External validation of the ISARIC 4C Mortality Score for hospitalized patients with COVID-19 in Tunisia

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Research Article

Keywords:

Posted Date: September 1st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3290410/v1

Abstract

Estimating mortality risk in hospitalized patients with COVID-19 infection may help clinicians to early triage patients with poor prognostic outcome. The Coronavirus Clinical Characterization Consortium Mortality Score (4C Score) is one of the predictive models that was externally validated in large cohorts. However, its use may be limited in population with quite different demographic and epidemiologic features.

Objective

To externally validate the 4 C score in a large Tunisian population

Methods

Multicenter retrospective cohort study of patients aged ≥ 14 years, hospitalized with the diagnosis of COVID-19. The primary outcome was in-hospital mortality, need for ICU admission and combined outcome (in-hospital mortality and/or ICU admission). We calculated the area under the receiver operating characteristic (ROC) curve (C statistics) for the 4C Mortality Score to assess the discriminatory power of the 4C Mortality Score for predicting outcomes. To assess calibration of the model, we used the Hosmer-Lemeshow goodness-of-fit test.

Results

2327 patients with diagnosis of COVID-19 based on positive RT-PCR assay or rapid antigen test of a nasopharyngeal swab were included for final analysis. Median time between symptoms start and hospital admission was 4 days [2-7], and 69.2% needed oxygen therapy at hospital admission. In-hospital mortality was 15.4% (n=358); most deaths (11%, n=257) occurred in the ICU. Mortality rates within the 4C Mortality Score risk groups were 0.6% (Low), 8.7% (Intermediate), 53.1% (High), and 37.7% (Very High). The score achieved a good estimated discrimination when predicting death (C-statistic:0.86; 95%, CI [0.84-0.88]), ICU admission (C-statistic: 0.69; 95%, CI [0.65-0.72]) and the combined outcome (C-statistic:0.79; 95%, CI [0.77-0.81]). The calibration plot indicated good calibration for both in-hospial mortality and combined outcome (HosmerLemeshow goodness-of-fit test p value of 0.86 and 0.28 respectively).

Our study represents a new external validation of the 4C score in COVID-19 patients with high reliability in predicting disease severity. These findings imply that the 4C Mortality Score may be generalized to patients with COVID-19 regardless of ethnicity and healthcare system.

Introduction

Coronavirus disease 2019 (COVID-19) is one of the most recent and ongoing viral disease that have severely threatened public health worldwide.(1, 2) On May 2022, the WHO estimated the number of excess deaths to be 14.9 million, with most of the unreported deaths believed to be directly due the virus.

(3) Stratification of COVID-19 patients based on their severity risk and can help physicians to triage and manage patients. This will reduce time to appropriate interventions and improve patients' outcomes. (4, 5) Multiple prognostic models have been proposed but, for most of them, the predictive accuracy remains uncertain.(6) The Coronavirus Clinical Characterization Consortium Mortality Score (4C Mortality Score) is one of the proposed risk assessment tools developed by the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC); it is an accessible simple score based on eight different clinical and biological parameters.(7) It was derived and internally validated on a large cohort of patients within and outside the United Kingdom.(8–14) However, its performance may be limited in patients with quite different demographic and epidemiologic features compared to the original population. The decision to apply 4C Mortality score in different setting should ideally be based on objective and specific validation. In this study we aimed to externally validate the prognostic performance of the 4C Mortality Score within the setting of five Tunisian University hospitals and two regional hospitals.

PATIENTS AND METHODS

Study design and population

This is a multicenter retrospective cohort study of patients admitted to five Tunisian university hospitals (Fattouma Bourguiba Hospital Monastir, Sahloul Hospital Sousse, Farhat Hached Hospital Sousse, Taher Sfar Hospital Mahdia, Habib Bourguiba Hospital Sfax) and two regional hospitals (Haj Ali Soua Regional Hospital and Ben Arous Traumatology and Burns Regional Hospital). Data of patients with COVID-19 admitted to hospital between July 2020 and April 2022 were extracted from an electronic health record using a combination of electronic download for routinely collected, coded variables (eg, age, vital signs, and laboratory values), supplemented by chart review by principal investigators. The study adhered to the principles of the National Data Protection Authority requirements, and the Declaration of Helsinki. The protocol was approved by the ethics committee of the faculty of medicine of Monastir University which waives the consent requirements.

Inclusion and exclusion criteria

We included subjects aged ≥ 14 years, hospitalized with the diagnosis of COVID-19 based on positive reverse transcription polymerase chain reaction (RT-PCR) assay or rapid antigen test of a nasopharyngeal swab. We excluded patients whose test results for RT-PCR were negative, patients with incomplete electronic records and patients needing immediate ICU admission.

Data collection

Clinical records of each participating centre were requested to provide information about demographic details, presenting clinical features, underlying comorbidities, laboratory markers, treatment and hospital outcomes. Physician coordinator and associate of each participating center collected data using a validated electronic case report form (eCRF). All eCRF users were trained according to the completion guidelines. Data for included cases were reviewed by at least two authors to check their validity.

4C Mortality Score calculation

The 4C Mortality score incorporates age, sex, comorbidities, respiratory rate, peripheral oxygen saturation, Glasgow coma score, blood urea nitrogen, and C-reactive protein (CRP). The 4C Mortality Score ranges from 0 to 21 with risk groups defined by Knight et al as low (0–3), intermediate (4–8), high (9–14), and very high (≥ 15).(7) When more than one value within the first 24 hours from hospital admission were available, the first one was used. The comorbidities considered in this score were chronic cardiac disease, chronic respiratory disease (excluding asthma), chronic renal disease (estimated glomerular filtration rate ≤ 30), mild to severe liver disease, dementia, chronic neurological conditions, connective tissue disease, diabetes mellitus (diet, tablet, or insulin controlled), HIV or AIDS, and malignancy.

Outcome criteria

Outcome criteria include in-hospital mortality, need for ICU admission and combined outcome (in-hospital mortality and/or ICU admission).

Statistical analysis

The statistical analysis was based on a descriptive analysis using qualitative and quantitative variables. For the description of qualitative variables, we used percentages and 95% confidence intervals. Quantitative variables, were expressed as mean and standard deviations or median and interquartile range (IQR) according to the data distribution. Comparative results were tested with chi-square test for comparison of percentages (with Fisher's test if appropriate) among categorical variables. Mann-Whitney test was used to compare two means or non-parametric tests for non-normal distributed data. Comparative results are presented with corresponding 95% confidence interval (CI). We calculated the area under the receiver operating characteristic (ROC) curve (C statistics) to assess the discriminatory power of the 4C Mortality Score for predicting outcomes. A value of 0.5 indicates no predictive ability, 0.8 is considered good, and 1.0 is perfect. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated. To assess calibration of the model, we used the Hosmer-Lemeshow goodness-of-fit test. All p-value analyses were two-sided, and a p-value of less than 0.05 was considered to be significant. The data were analyzed using SPSS Statistics version 22.0. The study is registered with ClinicalTrials.gov, number NCT05498324. There was no funding source for this study.

RESULTS

We included 2327 patients with diagnosis of COVID-19. We excluded patients with incomplete electronic records (2066), pregnant patients (5), patients aged less than 14 years (2), patients whose test results for RT-PCR were negative (232), and patients with an immediate need for ICU admission (180) (Fig. 1). The age of participants ranged between 16 and 96 years with a sex-ratio ratio (M/F) of 1:27. Almost two third of patients (64.5%) had at least one comorbidity; hypertension is the most common one (37.3%) followed by diabetes (33.5%) and chronic heart failure (9.3%). Median time between symptoms start and hospital admission was 4 days [range 2–7], and 69.2% needed oxygen therapy at hospital admission. Table 1

summarizes demographic characteristics and distribution of main clinical and biological findings of the overall population. Antibiotics were prescribed in 1137 patients (48.9%), corticosteroids in 1237 patients (53.2%) and anticoagulants in 1640 patients (70.5%). Vaccination rate was …%. In-hospital mortality was 15.4% (n = 358); most deaths occurred in the ICU (n = 257). Distribution of patients across range of 4C Mortality Score is shown in Fig. 2. The mean value of the risk score was higher in the non-survivors (13.09 ± 3.21) compared to survivors (7.21 ± 4.05) ($p < 0.0001$). Mortality rates within the 4C Mortality Score risk groups were 0.6% (Low), 8.7% (Intermediate), 53.1% (High), and 37.7% (Very High) (Table 3). The mean values of the risk score were higher in the ICU admitted group compared to non-ICU group (10.34 ± 3.73 versus 7.43 ± 0.1 in; $p < 0.0001$). The ROC curves for in-hospital mortality, ICU admission and combined outcome for the 4C Mortality Score are shown in Figs. 3. The score achieved a good estimated discrimination when predicting death (C-statistic: 0.86; 95%, CI [0.84–0.88]), ICU admission (C-statistic: 0.69; 95%, CI [0.65–0.72]) and combined outcome (C-statistic: 0.79; 95%, CI [0.77–0.81]). Table 4 shows the mortality accuracy measures for 4C Mortality Score cut-offs at 3, 8, 11, and 14. The sensitivity at each cut-off ranged from 99% for 4C Mortality Score > 3 to 37% for a cut-off > 14. Specificity ranged from 23% for a cut-off > 3 to 97% for a cut-off > 14. The calibration plot indicated good calibration for both in-hospital mortality and combined outcome (HosmerLemeshow goodness-of-fit test p value of 0.86 and 0.28 respectively).

Table 1
Demographics and baseline characteristics

	Overall
Age, (Years), median, IQR	61[47–71]
Sex-ratio, M/F	1303/1024
Smoking, n (%)	530 (22.7)
Body mass index, kg/m2, median [IQR]	25.95[23.67–29.26]
Previous Medical history, n (%)	1500 (64.5)
Hypertension	869 (37.3)
Diabetes	779 (33.5)
Chronic heart failure	216 (9.3)
COPD	203 (8.7)
Acute coronary syndrome	142 (6.1)
Asthma	39 (5.6)
Chronic renal failure	138 (5.9)
Hemodialysis	10 (0.4)
Symptoms, n (%)	
Symptomatic with need of Oxygen	1610(61610 (69.2)
Dry cough	1241 (61.7)
Asthenia	833 (60.9)
Fever	111 (48.0)
Headache	422 (31.7)
Vomiting	133 (28.4)
Myalgia	342 (25.2)
Polypnea > 22	219 (16.3)
Chest pain	203 (15.5)
Abdominal pain	272 (13.7)
Diarrhea	175 (12.8)
Anosmia	119 (6.2)

	Overall
Agueusia	53 (2.9)
Cutaneous shock signs	13 (0.9)
Vital signs on admission	
Glasgow Score (15 = yes), n (%)	2238 (96.2)
Oxygen pulse saturation, median [IQR]	90[87–96]
Respiratory rate, cpm, median [IQR]	21[18–25]
Heart rate, bpm, median [IQR]	88 [80–100]
SBP, mmHg, median [IQR]	128 [120–140]
DBP, mmHg, median [IQR]	74 [66–80]

Table 2
Biological findings

Biological values on admission	Overall
Hemoglobine, g/dl, median [IQR]	12 [11-13.4]
Leukocytes, g/l, median [IQR]	8.24 [6-11.24]
Lymphocytes, g/l, median [IQR]	1.02 [0.69–1.66]
Platelets count, g/l, median [IQR]	233 [169–303]
C-reactive protein, mg/l, median [IQR]	62 [28–115]
Urea, mmol/l, median [IQR]	6.7 [5–10]
Serum creatinine, µmol/l, median [IQR]	73.0 [62–94]
D-dimers, µg/l, median [IQR]	802 [446–1779]
Glucose, g/l, median [IQR]	9.33 [6.6-16.02]

Table 3
4C score risk groups

Risk Group	Overall (n = 2327)	Dead (n = 358)
Low (0–3), n (%)	462 (19.9)	2 (0.6)
Intermediate (4–8), n (%)	748 (32.1)	31 (8.7)
High (9–14), n (%)	930 (40.0)	190 (53.1)
Very high (> = 15), n (%)	187 (8.0)	135 (37.7)

Table 4
The mortality accuracy measures for cut-offs at the 4C Mortality Score.

Cut-off value	No of patients	FP (%)	FN (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥ 3	1865	80.91	0.43	99.44	23.36	19.09	99.57
≥ 8	1117	70.9	2.73	90.78	59.78	29.1	97.27
≥ 11	581	56.8	6.13	70.11	83.24	43.2	93.87
≥ 14	187	27.81	10.42	37.71	97.36	72.19	89.58

DISCUSSION

The present validation study demonstrated that, for Tunisian hospitalized patients with confirmed COVID-19, the 4C Mortality Score had good performance in predicting in-hospital mortality and ICU admission. Its discrimination and calibration were good.

Several studies proposed prediction models combining clinical, laboratory, and imaging variables to early identify COVID-19 patients at high-risk of serious complications in order to guide decisions regarding disposition, diagnostic workup, and therapy. However, most of these models were developed from studies with serious methodological issues and they lack external validation. (6) One of the most performant and validated scores to predict outcome in patients with COVID-19 is the 4C Mortality Score (6, 7) for which several studies reported an adequate external validation.(6, 15–17) However, there is still a doubt whether this score could be applied worldwide in populations with significant differences in demographic characteristics and frequency of the outcome compared with those of the original research. (18) Our findings were in line with the studies reported previously suggesting that the 4C Mortality Score could be a useful tool for our population. The large sample size, the number and diversity of the participating sites and a comprehensive list of data elements are major strengths of this study. In addition, in our study we assessed the 4C Mortality Score performance using both discrimination and calibration tests. Although it is frequently overlooked, calibration is a critical component of accuracy with particular relevance for prognostic models and risk-assessment tools. Calibration is especially important when the aim is to support decision-making. Reporting on calibration performance is recommended by the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guidelines for prediction modeling studies.(19) A recent validation study demonstrated that the 4C Mortality Score could be simplified by deleting CRP item which is favorable to its widespread use. This needs to be confirmed by further studies. It would also be interesting to compare the 4C Mortality Score with other available scores.(20–22) One simple prognostic clinical risk prediction score specific for COVID-19 is of particular interest in this issue, the Quick COVID-19 Severity Index (qCSI). Including only three items, respiratory rate, pulse oximetry, and supplemental oxygen flow rate, the qCSI may even outperform the 4C Mortality Score according to available data.(23, 24) This study has several limitations. First, the management of SARS-CoV-2 CAP is constantly evolving and changed markedly with

vaccination, corticosteroids, and other antiviral interventions which could influence outcome and score performance. Ongoing prospective validation is therefore necessary to ensure adequate performance and inform the need for temporal recalibration. Second, there were several missing values in our data set, and we analysed only complete cases in this study, which may have led to potential selection bias. Finally, the question whether the 4C Mortality Score has sufficient clinical utility to inform clinical decision-making is not unanswered. Currently, no study has clearly shown one prognostic model to improve clinical practice in effectiveness terms. Although Tunisian clinicians may apply this score in routine practice, more research is probably warranted to objectively establish its benefit.

In summary, our study represents a new external validation of the 4C Mortality Score in COVID-19 patients. We demonstrate that this score has high reliability in predicting disease severity. These findings imply that the 4C Mortality Score is generalizable to patients with COVID-19 regardless of ethnicity and healthcare system. It could assist with rapid and effective triage decisions, prognostic information, and better use of limited healthcare resources.

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Figures

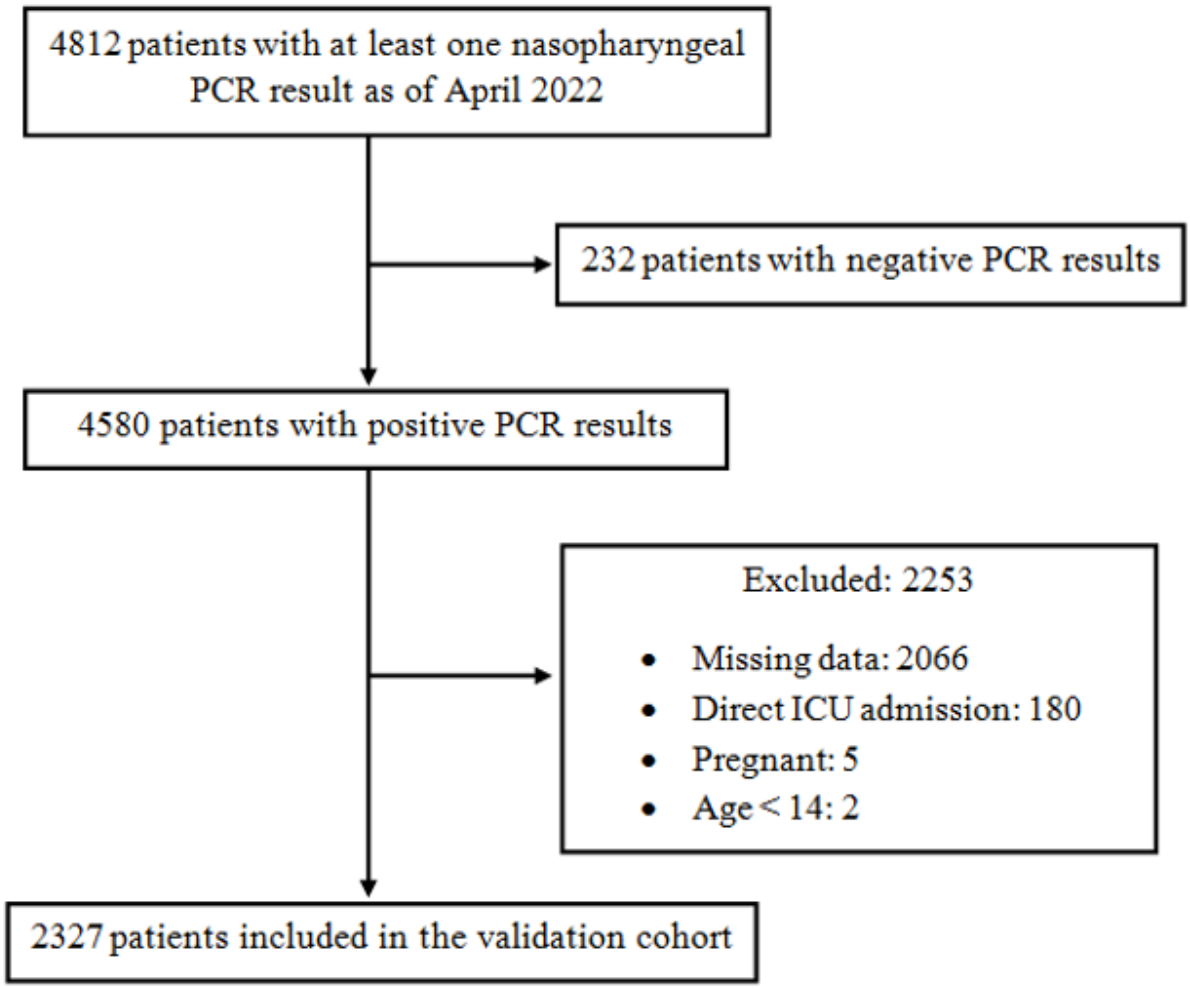


Figure 1

Flow chart of COVID-19 patients included in the study

PCR : Polymerase Chain Reaction, ICU: Intensive care unit.

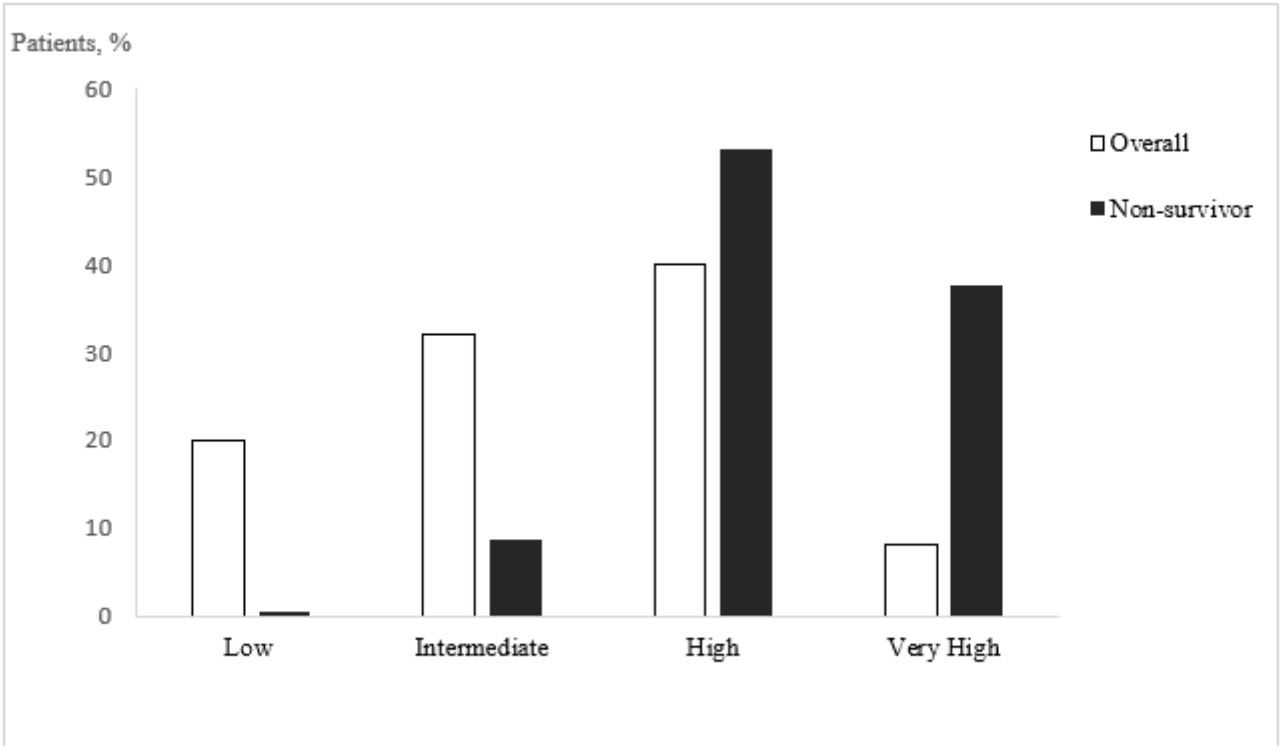


Figure 2

Mortality among 4C score risk groups.

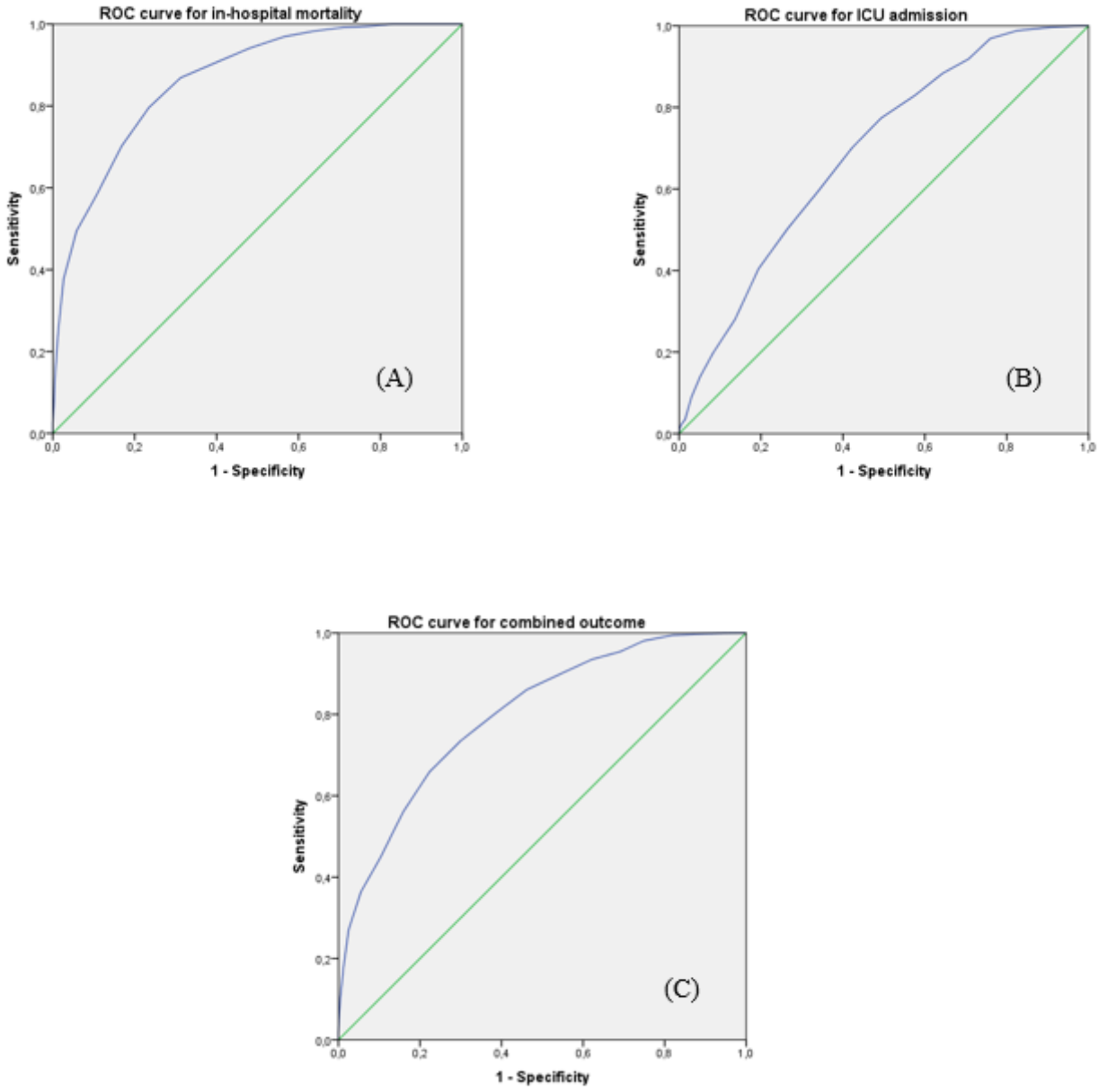
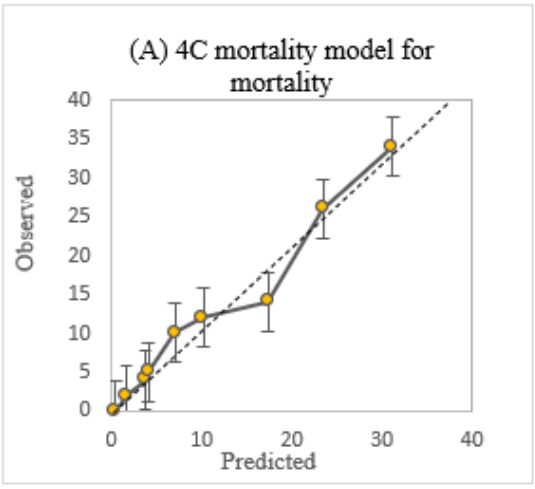
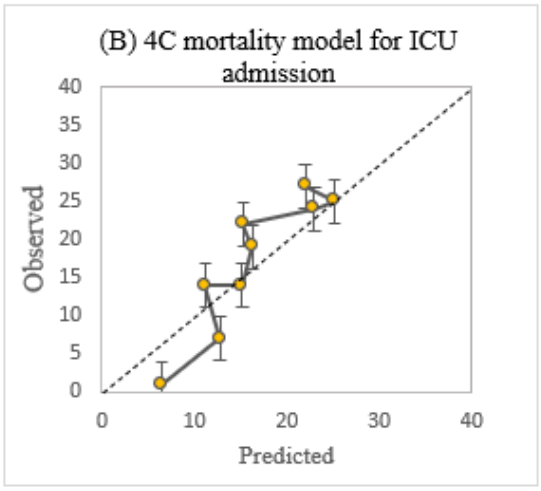


Figure 3

ROC Curve Of the 4C prognostic score for in-hospital mortality (A), ICU admission (B) and combined combined outcome (C).

ROC: Receiver Operating Characteristic, ICU: Intensive care unit.





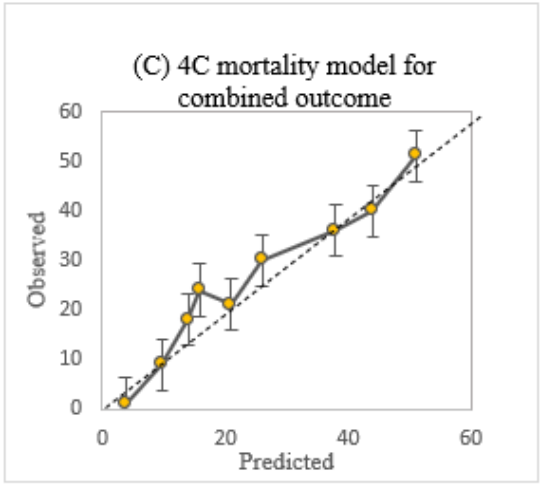


Figure 4

Calibration plot of the 4C Mortality Score models for in-hospital mortality (A), ICU admission rate (B) and combined outcome (C).

ICU: Intensive care unit.