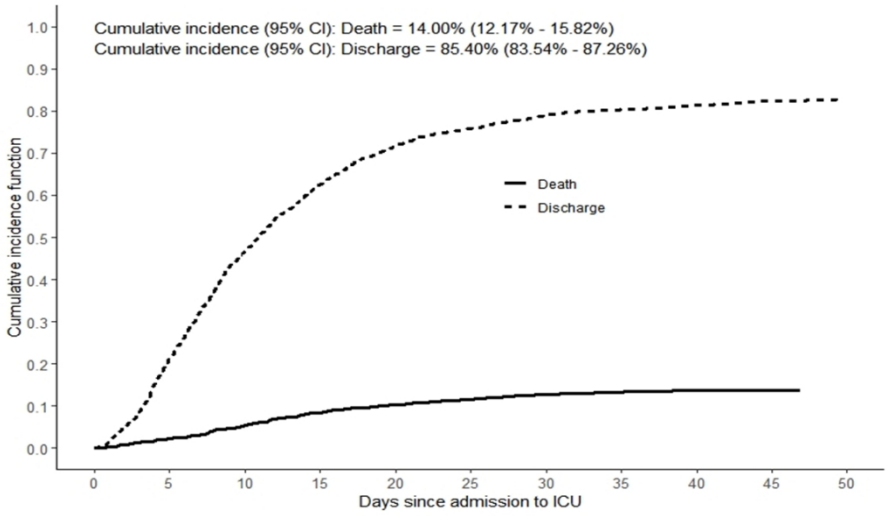

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

338x190mm (96 x 96 DPI)

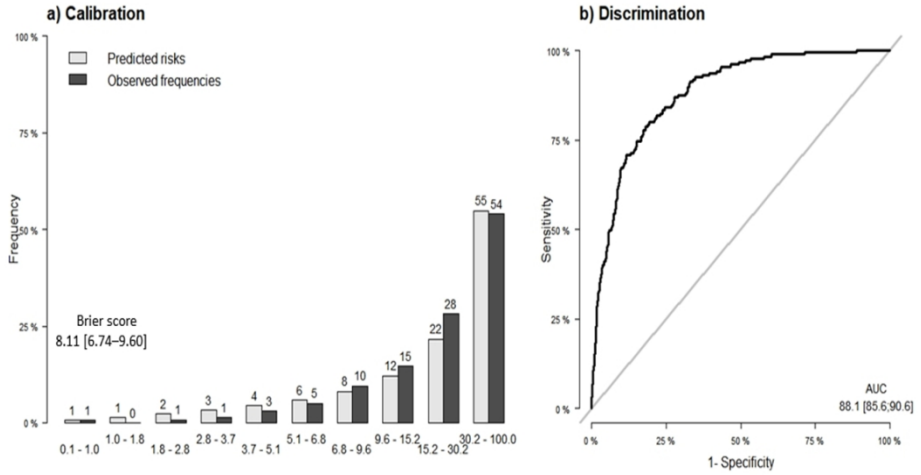

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

338x190mm (96 x 96 DPI)

Supplementary Material

Salem AlKaabi et al. A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

eTable 1. Univariate competing risk models on candidate predictors.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.

eFigure 2. Mortality curves according to risk factors retained in LASSO.

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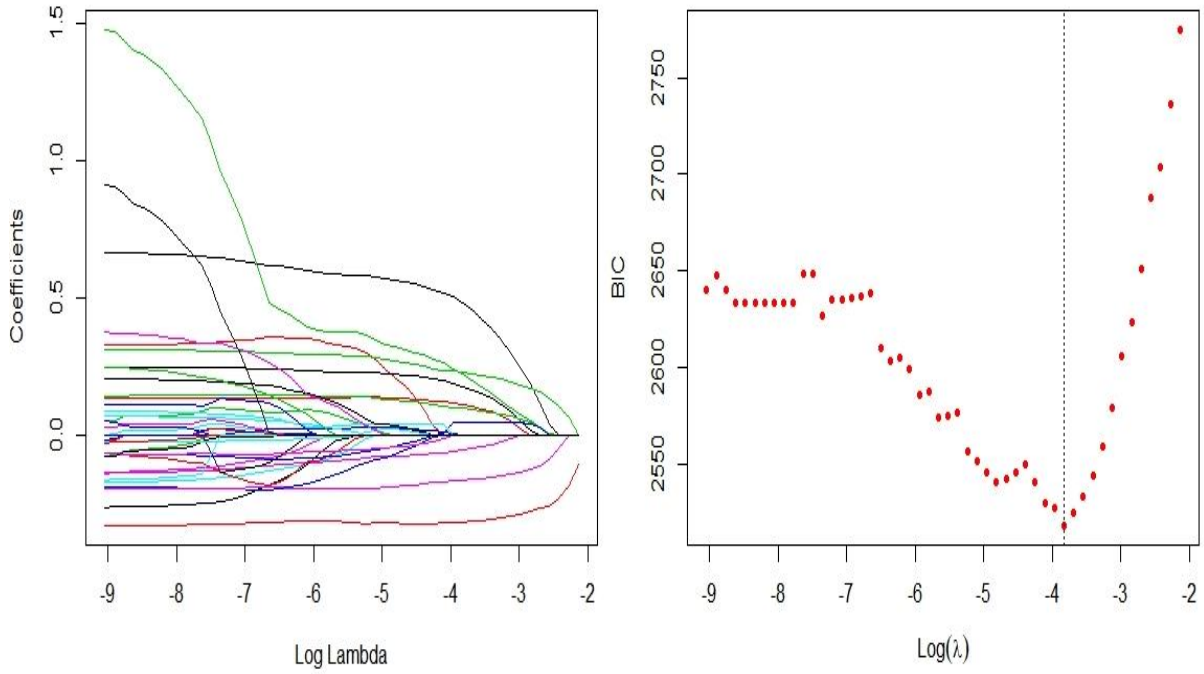
eTable 1. Univariate competing risk models on candidate predictors.

Variable	HR (95% CI)	P-value	AUC (95% CI)
Age	1.83 (1.61, 2.09)	<.001	67.22 (63.11, 71.33)
Male sex	1.02 (0.68, 1.53)	0.92	49.95 (47.20, 52.71)
Diabetes	1.69 (1.28, 2.24)	<.001	56.86 (52.91, 60.80)
Hypertension	1.70 (1.28, 2.26)	<.001	56.31 (52.37, 60.24)
Respiratory disease	1.32 (0.90, 1.94)	0.16	50.82 (48.10, 53.54)
Cardiovascular disease	2.10 (1.58, 2.77)	<.001	58.02 (54.09, 61.95)
Chronic kidney disease	2.36 (1.65, 3.37)	<.001	54.85 (51.87, 57.82)
Cancer	1.72 (0.97, 3.05)	0.062	51.45 (49.51, 53.39)
Liver disease	1.65 (1.07, 2.55)	0.023	51.40 (49.06, 53.73)
Chloride	0.94 (0.78, 1.14)	0.55	52.46 (47.39, 57.52)
Bicarbonate	0.63 (0.55, 0.72)	<.001	67.62 (62.91, 72.33)
Hemoglobin	0.74 (0.65, 0.83)	<.001	59.28 (54.81, 63.76)
Monocytes percentage	0.42 (0.29, 0.61)	<.001	73.55 (69.54, 77.56)
Neutrophil percentage	3.31 (2.57, 4.25)	<.001	76.94 (73.36, 80.51)
Platelets	0.77 (0.65, 0.93)	0.0052	56.86 (52.15, 61.58)
Potassium	1.34 (1.15, 1.57)	<.001	54.51 (49.45, 59.58)
Red blood cell width	1.25 (1.14, 1.38)	<.001	60.02 (55.74, 64.30)
White blood cell	1.55 (1.44, 1.66)	<.001	66.32 (61.80, 70.84)
Creatinine	1.21 (1.12, 1.32)	<.001	61.37 (56.39, 66.34)
Lactate dehydrogenase	1.34 (1.18, 1.51)	<.001	79.00 (75.62, 82.38)
Ferritin	1.26 (1.16, 1.37)	<.001	65.05 (60.92, 69.18)
Systolic blood pressure	0.95 (0.79, 1.13)	0.53	53.33 (48.28, 58.39)
Diastolic blood pressure	0.73 (0.62, 0.85)	<.001	58.82 (53.97, 63.67)
Respiratory rate	1.49 (1.35, 1.64)	<.001	69.45 (65.44, 73.47)
Glasgow coma scale	0.57 (0.52, 0.62)	<.001	67.89 (64.10, 71.68)
C-reactive protein	1.74 (1.55, 1.96)	<.001	71.21 (67.13, 75.30)
Neutrophil-lymphocyte ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.06, 79.27)
Neutrophil-lymphocyte percentage ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.07, 79.28)
Minimum SpO2	0.68 (0.63, 0.74)	<.001	75.82 (71.75, 79.89)
Sodium	1.00 (0.82, 1.22)	0.99	46.84 (41.81, 51.88)
Hematocrit	0.77 (0.67, 0.88)	<.001	57.83 (53.24, 62.43)
Red blood cell	0.76 (0.65, 0.88)	<.001	58.08 (53.38, 62.78)
Lymphocytes count	0.44 (0.33, 0.57)	<.001	68.28 (64.11, 72.44)
Neutrophils count	1.61 (1.49, 1.73)	<.001	70.90 (66.79, 75.02)
Monocytes count	0.94 (0.58, 1.51)	0.79	60.74 (55.92, 65.57)
Lymphocytes percentage	0.29 (0.23, 0.38)	<.001	75.40 (71.78, 79.01)

Abbreviations: HR, hazard ratios; CI, confidence interval; AUC, area under the receiver operating characteristics curve; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.



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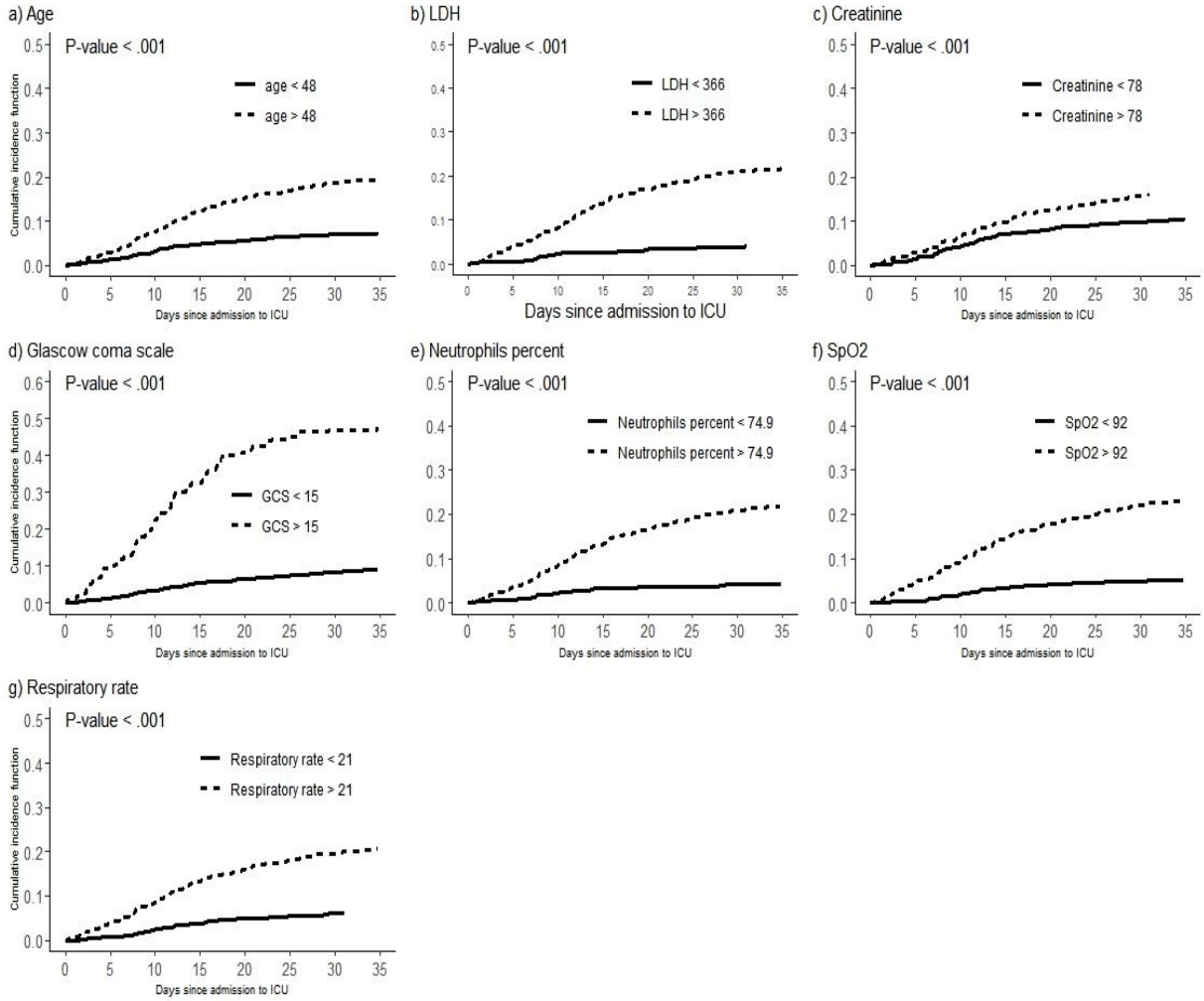
eFigure 2. Mortality curves according to risk factors retained in LASSO



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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7-8
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	9-10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	12
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10-11
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	11
	15b	D	Explain how to the use the prediction model.	12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	11-12
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	4, 13
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	11-12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

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Manuscript Word Count: 3241

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ABSTRACT

OBJECTIVES: To identify factors influencing the mortality risk in critically ill patients with COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit (ICU).

DESIGN: A multicentre cohort study

SETTING AND PARTICIPANTS: 1542 patients with COVID-19 admitted to ICUs in public hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.

MAIN OUTCOMES AND MEASURES: The primary outcome was time from ICU admission until death. We used competing risk regression models and Least Absolute Shrinkage and Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the score was assessed by the area under the receiver operating characteristic curve (AUC), and the Brier score using 500 bootstraps replications.

RESULTS: Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged, and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95% confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven factors associated with mortality, and included in the risk score: age (adjusted hazard ratio [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31), lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI, 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95% CI, 0.63–0.78), and oxygen saturation (SpO_2) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed a freely available web-based risk calculator (https://icumortalityrisk.shinyapps.io/ICUrisk/).

CONCLUSION: In critically ill patients with COVID-19, we identified factors associated with mortality, and developed a risk prediction tool that showed high predictive ability. This tool may

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have utility in clinical settings to guide decision-making, and may facilitate the identification of supportive therapies to improve outcomes.

Key words: COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical care

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Strengths and limitations of this study

- Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of in-hospital mortality, however, limited data is available regarding the risk prediction scores in this population.
- Our clinical risk score includes clinical features which are readily available at ICU admission, thus amplifying its clinical applicability.
- The score showed high predictive ability for in-hospital mortality.
- A major limitation is the generalizability of risk prediction score to other settings, and external validation should be the next step.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million patients, and more than 3.1 million have died, as of May 04, 2021[1]. A wide spectrum of clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure leading to hospital admission and death[2 3].

The preventive and treatment challenge of COVID-19 is very high because of the complexity of its transmission, substantial heterogeneity in the progression of disease, and lack of proven treatment[4 5]. Several studies have attempted to address this by predicting clinical outcomes using statistical association analyses or prediction model development methods in order to guide the management and prognostication of patients with COVID-19[6-17]. Based on patient characteristics at the time of hospital admission, Liang et al.[7] proposed a risk score to predict critical illness defined as a composite of intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19 patients which consisted of six parameters assessed at the time of hospital admission[12].

A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU admission has also shown higher mortality in COVID-19 patients with high nutritional risk compared with those with low nutritional risk[14]. Further, a prognostic score using machine learning methods has been shown to predict death in ICU patients with COVID-19[15]. Additionally, various demographics, clinical and hospital level risk factors have been reported to be associated with death in patients admitted to ICU[8].

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A recent meta-analysis showed that more than one-fourth of patients with COVID-19 were admitted to ICU globally, and the prevalence of mortality among these patients was very high (31%)[18]. However, limited data is available related to prognostic risk score of in-hospital mortality in critically ill patients with COVID-19 who were admitted to ICU. Therefore, the aim of the present study was to identify the risk factors and the set of clinical markers that increase the risk of death among ICU admitted COVID-19 patients, and to develop a risk prediction score that may facilitate the identification of supportive therapies to improve outcomes. We also aim to develop an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator will provide stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity.

METHODS

Study design and Data sources

This is a multicentre cohort study in which data of all laboratory confirmed COVID-19 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE) between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical records. The data was collected from four major hospitals as well as newly developed field hospitals operating with some ICU bed capacity. The estimated bed capacity for ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We included patients who were admitted to a regular ICU room or to a HDU or if they were consistently receiving any form of oxygen therapy during their hospital stay in a make-

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shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Outcomes

The primary outcome of this study is the survival time defined as the duration of time, from the date of ICU admission, until the date of death. Patients still hospitalized at the date of data extraction were considered as right censored and those discharged alive from the hospital were considered as competing events to death due to COVID-19.

Statistical Analyses

Baseline characteristics were summarized using descriptive statistics including mean and standard deviation for continuous measures, and frequencies tables for categorical variables. We compared categorical variables using the chi-square or Fisher's exact test, and continuous variables using the unpaired t-test or its non-parametric equivalent (Wilcoxon rank sum test) in case the normality assumption is violated.

Potential predictive variables

We considered 36 patient's characteristics assessed at the time of ICU admission as potential predictors based on demographics, clinical signs and symptoms, medical history and laboratory findings. Demographic variables included age and sex. Clinical signs and symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate, Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen saturation (SpO_2). Medical history included status of coexisting conditions: diabetes, hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer, and liver disease. Laboratory findings included white blood cells, monocytes count,

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monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count, lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride, bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with available data on these characteristics were included in the final analysis.

The statistical model

We used the competing risk regression model to investigate the association between death due to COVID-19 and all potential risk factors. We have chosen to use this model, instead of the standard Cox proportional hazard model, because discharge alive or recovery is clearly a competing event to death due to COVID-19[19 20]. Ignoring this property will lead to biased estimates of the hazard ratios and the survival curves. We estimated and plotted the survival curves using the cumulative incidence function taking into account competing risks. Cumulative incidence curves of different groups were compared using the Gray's test[21] for sub-distribution hazards, an equivalent of the log-rank test in the case of competing events. We used the Fine & Gray proportional hazards regression models[22] to investigate the association between potential risk factors and the primary outcome, and also to derive the risk prediction score. All statistical analysis and data management carried out in this paper were done using the R software version 3.6.3 and *P*-values <0.05 were considered as statistically significant.

Variables selection method and derivation of the risk prediction score

We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes Information criterion (BIC) for variables selection[23 24]. This method uses a shrinking

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parameter to penalize non-significant coefficients of the Fine and Gray competing risk regression model. Larger shrinking parameters make the coefficients of non-significant risk factors to shrink towards zero, so that only the strongest predictors remain in the survival model. Unlike the standard selection methods, such as stepwise forward or backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36 potential predictors were scaled using the z-score transformation, and were entered in the selection process. The most predictive covariates were selected by choosing the shrinking parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were statistically significant were retained to construct the risk prediction score. We also investigated all statistical interactions between pairs of the retained predictors.

Validation of the risk prediction score

We derived the 28-day risk of in-hospital death using the estimates obtained from the Fine & Gray competing risk regression model. The predictive ability of this proposed risk prediction score was assessed using discrimination and calibration. Discrimination refers to how well the predictive model is capable of discriminating between individuals who died and those who were discharged alive, whereas calibration refers to the agreement between observed and predicted number of deaths. Discrimination was assessed via the time-dependent area under the receiver-operator characteristic curve (AUC). Calibration was assessed via the time-dependent Brier score, and visually by plotting expected versus observed deaths. To reduce overfitting and optimism bias, we carried out internal validation of the risk prediction score by estimating the AUC and Brier score using 500 bootstraps replications. This method allows all of the original data to be used in the

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model development while providing insight into the extent to which the original model is overfitting or too optimistic.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 1695 patients were eligible for the study entry among which 1542 had complete information on all the potential predictors and hence were included in the analysis. The characteristics of the 153 patients who were excluded from the analysis (due to heavy missing values) were not different from those who were included in the current analysis. Almost, three fourth of the study patients were Asians, and nearly one fourth were Arabs which is consistent with the demographic composition of entire population of Abu Dhabi. Of the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%) were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the date of data extraction). Taking into account right-censored observations, the cumulative incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI, 83.54–87.26) (Figure 1).

The demographic and clinical characteristics of the patients are presented in Table 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168 (12.7%) died. Compared with patients who were discharged alive, those who died were older and had higher prevalence of diabetes, hypertension, chronic kidney disease,

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cardiovascular disease, and liver disease; lower diastolic blood pressure, higher respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO_2 and a higher percentage of patients requiring oxygen therapy.

The laboratory findings of the patients included in our study are presented in Table 2. Compared with patients who were discharged alive, those who died had unfavourable laboratory profile on almost all variables including levels of C-reactive protein, creatinine, LDH, red blood cell distribution width, white blood cell count, potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count, haemoglobin, haematocrit, and serum bicarbonates.

The results of the univariate competing risk model for each of the 36 potential predictors measured at ICU admission are presented in the supplement (eTable 1). Of these 36 variables, seven statistically significant predictors of mortality were retained by the LASSO selection procedure in the multivariable competing risk regression model (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals of these significant variables are presented in Table 3. The significant predictors increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–2.31]; *P*<.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<.001), higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), higher respiratory rate (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), and high levels of creatinine (HR, 1.19 [95% CI, 1.11– 1.28]; *P*<.001). The significant predictors lowering the risk of death included higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<.001) and higher SpO_2 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<.001). We found no statistically significant interaction terms between pairs of the retained predictors.

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The cumulative incidence function of these 7 predictors retained by LASSO in the multivariable model is shown in the supplement (eFigure 2). For graphical presentation, we created a binary variable based on the median split in case of continuous risk factors.

Validation of the risk prediction score

The results of the internal validation using 500 bootstrap samples are shown in Figure 2. The predictive ability of the derived risk prediction score was quite promising. Indeed, regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2 also shows the calibration plot for the risk prediction score, in which the predicted frequencies of deaths were plotted against the observed ones.

From Figure 2, it is evident that the predicted frequencies of death were very close to the observed ones suggesting a very good calibration. The risk prediction score provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.

We also developed an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator also provides stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity. The online risk calculator is freely available at (https://icumortalityrisk.shinyapps.io/ICUrisk/).

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DISCUSSION

We developed and validated a clinical risk prediction score and a web-based risk calculator to predict the risk of in-hospital death in adult patients with confirmed COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect similarity between predicted and expected deaths. We identified seven readily available clinical features at ICU admission to be used for risk prediction of in-hospital mortality namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings, neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these variables in an easy-to use web-based risk calculator has the potential to accurately classify ICU admitted patients as likely to be discharged alive or die.

A major strength of this study is the relatively large number of laboratory confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk prediction score includes clinical features that are readily available at ICU admission that increases its clinical applicability. An obvious limitation of this study is the generalizability of risk prediction score in other settings, and we acknowledge that external validation of our risk prediction score in other populations is the next step in model development. Further, the participants included in this study were younger compared with other studies using the data at the time of hospital admission[8 12-17], which may in turn limit the generalizability in older patients.

Previous studies have reported risk prediction scores of mortality based on the clinical features at the time of hospital or ICU admission, including patients with mild,

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moderate or severe forms of disease[6 7 9 10 12-17]. For instance, using data of 4711 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was developed and validated, and consisted of six variables (age, oxygen saturation, mean arterial pressure, blood urea nitrogen, C-Reactive protein, and the international normalized ratio) assessed at the time of hospital admission[12]. Moreover, 10 variables (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct bilirubin) were found to be independent predictive factors, and were included in the risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19[7]. The International Severe Respiratory and emerging Infections Consortium (ISARIC) developed and validated a mortality score consisting of eight variables (age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein) that were available at the initial hospital assessment[9]. In line with this, methods using machine learning have identified 8 important risk factors to predict mortality in ICU admitted patients with COVID-19[15]. Interestingly, nutritional status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time of ICU admission predicted twice the probability of death in patients with high nutritional risk than low risk patients[14]. The difference in the number and types of independent clinical features associated with mortality between our study and others may be explained by the differences in the baseline characteristics of the population or the choice of the statistical analyses. Indeed, we have chosen to use the competing risk regression model instead of the standard Cox proportional hazard model or the logistic regression model because recovery is clearly a competing event to in-hospital death due to COVID-19[19 20].

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Ignoring this property will definitely lead to biased effect estimates. Another plausible reason for this difference in the results is the younger age of the participants in our study compared to other studies[12-17], which could likely influence the clinical features to be included in the risk prediction score.

Other statistical association analyses have been published to investigate the factors affecting mortality due to COVID-19 in patients admitted to ICU[8 11]. For instance, a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted to ICU in the US identified 9 risk factors independently associated with the 28-days mortality. These risk factors included age, sex, body mass index, coronary artery disease, active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the number of hospital ICU beds[8]. In our risk score, none of the comorbid conditions achieved statistical significance for in-hospital mortality, however, other significant laboratory findings such as increased LDH and increased creatinine levels may represent underlying diseases such as liver disease, lung disease or kidney dysfunction.

Interestingly, a non COVID-19 prediction score named Waterlow score has shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly patients[25]. The Waterlow score is a multidimensional pressure ulcer risk assessment tool and includes age, nutritional status, weight, mobility, gender, smoking status, comorbidities, use of medication and continence[25]. One of the significant predictors of mortality included in our risk score is Glasgow Coma Scale which is an objective and reliable way of recording the initial and subsequent level of consciousness, and could be used as a proxy to continence. Although, the association between Waterlow score and mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac

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and stroke conditions, its application in patients with confirmed COVID-19 warrants further investigations.

The recent COVID-19 epidemiological update from WHO, as of May 04, 2021, reported over 5.7 million new weekly cases worldwide which is at the highest level since the beginning of the pandemic[1]. The WHO European and American regions accounted for 20% and 23% of new weekly cases, respectively. The largest increase accounting for 47% of new weekly cases was noted in South East Asia region particularly in India which accounted for over 90% of both cases and deaths in the region. The Eastern Mediterranean region that includes UAE accounted for 6% of new weekly cases[1]. Earlier studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases ranging between 2% and 81%[18 26 27], and high mortality prevalence among ICU patients ranging between 5% and 83%[3 18 28]. A meta-analysis of twenty-five studies with 24,677 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence among patients admitted to ICU with a severe form of COVID-19[18]. The relative high number of deaths in the ICU presents an enormous challenge to the prognostication and management of patients with COVID-19. We believe that the risk tool provided in this study may have utility in clinical settings to guide decision-making, and may facilitate the early identification of patients at high risk of death, and may be used as a guidance in busy ICU units to stratify patients according to their risk in order to deliver the best available supportive care. The parameters selected are easily available at the time of ICU admission.

Conclusion

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We developed and validated a risk tool for predicting in-hospital death among COVID-19 patients admitted to ICU, which shows high predictive accuracy. This tool can assist in early identification of patients during ICU admission who are at high risks of death, and consequently can facilitate optimal delivery of supportive care for these patients.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: The study was approved by the Department of Health of Abu Dhabi COVID-19 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Data availability statement: To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the data is according to the information and rules and regulations of Abu Dhabi Health Services - SEHA and Cerner.

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Competing interest statement: All authors have completed the ICMJE uniform disclosure form and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Figure legends

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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Table 1. Demographics and Clinical Characteristics among Critically Ill Patients with COVID-19.

Characteristics	Total	Died	Alive	*P*-value†
No. (%)	1542 (100)	196 (13)	1346 (87)	
Female sex, n (%)	221 (14.3)	28 (14.3)	193 (14.3)	
Age, mean (SD), years	48.9 (12.7)	56.7 (13.3)	47.8 (12.1)	<.001
Systolic blood pressure, mean (SD), mmHg	126.2 (17.4)	125.5 (21.1)	126.3 (16.8)	0.286
Diastolic blood pressure, mean (SD), mmHg	75.5 (12.1)	72.2 (12.5)	76.0 (12.0)	<.001
Respiratory rate, mean (SD), breaths/min	23.3 (6.7)	27.1 (7.4)	22.7 (6.4)	<.001
Oxygen saturation (SpO_2), n (%)				
<90	487 (31.6)	138 (70.4)	349 (25.9)	
90-94	569 (36.9)	39 (19.9)	530 (39.4)	
≥95	486 (31.5)	19 (9.7)	467 (34.7)	
Oxygen therapy*, n (%)				
Hypoxic respiratory failure requiring supplemental oxygen	736 (47.7)	18 (9.2)	718 (53.3)	
Hypoxic respiratory failure requiring none-invasive mechanical ventilation	76 (4.9)	11 (5.6)	65 (4.8)	
Hypoxic respiratory failure requiring invasive mechanical ventilation	519 (33.7)	167 (85.2)	352 (26.2)	<.001
Coexisting conditions, n (%)				
0	498 (32.3)	39 (19.9)	459 (34.1)	
1	403 (26.1)	45 (23.0)	358 (26.6)	
≥2	641 (41.6)	112 (57.1)	529 (39.3)	<.001
Diabetes, n (%)				
No	874 (56.7)	86 (43.9)	788 (58.5)	
Yes	668 (43.3)	110 (56.1)	558 (41.5)	<.001
Hypertension, n (%)				
No	854 (55.4)	82 (41.8)	772 (57.4)	
Yes	688 (44.6)	114 (58.2)	574 (42.6)	<.001
Respiratory disease, n (%)				
No	1,361 (88.3)	166 (84.7)	1,195 (88.8)	
Yes	181 (11.7)	30 (15.3)	151 (11.2)	0.123

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Characteristics	Total	Died	Alive	*P*-value[†]
Cardiovascular Disease, n (%)				
No	1,053 (68.3)	100 (51.0)	953 (70.8)	
Yes	489 (31.7)	96 (49.0)	393 (29.2)	<.001
Chronic Kidney Disease, n (%)				
No	1,397 (90.6)	159 (81.1)	1,238 (92.0)	
Yes	145 (9.4)	37 (18.9)	108 (8.0)	<.001
Cancer, n (%)				
No	1,479 (95.9)	183 (93.4)	1,296 (96.3)	
Yes	63 (4.1)	13 (6.6)	50 (3.7)	0.083
Liver disease, n (%)				
No	1,437 (93.2)	174 (88.8)	1,263 (93.8)	
Yes	105 (6.8)	22 (11.2)	83 (6.2)	0.013
Glasgow Coma Scale, mean (SD)	13.83 (±3.42)	11.94 (±5.07)	14.28 (±2.71)	<.001
Mild, n (%)	1,391 (90.2)	121 (61.7)	1,270 (94.4)	
Moderate, n (%)	21 (1.4)	7 (3.6)	14 (1.0)	
Severe, n (%)	130 (8.4)	68 (34.7)	62 (4.6)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.
[†]Continuous variables were compared using the t-test or Wilcoxon-rank-sum test, while categorical variables were compared using the Chi-square or Fisher's exact test.
Glasgow Coma Scale: Mild (14-15), Moderate (9-13) or Severe (3-8).
*The percentages do not sum up to 100% because there are patients not requiring any form of oxygen therapy.

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Table 2. Laboratory Findings among Critically Ill Patients with COVID-19.

Variable	Total	Died	Alive	*P*-value
Number. (%)	1542 (100)	196 (13)	1346 (87)	
White blood cells, mean (SD), $^{x}10^{9}$/L	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $^{x}10^{9}$/L	1.28 (0.71)	0.93 (0.57)	1.33 (0.72)	<.001
Lymphocyte percent, mean (SD), %	18.76 (10.74)	10.86 (6.93)	19.92 (10.72)	<.001
Neutrophil count, mean (SD), $^{x}10^{9}$/L	6.00 (3.77)	8.85 (5.65)	5.58 (3.21)	<.001
Neutrophil percent, mean (SD), %	73.04 (13.28)	83.29 (9.96)	71.55 (13.05)	<.001
Neutrophil-lymphocyte count ratio	6.81 (9.39)	13.66 (18.16)	5.82 (6.73)	<.001
Neutrophil-lymphocyte percent ratio	6.82 (9.46)	13.69 (18.33)	5.82 (6.77)	<.001
Monocytes count, mean (SD), $^{x}10^{9}$/L	0.51 (0.36)	0.50 (0.72)	0.51 (0.28)	0.769
Monocytes percent, mean (SD), %	6.93 (3.67)	4.94 (4.99)	7.22 (3.34)	<.001
Platelet count, mean (SD), $^{x}10^{9}$/L	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $^{x}10^{12}$/L	4.75 (0.71)	4.56 (0.80)	4.78 (0.70)	<.001
Red blood cell distribution width, %	13.49 (1.60)	13.97 (1.76)	13.42 (1.56)	<.001
Haemoglobin level, mean (SD), g/L	131.90 (18.24)	126.18 (19.59)	132.73 (17.89)	<.001
Haematocrit, mean (SD), L/L	0.39 (0.05)	0.38 (0.06)	0.40 (0.05)	<.001
Creatinine level, mean (SD), µmol/L	97.76 (111.80)	149.97 (188.91)	90.15 (93.23)	<.001
C-reactive protein level, mean (SD), mg/L	102.13 (94.00)	173.05 (112.06)	91.80 (86.39)	<.001
Lactate dehydrogenase, mean (SD), IU/L	409.32 (223.16)	605.80 (291.22)	380.71 (195.74)	<.001
Serum Chloride, mean (SD), mmol/L	99.25 (4.50)	99.05 (5.97)	99.28 (4.25)	0.600
Serum bicarbonate, mean (SD), mmol/L	22.80 (3.28)	21.02 (4.23)	23.06 (3.04)	<.001
Potassium, mean (SD), mmol/L	4.05 (0.55)	4.21 (0.76)	4.03 (0.50)	0.002
Sodium, mean (SD), mmol/L	136.98 (4.36)	136.97 (5.80)	136.98 (4.11)	0.984
Ferritin, mean (SD), ng/mL	1209.37 (1374.60)	1779.63 (1930.98)	1126.33 (1252.99)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.

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Table 3. Multivariable Adjusted Competing Risk Regression Model for Mortality.

Variables	HR (95% CI)	P-value
Age, years	1.98 (1.71 to 2.31)	<.001
Neutrophils $^{x}10^{9}$/L, percentage	1.71 (1.27 to 2.31)	<.001
Lactate dehydrogenase, IU/L	1.31 (1.15 to 1.49)	<.001
Respiratory rate, breaths/min	1.31 (1.15 to 1.49)	<.001
Glasgow Coma Scale	0.70 (0.63 to 0.78)	<.001
Oxygen saturation (SpO_2)	0.82 (0.74 to 0.91)	<.001
Creatinine, µmol/L	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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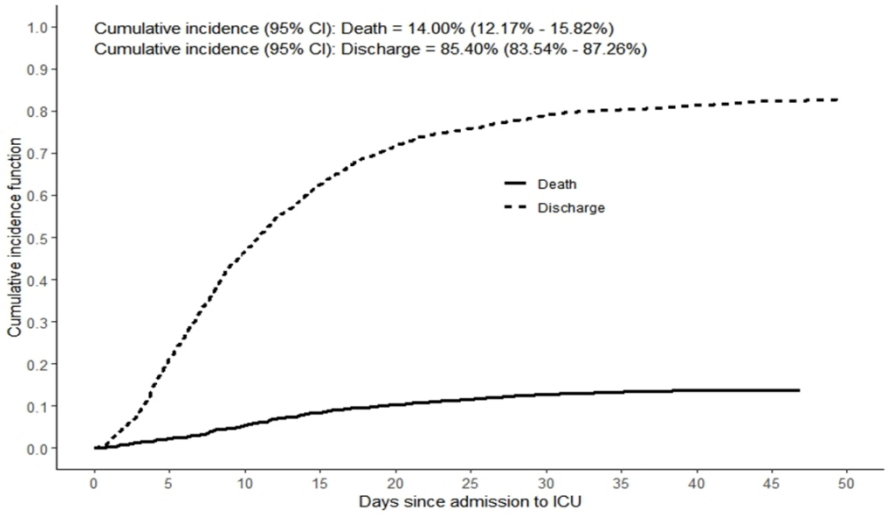

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

338x190mm (96 x 96 DPI)

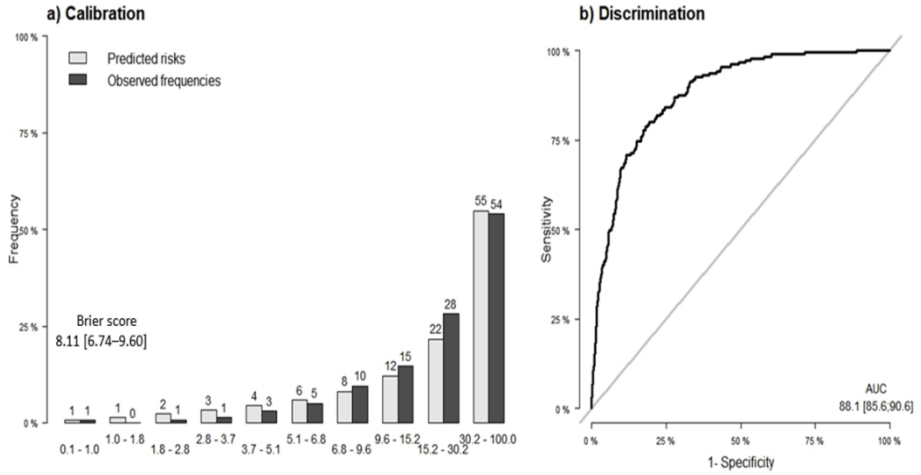

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

338x190mm (96 x 96 DPI)

Supplementary Material

Salem AlKaabi et al. A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

eTable 1. Univariate competing risk models on candidate predictors.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.

eFigure 2. Mortality curves according to risk factors retained in LASSO.

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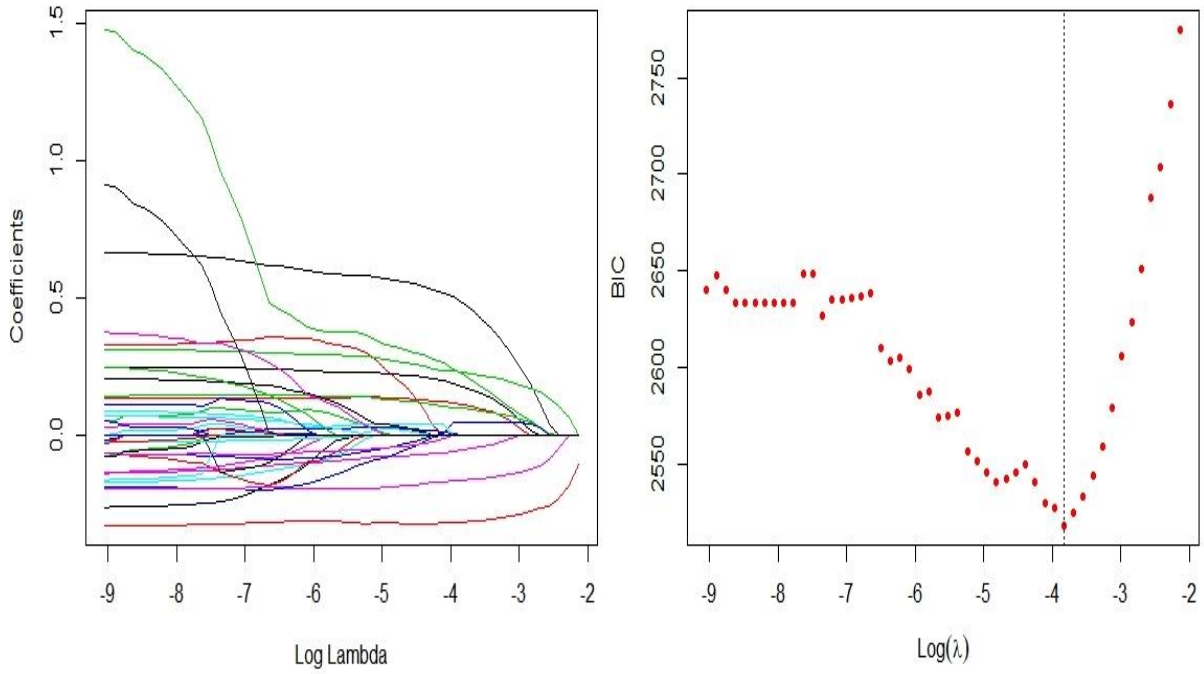
eTable 1. Univariate competing risk models on candidate predictors.

Variable	HR (95% CI)	P-value	AUC (95% CI)
Age	1.83 (1.61, 2.09)	<.001	67.22 (63.11, 71.33)
Male sex	1.02 (0.68, 1.53)	0.92	49.95 (47.20, 52.71)
Diabetes	1.69 (1.28, 2.24)	<.001	56.86 (52.91, 60.80)
Hypertension	1.70 (1.28, 2.26)	<.001	56.31 (52.37, 60.24)
Respiratory disease	1.32 (0.90, 1.94)	0.16	50.82 (48.10, 53.54)
Cardiovascular disease	2.10 (1.58, 2.77)	<.001	58.02 (54.09, 61.95)
Chronic kidney disease	2.36 (1.65, 3.37)	<.001	54.85 (51.87, 57.82)
Cancer	1.72 (0.97, 3.05)	0.062	51.45 (49.51, 53.39)
Liver disease	1.65 (1.07, 2.55)	0.023	51.40 (49.06, 53.73)
Chloride	0.94 (0.78, 1.14)	0.55	52.46 (47.39, 57.52)
Bicarbonate	0.63 (0.55, 0.72)	<.001	67.62 (62.91, 72.33)
Hemoglobin	0.74 (0.65, 0.83)	<.001	59.28 (54.81, 63.76)
Monocytes percentage	0.42 (0.29, 0.61)	<.001	73.55 (69.54, 77.56)
Neutrophil percentage	3.31 (2.57, 4.25)	<.001	76.94 (73.36, 80.51)
Platelets	0.77 (0.65, 0.93)	0.0052	56.86 (52.15, 61.58)
Potassium	1.34 (1.15, 1.57)	<.001	54.51 (49.45, 59.58)
Red blood cell width	1.25 (1.14, 1.38)	<.001	60.02 (55.74, 64.30)
White blood cell	1.55 (1.44, 1.66)	<.001	66.32 (61.80, 70.84)
Creatinine	1.21 (1.12, 1.32)	<.001	61.37 (56.39, 66.34)
Lactate dehydrogenase	1.34 (1.18, 1.51)	<.001	79.00 (75.62, 82.38)
Ferritin	1.26 (1.16, 1.37)	<.001	65.05 (60.92, 69.18)
Systolic blood pressure	0.95 (0.79, 1.13)	0.53	53.33 (48.28, 58.39)
Diastolic blood pressure	0.73 (0.62, 0.85)	<.001	58.82 (53.97, 63.67)
Respiratory rate	1.49 (1.35, 1.64)	<.001	69.45 (65.44, 73.47)
Glasgow coma scale	0.57 (0.52, 0.62)	<.001	67.89 (64.10, 71.68)
C-reactive protein	1.74 (1.55, 1.96)	<.001	71.21 (67.13, 75.30)
Neutrophil-lymphocyte ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.06, 79.27)
Neutrophil-lymphocyte percentage ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.07, 79.28)
Minimum SpO2	0.68 (0.63, 0.74)	<.001	75.82 (71.75, 79.89)
Sodium	1.00 (0.82, 1.22)	0.99	46.84 (41.81, 51.88)
Hematocrit	0.77 (0.67, 0.88)	<.001	57.83 (53.24, 62.43)
Red blood cell	0.76 (0.65, 0.88)	<.001	58.08 (53.38, 62.78)
Lymphocytes count	0.44 (0.33, 0.57)	<.001	68.28 (64.11, 72.44)
Neutrophils count	1.61 (1.49, 1.73)	<.001	70.90 (66.79, 75.02)
Monocytes count	0.94 (0.58, 1.51)	0.79	60.74 (55.92, 65.57)
Lymphocytes percentage	0.29 (0.23, 0.38)	<.001	75.40 (71.78, 79.01)

Abbreviations: HR, hazard ratios; CI, confidence interval; AUC, area under the receiver operating characteristics curve; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.



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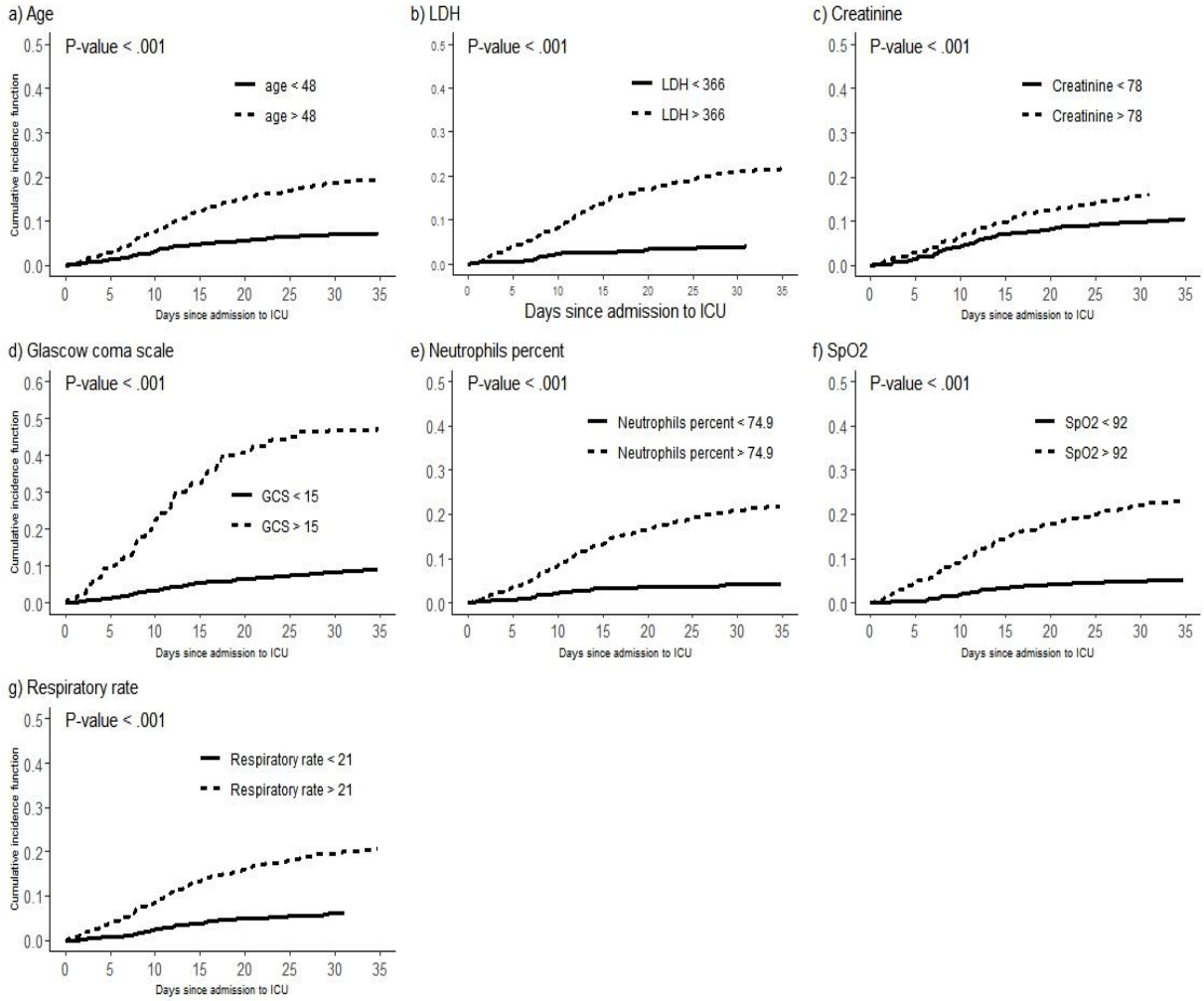
eFigure 2. Mortality curves according to risk factors retained in LASSO



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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7-8
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	9-10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	12
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10-11
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	11
	15b	D	Explain how to the use the prediction model.	12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	11-12
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	4, 13
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	11-12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study.

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A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

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ABSTRACT

OBJECTIVES: To identify factors influencing the mortality risk in critically ill patients with COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit (ICU).

DESIGN: A multicentre cohort study

SETTING AND PARTICIPANTS: 1542 patients with COVID-19 admitted to ICUs in public hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.

MAIN OUTCOMES AND MEASURES: The primary outcome was time from ICU admission until death. We used competing risk regression models and Least Absolute Shrinkage and Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the score was assessed by the area under the receiver operating characteristic curve (AUC), and the Brier score using 500 bootstraps replications.

RESULTS: Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged, and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95% confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven factors associated with mortality, and included in the risk score: age (adjusted hazard ratio [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31), lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI, 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95% CI, 0.63–0.78), and oxygen saturation (SpO_2) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed a freely available web-based risk calculator (https://icumortalityrisk.shinyapps.io/ICUrisk/).

CONCLUSION: In critically ill patients with COVID-19, we identified factors associated with mortality, and developed a risk prediction tool that showed high predictive ability. This tool may

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have utility in clinical settings to guide decision-making, and may facilitate the identification of supportive therapies to improve outcomes.

Key words: COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical care

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Strengths and limitations of this study

- Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of in-hospital mortality, however, limited data is available regarding the risk prediction scores in this population.
- Our clinical risk score includes clinical features which are readily available at ICU admission, thus amplifying its clinical applicability.
- A major limitation is the generalizability of risk prediction score to other settings, and external validation should be the next step.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million patients, and more than 3.1 million have died, as of May 04, 2021[1]. A wide spectrum of clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory failure leading to hospital admission and death[2 3].

The preventive and treatment challenge of COVID-19 is very high because of the complexity of its transmission, substantial heterogeneity in the progression of disease, and lack of proven treatment[4 5]. Several studies have attempted to address this by predicting clinical outcomes using statistical association analyses or prediction model development methods in order to guide the management and prognostication of patients with COVID-19[6-17]. Based on patient characteristics at the time of hospital admission, Liang et al.[7] proposed a risk score to predict critical illness defined as a composite of intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19 patients which consisted of six parameters assessed at the time of hospital admission[12].

A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU admission has also shown higher mortality in COVID-19 patients with high nutritional risk compared with those with low nutritional risk[14]. Further, a prognostic score using machine learning methods has been shown to predict death in ICU patients with COVID-19[15]. Additionally, various demographics, clinical and hospital level risk factors have been reported to be associated with death in patients admitted to ICU[8].

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A recent meta-analysis showed that more than one-fourth of patients with COVID-19 were admitted to ICU globally, and the prevalence of mortality among these patients was very high (31%)[18]. However, limited data is available related to prognostic risk score of in-hospital mortality in critically ill patients with COVID-19 who were admitted to ICU. Therefore, the aim of the present study was to identify the risk factors and the set of clinical markers that increase the risk of death among ICU admitted COVID-19 patients, and to develop a risk prediction score that may facilitate the identification of supportive therapies to improve outcomes. We also aim to develop an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator will provide stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity.

METHODS

Study design and Data sources

This is a multicentre cohort study in which data of all laboratory confirmed COVID-19 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE) between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical records. The data was collected from four major hospitals as well as newly developed field hospitals operating with some ICU bed capacity. The estimated bed capacity for ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We included patients who were admitted to a regular ICU room or to a HDU or if they were consistently receiving any form of oxygen therapy during their hospital stay in a make-

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shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Outcomes

The primary outcome of this study is the survival time defined as the duration of time, from the date of ICU admission, until the date of death. Patients still hospitalized at the date of data extraction were considered as right censored and those discharged alive from the hospital were considered as competing events to death due to COVID-19.

Statistical Analyses

Baseline characteristics were summarized using descriptive statistics including mean and standard deviation for continuous measures, and frequencies tables for categorical variables. We compared categorical variables using the chi-square or Fisher's exact test, and continuous variables using the unpaired t-test or its non-parametric equivalent (Wilcoxon rank sum test) in case the normality assumption is violated.

Potential predictive variables

We considered 36 patient's characteristics assessed at the time of ICU admission as potential predictors based on demographics, clinical signs and symptoms, medical history and laboratory findings. Demographic variables included age and sex. Clinical signs and symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate, Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen saturation (SpO_2). Medical history included status of coexisting conditions: diabetes, hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer, and liver disease. Laboratory findings included white blood cells, monocytes count,

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monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count, lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride, bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with available data on these characteristics were included in the final analysis.

The statistical model

We used the competing risk regression model to investigate the association between death due to COVID-19 and all potential risk factors. We have chosen to use this model, instead of the standard Cox proportional hazard model, because discharge alive or recovery is clearly a competing event to death due to COVID-19[19 20]. Ignoring this property will lead to biased estimates of the hazard ratios and the survival curves. We estimated and plotted the survival curves using the cumulative incidence function taking into account competing risks. Cumulative incidence curves of different groups were compared using the Gray's test[21] for sub-distribution hazards, an equivalent of the log-rank test in the case of competing events. We used the Fine & Gray proportional hazards regression models[22] to investigate the association between potential risk factors and the primary outcome, and also to derive the risk prediction score. All statistical analysis and data management carried out in this paper were done using the R software version 3.6.3 and *P*-values <0.05 were considered as statistically significant.

Variables selection method and derivation of the risk prediction score

We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes Information criterion (BIC) for variables selection[23 24]. This method uses a shrinking

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parameter to penalize non-significant coefficients of the Fine and Gray competing risk regression model. Larger shrinking parameters make the coefficients of non-significant risk factors to shrink towards zero, so that only the strongest predictors remain in the survival model. Unlike the standard selection methods, such as stepwise forward or backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36 potential predictors were scaled using the z-score transformation, and were entered in the selection process. The most predictive covariates were selected by choosing the shrinking parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were statistically significant were retained to construct the risk prediction score. We also investigated all statistical interactions between pairs of the retained predictors.

Validation of the risk prediction score

We derived the 28-day risk of in-hospital death using the estimates obtained from the Fine & Gray competing risk regression model. The predictive ability of this proposed risk prediction score was assessed using discrimination and calibration. Discrimination refers to how well the predictive model is capable of discriminating between individuals who died and those who were discharged alive, whereas calibration refers to the agreement between observed and predicted number of deaths. Discrimination was assessed via the time-dependent area under the receiver-operator characteristic curve (AUC). Calibration was assessed via the time-dependent Brier score, and visually by plotting expected versus observed deaths. To reduce overfitting and optimism bias, we carried out internal validation of the risk prediction score by estimating the AUC and Brier score using 500 bootstraps replications. This method allows all of the original data to be used in the

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model development while providing insight into the extent to which the original model is overfitting or too optimistic.

Patient and Public Involvement:

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

A total of 1695 patients were eligible for the study entry among which 1542 had complete information on all the potential predictors and hence were included in the analysis. The characteristics of the 153 patients who were excluded from the analysis (due to missing values) were not different from those who were included in the current analysis (eTable 1 in the supplement). Almost three quarters of the study patients were Asians and nearly one quarter were Arabs, which is consistent with the demographic composition of the entire population of Abu Dhabi. Of the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%) were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the date of data extraction). Taking into account right-censored observations, the cumulative incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI, 83.54–87.26) (Figure 1).

The demographic and clinical characteristics of the patients are presented in Table 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168 (12.7%) died. Compared with patients who were discharged alive, those who died were older and had higher prevalence of diabetes, hypertension, chronic kidney disease,

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cardiovascular disease, and liver disease; lower diastolic blood pressure, higher respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO_2 and a higher percentage of patients requiring oxygen therapy.

The laboratory findings of the patients included in our study are presented in Table 2. Compared with patients who were discharged alive, those who died had unfavourable laboratory profile on almost all variables including levels of C-reactive protein, creatinine, LDH, red blood cell distribution width, white blood cell count, potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count, haemoglobin, haematocrit, and serum bicarbonates.

The results of the univariate competing risk model for each of the 36 potential predictors measured at ICU admission are presented in the supplement (eTable 2). Of these 36 variables, seven statistically significant predictors of mortality were retained by the LASSO selection procedure in the multivariable competing risk regression model (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals of these significant variables are presented in Table 3. The significant predictors increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–2.31]; *P*<.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<.001), higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), higher respiratory rate (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), and high levels of creatinine (HR, 1.19 [95% CI, 1.11– 1.28]; *P*<.001). The significant predictors lowering the risk of death included higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<.001) and higher SpO_2 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<.001). We found no statistically significant interaction terms between pairs of the retained predictors.

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The cumulative incidence function of these 7 predictors retained by LASSO in the multivariable model is shown in the supplement (eFigure 2). For graphical presentation, we created a binary variable based on the median split in case of continuous risk factors.

Validation of the risk prediction score

The results of the internal validation using 500 bootstrap samples are shown in Figure 2. The predictive ability of the derived risk prediction score was quite promising. Indeed, regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2 also shows the calibration plot for the risk prediction score, in which the predicted frequencies of deaths were plotted against the observed ones.

From Figure 2, it is evident that the predicted frequencies of death were very close to the observed ones suggesting a very good calibration. The risk prediction score provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.

We also developed an easy-to-use web-based risk calculator implementing the derived risk prediction score to allow clinicians enter the values of the selected variables required for the risk calculation of mortality in patients admitted to ICU with COVID-19. The online calculator also provides stratification of patients into high and low risk categories based on an estimated cut-off risk corresponding to optimal performance measures of sensitivity and specificity. The online risk calculator is freely available at (https://icumortalityrisk.shinyapps.io/ICUrisk/).

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DISCUSSION

We developed and internally validated a clinical risk prediction score and a web-based risk calculator to predict the risk of in-hospital death in adult patients with confirmed COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect similarity between predicted and expected deaths. We identified seven readily available clinical features at ICU admission to be used for risk prediction of in-hospital mortality namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings, neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these variables in an easy-to use web-based risk calculator has the potential to accurately classify ICU admitted patients as likely to be discharged alive or die.

A major strength of this study is the relatively large number of laboratory confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk prediction score includes clinical features that are readily available at ICU admission that increases its clinical applicability. An obvious limitation of this study is the generalizability of risk prediction score in other settings, and we acknowledge that external validation of our risk prediction score in other populations is the next step in model development. Further, the participants included in this study were younger compared with other studies using the data at the time of hospital admission[8 12-17], which may in turn limit the generalizability in older patients.

Previous studies have reported risk prediction scores of mortality based on the clinical features at the time of hospital or ICU admission, including patients with mild,

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moderate or severe forms of disease[6 7 9 10 12-17]. For instance, using data of 4711 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was developed and validated, and consisted of six variables (age, oxygen saturation, mean arterial pressure, blood urea nitrogen, C-Reactive protein, and the international normalized ratio) assessed at the time of hospital admission[12]. Moreover, 10 variables (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct bilirubin) were found to be independent predictive factors, and were included in the risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19[7]. The International Severe Respiratory and emerging Infections Consortium (ISARIC) developed and validated a mortality score consisting of eight variables (age, sex, number of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness, urea level, and C reactive protein) that were available at the initial hospital assessment[9]. In line with this, methods using machine learning have identified 8 important risk factors to predict mortality in ICU admitted patients with COVID-19[15]. Interestingly, nutritional status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time of ICU admission predicted twice the probability of death in patients with high nutritional risk than low risk patients[14]. The difference in the number and types of independent clinical features associated with mortality between our study and others may be explained by the differences in the baseline characteristics of the population or the choice of the statistical analyses. Indeed, we have chosen to use the competing risk regression model instead of the standard Cox proportional hazard model or the logistic regression model because recovery is clearly a competing event to in-hospital death due to COVID-19[19 20].

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Ignoring this property will definitely lead to biased effect estimates. Another plausible reason for this difference in the results is the younger age of the participants in our study compared to other studies[12-17], which could likely influence the clinical features to be included in the risk prediction score.

Other statistical association analyses have been published to investigate the factors affecting mortality due to COVID-19 in patients admitted to ICU[8 11]. For instance, a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted to ICU in the US identified 9 risk factors independently associated with the 28-days mortality. These risk factors included age, sex, body mass index, coronary artery disease, active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the number of hospital ICU beds[8]. In our risk score, none of the comorbid conditions achieved statistical significance for in-hospital mortality, however, other significant laboratory findings such as increased LDH and increased creatinine levels may represent underlying diseases such as liver disease, lung disease or kidney dysfunction.

Interestingly, a non COVID-19 prediction score named Waterlow score has shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly patients[25]. The Waterlow score is a multidimensional pressure ulcer risk assessment tool and includes age, nutritional status, weight, mobility, gender, smoking status, comorbidities, use of medication and continence[25]. One of the significant predictors of mortality included in our risk score is Glasgow Coma Scale which is an objective and reliable way of recording the initial and subsequent level of consciousness, and could be used as a proxy to continence. Although, the association between Waterlow score and mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac

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and stroke conditions, its application in patients with confirmed COVID-19 warrants further investigations.

The recent COVID-19 epidemiological update from WHO, as of May 04, 2021, reported over 5.7 million new weekly cases worldwide which is at the highest level since the beginning of the pandemic[1]. The WHO European and American regions accounted for 20% and 23% of new weekly cases, respectively. The largest increase accounting for 47% of new weekly cases was noted in South East Asia region particularly in India which accounted for over 90% of both cases and deaths in the region. The Eastern Mediterranean region that includes UAE accounted for 6% of new weekly cases[1]. Earlier studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases ranging between 2% and 81%[18 26 27], and high mortality prevalence among ICU patients ranging between 5% and 83%[3 18 28]. A meta-analysis of twenty-five studies with 24,677 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence among patients admitted to ICU with a severe form of COVID-19[18]. The relative high number of deaths in the ICU presents an enormous challenge to the prognostication and management of patients with COVID-19. We believe that the risk tool provided in this study may have utility in clinical settings to guide decision-making, and may facilitate the early identification of patients at high risk of death, and may be used as a guidance in busy ICU units to stratify patients according to their risk in order to deliver the best available supportive care. The parameters selected are easily available at the time of ICU admission.

Conclusion

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We developed and internally validated a risk tool for predicting in-hospital death among COVID-19 patients admitted to ICU, which shows high predictive accuracy. This tool can assist in early identification of patients during ICU admission who are at high risks of death, and consequently can facilitate optimal delivery of supportive care for these patients.

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The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Ethical approval: The study was approved by the Department of Health of Abu Dhabi COVID-19 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

Data availability statement: To guarantee the confidentiality of personal and health information, only the authors have had access to the data during the study in accordance with the relevant licence agreements. Access to the data is according to the information and rules and regulations of Abu Dhabi Health Services - SEHA and Cerner.

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Figure legends

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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Table 1. Demographics and Clinical Characteristics among Critically Ill Patients with COVID-19.

Characteristics	Total	Died	Alive	*P*-value†
No. (%)	1542 (100)	196 (13)	1346 (87)	
Female sex, n (%)	221 (14.3)	28 (14.3)	193 (14.3)	
Age, mean (SD), years	48.9 (12.7)	56.7 (13.3)	47.8 (12.1)	<.001
Systolic blood pressure, mean (SD), mmHg	126.2 (17.4)	125.5 (21.1)	126.3 (16.8)	0.286
Diastolic blood pressure, mean (SD), mmHg	75.5 (12.1)	72.2 (12.5)	76.0 (12.0)	<.001
Respiratory rate, mean (SD), breaths/min	23.3 (6.7)	27.1 (7.4)	22.7 (6.4)	<.001
Oxygen saturation (SpO_2), n (%)				
<90	487 (31.6)	138 (70.4)	349 (25.9)	
90-94	569 (36.9)	39 (19.9)	530 (39.4)	
≥95	486 (31.5)	19 (9.7)	467 (34.7)	
Oxygen therapy*, n (%)				
Hypoxic respiratory failure requiring supplemental oxygen	736 (47.7)	18 (9.2)	718 (53.3)	
Hypoxic respiratory failure requiring none-invasive mechanical ventilation	76 (4.9)	11 (5.6)	65 (4.8)	
Hypoxic respiratory failure requiring invasive mechanical ventilation	519 (33.7)	167 (85.2)	352 (26.2)	<.001
Coexisting conditions, n (%)				
0	498 (32.3)	39 (19.9)	459 (34.1)	
1	403 (26.1)	45 (23.0)	358 (26.6)	
≥2	641 (41.6)	112 (57.1)	529 (39.3)	<.001
Diabetes, n (%)				
No	874 (56.7)	86 (43.9)	788 (58.5)	
Yes	668 (43.3)	110 (56.1)	558 (41.5)	<.001
Hypertension, n (%)				
No	854 (55.4)	82 (41.8)	772 (57.4)	
Yes	688 (44.6)	114 (58.2)	574 (42.6)	<.001
Respiratory disease, n (%)				
No	1,361 (88.3)	166 (84.7)	1,195 (88.8)	
Yes	181 (11.7)	30 (15.3)	151 (11.2)	0.123

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Characteristics	Total	Died	Alive	*P*-value[†]
Cardiovascular Disease, n (%)				
No	1,053 (68.3)	100 (51.0)	953 (70.8)	
Yes	489 (31.7)	96 (49.0)	393 (29.2)	<.001
Chronic Kidney Disease, n (%)				
No	1,397 (90.6)	159 (81.1)	1,238 (92.0)	
Yes	145 (9.4)	37 (18.9)	108 (8.0)	<.001
Cancer, n (%)				
No	1,479 (95.9)	183 (93.4)	1,296 (96.3)	
Yes	63 (4.1)	13 (6.6)	50 (3.7)	0.083
Liver disease, n (%)				
No	1,437 (93.2)	174 (88.8)	1,263 (93.8)	
Yes	105 (6.8)	22 (11.2)	83 (6.2)	0.013
Glasgow Coma Scale, mean (SD)	13.83 (±3.42)	11.94 (±5.07)	14.28 (±2.71)	<.001
Mild, n (%)	1,391 (90.2)	121 (61.7)	1,270 (94.4)	
Moderate, n (%)	21 (1.4)	7 (3.6)	14 (1.0)	
Severe, n (%)	130 (8.4)	68 (34.7)	62 (4.6)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.
[†]Continuous variables were compared using the t-test or Wilcoxon-rank-sum test, while categorical variables were compared using the Chi-square or Fisher's exact test.
Glasgow Coma Scale: Mild (14-15), Moderate (9-13) or Severe (3-8).
*The percentages do not sum up to 100% because there are patients not requiring any form of oxygen therapy.

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Table 2. Laboratory Findings among Critically Ill Patients with COVID-19.

Variable	Total	Died	Alive	*P*-value
Number. (%)	1542 (100)	196 (13)	1346 (87)	
White blood cells, mean (SD), $^{x}10^{9}$/L	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $^{x}10^{9}$/L	1.28 (0.71)	0.93 (0.57)	1.33 (0.72)	<.001
Lymphocyte percent, mean (SD), %	18.76 (10.74)	10.86 (6.93)	19.92 (10.72)	<.001
Neutrophil count, mean (SD), $^{x}10^{9}$/L	6.00 (3.77)	8.85 (5.65)	5.58 (3.21)	<.001
Neutrophil percent, mean (SD), %	73.04 (13.28)	83.29 (9.96)	71.55 (13.05)	<.001
Neutrophil-lymphocyte count ratio	6.81 (9.39)	13.66 (18.16)	5.82 (6.73)	<.001
Neutrophil-lymphocyte percent ratio	6.82 (9.46)	13.69 (18.33)	5.82 (6.77)	<.001
Monocytes count, mean (SD), $^{x}10^{9}$/L	0.51 (0.36)	0.50 (0.72)	0.51 (0.28)	0.769
Monocytes percent, mean (SD), %	6.93 (3.67)	4.94 (4.99)	7.22 (3.34)	<.001
Platelet count, mean (SD), $^{x}10^{9}$/L	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $^{x}10^{12}$/L	4.75 (0.71)	4.56 (0.80)	4.78 (0.70)	<.001
Red blood cell distribution width, %	13.49 (1.60)	13.97 (1.76)	13.42 (1.56)	<.001
Haemoglobin level, mean (SD), g/L	131.90 (18.24)	126.18 (19.59)	132.73 (17.89)	<.001
Haematocrit, mean (SD), L/L	0.39 (0.05)	0.38 (0.06)	0.40 (0.05)	<.001
Creatinine level, mean (SD), µmol/L	97.76 (111.80)	149.97 (188.91)	90.15 (93.23)	<.001
C-reactive protein level, mean (SD), mg/L	102.13 (94.00)	173.05 (112.06)	91.80 (86.39)	<.001
Lactate dehydrogenase, mean (SD), IU/L	409.32 (223.16)	605.80 (291.22)	380.71 (195.74)	<.001
Serum Chloride, mean (SD), mmol/L	99.25 (4.50)	99.05 (5.97)	99.28 (4.25)	0.600
Serum bicarbonate, mean (SD), mmol/L	22.80 (3.28)	21.02 (4.23)	23.06 (3.04)	<.001
Potassium, mean (SD), mmol/L	4.05 (0.55)	4.21 (0.76)	4.03 (0.50)	0.002
Sodium, mean (SD), mmol/L	136.98 (4.36)	136.97 (5.80)	136.98 (4.11)	0.984
Ferritin, mean (SD), ng/mL	1209.37 (1374.60)	1779.63 (1930.98)	1126.33 (1252.99)	<.001

Abbreviations: COVID-19; coronavirus disease 2019, SD; standard deviation.

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Table 3. Multivariable Adjusted Competing Risk Regression Model for Mortality.

Variables	HR (95% CI)	P-value
Age, years	1.98 (1.71 to 2.31)	<.001
Neutrophils $^{x}10^{9}$/L, percentage	1.71 (1.27 to 2.31)	<.001
Lactate dehydrogenase, IU/L	1.31 (1.15 to 1.49)	<.001
Respiratory rate, breaths/min	1.31 (1.15 to 1.49)	<.001
Glasgow Coma Scale	0.70 (0.63 to 0.78)	<.001
Oxygen saturation (SpO_2)	0.82 (0.74 to 0.91)	<.001
Creatinine, μmol/L	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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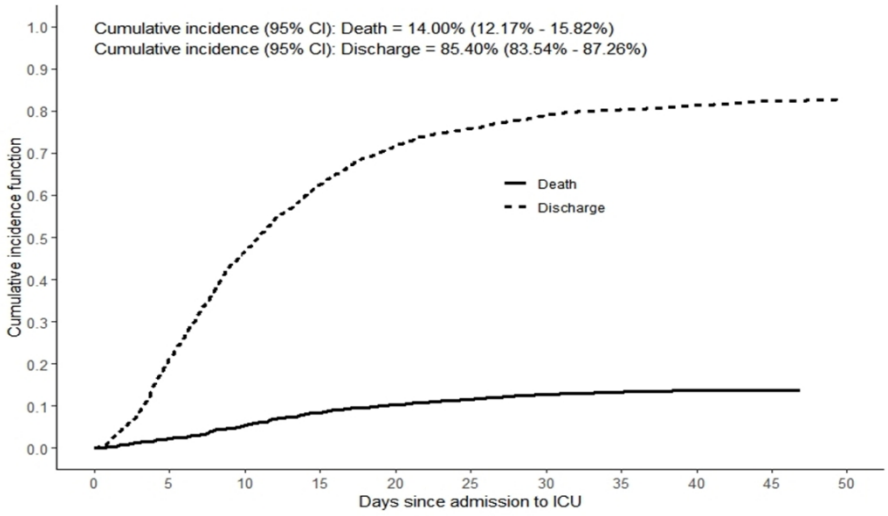

Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

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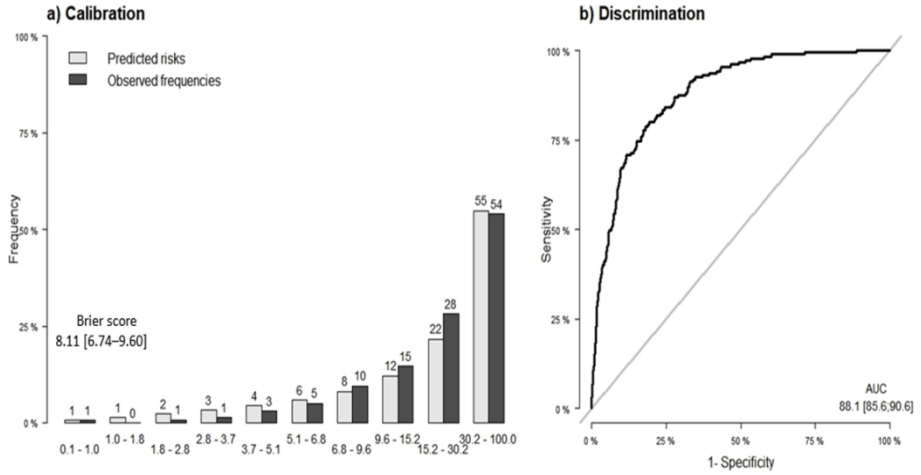

Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

338x190mm (96 x 96 DPI)

Supplementary Material

Salem AlKaabi et al. A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill Patients with COVID-19: A Retrospective Cohort Study

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eTable 1. Comparison of patients who were included in the study analyses vs those who were excluded.

Variables	Included 1,542 (90.97%)	Excluded 153 (9.03%)	P-value†
Age	48.94 (±12.66)	48.63 (±14.42)	0.656
Gender, n (%)			
Female	221 (14.33%)	25 (16.34%)	0.581
Male	1,321 (85.67%)	128 (83.66%)	
Diabetes, n (%)			
No	874 (56.68%)	77 (50.33%)	0.154
Yes	668 (43.32%)	76 (49.67%)	
Hypertension, n (%)			
No	854 (55.38%)	86 (56.21%)	0.912
Yes	688 (44.62%)	67 (43.79%)	
Respiratory disease, n (%)			
No	1,361 (88.26%)	134 (87.58%)	0.907
Yes	181 (11.74%)	19 (12.42%)	
Cardiovascular disease, n (%)			
No	1,053 (68.29%)	103 (67.32%)	0.877
Yes	489 (31.71%)	50 (32.68%)	
Chronic kidney disease, n (%)			
No	1,397 (90.60%)	140 (91.50%)	0.824
Yes	145 (9.40%)	13 (8.50%)	
Cancer, n (%)			
No	1,479 (95.91%)	147 (96.08%)	1.000
Yes	63 (4.09%)	6 (3.92%)	
Liver disease, n (%)			
No	1,437 (93.19%)	143 (93.46%)	1.000
Yes	105 (6.81%)	10 (6.54%)	
Coexisting conditions, n (%)			
0	498 (32.30%)	56 (36.60%)	0.05
1	403 (26.13%)	26 (16.99%)	
≥ 2	641 (41.57%)	71 (46.41%)	
Systolic blood pressure, Mean (±SD)	126.16 (±17.37)	124.86 (±18.19)	0.137
Missing	0 (0%)	5 (3.27%)	
Diastolic blood pressure, Mean (±SD)	75.54 (±12.12)	73.66 (±9.86)	0.070
Missing	0 (0%)	5 (3.27%)	
Respiratory rate, Mean (±SD)	23.26 (±6.70)	22.32 (±6.62)	0.097
Glasgow Coma Scale, Mean (±SD)	13.96 (±3.25)	13.92 (±3.25)	0.635
Missing	0 (0%)	28 (18.30%)	
Glasgow Coma Scale, n (%)			
Mild	1,391 (90.21%)	112 (73.20%)	0.639
Moderate	21 (1.36%)	3 (1.96%)	
Severe	130 (8.43%)	10 (6.54%)	
Missing	0 (0.00%)	28 (18.30%)	
Chloride, Mean (±SD)	99.25 (±4.50)	99.42 (±4.97)	0.675
Missing	0 (0%)	61 (39.87%)	
Bicarbonates, Mean (±SD)	22.80 (±3.28)	22.62 (±3.54)	0.210
Missing	0 (0%)	61 (39.87%)	
Hemoglobin, Mean (±SD)	131.90 (±18.24)	130.04 (±21.45)	0.814
Missing	0 (0%)	68 (44.44%)	
Monocytes percent, Mean (±SD)	6.93 (±3.67)	6.63 (±3.31)	0.474
Missing	0 (0%)	69 (45.10%)	
Neutrophil percent, Mean (±SD)	73.04 (±13.28)	72.58 (±14.16)	0.865
Missing	0 (0%)	69 (45.10%)	

eTable 1. Comparison of patients who were included in the study analyses vs those who were excluded.

Variables	Included 1,542 (90.97%)	Excluded 153 (9.03%)	P-value†
Platelets count, Mean (±SD)	263.57 (±107.94)	257.51 (±118.38)	0.359
Missing	0 (0%)	69 (45.10%)	
Potassium, Mean (±SD)	4.05 (±0.55)	4.05 (±0.55)	0.980
Missing	0 (0%)	61 (39.87%)	
Red blood cell distribution width, Mean (±SD)	13.49 (±1.60)	13.74 (±2.27)	0.829
Missing	0 (0%)	67 (43.79%)	
White blood cells, Mean (±SD)	7.89 (±3.92)	9.21 (±6.08)	0.257
Missing	0 (0%)	68 (44.44%)	
Creatinine, Mean (±SD)	97.76 (±111.80)	95.09 (±71.56)	0.300
Missing	0 (0%)	59 (38.56%)	
Lactate dehydrogenase, Mean (±SD)	409.32 (±223.16)	400.00 (±125.96)	0.431
Missing	0 (0%)	121 (79.08%)	
Ferritin, Mean (±SD)	1209.37 (±1374.60)	1031.91 (±996.80)	0.400
Missing	0 (0%)	116 (75.82%)	
C-reactive protein level, Mean (±SD)	102.13 (±94.00)	88.42 (±94.52)	0.057
Missing	0 (0%)	76 (49.67%)	
Sodium, Mean (±SD)	136.98 (±4.36)	136.87 (±4.76)	0.446
Missing	0 (0%)	61 (39.87%)	
Hematocrit, Mean (±SD)	0.39 (±0.05)	0.39 (±0.06)	0.462
Missing	0 (0%)	67 (43.79%)	
Red blood cells, Mean (±SD)	4.75 (±0.71)	4.64 (±0.73)	0.542
Missing	0 (0%)	67 (43.79%)	
Lymphocytes count, Mean (±SD)	1.28 (±0.71)	1.38 (±0.90)	0.440
Missing	0 (0%)	69 (45.10%)	
Neutrophils count, Mean (±SD)	6.00 (±3.77)	6.94 (±4.87)	0.376
Missing	0 (0%)	69 (45.10%)	
Monocyte count, Mean (±SD)	0.51 (±0.36)	0.54 (±0.33)	0.514
Missing	0 (0%)	69 (45.10%)	
Lymphocyte percent, Mean (±SD)	18.76 (±10.74)	18.72 (±11.70)	0.824
Missing	0 (0%)	69 (45.10%)	
Neutrophil-lymphocyte percent ratio, Mean (±SD)	6.82 (±9.46)	8.09 (±11.18)	0.828
Missing	0 (0%)	69 (45.10%)	
Neutrophil-lymphocyte count ratio, Mean (±SD)	6.81 (±9.39)	8.09 (±11.18)	0.830
Missing	0 (0%)	69 (45.10%)	

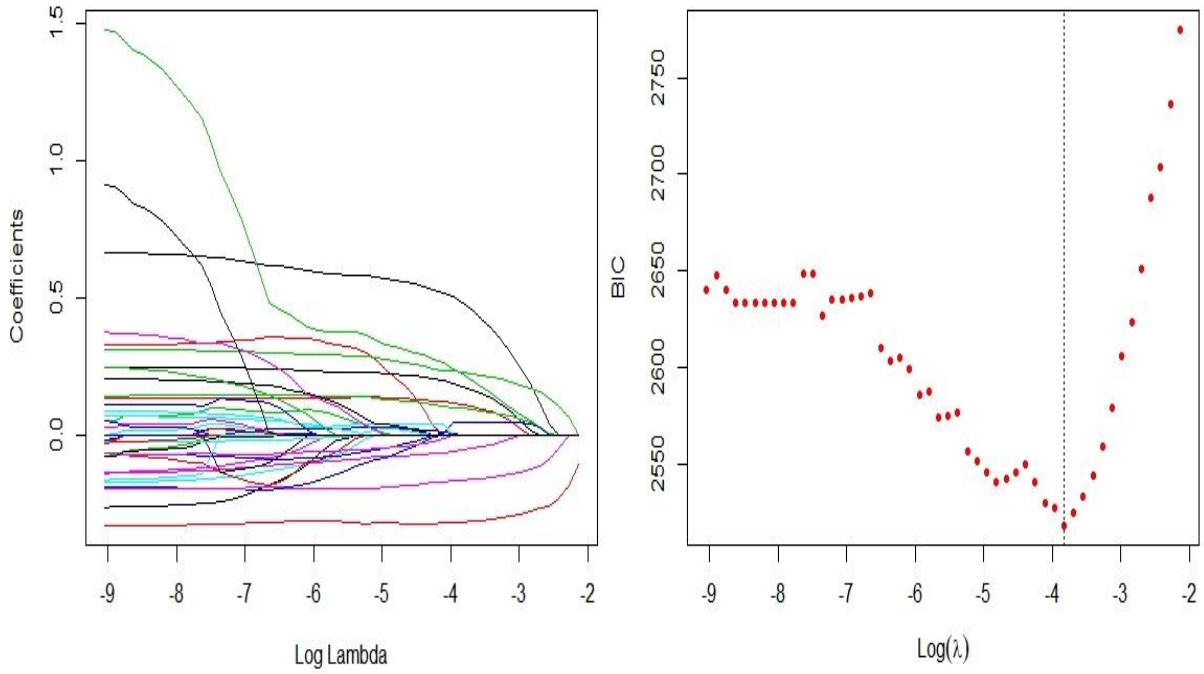
†Continuous variables were compared using the t-test Wilcoxon-rank-sum test, while discrete variables were compared using the Chi-square test Fisher's exact test.

eTable 2. Univariate competing risk models on candidate predictors.

Variable	HR (95% CI)	P-value	AUC (95% CI)
Age	1.83 (1.61, 2.09)	<.001	67.22 (63.11, 71.33)
Male sex	1.02 (0.68, 1.53)	0.92	49.95 (47.20, 52.71)
Diabetes	1.69 (1.28, 2.24)	<.001	56.86 (52.91, 60.80)
Hypertension	1.70 (1.28, 2.26)	<.001	56.31 (52.37, 60.24)
Respiratory disease	1.32 (0.90, 1.94)	0.16	50.82 (48.10, 53.54)
Cardiovascular disease	2.10 (1.58, 2.77)	<.001	58.02 (54.09, 61.95)
Chronic kidney disease	2.36 (1.65, 3.37)	<.001	54.85 (51.87, 57.82)
Cancer	1.72 (0.97, 3.05)	0.062	51.45 (49.51, 53.39)
Liver disease	1.65 (1.07, 2.55)	0.023	51.40 (49.06, 53.73)
Chloride	0.94 (0.78, 1.14)	0.55	52.46 (47.39, 57.52)
Bicarbonate	0.63 (0.55, 0.72)	<.001	67.62 (62.91, 72.33)
Hemoglobin	0.74 (0.65, 0.83)	<.001	59.28 (54.81, 63.76)
Monocytes percentage	0.42 (0.29, 0.61)	<.001	73.55 (69.54, 77.56)
Neutrophil percentage	3.31 (2.57, 4.25)	<.001	76.94 (73.36, 80.51)
Platelets	0.77 (0.65, 0.93)	0.0052	56.86 (52.15, 61.58)
Potassium	1.34 (1.15, 1.57)	<.001	54.51 (49.45, 59.58)
Red blood cell width	1.25 (1.14, 1.38)	<.001	60.02 (55.74, 64.30)
White blood cell	1.55 (1.44, 1.66)	<.001	66.32 (61.80, 70.84)
Creatinine	1.21 (1.12, 1.32)	<.001	61.37 (56.39, 66.34)
Lactate dehydrogenase	1.34 (1.18, 1.51)	<.001	79.00 (75.62, 82.38)
Ferritin	1.26 (1.16, 1.37)	<.001	65.05 (60.92, 69.18)
Systolic blood pressure	0.95 (0.79, 1.13)	0.53	53.33 (48.28, 58.39)
Diastolic blood pressure	0.73 (0.62, 0.85)	<.001	58.82 (53.97, 63.67)
Respiratory rate	1.49 (1.35, 1.64)	<.001	69.45 (65.44, 73.47)
Glasgow coma scale	0.57 (0.52, 0.62)	<.001	67.89 (64.10, 71.68)
C-reactive protein	1.74 (1.55, 1.96)	<.001	71.21 (67.13, 75.30)
Neutrophil-lymphocyte ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.06, 79.27)
Neutrophil-lymphocyte percentage ratio	1.31 (1.25, 1.38)	<.001	75.67 (72.07, 79.28)
Minimum SpO2	0.68 (0.63, 0.74)	<.001	75.82 (71.75, 79.89)
Sodium	1.00 (0.82, 1.22)	0.99	46.84 (41.81, 51.88)
Hematocrit	0.77 (0.67, 0.88)	<.001	57.83 (53.24, 62.43)
Red blood cell	0.76 (0.65, 0.88)	<.001	58.08 (53.38, 62.78)
Lymphocytes count	0.44 (0.33, 0.57)	<.001	68.28 (64.11, 72.44)
Neutrophils count	1.61 (1.49, 1.73)	<.001	70.90 (66.79, 75.02)
Monocytes count	0.94 (0.58, 1.51)	0.79	60.74 (55.92, 65.57)
Lymphocytes percentage	0.29 (0.23, 0.38)	<.001	75.40 (71.78, 79.01)

Abbreviations: HR, hazard ratios; CI, confidence interval; AUC, area under the receiver operating characteristics curve; SpO_2, peripheral capillary oxygen saturation.
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

eFigure 1. Feature selection using the least absolute shrinkage and selection operator (LASSO) competing risk survival model.



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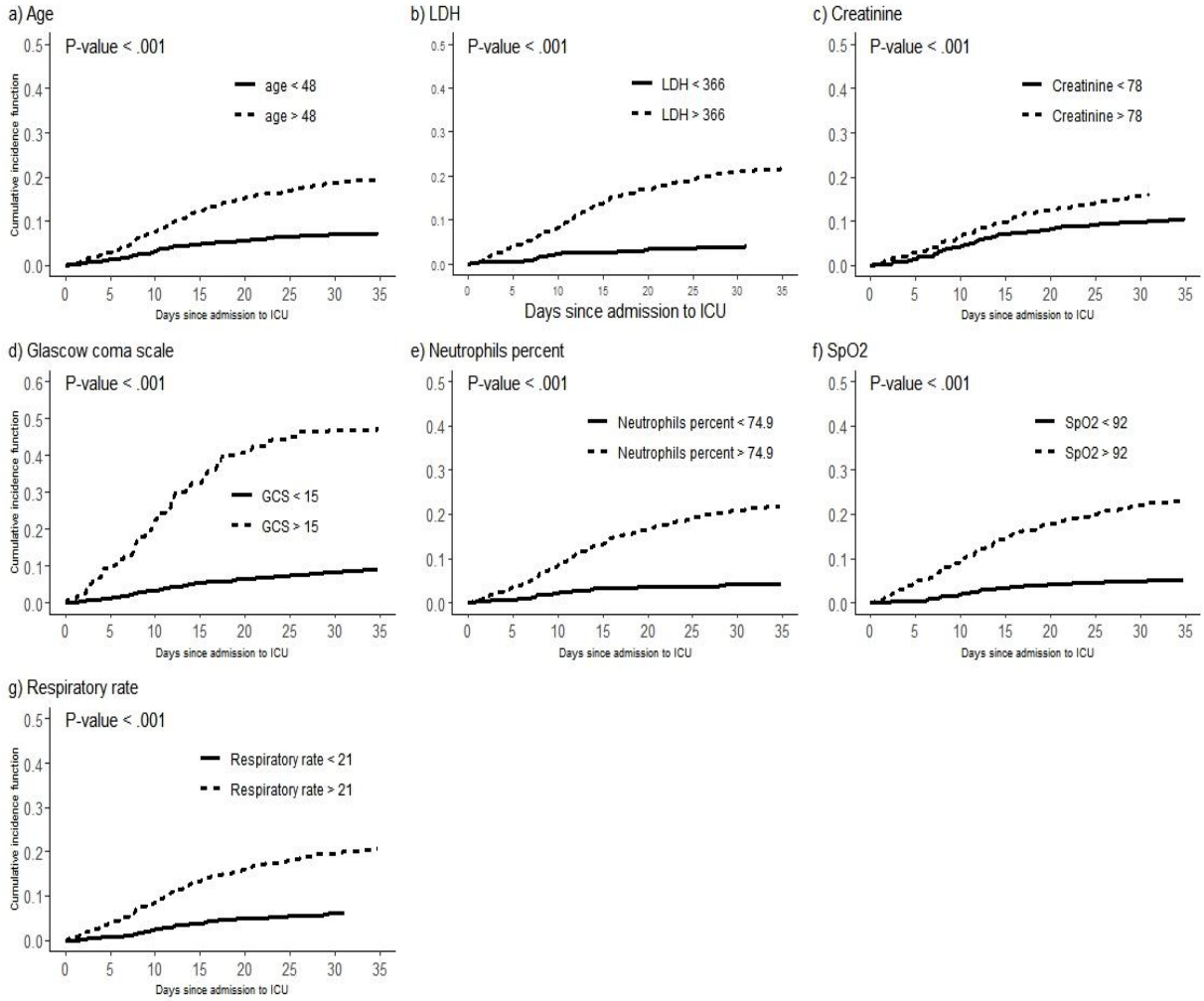
eFigure 2. Mortality curves according to risk factors retained in LASSO



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TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2-3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	6
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6
	5b	D;V	Describe eligibility criteria for participants.	6
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	7
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7-8
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	6
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	8
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	8-9
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8-9
	10c	V	For validation, describe how the predictions were calculated.	9-10
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	9-10
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	12
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	NA
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	10
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	10-11
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	NA
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	10
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	11
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	11
	15b	D	Explain how to the use the prediction model.	12
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	11-12
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	4, 13
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	NA
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	13-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	11-12
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.