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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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3 Identification of Factors and Development of a Clinical Risk Score to
4 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 (SpO₂) (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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2 have utility in clinical settings to guide decision-making, and may facilitate the identification of
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4 supportive therapies to improve outcomes.
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6 **Key words:** COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical
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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.

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, 2020¹. 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-19⁶⁻¹¹. 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 ICU⁸.

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-19¹⁴.

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.

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 test¹⁸ 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 models¹⁹ 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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3 data management carried out in this paper were done using the R software version 3.6.3
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5 and P -values <0.05 were considered as statistically significant.
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8 9 ***Potential predictive variables***

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

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44 We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes
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46 Information criterion (BIC) for variables selection^{20 21}. This method uses a shrinking
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48 parameter to penalize non-significant coefficients of the Fine and Gray competing risk
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50 regression model. Larger shrinking parameters make the coefficients of non-significant
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52 risk factors to shrink towards zero, so that only the strongest predictors remain in the
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54 survival model. Unlike the standard selection methods, such as stepwise forward or
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3 backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36
4 potential predictors were scaled using the z-score transformation, and were entered in the
5 selection process. The most predictive covariates were selected by choosing the shrinking
6 parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were
7 statistically significant were retained to construct the risk prediction score.
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15 *Validation of the risk prediction score*

17 We derived the risk of death using the estimates obtained from the Fine & Gray
18 competing risk regression model. The predictive ability of this proposed risk prediction
19 score was assessed using discrimination and calibration. Discrimination refers to how
20 well the predictive model is capable of discriminating between individuals who died and
21 those who were discharged alive, whereas calibration refers to the agreement between
22 observed and predicted number of deaths. Discrimination was assessed via the time-
23 dependent area under the receiver-operator characteristic curve (AUC). Calibration was
24 assessed via the time-dependent Brier score, and visually by plotting expected versus
25 observed deaths. To reduce overfitting and optimism bias, we carried out internal
26 validation of the risk prediction score by estimating the AUC and Brier score using 500
27 bootstraps replications. This method allows all of the original data to be used in the
28 model development while providing insight into the extent to which the original model is
29 overfitting or too optimistic.
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47 We also developed an easy-to-use web-based risk calculator implementing the
48 derived risk prediction score to allow clinicians enter the values of the selected variables
49 required for the risk calculation of mortality in patients admitted to ICU with COVID-19.
50 The online calculator also provides stratification of patients into high and low risk
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3 categories based on an estimated cutoff risk corresponding to optimal performance
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5 measures of sensitivity and specificity.
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8 9 **RESULTS**

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11 Among the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%)
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13 were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the
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15 date of data extraction). Taking into account right-censored observations, the cumulative
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17 incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–
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19 15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI,
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21 83.54–87.26) (Figure 1).
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25 The demographic and clinical characteristics of the patients are presented in Table
26
27 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168
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29 (12.7%) died. Compared with patients who were discharged alive, those who died were
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31 older and had higher prevalence of diabetes, hypertension, chronic kidney disease,
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33 cardiovascular disease, and liver disease; lower diastolic blood pressure, higher
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35 respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO₂ and a higher
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37 percentage of patients requiring oxygen therapy.
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41 The laboratory findings of these patients are presented in Table 2. Compared with
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43 patients who were discharged alive, those who died had unfavorable laboratory profile on
44
45 almost all variables including levels of C-reactive protein, creatinine, LDH, red blood cell
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47 distribution width, white blood cell count, potassium, ferritin, values of red blood cells,
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49 lymphocytes, monocytes, platelets count, hemoglobin, hematocrit, and serum
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51 bicarbonates.
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3 The results of the univariate competing risk model for each of the 36 potential predictors
4 measured at ICU admission are presented in the supplement (eTable 1). Of these 36
5 variables, seven statistically significant predictors of mortality were retained by the
6
7 LASSO selection procedure in the multivariable competing risk regression model
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9 (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals
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11 of these significant variables are presented in Table 3. The significant predictors
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13 increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–
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15 2.31]; *P*<0.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<0.001),
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17 higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<0.001), higher respiratory rate
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19 (HR, 1.31 [95% CI, 1.15–1.49]; *P*<0.001), and high levels of creatinine (HR, 1.19 [95%
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21 CI, 1.11–1.28]; *P*<0.001). The significant predictors lowering the risk of death included
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23 higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63–0.78]; *P*<0.001) and higher SpO₂
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25 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<0.001).
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33 The cumulative incidence function of these 7 predictors retained by LASSO in the
34 multivariable model is shown in the supplement (eFigure 2). In case of continuous risk
35 factors, we created a binary variable based on the median split.
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41 ***Validation of the risk prediction score***

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43 The results of the internal validation using 500 bootstrap samples are shown in Figure 2.
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45 The predictive ability of the derived risk prediction score was quite promising. Indeed,
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47 regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the
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49 Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2
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51 also shows the calibration plot for the risk prediction score, in which the predicted
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53 frequencies of deaths were plotted against the observed ones.
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3 From Figure 2, it is evident that the predicted frequencies of death were very close to the
4 observed ones suggesting a very good calibration. The risk prediction score provided a
5 sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%. The online risk
6 calculator derived from the risk prediction score for the calculation of mortality in
7 patients admitted to ICU with COVID-19 is freely available at
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15 (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).

18 DISCUSSION

20 We developed and validated a clinical risk prediction score and a web-based risk
21 calculator to predict the risk of death in adult patients with confirmed COVID-19
22 admitted to ICUs. The risk prediction score shows high accuracy in terms of
23 discrimination (AUC = 88.1) and calibration (Brier score = 8.11) with an almost perfect
24 similarity between predicted and expected deaths. We identified seven readily available
25 clinical features at ICU admission to be used for risk prediction of mortality namely age,
26 minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings, neutrophil
27 percentage, LDH, and creatinine levels. Our work shows that input of these variables in
28 an easy-to use web-based risk calculator has the potential to accurately classify ICU
29 admitted patients as likely to be discharged alive or die.
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44 A major strength of this study is the relatively large number of laboratory
45 confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a
46 broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk
47 prediction score includes clinical features that are readily available at ICU admission that
48 increases its clinical applicability. An obvious limitation of this study is the
49 generalizability of risk prediction score in other settings, and we acknowledge that
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3 external validation of our risk prediction score in other populations is the next step in
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5 model development.
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8 To the best of our knowledge, our study is the first one to provide a risk
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10 prediction score of mortality for COVID-19 patients admitted to ICU. Previous studies
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12 have reported risk prediction scores of mortality based on the clinical features at the time
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14 of hospital admission, not ICU admission, including patients with mild, moderate or
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16 severe forms of disease^{6 7 9 10} Meanwhile, other statistical association analyses have been
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18 published to investigate the factors affecting mortality due to COVID-19 in patients
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20 admitted to ICU¹¹. For instance, a multicenter cohort study of 2215 adults with
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22 laboratory-confirmed COVID-19 admitted to ICU in the US identified 9 risk factors
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24 independently associated with the 28-days mortality. These risk factors included age, sex,
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26 body mass index, coronary artery disease, active cancer, presence of hypoxemia, liver
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28 dysfunction, kidney dysfunction, and the number of hospital ICU beds⁸. The difference in
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30 the number and types of independent clinical features associated with ICU mortality
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32 between our study and others may be explained by the differences in the baseline
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34 characteristics of the population or the choice of the statistical analyses. Indeed, we have
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36 chosen to use the competing risk regression model instead of the standard Cox
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38 proportional hazard model or the logistic regression model because recovery is clearly a
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40 competing event to death due to COVID-19^{16 17}. Ignoring this property will definitely
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42 lead to biased effect estimates.
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49 A recent meta-analysis showed that more than one-fourth of patients with
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51 COVID-19 were admitted to ICU globally, and the prevalence of mortality among these
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53 patients was very high (31%)¹⁴. The relative high number of deaths in the ICU presents
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3 an enormous challenge to the prognostication and management of patients with COVID-
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5 19. We believe that the results of our study and the stratification of ICU admitted patients
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7 into high and low risk categories throughout the patient's encounter may facilitate the
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9 clinical and ICU teams to identify and promptly focus on the medications and supportive
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11 therapies to prevent deaths.
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14 15 **Conclusion**

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17 We developed and validated a risk tool for predicting death among COVID-19 patients
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19 admitted to ICU, which shows high predictive accuracy. This tool may have utility in
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21 clinical settings to guide decision-making, and may facilitate the identification of
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23 medications and supportive therapies to improve outcomes. To the best of our
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25 knowledge, this is the first mortality prediction model for patients admitted to ICU due to
26
27 COVID-19. The parameters selected are easily available at the time of ICU admission.
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29 The freely available web-based calculator may facilitate the early identification of
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31 patients at high risk of death, and may be used as a guidance in busy ICU units to stratify
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33 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.

Conflict of interest: None reported.

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3 preparation, review, or approval of the manuscript; and decision to submit the manuscript
4 for publication.
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7 **Competing interest statement:** All authors have completed the ICMJE uniform
8 disclosure form and declare: no support from any organisation for the submitted work; no
9 financial relationships with any organisations that might have an interest in the submitted
10 work in the previous three years , no other relationships or activities that could appear to
11 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.

For peer review only

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 non-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)	

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)				
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).

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), $\times 10^9/L$	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	0.000
Lymphocyte count, mean (SD), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $\times 10^{12}/L$	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), $\mu\text{mol}/L$	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.

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 $\times 10^9/L$, 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, $\mu\text{mol/L}$	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO₂, 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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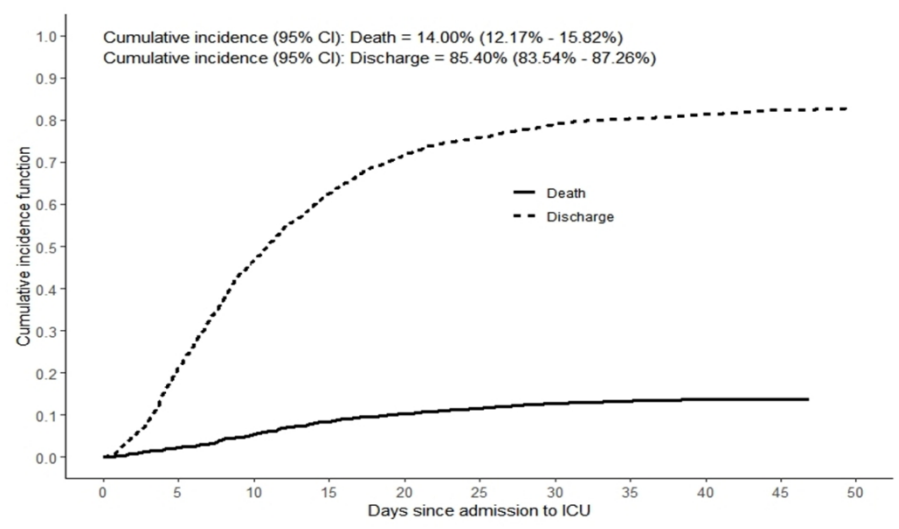


Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

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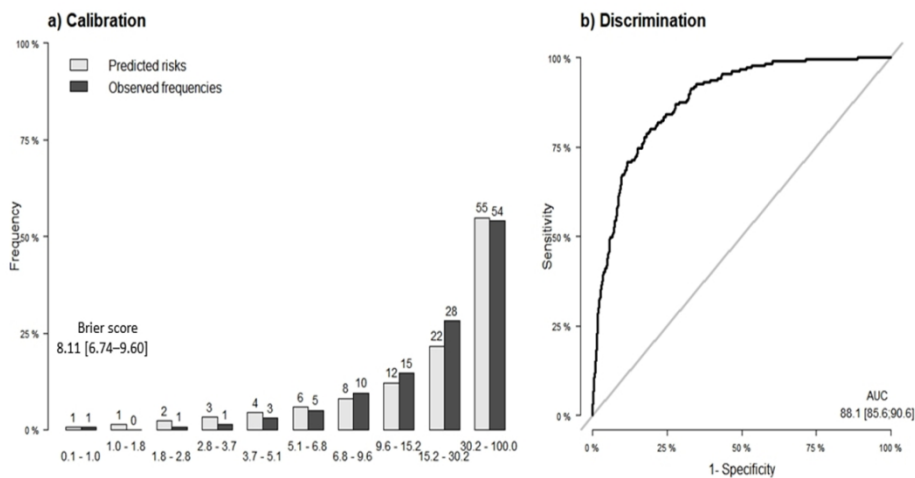


Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

338x190mm (96 x 96 DPI)

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.

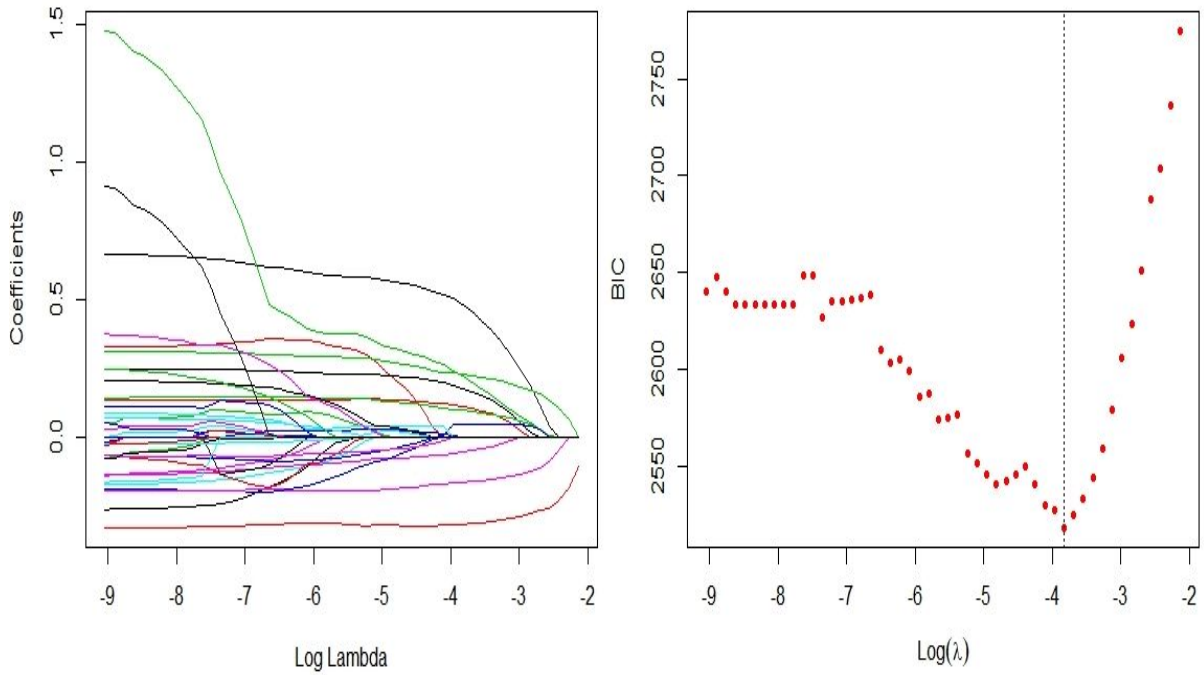
eTable 1. Univariate competing risk models on candidate predictors.

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 SpO ₂	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; SpO₂, peripheral capillary oxygen saturation.

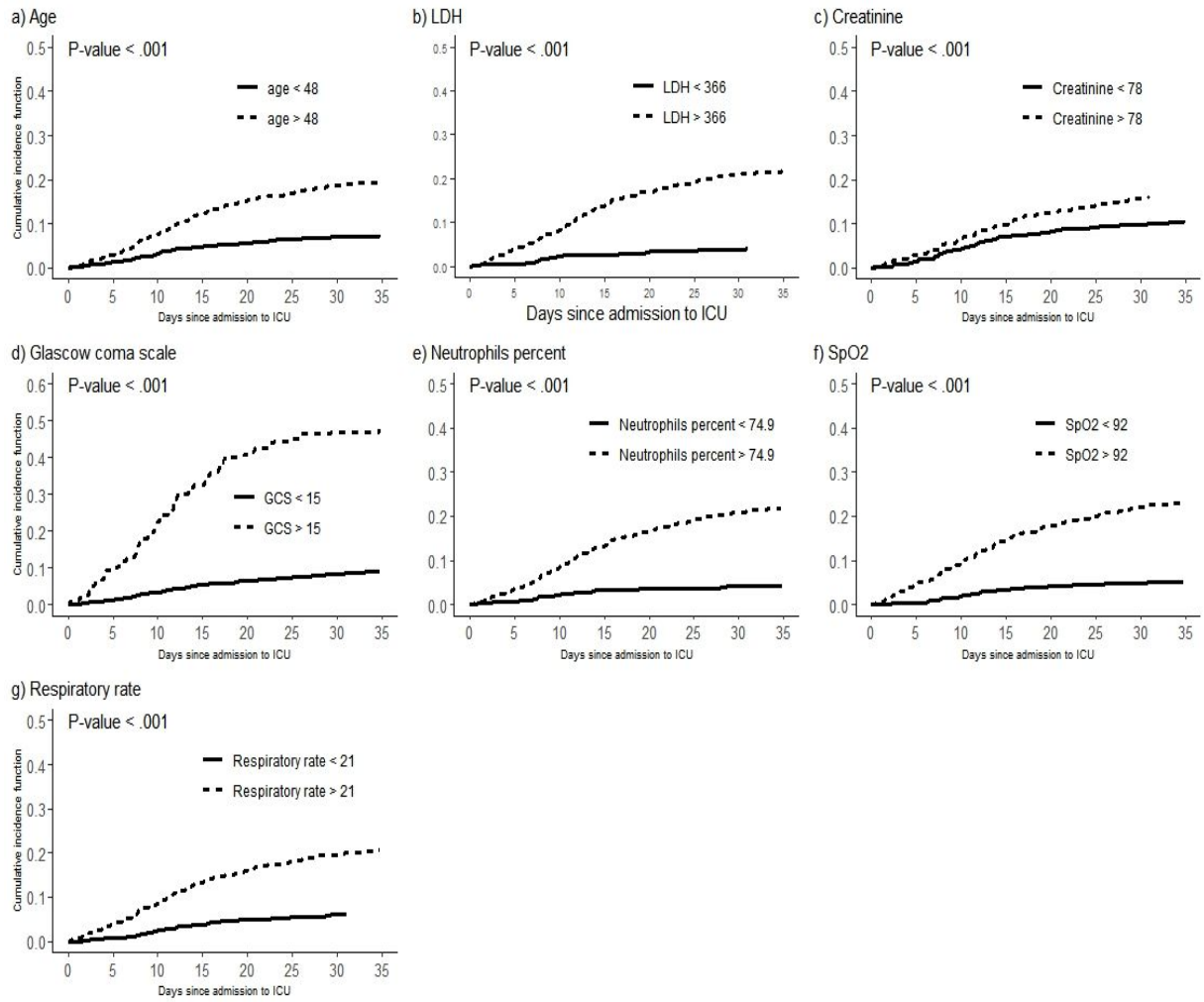
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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



view only

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



Only

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
		(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	
Participants	6	<i>Case-control study</i> —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	6
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
		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
		(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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	
Statistical methods	12	<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	7
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-048770.R1
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Secondary Subject Heading:	Emergency medicine, Intensive care, Infectious diseases
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1 A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill
2 Patients with COVID-19: A Retrospective Cohort Study

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1
2 25 **ABSTRACT**
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4 26 **OBJECTIVES:** To identify factors influencing the mortality risk in critically ill patients with
5
6 27 COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit
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9 28 (ICU).
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11 29 **DESIGN:** A multicentre cohort study
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13 30 **SETTING AND PARTICIPANTS:** 1542 patients with COVID-19 admitted to ICUs in public
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16 31 hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.
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18 32 **MAIN OUTCOMES AND MEASURES:** The primary outcome was time from ICU admission
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20 33 until death. We used competing risk regression models and Least Absolute Shrinkage and
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22 34 Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the
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24 35 score was assessed by the area under the receiver operating characteristic curve (AUC), and the
25
26 36 Brier score using 500 bootstraps replications.
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29 37 **RESULTS:** Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged,
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31 38 and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95%
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33 39 confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven
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35 40 factors associated with mortality, and included in the risk score: age (adjusted hazard ratio
36
37 41 [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31),
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39 42 lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI,
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41 43 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95%
42
43 44 CI, 0.63–0.78), and oxygen saturation (SpO₂) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC
44
45 45 was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed
46
47 46 a freely available web-based risk calculator (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).
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50 47 **CONCLUSION:** In critically ill patients with COVID-19, we identified factors associated with
51
52 48 mortality, and developed a risk prediction tool that showed high predictive ability. This tool may
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2 49 have utility in clinical settings to guide decision-making, and may facilitate the identification of
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4 50 supportive therapies to improve outcomes.
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6 51 **Key words:** COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical
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9 52 care
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2 53 **Strengths and limitations of this study**
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- 4 54 • Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of
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6 55 in-hospital mortality, however, limited data is available regarding the risk prediction
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8 56 scores in this population.
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11 57 • Our clinical risk score includes clinical features which are readily available at ICU
12
13 58 admission, thus amplifying its clinical applicability.
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16 59 • The score showed high predictive ability for in-hospital mortality.
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18 60 • A major limitation is the generalizability of risk prediction score to other settings, and
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20 61 external validation should be the next step.
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62 INTRODUCTION

63 The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute
64 respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million
65 patients, and more than 3.1 million have died, as of May 04, 2021¹. A wide spectrum of
66 clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic
67 infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory
68 failure leading to hospital admission and death^{2,3}.

69 The preventive and treatment challenge of COVID-19 is very high because of the
70 complexity of its transmission, substantial heterogeneity in the progression of disease,
71 and lack of proven treatment^{4,5}. Several studies have attempted to address this by
72 predicting clinical outcomes using statistical association analyses or prediction model
73 development methods in order to guide the management and prognostication of patients
74 with COVID-19⁶⁻¹⁵. Based on patient characteristics at the time of hospital admission,
75 Liang et al.⁷ proposed a risk score to predict critical illness defined as a composite of
76 intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity
77 score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19
78 patients which consisted of six parameters assessed at the time of hospital admission¹².

79 A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU
80 admission has also shown higher mortality in COVID-19 patients with high nutritional
81 risk compared with those with low nutritional risk¹⁴. Further, a prognostic score using
82 machine learning methods has been shown to predict death in ICU patients with COVID-
83 19¹⁵. Additionally, various demographics, clinical and hospital level risk factors have
84 been reported to be associated with death in patients admitted to ICU⁸.

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3 85 A recent meta-analysis showed that more than one-fourth of patients with
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5 86 COVID-19 were admitted to ICU globally, and the prevalence of mortality among these
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7 87 patients was very high (31%)¹⁶. However, limited data is available related to prognostic
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9 88 risk score of in-hospital mortality in critically ill patients with COVID-19 who were
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11 89 admitted to ICU. Therefore, the aim of the present study was to identify the risk factors
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13 90 and the set of clinical markers that increase the risk of death among ICU admitted
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15 91 COVID-19 patients, and to develop a risk prediction score that may facilitate the
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17 92 identification of supportive therapies to improve outcomes. We also aim to develop an
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19 93 easy-to-use web-based risk calculator implementing the derived risk prediction score to
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21 94 allow clinicians enter the values of the selected variables required for the risk calculation
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23 95 of mortality in patients admitted to ICU with COVID-19. The online calculator will
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25 96 provide stratification of patients into high and low risk categories based on an estimated
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27 97 cut-off risk corresponding to optimal performance measures of sensitivity and specificity.
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34 98 **METHODS**

35 99 **Study design and Data sources**

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38 100 This is a multicentre cohort study in which data of all laboratory confirmed COVID-19
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40 101 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE)
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42 102 between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical
43
44 103 records. The data was collected from four major hospitals as well as newly developed
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46 104 field hospitals operating with some ICU bed capacity. The estimated bed capacity for
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48 105 ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We
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50 106 included patients who were admitted to a regular ICU room or to a HDU or if they were
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52 107 consistently receiving any form of oxygen therapy during their hospital stay in a make-
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3 108 shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9
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5 109 IRB ethical committee (Ref#DOH/CVDC/2020/1116).
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8 110 **Outcomes**

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10 111 The primary outcome of this study is the survival time defined as the duration of time,
11
12 112 from the date of ICU admission, until the date of death. Patients still hospitalized at the
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14 113 date of data extraction were considered as right censored and those discharged alive from
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16 114 the hospital were considered as competing events to death due to COVID-19.
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20 115 **Statistical Analyses**

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22 116 Baseline characteristics were summarized using descriptive statistics including mean and
23
24 117 standard deviation for continuous measures, and frequencies tables for categorical
25
26 118 variables. We compared categorical variables using the chi-square or Fisher's exact test,
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28 119 and continuous variables using the unpaired t-test or its non-parametric equivalent
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30 120 (Wilcoxon rank sum test) in case the normality assumption is violated.
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35 121 ***Potential predictive variables***

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37 122 We considered 36 patient's characteristics assessed at the time of ICU admission as
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39 123 potential predictors based on demographics, clinical signs and symptoms, medical history
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41 124 and laboratory findings. Demographic variables included age and sex. Clinical signs and
42
43 125 symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate,
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45 126 Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen
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47 127 saturation (SpO₂). Medical history included status of coexisting conditions: diabetes,
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49 128 hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer,
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51 129 and liver disease. Laboratory findings included white blood cells, monocytes count,
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3 130 monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count,
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5 131 lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count
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8 132 ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate
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10 133 dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride,
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12 134 bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with
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15 135 available data on these characteristics were included in the final analysis.
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17 18 136 ***The statistical model***

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20 137 We used the competing risk regression model to investigate the association between
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22 138 death due to COVID-19 and all potential risk factors. We have chosen to use this model,
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24 139 instead of the standard Cox proportional hazard model, because discharge alive or
25
26 140 recovery is clearly a competing event to death due to COVID-19^{17 18}. Ignoring this
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28 141 property will lead to biased estimates of the hazard ratios and the survival curves. We
29
30 142 estimated and plotted the survival curves using the cumulative incidence function taking
31
32 143 into account competing risks. Cumulative incidence curves of different groups were
33
34 144 compared using the Gray's test¹⁹ for sub-distribution hazards, an equivalent of the log-
35
36 145 rank test in the case of competing events. We used the Fine & Gray proportional hazards
37
38 146 regression models²⁰ to investigate the association between potential risk factors and the
39
40 147 primary outcome, and also to derive the risk prediction score. All statistical analysis and
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42 148 data management carried out in this paper were done using the R software version 3.6.3
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44 149 and *P*-values <0.05 were considered as statistically significant.
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50 51 150 ***Variables selection method and derivation of the risk prediction score***

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53 151 We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes
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55 152 Information criterion (BIC) for variables selection^{21 22}. This method uses a shrinking
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3 153 parameter to penalize non-significant coefficients of the Fine and Gray competing risk
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5 154 regression model. Larger shrinking parameters make the coefficients of non-significant
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7 155 risk factors to shrink towards zero, so that only the strongest predictors remain in the
8
9 156 survival model. Unlike the standard selection methods, such as stepwise forward or
10
11 157 backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36
12
13 158 potential predictors were scaled using the z-score transformation, and were entered in the
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15 159 selection process. The most predictive covariates were selected by choosing the shrinking
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17 160 parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were
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19 161 statistically significant were retained to construct the risk prediction score. We also
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21 162 investigated all statistical interactions between pairs of the retained predictors.
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27 163 *Validation of the risk prediction score*

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29 164 We derived the 28-day risk of in-hospital death using the estimates obtained from the
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31 165 Fine & Gray competing risk regression model. The predictive ability of this proposed risk
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33 166 prediction score was assessed using discrimination and calibration. Discrimination refers
34
35 167 to how well the predictive model is capable of discriminating between individuals who
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37 168 died and those who were discharged alive, whereas calibration refers to the agreement
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39 169 between observed and predicted number of deaths. Discrimination was assessed via the
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41 170 time-dependent area under the receiver-operator characteristic curve (AUC). Calibration
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43 171 was assessed via the time-dependent Brier score, and visually by plotting expected versus
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45 172 observed deaths. To reduce overfitting and optimism bias, we carried out internal
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47 173 validation of the risk prediction score by estimating the AUC and Brier score using 500
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49 174 bootstraps replications. This method allows all of the original data to be used in the
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175 model development while providing insight into the extent to which the original model is
176 overfitting or too optimistic.

177 **Patient and Public Involvement:**

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

180 **RESULTS**

181 Among the 1542 COVID-19 patients admitted to ICU, 196 (12.7 %) died, 1215 (78.8%)
182 were discharged alive and 131 (8.5%) were right-censored (i.e., still hospitalized at the
183 date of data extraction). Taking into account right-censored observations, the cumulative
184 incidence of mortality was estimated at 14% (95% confidence interval [CI], 12.17%–
185 15.82%), and the cumulative incidence of discharge was estimated to 85.40% (95% CI,
186 83.54–87.26) (Figure 1).

187 The demographic and clinical characteristics of the patients are presented in Table
188 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168
189 (12.7%) died. Compared with patients who were discharged alive, those who died were
190 older and had higher prevalence of diabetes, hypertension, chronic kidney disease,
191 cardiovascular disease, and liver disease; lower diastolic blood pressure, higher
192 respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO₂ and a higher
193 percentage of patients requiring oxygen therapy.

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

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

200 The results of the univariate competing risk model for each of the 36 potential
201 predictors measured at ICU admission are presented in the supplement (eTable 1). Of
202 these 36 variables, seven statistically significant predictors of mortality were retained by
203 the LASSO selection procedure in the multivariable competing risk regression model
204 (eFigure 1 in the supplement). The hazard ratios, P -values and 95% confidence intervals
205 of these significant variables are presented in Table 3. The significant predictors
206 increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–
207 2.31]; $P<.001$), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; $P<.001$),
208 higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; $P<.001$), higher respiratory rate (HR,
209 1.31 [95% CI, 1.15–1.49]; $P<.001$), and high levels of creatinine (HR, 1.19 [95% CI,
210 1.11– 1.28]; $P<.001$). The significant predictors lowering the risk of death included
211 higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; $P<.001$) and higher SpO₂
212 levels (HR, 0.82 [95% CI, 0.74–0.91]; $P<.001$). We found no statistically significant
213 interaction terms between pairs of the retained predictors.

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

217 ***Validation of the risk prediction score***

218 The results of the internal validation using 500 bootstrap samples are shown in Figure 2.

219 The predictive ability of the derived risk prediction score was quite promising. Indeed,

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3 220 regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the
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5 221 Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2
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7 222 also shows the calibration plot for the risk prediction score, in which the predicted
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9 223 frequencies of deaths were plotted against the observed ones.

12 224 From Figure 2, it is evident that the predicted frequencies of death were very
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14 225 close to the observed ones suggesting a very good calibration. The risk prediction score
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16 226 provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.

19 227 We also developed an easy-to-use web-based risk calculator implementing the
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21 228 derived risk prediction score to allow clinicians enter the values of the selected variables
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23 229 required for the risk calculation of mortality in patients admitted to ICU with COVID-19.
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25 230 The online calculator also provides stratification of patients into high and low risk
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27 231 categories based on an estimated cut-off risk corresponding to optimal performance
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29 232 measures of sensitivity and specificity. The online risk calculator is freely available at
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31 233 (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).

37 234 **DISCUSSION**

39 235 We developed and validated a clinical risk prediction score and a web-based risk
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41 236 calculator to predict the risk of in-hospital death in adult patients with confirmed
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43 237 COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of
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45 238 discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect
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47 239 similarity between predicted and expected deaths. We identified seven readily available
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49 240 clinical features at ICU admission to be used for risk prediction of in-hospital mortality
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51 241 namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings,
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53 242 neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these
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3 243 variables in an easy-to use web-based risk calculator has the potential to accurately
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5 244 classify ICU admitted patients as likely to be discharged alive or die.
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8 245 A major strength of this study is the relatively large number of laboratory
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10 246 confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a
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12 247 broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk
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14 248 prediction score includes clinical features that are readily available at ICU admission that
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16 249 increases its clinical applicability. An obvious limitation of this study is the
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18 250 generalizability of risk prediction score in other settings, and we acknowledge that
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20 251 external validation of our risk prediction score in other populations is the next step in
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22 252 model development. Further, the participants included in this study were younger
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24 253 compared with other studies using the data at the time of ICU admission^{8 12-15}, which may
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26 254 in turn limit the generalizability in older patients.
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31 255 Previous studies have reported risk prediction scores of mortality based on the
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33 256 clinical features at the time of hospital or ICU admission, including patients with mild,
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35 257 moderate or severe forms of disease^{6 7 9 10 12-15}. For instance, using data of 4711
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37 258 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was
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39 259 developed and validated, and consisted of six variables (age, oxygen saturation, mean
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41 260 arterial pressure, blood urea nitrogen, C-Reactive protein, and the international
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43 261 normalized ratio) assessed at the time of hospital admission¹². Moreover, 10 variables
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45 262 (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number
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47 263 of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct
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49 264 bilirubin) were found to be independent predictive factors, and were included in the risk
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51 265 score to predict the occurrence of critical illness in hospitalized patients with COVID-
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3 266 19⁷. The International Severe Respiratory and emerging Infections Consortium (ISARIC)
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5 267 developed and validated a mortality score consisting of eight variables (age, sex, number
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7 268 of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness,
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10 269 urea level, and C reactive protein) that were available at the initial hospital assessment⁹.
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12 270 In line with this, methods using machine learning have identified 8 important risk factors
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14 271 to predict mortality in ICU admitted patients with COVID-19¹⁵. Interestingly, nutritional
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16 272 status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time
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18 273 of ICU admission predicted twice the probability of death in patients with high nutritional
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20 274 risk than low risk patients¹⁴. The difference in the number and types of independent
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22 275 clinical features associated with mortality between our study and others may be explained
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24 276 by the differences in the baseline characteristics of the population or the choice of the
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26 277 statistical analyses. Indeed, we have chosen to use the competing risk regression model
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28 278 instead of the standard Cox proportional hazard model or the logistic regression model
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30 279 because recovery is clearly a competing event to in-hospital death due to COVID-19^{17 18}.
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32 280 Ignoring this property will definitely lead to biased effect estimates. Another plausible
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34 281 reason for this difference in the results is the younger age of the participants in our study
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36 282 compared to other studies¹²⁻¹⁵, which could likely influence the clinical features to be
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38 283 included in the risk prediction score.
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44 284 Other statistical association analyses have been published to investigate the
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46 285 factors affecting mortality due to COVID-19 in patients admitted to ICU^{8 11}. For instance,
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48 286 a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted
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50 287 to ICU in the US identified 9 risk factors independently associated with the 28-days
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52 288 mortality. These risk factors included age, sex, body mass index, coronary artery disease,
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3 289 active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the
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5 290 number of hospital ICU beds⁸. In our risk score, none of the comorbid conditions
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7 291 achieved statistical significance for in-hospital mortality, however, other significant
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9 292 laboratory findings such as increased LDH and increased creatinine levels may represent
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11 293 underlying diseases such as liver disease, lung disease or kidney dysfunction.
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15 294 Interestingly, a non COVID-19 prediction score named Waterlow score has
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17 295 shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly
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19 296 patients²³. The Waterlow score is a multidimensional pressure ulcer risk assessment tool
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21 297 and includes age, nutritional status, weight, mobility, gender, smoking status,
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23 298 comorbidities, use of medication and continence²³. One of the significant predictors of
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25 299 mortality included in our risk score is Glasgow Coma Scale which is an objective and
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27 300 reliable way of recording the initial and subsequent level of consciousness, and could be
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29 301 used as a proxy to continence. Although, the association between Waterlow score and
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31 302 mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac
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33 303 and stroke conditions, its application in patients with confirmed COVID-19 warrants
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35 304 further investigations.
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40 305 The recent COVID-19 epidemiological update from WHO, as of May 04, 2021,
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42 306 reported over 5.7 million new weekly cases worldwide which is at the highest level since
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44 307 the beginning of the pandemic¹. The WHO European and American regions accounted
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46 308 for 20% and 23% of new weekly cases, respectively. The largest increase accounting for
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48 309 47% of new weekly cases was noted in South East Asia region particularly in India which
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50 310 accounted for over 90% of both cases and deaths in the region. The Eastern
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52 311 Mediterranean region that includes UAE accounted for 6% of new weekly cases¹. Earlier
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3 312 studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases
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5 313 ranging between 2% and 81%^{16 24 25}, and high mortality prevalence among ICU patients
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7 314 ranging between 5% and 83%^{3 16 26}. A meta-analysis of twenty-five studies with 24,677
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9 315 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence
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11 316 among patients admitted to ICU with a severe form of COVID-19¹⁶. The relative high
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13 317 number of deaths in the ICU presents an enormous challenge to the prognostication and
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15 318 management of patients with COVID-19. We believe that the risk tool provided in this
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17 319 study may have utility in clinical settings to guide decision-making, and may facilitate the
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19 320 early identification of patients at high risk of death, and may be used as a guidance in
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21 321 busy ICU units to stratify patients according to their risk in order to deliver the best
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23 322 available supportive care. The parameters selected are easily available at the time of ICU
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31 324 **Conclusion**

32 325 We developed and validated a risk tool for predicting in-hospital death among COVID-19
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34 326 patients admitted to ICU, which shows high predictive accuracy. This tool can assist in
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36 327 early identification of patients during ICU admission who are at high risks of death, and
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38 328 consequently can facilitate optimal delivery of supportive care for these patients.
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13
14 334 advanced statistical aspects. SA, AA, MAH, MAA, RG, II and AO were involved in data
15
16 335 specification, curation, and collection. AO did data management and statistical analyses,
17
18 336 which were checked by SA, AA, MAH, and JN. SA, AA, MAH, MAA, RG, II, JN and
19
20 337 AO contributed to the interpretation of the results. SA, AA, JN and AO wrote the first
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23
24 339 revision of the manuscript for important intellectual content and approved the final
25
26 340 version of the manuscript. AO developed the software for the web calculator. The
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28 341 corresponding author attests that all listed authors meet authorship criteria and that no
29
30 342 others meeting the criteria have been omitted. AO is the guarantor.

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32 343 The lead author affirms that the manuscript is an honest, accurate, and transparent
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34 344 account of the study being reported; that no important aspects of the study have been
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36 345 omitted; and that any discrepancies from the study as planned (and, if relevant,
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38 346 registered) have been explained.

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40 347 **Ethical approval:** The study was approved by the Department of Health of Abu Dhabi
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42 348 COVID-9 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

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44 349 **Data availability statement:** To guarantee the confidentiality of personal and health
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46 350 information, only the authors have had access to the data during the study in accordance
47
48 351 with the relevant licence agreements. Access to the data is according to the information
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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 non-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)	

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)				
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.

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), $\times 10^9/L$	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $\times 10^{12}/L$	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), $\mu\text{mol}/L$	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.

363 **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 $\times 10^9/L$, 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, $\mu\text{mol/L}$	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO₂, 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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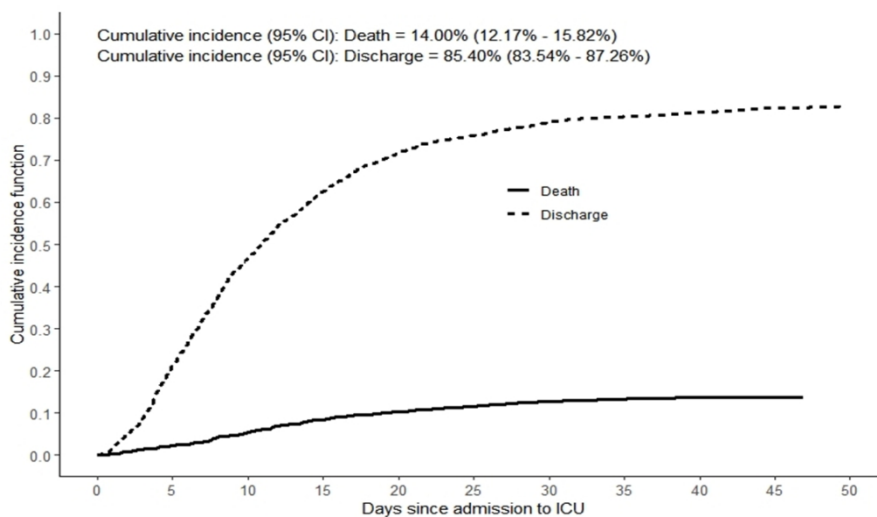


Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

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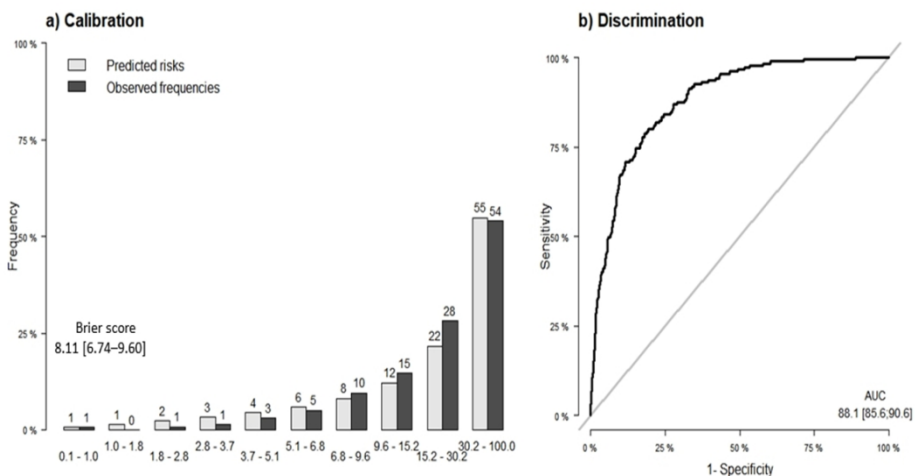


Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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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.

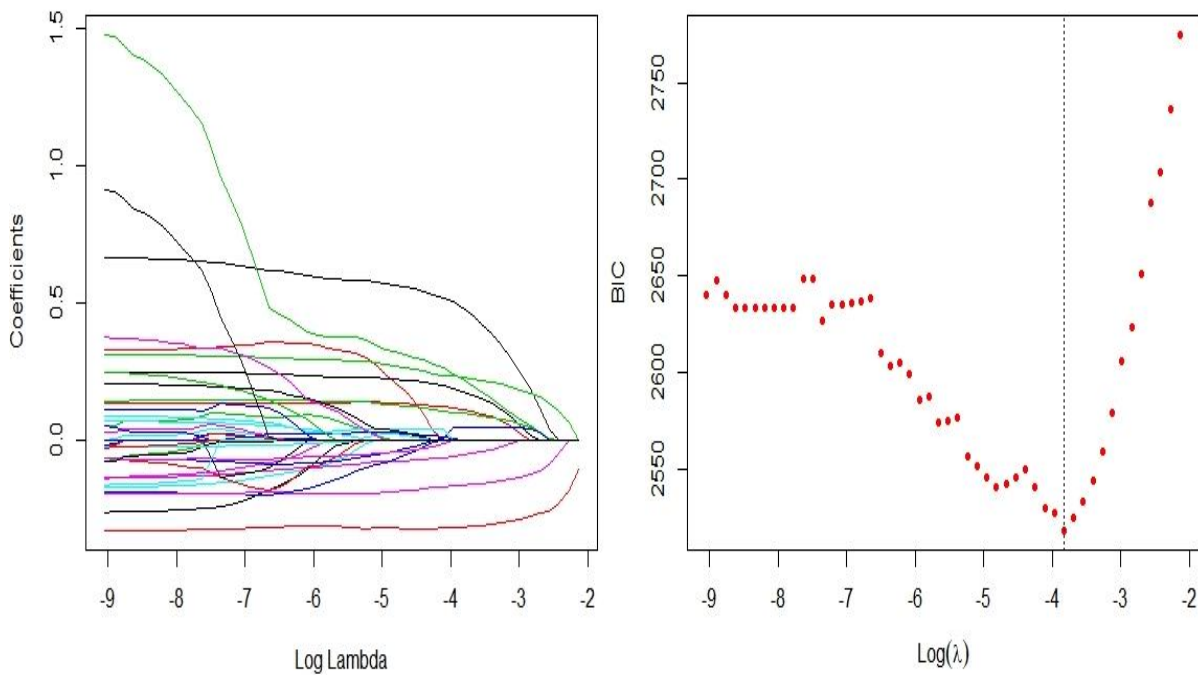
eTable 1. Univariate competing risk models on candidate predictors.

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 SpO ₂	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)

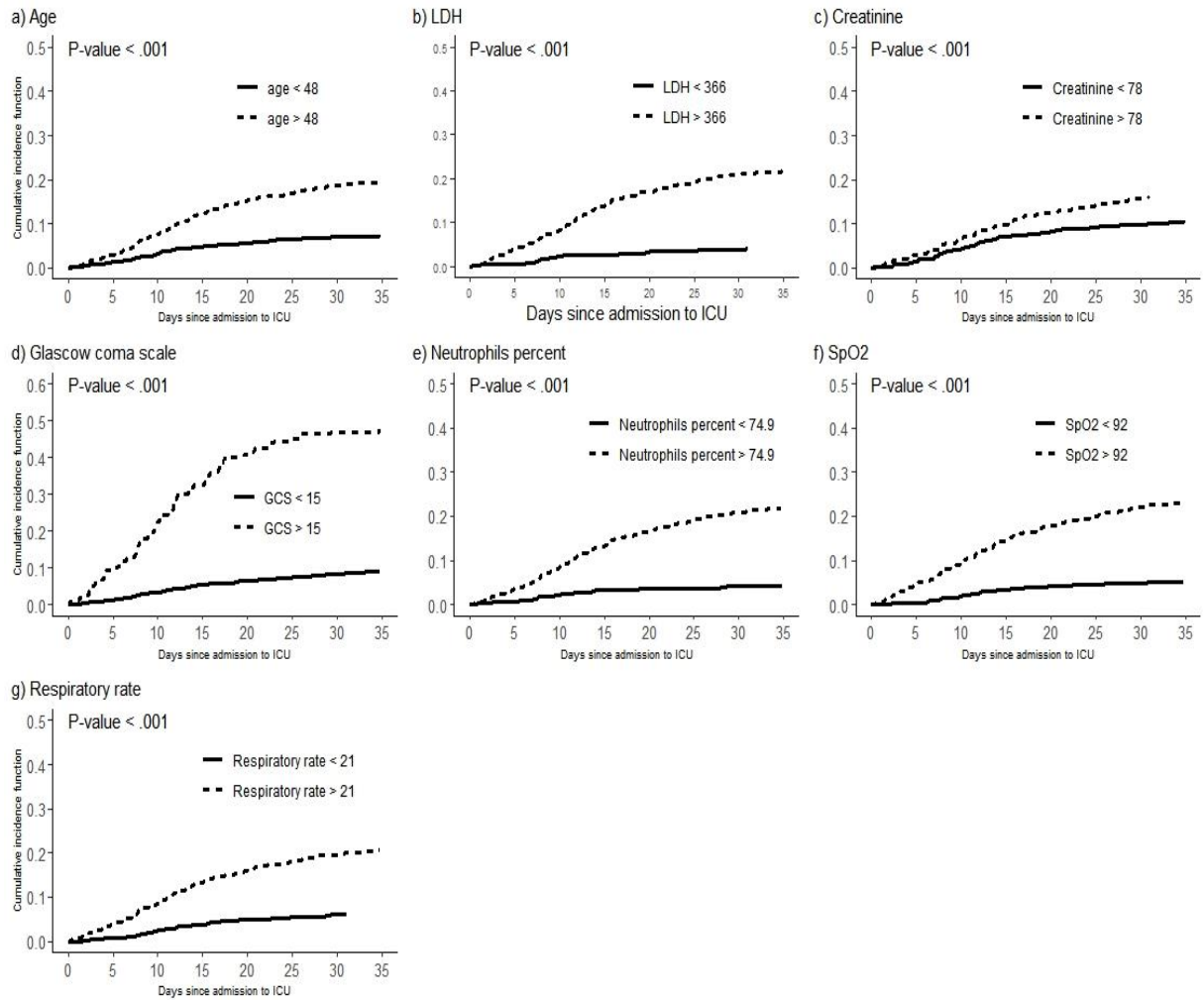
Abbreviations: HR, hazard ratios; CI, confidence interval; AUC, area under the receiver operating characteristics curve; SpO₂, peripheral capillary oxygen saturation.

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.



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



Only



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 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.

BMJ Open

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

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3 1 A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill
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5 2 Patients with COVID-19: A Retrospective Cohort Study
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1
2 25 **ABSTRACT**
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4 26 **OBJECTIVES:** To identify factors influencing the mortality risk in critically ill patients with
5
6 27 COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit
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9 28 (ICU).
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11 29 **DESIGN:** A multicentre cohort study
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13 30 **SETTING AND PARTICIPANTS:** 1542 patients with COVID-19 admitted to ICUs in public
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16 31 hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.
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18 32 **MAIN OUTCOMES AND MEASURES:** The primary outcome was time from ICU admission
19
20 33 until death. We used competing risk regression models and Least Absolute Shrinkage and
21
22 34 Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the
23
24 35 score was assessed by the area under the receiver operating characteristic curve (AUC), and the
25
26 36 Brier score using 500 bootstraps replications.
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29 37 **RESULTS:** Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged,
30
31 38 and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95%
32
33 39 confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven
34
35 40 factors associated with mortality, and included in the risk score: age (adjusted hazard ratio
36
37 41 [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31),
38
39 42 lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI,
40
41 43 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95%
42
43 44 CI, 0.63–0.78), and oxygen saturation (SpO₂) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC
44
45 45 was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed
46
47 46 a freely available web-based risk calculator (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).
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49

50 47 **CONCLUSION:** In critically ill patients with COVID-19, we identified factors associated with
51
52 48 mortality, and developed a risk prediction tool that showed high predictive ability. This tool may
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1
2 49 have utility in clinical settings to guide decision-making, and may facilitate the identification of
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4 50 supportive therapies to improve outcomes.
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6 51 **Key words:** COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical
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9 52 care
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For peer review only

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2 53 **Strengths and limitations of this study**
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- 4 54 • Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of
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6 55 in-hospital mortality, however, limited data is available regarding the risk prediction
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8 56 scores in this population.
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11 57 • Our clinical risk score includes clinical features which are readily available at ICU
12
13 58 admission, thus amplifying its clinical applicability.
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16 59 • The score showed high predictive ability for in-hospital mortality.
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18 60 • A major limitation is the generalizability of risk prediction score to other settings, and
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20 61 external validation should be the next step.
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62 INTRODUCTION

63 The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute
64 respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million
65 patients, and more than 3.1 million have died, as of May 04, 2021¹. A wide spectrum of
66 clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic
67 infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory
68 failure leading to hospital admission and death^{2,3}.

69 The preventive and treatment challenge of COVID-19 is very high because of the
70 complexity of its transmission, substantial heterogeneity in the progression of disease,
71 and lack of proven treatment^{4,5}. Several studies have attempted to address this by
72 predicting clinical outcomes using statistical association analyses or prediction model
73 development methods in order to guide the management and prognostication of patients
74 with COVID-19⁶⁻¹⁷. Based on patient characteristics at the time of hospital admission,
75 Liang et al.⁷ proposed a risk score to predict critical illness defined as a composite of
76 intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity
77 score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19
78 patients which consisted of six parameters assessed at the time of hospital admission¹².

79 A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU
80 admission has also shown higher mortality in COVID-19 patients with high nutritional
81 risk compared with those with low nutritional risk¹⁴. Further, a prognostic score using
82 machine learning methods has been shown to predict death in ICU patients with COVID-
83 19¹⁵. Additionally, various demographics, clinical and hospital level risk factors have
84 been reported to be associated with death in patients admitted to ICU⁸.

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3 85 A recent meta-analysis showed that more than one-fourth of patients with
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5 86 COVID-19 were admitted to ICU globally, and the prevalence of mortality among these
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7 87 patients was very high (31%)¹⁸. However, limited data is available related to prognostic
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9 88 risk score of in-hospital mortality in critically ill patients with COVID-19 who were
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11 89 admitted to ICU. Therefore, the aim of the present study was to identify the risk factors
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13 90 and the set of clinical markers that increase the risk of death among ICU admitted
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15 91 COVID-19 patients, and to develop a risk prediction score that may facilitate the
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17 92 identification of supportive therapies to improve outcomes. We also aim to develop an
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19 93 easy-to-use web-based risk calculator implementing the derived risk prediction score to
20
21 94 allow clinicians enter the values of the selected variables required for the risk calculation
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23 95 of mortality in patients admitted to ICU with COVID-19. The online calculator will
24
25 96 provide stratification of patients into high and low risk categories based on an estimated
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27 97 cut-off risk corresponding to optimal performance measures of sensitivity and specificity.
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34 98 **METHODS**

35 99 **Study design and Data sources**

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38 100 This is a multicentre cohort study in which data of all laboratory confirmed COVID-19
39
40 101 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE)
41
42 102 between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical
43
44 103 records. The data was collected from four major hospitals as well as newly developed
45
46 104 field hospitals operating with some ICU bed capacity. The estimated bed capacity for
47
48 105 ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We
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50 106 included patients who were admitted to a regular ICU room or to a HDU or if they were
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52 107 consistently receiving any form of oxygen therapy during their hospital stay in a make-
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3 108 shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9
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5 109 IRB ethical committee (Ref#DOH/CVDC/2020/1116).
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8 110 **Outcomes**

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10 111 The primary outcome of this study is the survival time defined as the duration of time,
11
12 112 from the date of ICU admission, until the date of death. Patients still hospitalized at the
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14 113 date of data extraction were considered as right censored and those discharged alive from
15
16 114 the hospital were considered as competing events to death due to COVID-19.
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20 115 **Statistical Analyses**

21
22 116 Baseline characteristics were summarized using descriptive statistics including mean and
23
24 117 standard deviation for continuous measures, and frequencies tables for categorical
25
26 118 variables. We compared categorical variables using the chi-square or Fisher's exact test,
27
28 119 and continuous variables using the unpaired t-test or its non-parametric equivalent
29
30 120 (Wilcoxon rank sum test) in case the normality assumption is violated.
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35 121 ***Potential predictive variables***

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37 122 We considered 36 patient's characteristics assessed at the time of ICU admission as
38
39 123 potential predictors based on demographics, clinical signs and symptoms, medical history
40
41 124 and laboratory findings. Demographic variables included age and sex. Clinical signs and
42
43 125 symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate,
44
45 126 Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen
46
47 127 saturation (SpO₂). Medical history included status of coexisting conditions: diabetes,
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49 128 hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer,
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51 129 and liver disease. Laboratory findings included white blood cells, monocytes count,
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3 130 monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count,
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5 131 lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count
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8 132 ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate
9
10 133 dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride,
11
12 134 bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with
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14
15 135 available data on these characteristics were included in the final analysis.
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17 18 136 *The statistical model*

19
20 137 We used the competing risk regression model to investigate the association between
21
22 138 death due to COVID-19 and all potential risk factors. We have chosen to use this model,
23
24 139 instead of the standard Cox proportional hazard model, because discharge alive or
25
26 140 recovery is clearly a competing event to death due to COVID-19^{19 20}. Ignoring this
27
28 141 property will lead to biased estimates of the hazard ratios and the survival curves. We
29
30 142 estimated and plotted the survival curves using the cumulative incidence function taking
31
32 143 into account competing risks. Cumulative incidence curves of different groups were
33
34 144 compared using the Gray's test²¹ for sub-distribution hazards, an equivalent of the log-
35
36 145 rank test in the case of competing events. We used the Fine & Gray proportional hazards
37
38 146 regression models²² to investigate the association between potential risk factors and the
39
40 147 primary outcome, and also to derive the risk prediction score. All statistical analysis and
41
42 148 data management carried out in this paper were done using the R software version 3.6.3
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44 149 and *P*-values <0.05 were considered as statistically significant.
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50 51 150 *Variables selection method and derivation of the risk prediction score*

52
53 151 We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes
54
55 152 Information criterion (BIC) for variables selection^{23 24}. This method uses a shrinking
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2
3 153 parameter to penalize non-significant coefficients of the Fine and Gray competing risk
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5 154 regression model. Larger shrinking parameters make the coefficients of non-significant
6
7 155 risk factors to shrink towards zero, so that only the strongest predictors remain in the
8
9 156 survival model. Unlike the standard selection methods, such as stepwise forward or
10
11 157 backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36
12
13 158 potential predictors were scaled using the z-score transformation, and were entered in the
14
15 159 selection process. The most predictive covariates were selected by choosing the shrinking
16
17 160 parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were
18
19 161 statistically significant were retained to construct the risk prediction score. We also
20
21 162 investigated all statistical interactions between pairs of the retained predictors.
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27 163 *Validation of the risk prediction score*

28
29 164 We derived the 28-day risk of in-hospital death using the estimates obtained from the
30
31 165 Fine & Gray competing risk regression model. The predictive ability of this proposed risk
32
33 166 prediction score was assessed using discrimination and calibration. Discrimination refers
34
35 167 to how well the predictive model is capable of discriminating between individuals who
36
37 168 died and those who were discharged alive, whereas calibration refers to the agreement
38
39 169 between observed and predicted number of deaths. Discrimination was assessed via the
40
41 170 time-dependent area under the receiver-operator characteristic curve (AUC). Calibration
42
43 171 was assessed via the time-dependent Brier score, and visually by plotting expected versus
44
45 172 observed deaths. To reduce overfitting and optimism bias, we carried out internal
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47 173 validation of the risk prediction score by estimating the AUC and Brier score using 500
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49 174 bootstraps replications. This method allows all of the original data to be used in the
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175 model development while providing insight into the extent to which the original model is
176 overfitting or too optimistic.

177 **Patient and Public Involvement:**

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

180 **RESULTS**

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

193 The demographic and clinical characteristics of the patients are presented in Table
194 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168
195 (12.7%) died. Compared with patients who were discharged alive, those who died were
196 older and had higher prevalence of diabetes, hypertension, chronic kidney disease,

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3 197 cardiovascular disease, and liver disease; lower diastolic blood pressure, higher
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5 198 respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO₂ and a higher
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8 199 percentage of patients requiring oxygen therapy.
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10 200 The laboratory findings of the patients included in our study are presented in
11
12 201 Table 2. Compared with patients who were discharged alive, those who died had
13
14 202 unfavourable laboratory profile on almost all variables including levels of C-reactive
15
16 203 protein, creatinine, LDH, red blood cell distribution width, white blood cell count,
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18 204 potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count,
19
20 205 haemoglobin, haematocrit, and serum bicarbonates.
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24 206 The results of the univariate competing risk model for each of the 36 potential
25
26 207 predictors measured at ICU admission are presented in the supplement (eTable 1). Of
27
28 208 these 36 variables, seven statistically significant predictors of mortality were retained by
29
30 209 the LASSO selection procedure in the multivariable competing risk regression model
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32 210 (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals
33
34 211 of these significant variables are presented in Table 3. The significant predictors
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36 212 increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–
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38 213 2.31]; *P*<.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<.001),
39
40 214 higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), higher respiratory rate (HR,
41
42 215 1.31 [95% CI, 1.15–1.49]; *P*<.001), and high levels of creatinine (HR, 1.19 [95% CI,
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44 216 1.11– 1.28]; *P*<.001). The significant predictors lowering the risk of death included
45
46 217 higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<.001) and higher SpO₂
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48 218 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<.001). We found no statistically significant
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53 219 interaction terms between pairs of the retained predictors.
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3 220 The cumulative incidence function of these 7 predictors retained by LASSO in the
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5 221 multivariable model is shown in the supplement (eFigure 2). For graphical presentation,
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7
8 222 we created a binary variable based on the median split in case of continuous risk factors.
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10 11 223 *Validation of the risk prediction score*

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13 224 The results of the internal validation using 500 bootstrap samples are shown in Figure 2.
14
15 225 The predictive ability of the derived risk prediction score was quite promising. Indeed,
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17 226 regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the
18
19
20 227 Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2
21
22 228 also shows the calibration plot for the risk prediction score, in which the predicted
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24
25 229 frequencies of deaths were plotted against the observed ones.
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27 230 From Figure 2, it is evident that the predicted frequencies of death were very
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29 231 close to the observed ones suggesting a very good calibration. The risk prediction score
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31 232 provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.
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34 233 We also developed an easy-to-use web-based risk calculator implementing the
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36 234 derived risk prediction score to allow clinicians enter the values of the selected variables
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38 235 required for the risk calculation of mortality in patients admitted to ICU with COVID-19.
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41 236 The online calculator also provides stratification of patients into high and low risk
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43 237 categories based on an estimated cut-off risk corresponding to optimal performance
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45 238 measures of sensitivity and specificity. The online risk calculator is freely available at
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48 239 (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).
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3 240 **DISCUSSION**
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5 241 We developed and validated a clinical risk prediction score and a web-based risk
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7 242 calculator to predict the risk of in-hospital death in adult patients with confirmed
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9 243 COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of
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11 244 discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect
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13 245 similarity between predicted and expected deaths. We identified seven readily available
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15 246 clinical features at ICU admission to be used for risk prediction of in-hospital mortality
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17 247 namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings,
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19 248 neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these
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21 249 variables in an easy-to use web-based risk calculator has the potential to accurately
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23 250 classify ICU admitted patients as likely to be discharged alive or die.
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28 251 A major strength of this study is the relatively large number of laboratory
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30 252 confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a
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32 253 broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk
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34 254 prediction score includes clinical features that are readily available at ICU admission that
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36 255 increases its clinical applicability. An obvious limitation of this study is the
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38 256 generalizability of risk prediction score in other settings, and we acknowledge that
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40 257 external validation of our risk prediction score in other populations is the next step in
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42 258 model development. Further, the participants included in this study were younger
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44 259 compared with other studies using the data at the time of hospital admission^{8 12-17}, which
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46 260 may in turn limit the generalizability in older patients.
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51 261 Previous studies have reported risk prediction scores of mortality based on the
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53 262 clinical features at the time of hospital or ICU admission, including patients with mild,
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3 263 moderate or severe forms of disease^{6 7 9 10 12-17}. For instance, using data of 4711
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5 264 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was
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7 265 developed and validated, and consisted of six variables (age, oxygen saturation, mean
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9 266 arterial pressure, blood urea nitrogen, C-Reactive protein, and the international
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11 267 normalized ratio) assessed at the time of hospital admission¹². Moreover, 10 variables
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13 268 (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number
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15 269 of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct
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17 270 bilirubin) were found to be independent predictive factors, and were included in the risk
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19 271 score to predict the occurrence of critical illness in hospitalized patients with COVID-
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21 272 19⁷. The International Severe Respiratory and emerging Infections Consortium (ISARIC)
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23 273 developed and validated a mortality score consisting of eight variables (age, sex, number
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25 274 of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness,
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27 275 urea level, and C reactive protein) that were available at the initial hospital assessment⁹.
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29 276 In line with this, methods using machine learning have identified 8 important risk factors
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31 277 to predict mortality in ICU admitted patients with COVID-19¹⁵. Interestingly, nutritional
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33 278 status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time
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35 279 of ICU admission predicted twice the probability of death in patients with high nutritional
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37 280 risk than low risk patients¹⁴. The difference in the number and types of independent
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39 281 clinical features associated with mortality between our study and others may be explained
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41 282 by the differences in the baseline characteristics of the population or the choice of the
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43 283 statistical analyses. Indeed, we have chosen to use the competing risk regression model
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45 284 instead of the standard Cox proportional hazard model or the logistic regression model
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47 285 because recovery is clearly a competing event to in-hospital death due to COVID-19^{19 20}.
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3 286 Ignoring this property will definitely lead to biased effect estimates. Another plausible
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5 287 reason for this difference in the results is the younger age of the participants in our study
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8 288 compared to other studies¹²⁻¹⁷, which could likely influence the clinical features to be
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10 289 included in the risk prediction score.

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12 290 Other statistical association analyses have been published to investigate the
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14 291 factors affecting mortality due to COVID-19 in patients admitted to ICU^{8 11}. For instance,
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16 292 a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted
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18 293 to ICU in the US identified 9 risk factors independently associated with the 28-days
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20 294 mortality. These risk factors included age, sex, body mass index, coronary artery disease,
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22 295 active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the
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24 296 number of hospital ICU beds⁸. In our risk score, none of the comorbid conditions
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26 297 achieved statistical significance for in-hospital mortality, however, other significant
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28 298 laboratory findings such as increased LDH and increased creatinine levels may represent
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30 299 underlying diseases such as liver disease, lung disease or kidney dysfunction.

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33 300 Interestingly, a non COVID-19 prediction score named Waterlow score has
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35 301 shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly
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37 302 patients²⁵. The Waterlow score is a multidimensional pressure ulcer risk assessment tool
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39 303 and includes age, nutritional status, weight, mobility, gender, smoking status,
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41 304 comorbidities, use of medication and continence²⁵. One of the significant predictors of
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43 305 mortality included in our risk score is Glasgow Coma Scale which is an objective and
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45 306 reliable way of recording the initial and subsequent level of consciousness, and could be
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47 307 used as a proxy to continence. Although, the association between Waterlow score and
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49 308 mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac
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3 309 and stroke conditions, its application in patients with confirmed COVID-19 warrants
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5 310 further investigations.
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8 311 The recent COVID-19 epidemiological update from WHO, as of May 04, 2021,
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10 312 reported over 5.7 million new weekly cases worldwide which is at the highest level since
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12 313 the beginning of the pandemic¹. The WHO European and American regions accounted
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14 314 for 20% and 23% of new weekly cases, respectively. The largest increase accounting for
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16 315 47% of new weekly cases was noted in South East Asia region particularly in India which
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18 316 accounted for over 90% of both cases and deaths in the region. The Eastern
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20 317 Mediterranean region that includes UAE accounted for 6% of new weekly cases¹. Earlier
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22 318 studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases
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24 319 ranging between 2% and 81%^{18 26 27}, and high mortality prevalence among ICU patients
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26 320 ranging between 5% and 83%^{3 18 28}. A meta-analysis of twenty-five studies with 24,677
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28 321 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence
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30 322 among patients admitted to ICU with a severe form of COVID-19¹⁸. The relative high
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32 323 number of deaths in the ICU presents an enormous challenge to the prognostication and
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34 324 management of patients with COVID-19. We believe that the risk tool provided in this
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36 325 study may have utility in clinical settings to guide decision-making, and may facilitate the
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38 326 early identification of patients at high risk of death, and may be used as a guidance in
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40 327 busy ICU units to stratify patients according to their risk in order to deliver the best
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42 328 available supportive care. The parameters selected are easily available at the time of ICU
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44 329 admission.
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51
52 330 **Conclusion**
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3 331 We developed and validated a risk tool for predicting in-hospital death among COVID-19
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5 332 patients admitted to ICU, which shows high predictive accuracy. This tool can assist in
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7 333 early identification of patients during ICU admission who are at high risks of death, and
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9 334 consequently can facilitate optimal delivery of supportive care for these patients.
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8

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13
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15
16 341 specification, curation, and collection. AO did data management and statistical analyses,
17
18 342 which were checked by SA, AA, MAH, and JN. SA, AA, MAH, MAA, RG, II, JN and
19
20 343 AO contributed to the interpretation of the results. SA, AA, JN and AO wrote the first
21
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23
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25
26 346 version of the manuscript. AO developed the software for the web calculator. The
27
28 347 corresponding author attests that all listed authors meet authorship criteria and that no
29
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31
32 349 The lead author affirms that the manuscript is an honest, accurate, and transparent
33
34 350 account of the study being reported; that no important aspects of the study have been
35
36 351 omitted; and that any discrepancies from the study as planned (and, if relevant,
37
38 352 registered) have been explained.

39
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41
42 354 COVID-19 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

43
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45
46 356 information, only the authors have had access to the data during the study in accordance
47
48 357 with the relevant licence agreements. Access to the data is according to the information
49
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8
9
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11
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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 non-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

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)				
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.

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), $\times 10^9/L$	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $\times 10^{12}/L$	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), $\mu\text{mol}/L$	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.

369 **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 $\times 10^9/L$, 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, $\mu\text{mol/L}$	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO₂, 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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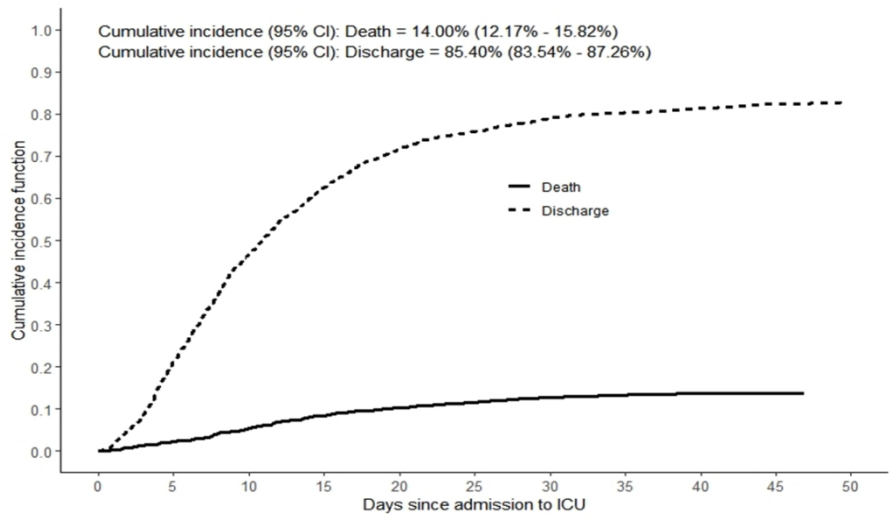


Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

338x190mm (96 x 96 DPI)

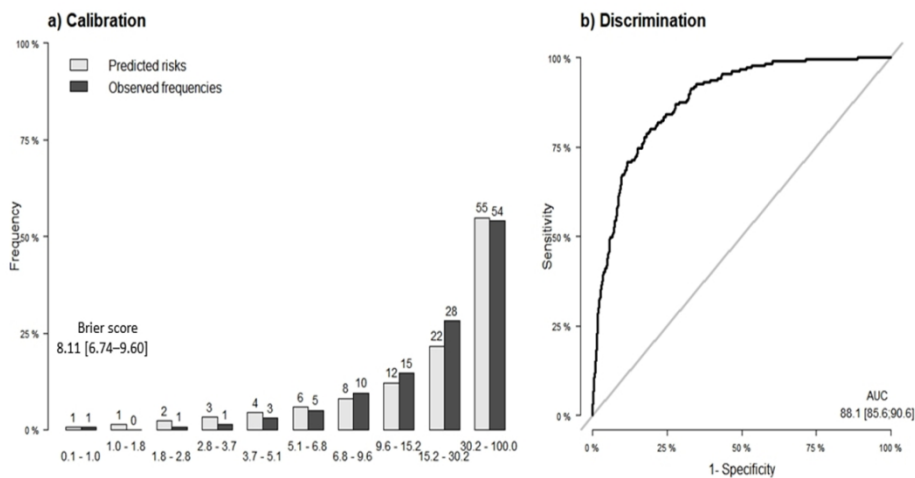


Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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.

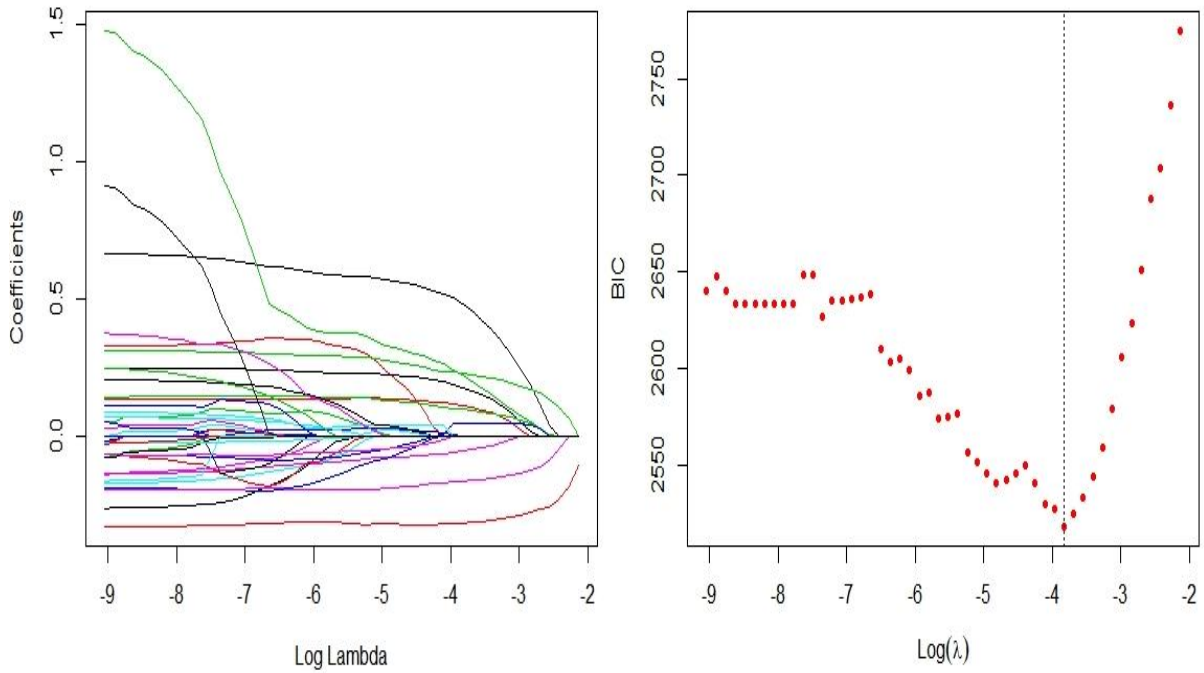
eTable 1. Univariate competing risk models on candidate predictors.

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 SpO ₂	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; SpO₂, peripheral capillary oxygen saturation.

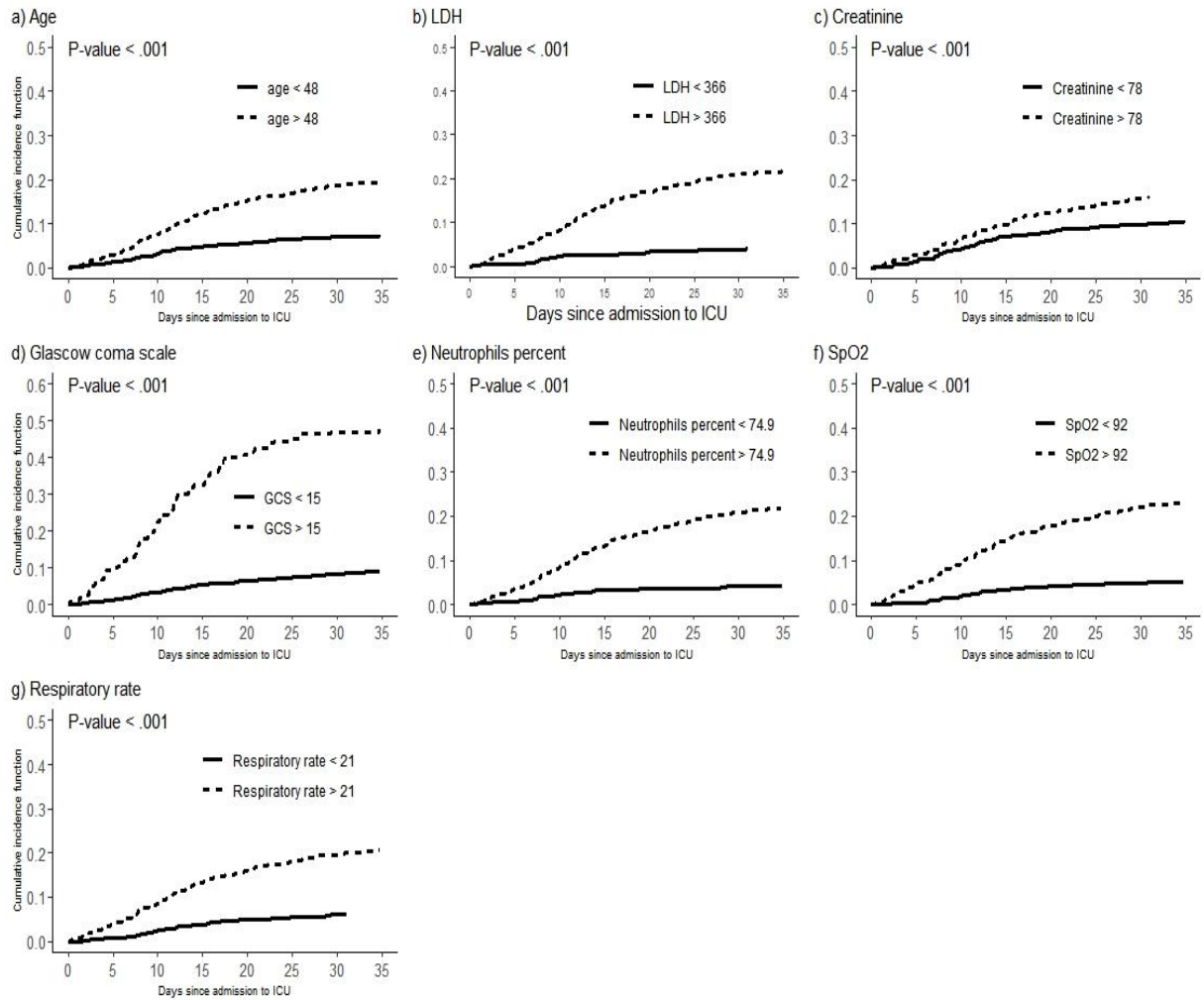
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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



view only

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



Only

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 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.

BMJ Open

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

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Emergency medicine, Intensive care, Infectious diseases
Keywords:	COVID-19, Epidemiology < INFECTIOUS DISEASES, Public health < INFECTIOUS DISEASES, INTENSIVE & CRITICAL CARE, PREVENTIVE MEDICINE

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3 1 A Clinical Risk Score to Predict in-hospital Mortality in Critically Ill
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5 2 Patients with COVID-19: A Retrospective Cohort Study
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1
2 25 **ABSTRACT**
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4 26 **OBJECTIVES:** To identify factors influencing the mortality risk in critically ill patients with
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6 27 COVID-19, and to develop a risk prediction score to be used at admission to intensive care unit
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9 28 (ICU).
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11 29 **DESIGN:** A multicentre cohort study
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13 30 **SETTING AND PARTICIPANTS:** 1542 patients with COVID-19 admitted to ICUs in public
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16 31 hospitals of Abu Dhabi, United Arab Emirates between March, 1st 2020 and July, 22nd 2020.
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18 32 **MAIN OUTCOMES AND MEASURES:** The primary outcome was time from ICU admission
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20 33 until death. We used competing risk regression models and Least Absolute Shrinkage and
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22 34 Selection Operator to identify the factors, and to construct a risk score. Predictive ability of the
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24 35 score was assessed by the area under the receiver operating characteristic curve (AUC), and the
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26 36 Brier score using 500 bootstraps replications.
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29 37 **RESULTS:** Among patients admitted to ICU, 196 (12.7%) died, 1215 (78.8%) were discharged,
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31 38 and 131 (8.5%) were right-censored. The cumulative mortality incidence was 14% (95%
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33 39 confidence interval [CI], 12.17%–15.82%). From 36 potential predictors, we identified seven
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35 40 factors associated with mortality, and included in the risk score: age (adjusted hazard ratio
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37 41 [AHR], 1.98; 95% CI, 1.71–2.31), neutrophil percentage (AHR, 1.71; 95% CI, 1.27–2.31),
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39 42 lactate dehydrogenase (AHR, 1.31; 95% CI, 1.15–1.49), respiratory rate (AHR, 1.31; 95% CI,
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41 43 1.15–1.49), creatinine (AHR, 1.19; 95% CI, 1.11–1.28), Glasgow Coma Scale (AHR, 0.70; 95%
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43 44 CI, 0.63–0.78), and oxygen saturation (SpO₂) (AHR, 0.82; 95% CI, 0.74–0.91). The mean AUC
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45 45 was 88.1 (95% CI, 85.6–91.6), and the Brier score was 8.11 (95% CI, 6.74–9.60). We developed
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47 46 a freely available web-based risk calculator (<https://icumortalityrisk.shinyapps.io/ICUrisk/>).
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50 47 **CONCLUSION:** In critically ill patients with COVID-19, we identified factors associated with
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52 48 mortality, and developed a risk prediction tool that showed high predictive ability. This tool may
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2 49 have utility in clinical settings to guide decision-making, and may facilitate the identification of
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4 50 supportive therapies to improve outcomes.
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6 51 **Key words:** COVID-19, SARS-CoV-2, risk prediction, mortality, ICU, intensive care, critical
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For peer review only

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2 53 **Strengths and limitations of this study**
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- 4 54 • Patients admitted to ICU with confirmed COVID-19 have relatively high prevalence of
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6 55 in-hospital mortality, however, limited data is available regarding the risk prediction
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8 56 scores in this population.
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11 57 • Our clinical risk score includes clinical features which are readily available at ICU
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13 58 admission, thus amplifying its clinical applicability.
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16 59 • A major limitation is the generalizability of risk prediction score to other settings, and
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18 60 external validation should be the next step.
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61 INTRODUCTION

62 The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute
63 respiratory syndrome coronavirus (SARS-CoV-2) has affected more than 151 million
64 patients, and more than 3.1 million have died, as of May 04, 2021¹. A wide spectrum of
65 clinical symptoms of SARS-CoV-2 has been reported, encompassing asymptomatic
66 infection, mild upper respiratory tract illness, and severe viral pneumonia with respiratory
67 failure leading to hospital admission and death^{2,3}.

68 The preventive and treatment challenge of COVID-19 is very high because of the
69 complexity of its transmission, substantial heterogeneity in the progression of disease,
70 and lack of proven treatment^{4,5}. Several studies have attempted to address this by
71 predicting clinical outcomes using statistical association analyses or prediction model
72 development methods in order to guide the management and prognostication of patients
73 with COVID-19⁶⁻¹⁷. Based on patient characteristics at the time of hospital admission,
74 Liang et al.⁷ proposed a risk score to predict critical illness defined as a composite of
75 intensive care unit (ICU) admission, invasive ventilation, or death. Similarly, a severity
76 score ranging from 0 to 10 is proposed to predict inpatient mortality in COVID-19
77 patients which consisted of six parameters assessed at the time of hospital admission¹².

78 A modified Nutrition Risk in the Critically ill (mNUTRIC) score assessed at ICU
79 admission has also shown higher mortality in COVID-19 patients with high nutritional
80 risk compared with those with low nutritional risk¹⁴. Further, a prognostic score using
81 machine learning methods has been shown to predict death in ICU patients with COVID-
82 19¹⁵. Additionally, various demographics, clinical and hospital level risk factors have
83 been reported to be associated with death in patients admitted to ICU⁸.

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3 84 A recent meta-analysis showed that more than one-fourth of patients with
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5 85 COVID-19 were admitted to ICU globally, and the prevalence of mortality among these
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7 86 patients was very high (31%)¹⁸. However, limited data is available related to prognostic
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10 87 risk score of in-hospital mortality in critically ill patients with COVID-19 who were
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12 88 admitted to ICU. Therefore, the aim of the present study was to identify the risk factors
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14 89 and the set of clinical markers that increase the risk of death among ICU admitted
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16 90 COVID-19 patients, and to develop a risk prediction score that may facilitate the
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18 91 identification of supportive therapies to improve outcomes. We also aim to develop an
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20 92 easy-to-use web-based risk calculator implementing the derived risk prediction score to
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22 93 allow clinicians enter the values of the selected variables required for the risk calculation
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24 94 of mortality in patients admitted to ICU with COVID-19. The online calculator will
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26 95 provide stratification of patients into high and low risk categories based on an estimated
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28 96 cut-off risk corresponding to optimal performance measures of sensitivity and specificity.
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34 97 **METHODS**

35 98 **Study design and Data sources**

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38 99 This is a multicentre cohort study in which data of all laboratory confirmed COVID-19
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40 100 patients admitted to ICU in the Emirate of Abu Dhabi, United Arab Emirates (UAE)
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42 101 between March, 1st 2020 and July, 22nd 2020 were retrieved from electronic medical
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44 102 records. The data was collected from four major hospitals as well as newly developed
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46 103 field hospitals operating with some ICU bed capacity. The estimated bed capacity for
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48 104 ICU and/or high-dependency unit (HDU) was around 550 across the Emirate. We
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50 105 included patients who were admitted to a regular ICU room or to a HDU or if they were
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52 106 consistently receiving any form of oxygen therapy during their hospital stay in a make-
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3 107 shift ICU. The study was approved by the Department of Health of Abu Dhabi COVID-9
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5 108 IRB ethical committee (Ref#DOH/CVDC/2020/1116).
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8 109 **Outcomes**

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10 110 The primary outcome of this study is the survival time defined as the duration of time,
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12 111 from the date of ICU admission, until the date of death. Patients still hospitalized at the
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14 112 date of data extraction were considered as right censored and those discharged alive from
15
16 113 the hospital were considered as competing events to death due to COVID-19.
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20 21 22 114 **Statistical Analyses**

23 115 Baseline characteristics were summarized using descriptive statistics including mean and
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25 116 standard deviation for continuous measures, and frequencies tables for categorical
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27 117 variables. We compared categorical variables using the chi-square or Fisher's exact test,
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29 118 and continuous variables using the unpaired t-test or its non-parametric equivalent
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31 119 (Wilcoxon rank sum test) in case the normality assumption is violated.
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35 36 37 120 ***Potential predictive variables***

38 121 We considered 36 patient's characteristics assessed at the time of ICU admission as
39
40 122 potential predictors based on demographics, clinical signs and symptoms, medical history
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42 123 and laboratory findings. Demographic variables included age and sex. Clinical signs and
43
44 124 symptoms included systolic blood pressure, diastolic blood pressure, respiratory rate,
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46 125 Glasgow Coma Scale ratings, and minimum level of peripheral capillary oxygen
47
48 126 saturation (SpO₂). Medical history included status of coexisting conditions: diabetes,
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50 127 hypertension, cardiovascular disease, respiratory diseases, chronic kidney disease, cancer,
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52 128 and liver disease. Laboratory findings included white blood cells, monocytes count,
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3 129 monocytes percentage, neutrophils count, neutrophils percentage, lymphocytes count,
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5 130 lymphocytes percentage, red blood cell, platelets count, neutrophils-lymphocytes count
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8 131 ratio, neutrophils-lymphocytes percentage ratio, levels of C-reactive protein, lactate
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10 132 dehydrogenase (LDH), ferritin, haemoglobin, haematocrit, sodium, potassium, chloride,
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12 133 bicarbonates, creatinine and red blood cell distribution width (RDW). Patients with
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15 134 available data on these characteristics were included in the final analysis.
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17 18 135 ***The statistical model***

19
20 136 We used the competing risk regression model to investigate the association between
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22 137 death due to COVID-19 and all potential risk factors. We have chosen to use this model,
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24 138 instead of the standard Cox proportional hazard model, because discharge alive or
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26 139 recovery is clearly a competing event to death due to COVID-19^{19 20}. Ignoring this
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28 140 property will lead to biased estimates of the hazard ratios and the survival curves. We
29
30 141 estimated and plotted the survival curves using the cumulative incidence function taking
31
32 142 into account competing risks. Cumulative incidence curves of different groups were
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34 143 compared using the Gray's test²¹ for sub-distribution hazards, an equivalent of the log-
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36 144 rank test in the case of competing events. We used the Fine & Gray proportional hazards
37
38 145 regression models²² to investigate the association between potential risk factors and the
39
40 146 primary outcome, and also to derive the risk prediction score. All statistical analysis and
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42 147 data management carried out in this paper were done using the R software version 3.6.3
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44 148 and *P*-values <0.05 were considered as statistically significant.
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50 51 149 ***Variables selection method and derivation of the risk prediction score***

52
53 150 We used the Least Absolute Shrinkage and Selection Operator (LASSO) with Bayes
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55 151 Information criterion (BIC) for variables selection^{23 24}. This method uses a shrinking
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3 152 parameter to penalize non-significant coefficients of the Fine and Gray competing risk
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5 153 regression model. Larger shrinking parameters make the coefficients of non-significant
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7 154 risk factors to shrink towards zero, so that only the strongest predictors remain in the
8
9 155 survival model. Unlike the standard selection methods, such as stepwise forward or
10
11 156 backward, the LASSO procedure can deal with issues of multi-collinearity. All the 36
12
13 157 potential predictors were scaled using the z-score transformation, and were entered in the
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15 158 selection process. The most predictive covariates were selected by choosing the shrinking
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17 159 parameter that minimizes the BIC. Predictors selected by the LASSO procedure that were
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19 160 statistically significant were retained to construct the risk prediction score. We also
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21 161 investigated all statistical interactions between pairs of the retained predictors.
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27 162 *Validation of the risk prediction score*

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29 163 We derived the 28-day risk of in-hospital death using the estimates obtained from the
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31 164 Fine & Gray competing risk regression model. The predictive ability of this proposed risk
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33 165 prediction score was assessed using discrimination and calibration. Discrimination refers
34
35 166 to how well the predictive model is capable of discriminating between individuals who
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37 167 died and those who were discharged alive, whereas calibration refers to the agreement
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39 168 between observed and predicted number of deaths. Discrimination was assessed via the
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41 169 time-dependent area under the receiver-operator characteristic curve (AUC). Calibration
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43 170 was assessed via the time-dependent Brier score, and visually by plotting expected versus
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45 171 observed deaths. To reduce overfitting and optimism bias, we carried out internal
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47 172 validation of the risk prediction score by estimating the AUC and Brier score using 500
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49 173 bootstraps replications. This method allows all of the original data to be used in the
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174 model development while providing insight into the extent to which the original model is
175 overfitting or too optimistic.

176 **Patient and Public Involvement:**

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

179 **RESULTS**

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

192 The demographic and clinical characteristics of the patients are presented in Table
193 1. Among 221 women patients, 28 (12.7%) have died, and among 1321 men, 168
194 (12.7%) died. Compared with patients who were discharged alive, those who died were
195 older and had higher prevalence of diabetes, hypertension, chronic kidney disease,

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3 196 cardiovascular disease, and liver disease; lower diastolic blood pressure, higher
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5 197 respiratory rate, lower scores of Glasgow Coma Scale, lower levels of SpO₂ and a higher
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8 198 percentage of patients requiring oxygen therapy.
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10 199 The laboratory findings of the patients included in our study are presented in
11
12 200 Table 2. Compared with patients who were discharged alive, those who died had
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14 201 unfavourable laboratory profile on almost all variables including levels of C-reactive
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16 202 protein, creatinine, LDH, red blood cell distribution width, white blood cell count,
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19 203 potassium, ferritin, values of red blood cells, lymphocytes, monocytes, platelets count,
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21 204 haemoglobin, haematocrit, and serum bicarbonates.
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24 205 The results of the univariate competing risk model for each of the 36 potential
25
26 206 predictors measured at ICU admission are presented in the supplement (eTable 2). Of
27
28 207 these 36 variables, seven statistically significant predictors of mortality were retained by
29
30 208 the LASSO selection procedure in the multivariable competing risk regression model
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32 209 (eFigure 1 in the supplement). The hazard ratios, *P*-values and 95% confidence intervals
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34 210 of these significant variables are presented in Table 3. The significant predictors
35
36 211 increasing the risk of death included older age (hazard ratio [HR], 1.98 [95% CI, 1.71–
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38 212 2.31]; *P*<.001), higher neutrophil percentage (HR, 1.71 [95% CI, 1.27–2.31]; *P*<.001),
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40 213 higher LDH levels (HR, 1.31 [95% CI, 1.15–1.49]; *P*<.001), higher respiratory rate (HR,
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42 214 1.31 [95% CI, 1.15–1.49]; *P*<.001), and high levels of creatinine (HR, 1.19 [95% CI,
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44 215 1.11– 1.28]; *P*<.001). The significant predictors lowering the risk of death included
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46 216 higher Glasgow Coma Scale (HR, 0.70 [95% CI, 0.63– 0.78]; *P*<.001) and higher SpO₂
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48 217 levels (HR, 0.82 [95% CI, 0.74–0.91]; *P*<.001). We found no statistically significant
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52 218 interaction terms between pairs of the retained predictors.
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3 219 The cumulative incidence function of these 7 predictors retained by LASSO in the
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5 220 multivariable model is shown in the supplement (eFigure 2). For graphical presentation,
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8 221 we created a binary variable based on the median split in case of continuous risk factors.
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10 11 222 *Validation of the risk prediction score*

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13 223 The results of the internal validation using 500 bootstrap samples are shown in Figure 2.
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15 224 The predictive ability of the derived risk prediction score was quite promising. Indeed,
16
17 225 regarding discrimination, the estimated AUC was 88.1 (95% CI, 85.6–90.6), and the
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20 226 Brier score, measuring calibration, was estimated to 8.11 (95% CI, 6.74–9.60). Figure 2
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22 227 also shows the calibration plot for the risk prediction score, in which the predicted
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25 228 frequencies of deaths were plotted against the observed ones.
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27 229 From Figure 2, it is evident that the predicted frequencies of death were very
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29 230 close to the observed ones suggesting a very good calibration. The risk prediction score
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31 231 provided a sensitivity of 81% and a specificity of 79% using a cutoff risk of 11.5%.
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34 232 We also developed an easy-to-use web-based risk calculator implementing the
35
36 233 derived risk prediction score to allow clinicians enter the values of the selected variables
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38 234 required for the risk calculation of mortality in patients admitted to ICU with COVID-19.
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41 235 The online calculator also provides stratification of patients into high and low risk
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43 236 categories based on an estimated cut-off risk corresponding to optimal performance
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45 237 measures of sensitivity and specificity. The online risk calculator is freely available at
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3 **239 DISCUSSION**
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6 240 We developed and internally validated a clinical risk prediction score and a web-based
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8 241 risk calculator to predict the risk of in-hospital death in adult patients with confirmed
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10 242 COVID-19 admitted to ICUs. The risk prediction score shows high accuracy in terms of
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12 243 discrimination (AUC = 88.1) and calibration (Bier score = 8.11) with an almost perfect
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14 244 similarity between predicted and expected deaths. We identified seven readily available
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16 245 clinical features at ICU admission to be used for risk prediction of in-hospital mortality
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18 246 namely age, minimum oxygen saturation, respiratory rate, Glasgow Coma Scale ratings,
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20 247 neutrophil percentage, LDH, and creatinine levels. Our work shows that input of these
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22 248 variables in an easy-to use web-based risk calculator has the potential to accurately
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24 249 classify ICU admitted patients as likely to be discharged alive or die.
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29 250 A major strength of this study is the relatively large number of laboratory
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31 251 confirmed COVID-19 patients admitted to ICU, and the inclusion of information on a
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33 252 broad range of demographic, clinical and laboratory characteristics. Furthermore, the risk
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35 253 prediction score includes clinical features that are readily available at ICU admission that
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37 254 increases its clinical applicability. An obvious limitation of this study is the
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39 255 generalizability of risk prediction score in other settings, and we acknowledge that
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41 256 external validation of our risk prediction score in other populations is the next step in
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43 257 model development. Further, the participants included in this study were younger
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45 258 compared with other studies using the data at the time of hospital admission^{8 12-17}, which
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47 259 may in turn limit the generalizability in older patients.
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51 260 Previous studies have reported risk prediction scores of mortality based on the
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53 261 clinical features at the time of hospital or ICU admission, including patients with mild,
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3 262 moderate or severe forms of disease^{6 7 9 10 12-17}. For instance, using data of 4711
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5 263 confirmed patients with COVID-19, a severity score to predict in-hospital mortality was
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7 264 developed and validated, and consisted of six variables (age, oxygen saturation, mean
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9 265 arterial pressure, blood urea nitrogen, C-Reactive protein, and the international
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11 266 normalized ratio) assessed at the time of hospital admission¹². Moreover, 10 variables
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13 267 (chest radiographic abnormality, age, haemoptysis, dyspnoea, unconsciousness, number
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15 268 of comorbidities, cancer history, neutrophil-to-lymphocyte ratio, LDH and direct
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17 269 bilirubin) were found to be independent predictive factors, and were included in the risk
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19 270 score to predict the occurrence of critical illness in hospitalized patients with COVID-
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21 271 19⁷. The International Severe Respiratory and emerging Infections Consortium (ISARIC)
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23 272 developed and validated a mortality score consisting of eight variables (age, sex, number
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25 273 of comorbidities, respiratory rate, peripheral oxygen saturation, level of consciousness,
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27 274 urea level, and C reactive protein) that were available at the initial hospital assessment⁹.
28
29 275 In line with this, methods using machine learning have identified 8 important risk factors
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31 276 to predict mortality in ICU admitted patients with COVID-19¹⁵. Interestingly, nutritional
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33 277 status of the critically ill COVID-19 patients ascertained by mNUTRIC score at the time
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35 278 of ICU admission predicted twice the probability of death in patients with high nutritional
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37 279 risk than low risk patients¹⁴. The difference in the number and types of independent
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39 280 clinical features associated with mortality between our study and others may be explained
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41 281 by the differences in the baseline characteristics of the population or the choice of the
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43 282 statistical analyses. Indeed, we have chosen to use the competing risk regression model
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45 283 instead of the standard Cox proportional hazard model or the logistic regression model
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47 284 because recovery is clearly a competing event to in-hospital death due to COVID-19^{19 20}.
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3 285 Ignoring this property will definitely lead to biased effect estimates. Another plausible
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5 286 reason for this difference in the results is the younger age of the participants in our study
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8 287 compared to other studies¹²⁻¹⁷, which could likely influence the clinical features to be
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10 288 included in the risk prediction score.

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12 289 Other statistical association analyses have been published to investigate the
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15 290 factors affecting mortality due to COVID-19 in patients admitted to ICU^{8 11}. For instance,
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17 291 a multicentre cohort study of 2215 adults with laboratory-confirmed COVID-19 admitted
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19 292 to ICU in the US identified 9 risk factors independently associated with the 28-days
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22 293 mortality. These risk factors included age, sex, body mass index, coronary artery disease,
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24 294 active cancer, presence of hypoxemia, liver dysfunction, kidney dysfunction, and the
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26 295 number of hospital ICU beds⁸. In our risk score, none of the comorbid conditions
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28 296 achieved statistical significance for in-hospital mortality, however, other significant
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31 297 laboratory findings such as increased LDH and increased creatinine levels may represent
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33 298 underlying diseases such as liver disease, lung disease or kidney dysfunction.

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35 299 Interestingly, a non COVID-19 prediction score named Waterlow score has
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38 300 shown to predict 30-day mortality and length of hospital stay in acutely admitted elderly
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40 301 patients²⁵. The Waterlow score is a multidimensional pressure ulcer risk assessment tool
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42 302 and includes age, nutritional status, weight, mobility, gender, smoking status,
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44 303 comorbidities, use of medication and continence²⁵. One of the significant predictors of
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47 304 mortality included in our risk score is Glasgow Coma Scale which is an objective and
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49 305 reliable way of recording the initial and subsequent level of consciousness, and could be
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51 306 used as a proxy to continence. Although, the association between Waterlow score and
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54 307 mortality is demonstrated in patients aged 65 and above especially for respiratory, cardiac

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3 308 and stroke conditions, its application in patients with confirmed COVID-19 warrants
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5 309 further investigations.
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8 310 The recent COVID-19 epidemiological update from WHO, as of May 04, 2021,
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10 311 reported over 5.7 million new weekly cases worldwide which is at the highest level since
11
12 312 the beginning of the pandemic¹. The WHO European and American regions accounted
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14 313 for 20% and 23% of new weekly cases, respectively. The largest increase accounting for
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16 314 47% of new weekly cases was noted in South East Asia region particularly in India which
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18 315 accounted for over 90% of both cases and deaths in the region. The Eastern
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20 316 Mediterranean region that includes UAE accounted for 6% of new weekly cases¹. Earlier
21
22 317 studies have reported rate of admission to ICU among confirmed SARS-CoV-2 cases
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24 318 ranging between 2% and 81%^{18 26 27}, and high mortality prevalence among ICU patients
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26 319 ranging between 5% and 83%^{3 18 28}. A meta-analysis of twenty-five studies with 24,677
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28 320 patients demonstrated a rate of 26% for ICU admission, and 31% mortality prevalence
29
30 321 among patients admitted to ICU with a severe form of COVID-19¹⁸. The relative high
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32 322 number of deaths in the ICU presents an enormous challenge to the prognostication and
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34 323 management of patients with COVID-19. We believe that the risk tool provided in this
35
36 324 study may have utility in clinical settings to guide decision-making, and may facilitate the
37
38 325 early identification of patients at high risk of death, and may be used as a guidance in
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40 326 busy ICU units to stratify patients according to their risk in order to deliver the best
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42 327 available supportive care. The parameters selected are easily available at the time of ICU
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44 328 admission.
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52 329 **Conclusion**
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3 330 We developed and internally validated a risk tool for predicting in-hospital death among
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5 331 COVID-19 patients admitted to ICU, which shows high predictive accuracy. This tool
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7 332 can assist in early identification of patients during ICU admission who are at high risks of
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9 333 death, and consequently can facilitate optimal delivery of supportive care for these
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11 334 patients.
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4

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6
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8

9
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11
12 339 development of the research question and study design. AO led the development of
13
14 340 advanced statistical aspects. SA, AA, MAH, MAA, RG, II and AO were involved in data
15
16 341 specification, curation, and collection. AO did data management and statistical analyses,
17
18 342 which were checked by SA, AA, MAH, and JN. SA, AA, MAH, MAA, RG, II, JN and
19
20 343 AO contributed to the interpretation of the results. SA, AA, JN and AO wrote the first
21
22 344 draft of the paper. SA, AA, MAH, MAA, RG, II, JN and AO contributed to the critical
23
24 345 revision of the manuscript for important intellectual content and approved the final
25
26 346 version of the manuscript. AO developed the software for the web calculator. The
27
28 347 corresponding author attests that all listed authors meet authorship criteria and that no
29
30 348 others meeting the criteria have been omitted. AO is the guarantor.

31
32 349 The lead author affirms that the manuscript is an honest, accurate, and transparent
33
34 350 account of the study being reported; that no important aspects of the study have been
35
36 351 omitted; and that any discrepancies from the study as planned (and, if relevant,
37
38 352 registered) have been explained.

39
40 353 **Ethical approval:** The study was approved by the Department of Health of Abu Dhabi
41
42 354 COVID-19 IRB ethical committee (Ref#DOH/CVDC/2020/1116).

43
44 355 **Data availability statement:** To guarantee the confidentiality of personal and health
45
46 356 information, only the authors have had access to the data during the study in accordance
47
48 357 with the relevant licence agreements. Access to the data is according to the information
49
50 358 and rules and regulations of Abu Dhabi Health Services - SEHA and Cerner.

51
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53
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55
56 361 conduct of the study; collection, management, analysis, and interpretation of the data;
57
58 362 preparation, review, or approval of the manuscript; and decision to submit the manuscript
59
60 363 for publication.

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2
3 364 **Competing interest statement:** All authors have completed the ICMJE uniform
4
5 365 disclosure form and declare: no support from any organisation for the submitted work; no
6
7 366 financial relationships with any organisations that might have an interest in the submitted
8
9
10 367 work in the previous three years, no other relationships or activities that could appear to
11
12 368 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

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)				
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.

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), $\times 10^9/L$	7.89 (3.92)	10.40 (6.01)	7.52 (3.36)	<.001
Lymphocyte count, mean (SD), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	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), $\times 10^9/L$	263.57 (107.94)	241.88 (104.12)	266.72 (108.17)	0.002
Red blood cell, mean (SD) $\times 10^{12}/L$	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), $\mu\text{mol}/L$	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.

369 **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 $\times 10^9/L$, 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, $\mu\text{mol/L}$	1.19 (1.11 to 1.28)	<.001

Abbreviations: HR, hazard ratios; CI, confidence interval; SpO₂, 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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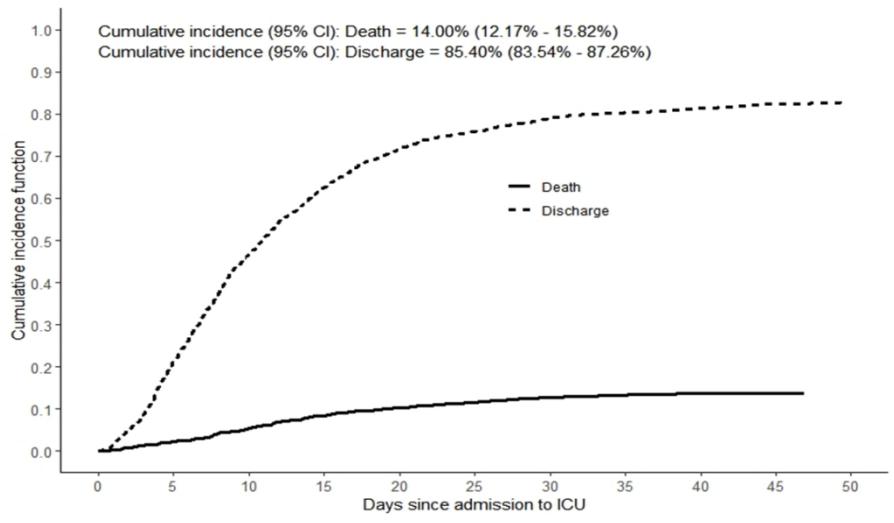


Figure 1. Mortality and Recovery Curves among Critically Ill Patients with COVID-19.

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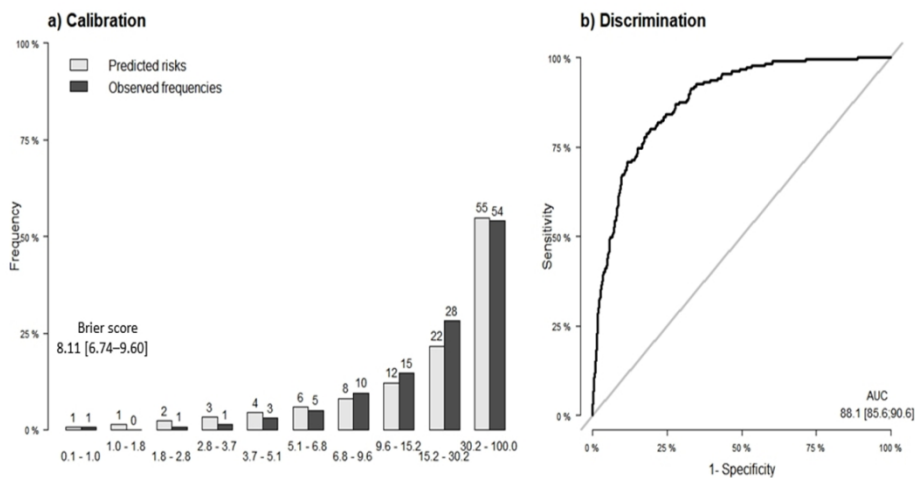


Figure 2. Calibration and Area under the Receiver-Operator Characteristic (ROC) Curve (AUC) of Predicting Death among Patients with COVID-19 admitted to ICU.

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

eTable 2. 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.

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.

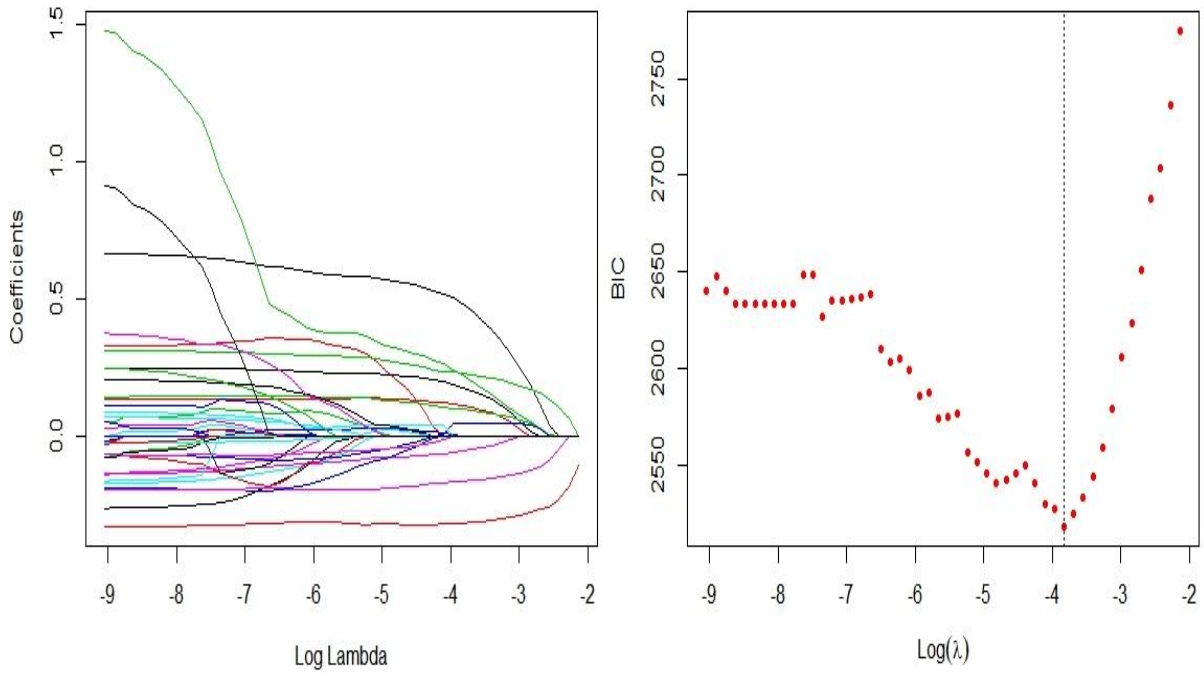
eTable 2. Univariate competing risk models on candidate predictors.

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 SpO ₂	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; SpO₂, peripheral capillary oxygen saturation.

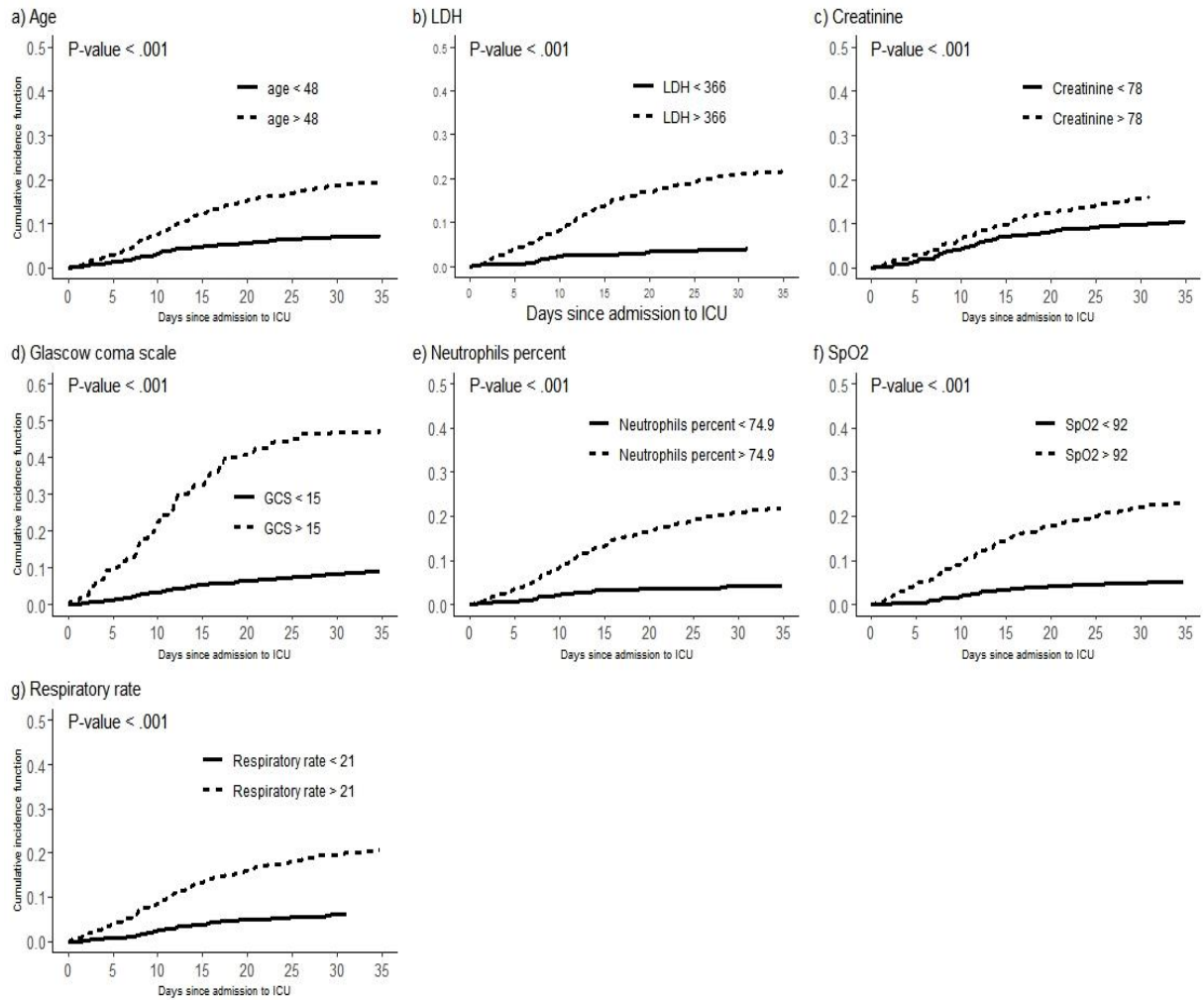
The predictors were scaled using z-score transformation, and hazard ratios should be interpreted as 1 SD change in the values of the parameters.

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 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.