

# Predictive value of serial evaluation of the Sequential Organ Failure Assessment (SOFA) score for intensive care unit mortality in critically ill patients with COVID-19: a retrospective cohort study

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## Abstract

**Background:** The Sequential Organ Failure Assessment (SOFA) score has been developed to score the severity of organ dysfunction in critically ill sepsis patients and has been proven to have a high predictive value for intensive care unit (ICU) mortality in severely ill patients. Our goal was to evaluate the prognostic value of the SOFA score as well as trends in SOFA score for ICU mortality in COVID-19 patients.

**Methods:** All consecutive patients with confirmed COVID-19 pneumonia admitted to the ICU between March 13<sup>th</sup>, 2020, and October 17<sup>th</sup>, 2020 were included in this retrospective cohort study. The worst SOFA score was evaluated daily. Multiple logistic regression models were used to evaluate the predictive value of SOFA in ICU mortality.

**Results:** 103 patients were included in this study. 30 patients (29%) died during their ICU stay and 73 (71%) patients were discharged alive. The ICU admission SOFA score was  $5.2 \pm 3.3$  in ICU non-survivors vs.  $4.3 \pm 2.9$  in ICU survivors ( $P = 0.15$ ). The maximum SOFA score in ICU non-survivors was  $11.7 \pm 4.7$  vs.  $7.4 \pm 4.3$  in ICU survivors. SOFA scores increased the first week in both survivors and non-survivors, but the increase was less pronounced in survivors. In the multiple logistic regression models, neither admission SOFA score nor combination with delta SOFA in the first 48 hours was statistically significantly related to ICU mortality. Only the maximum SOFA score remained significant (OR = 1.23, 95% CI: 1.11–1.37,  $P < 0.001$ ) in the multiple logistic models with an AUC of 0.91.

**Conclusions:** Evaluation of SOFA scores in the first 48 hours after ICU admission is not a good prognostic indicator in COVID-19 patients. Only the maximum SOFA score was predictive for ICU mortality.

**Key words:** COVID-19, SOFA, mortality, intensive care unit.

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Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first diagnosed in Wuhan, China, after a series of unexplained cases of severe pneumonia in December 2019 [1]. Despite important precautions that were taken, the virus spread rapidly worldwide and arrived in Belgium in February 2020. From the little experience and data of other countries, we knew that the presence of the infection was highly heterogeneous [2, 3]. The majority of the patients were asymptomatic or showed mild symptoms, but around 20% of the patients required hospitalization, of whom 5–10% became critically ill, requiring intensive care admission and mechanical ventilation, with still a high mortality rate [4].

Consequently, major concerns arose regarding bed and nurse capacity for all intensive care units (ICU) eligible patients during the first wave of the COVID-19 pandemic in Belgium. Due to the scarcity of guidelines for ICU admission and outcome data, mainly age and comorbidities were used as criteria for admission and decision making of coding. During the second wave of infections, with an even higher critical saturation of ICU beds and mortality rate, specific scoring systems to guide ICU admission or predict mortality for patients with SARS-CoV-2 infection were still lacking.

There are multiple scoring systems in use on the ICU that can help assess organ dysfunction or failure and are useful to evaluate morbidity in critically

ill patients. The Sequential Organ Failure Assessment (SOFA) score was initially designed in 1996 to sequentially assess and quantify the severity of organ dysfunction in patients who were critically ill from sepsis [5]. The SOFA uses six different variables, one for each of the major organ systems: respiratory, cardiovascular, liver, coagulation, kidneys, and central nervous system. The function of each organ system is scored from 0 to 4, with an increasing score reflecting worsening organ dysfunction [5, 6]. Although this scoring system was not developed to predict the outcome, an obvious relationship between organ failure and mortality has been demonstrated in several studies [6–8]. Therefore, it has been validated as a prognostic tool to predict mortality in severely ill patients [9, 10]. Additionally, the SOFA score is an increasingly important tool in evaluating the response to the change of therapy in the context of clinical trials [11].

This study aimed to evaluate the prognostic value of the SOFA score and evolution in SOFA score concerning ICU mortality in patients admitted to the ICU with severe SARS-CoV-2 infection.

## METHODS

This mono-centric, investigator-initiated, longitudinal, retrospective, observational cohort study was performed at the ICU department of the Jessa Hospital, Hasselt, Belgium. This study was approved by the ethical committee of Jessa Hospital, Hasselt, Belgium on 4<sup>th</sup> January 2021 and registered at [clinicaltrials.gov](https://clinicaltrials.gov) on September 30<sup>th</sup>, 2020 (NCT04713852). Written informed consent was waived in light of the urgent need to collect data on the ongoing pandemic. This study is reported according to the Transparent Reporting of a multi-variable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement [12].

### Study population

All adult patients diagnosed with COVID-19 pneumonia and admitted to the ICU between 13<sup>th</sup> March 2020 and 17<sup>th</sup> October 2020 were included in the study. Following the World Health Organization (WHO) protocol [13], laboratory confirmation of COVID-19 infection was defined as a positive result on polymerase chain reaction (PCR) assays of nasopharyngeal swab samples or bronchoalveolar lavage. Only laboratory-confirmed patients were included in the analysis. From March 13<sup>th</sup>, 2020, until October 17<sup>th</sup>, 2020, data from 116 consecutive patients admitted to the ICU were prospectively entered into a customized database that included medical history, demographic data, clinical symptoms and signs, laboratory results, and clinical outcomes. Body temperature was measured with an electronic inguinal

thermometer. A body temperature of 38°C was determined as the cut-off value for diagnosis of fever.

### Multi-organ failure variables

The SOFA score was calculated on admission and every 24 hours until ICU discharge or death for every included patient. The SOFA score includes components reflecting the status of coagulation and the hepatic, respiratory, cardiovascular, central nervous, and renal organ systems. Each component score ranges from 0 (normal organ function) to 4 (worst organ function). The SOFA score is the sum of all organ scores resulting in a range from 0 to 24 [5]. The SOFA score for each patient on a given ICU day was the sum of the worst values for all component organ failures in the 24 hours. In cases where the physiological parameters did not match any row, zero points were given. In cases where the physiological parameters matched more than one row, the row representing the highest score was selected [11]. All parameters included in the SOFA scores such as bilirubin, platelets and serum creatinine were measured daily. However, when a value was exceptionally missing, the value of the previous day was used to calculate the SOFA score (last observation carried forward approach) [14]. All COVID-19 patients admitted to the ICU were included in the analysis and the type of respiratory support, i.e., endotracheal tube, high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV) or nasal cannula, was documented as such. Almost all patients were treated at some stage in their care with a nasal cannula and HFNO, which deliver oxygen at variable inspired oxygen percentage or flow rates. For patients on nasal cannula oxygen, an estimated  $\text{FiO}_2$  was calculated for patients on a nasal cannula ( $\text{O}_2$  flow in litres per minute  $\times$  0.03 + 0.21) [11]. In sedated patients, we also applied 'a last observation carried forward approach' [11]. In the rare cases where the Glasgow Coma Scale (GCS) from before the start of sedation was not available, a value of 15/15 was recorded and carried over throughout the duration of sedation administration [11].

The admission SOFA score is defined as the sum of the most severe value for each sub-score at admission to the ICU. The maximum SOFA score is the highest daily SOFA score observed during ICU stay [10]. The change in SOFA score during the first 24/48 hours is calculated as SOFA at day 2/3 minus SOFA at day 1 (admission). We refer to this change as delta SOFA from day 1 to day 2/3.

### Outcome parameters

The primary endpoint is either ICU mortality or discharge from the ICU. Hence, the study population was divided into participants who died during their

ICU stay and participants who were discharged from the ICU alive. The data set was closed on November 10<sup>th</sup>, 2020. All participants reached the primary outcome.

### Explanatory variables

For the present study, a few variables were selected to test their predictive value for ICU mortality with multiple testing. First, it is widely recognized that mortality after SARS-CoV-2 infection increases exponentially in patients aged over 50 [15]. Second, in our hospital, also patients with a do-not-intubate (DNI) code were admitted to the ICU for high-flow oxygen therapy. Third, a therapy adjustment was implemented throughout the inclusion period: an intensified thromboprophylaxis protocol implemented on March 31<sup>st</sup> significantly reduced one-month mortality [16]. Thus, the time of admission (before or after 31.03.2020) was included as an explanatory variable.

### Statistical analysis

Continuous data are shown as mean  $\pm$  standard deviation (SD) and categorical data are represented as frequency (%). At ICU admission, Student's *t*-test or the Mann-Whitney *U* test (in the case of non-normally distributed data) was used to compare ICU survivors and ICU non-survivors for continuous variables, and the  $\chi^2$  test for categorical variables.

Linear mixed models for repeated measures were employed to compare the evolution of mean SOFA scores over time for ICU survivors and ICU non-survivors. For each patient, the SOFA scores of the first two weeks at the ICU were used. Day since ICU admission, group (ICU survivor or ICU non-survivor) and their interaction term were included as fixed effects. A non-linear evolution was allowed by including the quadratic term of day since ICU admission. The linear mixed model also included a random patient effect to take into account the correlation between SOFA scores of the same patient. Based on this model, changes within a group (survivor or non-survivor) and differences between the groups at specific time points or for differences in change were investigated. No correction of multiple testing was used.

The predictive value of the following SOFA variables for predicting ICU mortality was investigated using logistic regression models: SOFA score on day 1, the maximum SOFA score, combination of SOFA score on day 1, and change in SOFA score between days 1 and 2. The  $\chi^2$  test was used to evaluate the statistical significance of these variables. These logistic models were extended by incorporating the following variables: age, time of admission (before or after 31.03.2020), and DNI status. For each model,

the predictive significance of the variables, the OR (95% CI), and area under the receiver operating characteristic (AUC) curve are given. The ROC curve, the calibration plot, and the Hosmer-Lemeshow test are presented for the multiple logistic models when the SOFA variable is statistically significant. A *P*-value  $< 0.05$  is considered statistically significant. All analyses were conducted with SAS software, version 9.4 of the SAS System for Windows.

### RESULTS

The STROBE flowchart depicting inclusion and exclusion is presented in Figure 1. In total, 116 COVID-19 patients were admitted to the ICU from March 13<sup>th</sup> until October 17<sup>th</sup>, 2020. Patients admitted to the COVID ICU for reasons other than COVID-19 pneumonia (i.e., neurological trauma, diabetic ketoacidosis, complication after surgery) were excluded, resulting in 103 patients for the statistical analyses. The patients' baseline characteristics are presented in Table 1. Mean age was  $68.2 \pm 11.3$  years, ranging from 24 to 86 years for the total group. The majority of the patients were male (61.2%). A total of 30 patients (29%) died during their ICU stay and 73 (71%) patients were discharged alive. Arterial hypertension was the most common comorbidity in both groups (60.2% of all patients). Fever (80.6%), dry cough (79.6%), and dyspnoea (72.8%) were the most common symptoms on admission. Age was significantly associated with mortality (mean age 73.7 years versus 65.9 years in the survivor group; *P*-value 0.01). Other baseline variables associated with mortality were history of dementia (*P* = 0.02), fever at admission (*P*  $< 0.001$ ), higher systolic (*P* = 0.02) and diastolic (*P*  $< 0.01$ ) blood pressure at admission, lower P/F-ratio at admission (*P*  $< 0.01$ ), and higher clinical frailty index (*P* = 0.01). In the total group, the mean SOFA score was 4.5 (SD 3.0) on admission. In the ICU survival group, the mean admission SOFA score was 4.3 (SD 2.9) versus 5.2 (SD 3.3) in the ICU non-survival group (*P* = 0.10). The distribution of SOFA scores at admission, stratified for ICU survival, is shown in Figure 2.

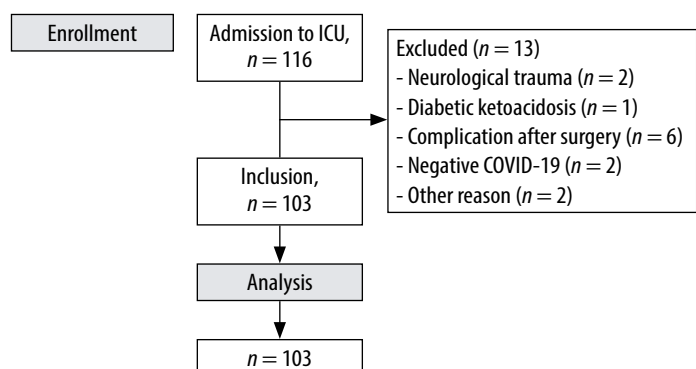
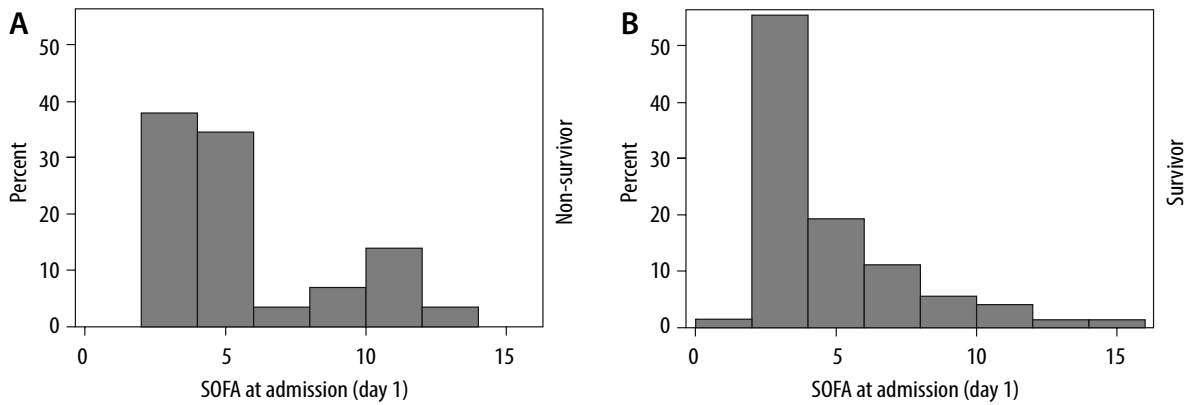


FIGURE 1. Study flow chart

TABLE 1. Demographics and clinical characteristics at admission to ICU

Factor	ICU survivors (n = 73)	ICU deceased (n = 30)	P-value
<b>Demographics</b>			
Age (years)	65.93 ± 11.55	73.73 ± 8.66	<b>0.01</b>
Gender (male/female)	17/13	46/27	0.55
BMI (kg m <sup>-2</sup> )	27.58 ± 4.67	29.15 ± 6.26	0.17
<b>Comorbidities, n (%)</b>			
Smoking	2 (2.74)	3 (10.00)	0.24
Arterial hypertension	40 (54.80)	22 (73.33)	0.08
Diabetes	20 (27.40)	13 (43.33)	0.11
Respiratory disease	12 (16.44)	8 (26.66)	0.23
Malignancy	5 (6.85)	6 (20.00)	0.05
Chronic kidney disease	10 (13.70)	5 (16.66)	0.70
Chronic liver disease	2 (2.74)	1 (3.33)	0.87
Cardiovascular disease	27 (36.99)	12 (40.00)	0.77
Chronic bowel disease	5 (6.85)	3 (10.00)	0.59
Chronic nervous disease	1 (1.37)	0 (0.00)	0.52
Cerebrovascular disease	13 (17.81)	5 (16.66)	0.89
Haematological disease	5 (6.85)	4 (13.33)	0.29
Rheumatological disease	8 (10.96)	0 (0.00)	0.06
Dementia	0 (0.00)	2 (6.66%)	<b>0.02</b>
HIV/AIDS	0 (0.00)	0 (0.00)	1.00
<b>Clinical parameters</b>			
Fever, n (%)	53 (72.60)	30 (100)	<b>&lt; 0.001</b>
Cough, n (%)	59 (80.82)	23 (76.67)	0.54
Dyspnoea, n (%)	54 (73.97)	21 (70.00)	0.60
Sputum production, n (%)	8 (10.96)	3 (10.00)	0.87
Myalgia, n (%)	38 (52.05)	14 (46.67)	0.57
Headache, n (%)	8 (10.96)	2 (6.66)	0.49
Diarrhoea, n (%)	14 (19.18)	5 (16.66)	0.74
Respiratory rate, n (%)	24.27 ± 6.38	26.97 ± 6.99	0.06
Systolic blood pressure (mmHg)	139.35 ± 23.72	152.00 ± 30.24	0.02
Diastolic blood pressure (mmHg)	87.05 ± 16.25	97.53 ± 17.70	<b>&lt; 0.01</b>
Heart rate	85.55 ± 16.23	93.20 ± 26.33	0.12
Urine output on day 1 (mL)	1284.62 ± 827.55	1252.33 ± 821.89	0.75
GCS (total)	14.19 ± 1.36	14.30 ± 1.29	0.62
P/F ratio	132.54 ± 84.93	74.46 ± 33.13	<b>&lt; 0.01</b>
<b>Laboratory findings</b>			
Red blood cell count (T L <sup>-1</sup> )	4.09 ± 0.70	4.07 ± 0.85	0.10
White blood cell count (G L <sup>-1</sup> )	8.86 ± 4.37	8.53 ± 6.57	0.18
Lymphocytes (%)	20.89 ± 40.33	17.25 ± 22.34	0.82
Platelets (G L <sup>-1</sup> )	251.55 ± 94.85	233.00 ± 117.51	0.31
Bilirubin (mg L <sup>-1</sup> )	0.64 ± 0.63	0.70 ± 0.49	0.22
Length of stay (before ICU) (days)	2.60 ± 4.90	4.30 ± 5.81	
SOFA (at admission)	4.25 ± 2.85	5.21 ± 3.25	0.10
Clinical Frailty Index	3.78 ± 1.57	4.57 ± 1.50	<b>0.01</b>
PaO <sub>2</sub> /FiO <sub>2</sub> ratio	132.54 ± 84.93	74.46 ± 33.12	<b>&lt; 0.001</b>
Invasive mechanical ventilation, n (%)	39 (53.40%)	20 (66.77%)	<b>&lt; 0.001</b>
ECMO, n (%)	3 (4.10%)	1 (3.3%)	<b>&lt; 0.001</b>

Data are presented as mean ± standard deviation or as number (%). Characteristics of ICU survivors and ICU non-survivors were compared with Student's *t*-test or Mann-Whitney *U* test for continuous variables and with the  $\chi^2$  test for categorical variables. A *P*-value < 0.05 is considered statistically significant. BMI – body mass index.



**FIGURE 2.** Distribution of baseline SOFA scores for ICU survivors (B) and ICU non-survivors (A)

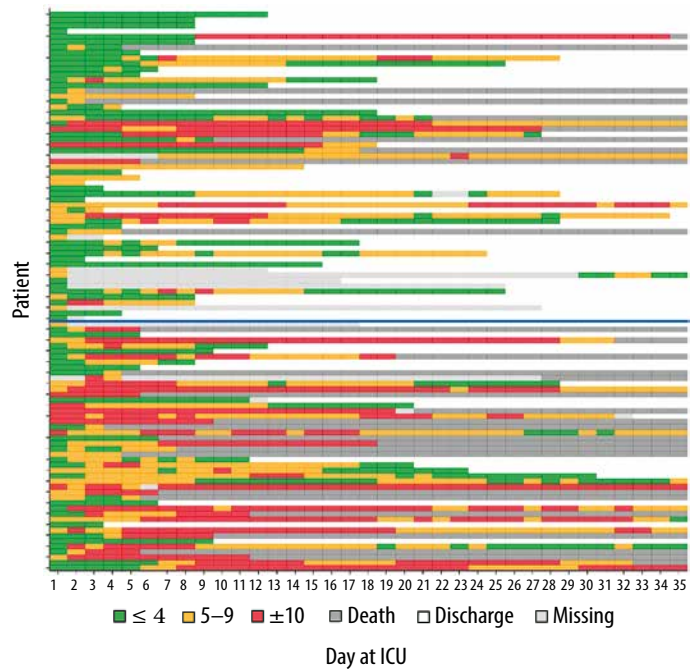
The mean maximum SOFA score for the ICU non-survivors was 11.7 (SD 4.7) compared to 7.4 (SD 4.3) for the survivors during their stay in the ICU ( $P < 0.001$ ). The individual course of the SOFA scores for ICU survivors and ICU non-survivors during ICU stay until day 35 is shown in Supplemental Figure 1.

Figure 3 displays the evolution of SOFA scores in time of consecutive patients. Each line corresponds to one patient's trajectory during their ICU hospitalization displayed until day 35 for those who survived and those who did not survive on the ICU.

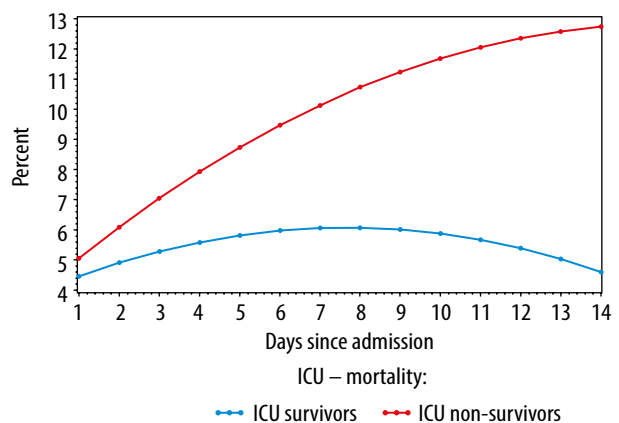
The average evolutions of the daily worst SOFA scores for ICU survivors and ICU non-survivors, estimated by the linear mixed model, are depicted in Figure 4.

On admission (day 1), the mean worst SOFA score did not differ between the two groups (difference = 0.60,  $P = 0.333$ ), whereas from day 2, the difference in mean worst SOFA scores gradually increased between both groups (difference at day 2 = 1.18,  $P = 0.055$ ). On day 3, the score of the ICU non-survivors is 1.76 points higher compared to the survivors ( $P < 0.01$ ). This difference further increased to 4.08 on day 7 ( $P < 0.001$ ). The figure demonstrates a rise in SOFA scores in the first week for the entire population; this rise is however less pronounced for the ICU survivors (an increase of 1.60 for survivors vs 5.08 for non-survivors,  $P < 0.001$ ). For both groups, the change in SOFA score from day 1 to day 2 (first 24 hours) was statistically significant. For the ICU non-survivors there was an increase in SOFA score of 1.03 points ( $P < 0.001$ ), for the survivors of 0.45 points ( $P < 0.001$ ). The same significant rise was observed from day 1 to day 3, with an increase in SOFA score of 1.98 points for the non-survivors ( $P < 0.001$ ) and 0.82 for the survivors ( $P < 0.001$ ). Hence, the increase in SOFA score in the non-survivor group was significantly stronger, with an additional increase of 0.58 from day 1 to 2 ( $P < 0.001$ ), 1.16 from day 1 to 3 ( $P < 0.001$ ), and 3.48 from day 1 to 7 ( $P < 0.001$ ).

The results of the logistic regression analyses with the SOFA variables as predicted variables are



**FIGURE 3.** Individual SOFA scores displayed in three categories with a colour code ( $\leq 4$ : green, 5–9: orange,  $\geq 9$ : red, discharge from ICU: white, deceased: grey, light grey: missing SOFA score). A lower SOFA score indicates less organ dysfunction. The patients are plotted according to their admission day: the first admitted patient corresponds to the lowest line. The blue line represents 30.03.2020, as the day that an intensified thromboprophylaxis protocol was implemented in the hospital



**FIGURE 4.** Average evolution of the daily worst SOFA scores stratified for survival (ICU survivors: blue and ICU non-survivors: red), estimated using a linear mixed model

**TABLE 2.** Overview of logistic regression analyses with different SOFA variables

	OR (95% CI)	AUC	P-value
Baseline SOFA score	1.11 (0.96–1.27)	0.60	0.15
Maximum SOFA score	1.23 (1.11–1.37)	0.76	< 0.001
Baseline SOFA score	1.12 (0.97–1.31)	0.64	0.13
Delta SOFA score 24 h	1.03 (0.83–1.28)		0.77

Results are presented as odds ratio with the 95% CI and area under curve. A *P*-value < 0.05 is considered statistically significant.

**TABLE 3. A)** A multiple logistic regression model with the maximum SOFA as an explanatory variable corrected for age, DNI status, and time of admission. **B)** Multiple logistic regression model with the maximum SOFA as explanatory variable corrected for age and time of admission. The area under the curve equals 0.91

A

	OR (95% CI)	P-value
Maximum SOFA score	1.53 (1.23–1.89)	< 0.001
Age	1.13 (1.03–1.23)	0.007
DNI status (intubate versus DNI)	0.02 (0.002–0.15)	< 0.0001
Time of admission (before 31.03.2020 vs. after)	2.48 (0.65–9.45)	0.18

B

	OR (95% CI)	P-value
Maximum SOFA score	1.28 (1.12–1.47)	< 0.001
Age	1.15 (1.06–1.24)	< 0.001
Time of admission (before 31.03.2020 vs. after)	2.00 (0.65–6.18)	0.23

Results are presented as odds ratio with the 95% CI and area under curve. A *P*-value < 0.05 is considered statistically significant.

presented in Table 2. Only the maximum SOFA score is significant (OR = 1.23, 95% CI: 1.11–1.37, *P* < 0.001).

This association remains significant after inclusion of age, DNI status and time of admission (before or after 31.03.2020) in the multiple logistic regression model (OR = 1.53, 95% CI: 1.23–1.89, *P* < 0.001) (Table 3).

The ROC curve (AUC = 0.91) and calibration plot of this multiple logistic model are shown in Figure 5. The Hosmer-Lemeshow test indicates good calibration (*P* = 0.838).

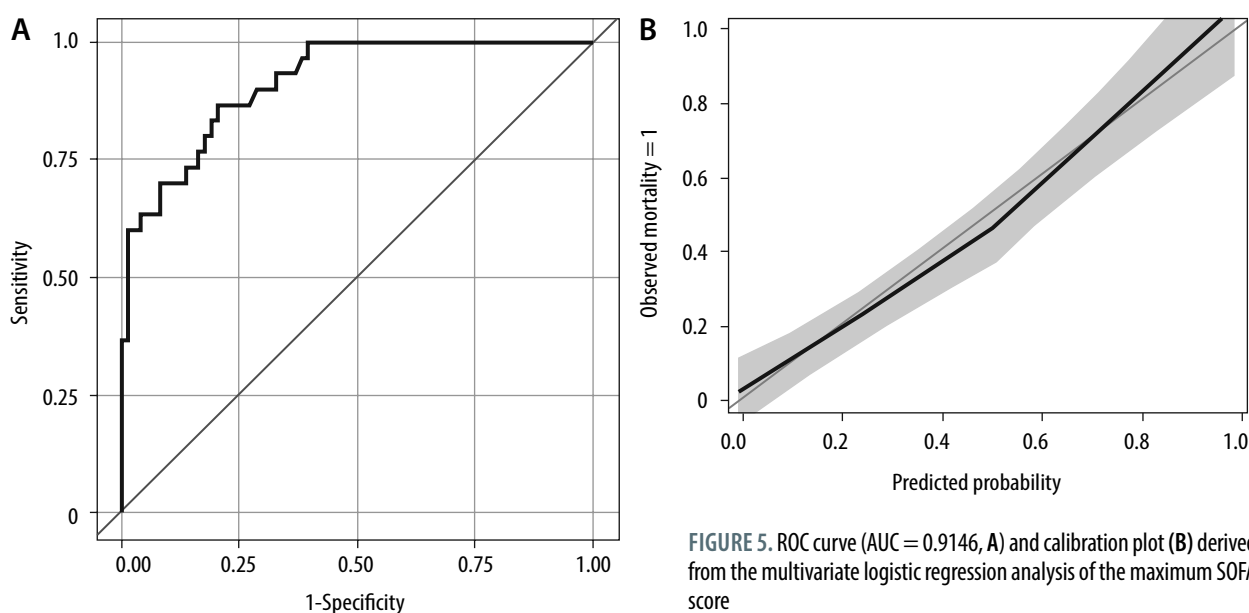
## DISCUSSION

In this cohort study including 103 consecutive patients admitted to the ICU with severe SARS-CoV-2 infection and investigating the predictive value of serial evaluation of the SOFA score for ICU mortality, we first noted an increase in SOFA scores in the first week for the entire population, but less pronounced for the ICU survivors. Secondly, no significant difference in the worst SOFA score on admission day between ICU survivors and non-survivors was observed. Thirdly, a combination of SOFA score on admission day and delta SOFA score in the first 48 hours lost its predictive value for ICU mortality. Finally, the association of the maximum SOFA score with ICU mortality remained present after inclusion of age, DNI status, and change of therapy protocol to the predictive model. Moreover, this multiple logistic regression model can discriminate between patients with and without ICU mortality with an AUC of 0.91. The calibration curve, shown in Figure 5, also indicates good calibration of this model.

To date, several studies have investigated the predictive value of the SOFA scoring system for poor outcomes in a COVID-19 population [4, 13, 15–17]. Of those, five focused on patients admitted to the ICU with mixed results [4, 18–21].

### The trend in SOFA score

A significant increase in SOFA scores in the first week was found in both the ICU survival and ICU non-survival groups. This increase was however less pronounced for ICU survivors. Based on an analysis



**FIGURE 5.** ROC curve (AUC = 0.9146, A) and calibration plot (B) derived from the multivariate logistic regression analysis of the maximum SOFA score

of 18 patients, Martinez *et al.* [20] concluded that an increase in SOFA score in the first 48 hours after admission is associated with significant ICU mortality. This study was underpowered to draw firm conclusions on the association in the evolution of SOFA scores over time and ICU mortality. Bels *et al.* [4] concluded in a cohort study including 93 mechanically ventilated participants with SARS-CoV-2 infection that a decrease of SOFA scores over time was associated with ICU survival, even after adjustment for age, sex, and comorbidities. However, it has to be pointed out that in this study, patients were only admitted to the ICU when intubation and mechanical ventilation were essential, resulting in higher SOFA scores on admission. At our institution, patients were already admitted to the ICU when in need of high-flow oxygen therapy. Furthermore, Bels *et al.* [4] drew their conclusions from the analysis of the evolution of SOFA scores over more than 30 days. In our cohort, a decrease of SOFA scores in the ICU survival group was also noted from day 8.

#### **Worst SOFA score on admission day and delta SOFA score in first 48 hours**

The observed absence of a significant difference in worst SOFA score on admission day between ICU survivors and non-survivors in this study is in line with the observations of Bels *et al.* [4]. However, two studies investigating SOFA scores on admission to hospital both came to an opposite result: in a multicentre cohort study, Zhou *et al.* [11] detected an increased risk of in-hospital death with higher SOFA score on admission, older age, and D-dimer greater than  $1 \mu\text{g mL}^{-1}$ . Liu *et al.* [22] also found that a SOFA score on admission of  $\leq 3$  was highly predictive of survival in COVID-19 patients admitted to the hospital ward. These opposite results might be explained by the fact that SOFA scores on admission are high in both ICU survivors and non-survivors, resulting in an impaired discriminative power for mortality of this SOFA variable in an ICU population. Another multicentre cohort study concluded that higher renal and cardiovascular SOFA score components and lower  $\text{PaO}_2/\text{FiO}_2$  ratio at ICU admission are independent predictors of 90-day mortality [21].

Evaluating and comparing the level of mean worst SOFA scores at ICU admission, and accordingly reflecting the severity of organ dysfunction of COVID-19 patients admitted to the ICU, may provide interesting insights. Martinez *et al.* [20] reported a mean SOFA score of  $6 (\pm 4.8)$  at ICU admission in the ICU non-survivor group compared to  $5.2 (\pm 3.3)$  in our study. Interestingly, Bels *et al.* [4] reported remarkably higher mean baseline SOFA scores for both ICU survivors ( $7.3$  [SD 1.9]) and ICU survivors ( $8.6$  [SD 2.8]) [3]. This difference is probably attrib-

utable to the limited availability of ICU beds in the Netherlands, which is only 6.4 compared to 15.9 per 100 000 inhabitants in Belgium [16], resulting in very restrictive admission criteria (only patients who require intubation and mechanical ventilation).

A combination of SOFA score on admission day and delta SOFA score in the first 48 hours was also not predictive for ICU mortality. In a non-COVID ICU population, however, an increase in SOFA score in the first 48 hours after ICU admission was highly effective in predicting ICU mortality [10]. Our results echo those of a large multicentre trial including 675 mechanically ventilated patients with SARS-CoV-2 pneumonia. This study also showed that the worst SOFA score within 48 hours before intubation was poorly predictive for mortality and was significantly inferior to simply using age [18].

#### **Maximum SOFA score during ICU stay**

In this study, the maximum SOFA score, or the worst SOFA score during the patient's ICU stay, was strongly associated with ICU mortality. Its predictive power for ICU mortality remained intact after including age, DNI status, and change of therapy protocol in the predictive model. This model comprising maximum SOFA score, age, DNI status, and change of therapy protocol is highly effective in discriminating between patients with and without ICU mortality and also showed good calibration. In a non-COVID ICU population, the maximum SOFA score was also found to be highly predictive for poor outcomes [10]. Other studies evaluating the predictive value for poor outcome of the SOFA scoring system in a COVID-19 population did not analyse the maximum SOFA score [3, 10, 19, 20, 22, 23]. Data on the maximum SOFA score are only available for post-hoc analysis. Consequently, this SOFA variable cannot be incorporated in a predictive model for poor outcomes of critically ill SARS-CoV-2 patients that can support physicians in decisions concerning ICU admission at times of critical saturation of ICU capacity.

Because of the novelty of the disease and its clinical progression, there were some therapy adjustments throughout the inclusion period. Especially an intensified thromboprophylaxis protocol implemented on March 31<sup>st</sup>, including augmented low-molecular-weight heparin dosing, individually tailored with anti-Xa measurements and twice-weekly ultrasonography screening for deep venous thrombosis (DVT), significantly reduced one-month mortality [16]. The response to this change of therapy concerning trends in SOFA score is clear in Figure 3: SOFA scores above 10 were less often seen after March 31<sup>st</sup>. In contrast, recent evidence does not support the use of intermediate-dose venous

thromboembolism (VTE) prophylaxis (INSPIRATION trial) [24]. The INSPIRATION trial was conducted in several hospitals in Iran between July and November 2020. In this trial, VTE events were only recorded in 19 (3.4%) patients enrolled and the risk of VTE was not significantly different between the intermediate-dose and standard-dose groups (3.3% vs. 3.5%) [24]. In contrast, several mono- and multicentre European first wave ICU cohorts reported incidences of above 40% of thrombotic complications [25–27]. These conflicting results may be explained by variability in disease severity and/or host immune response between different ethnic groups. The observed difference in COVID-19-associated hypercoagulability between European first wave cohorts and the INSPIRATION trial might also be explained by the genetic variation in the SARS-CoV-2 circulating in Europe in the first wave and Iran between July and November 2020. Finally, selection bias and/or detection bias may also explain the low observed incidence of VTE phenomena in the INSPIRATION trial, since 1200 out of 1800 patients were excluded from enrolment and VTE phenomena were not systematically assessed. This study also has some limitations. First, the interpretation of our findings might be limited by the small sample size with low statistical power and the single-centre approach. Second, interpretation of our findings might be further limited due to the retrospective design of this study. Also, a limited amount of laboratory tests was not available in all patients. Finally, since COVID-19 is a new disease with a lack of effective standard therapy, changes in therapy were made throughout the inclusion period which might have affected the patient outcome.

## CONCLUSIONS

Evaluation of the SOFA scores in the first 48 hours after ICU admission is not a good prognostic indicator in COVID-19 patients. Only the maximum SOFA score was highly predictive of ICU mortality. Since these data are only available for posthoc analysis, we can conclude that the SOFA scoring system is not useful for the triage of critically ill COVID-19 patients.

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