Biomarkers and prognosis in cardiac surgery in the ICU

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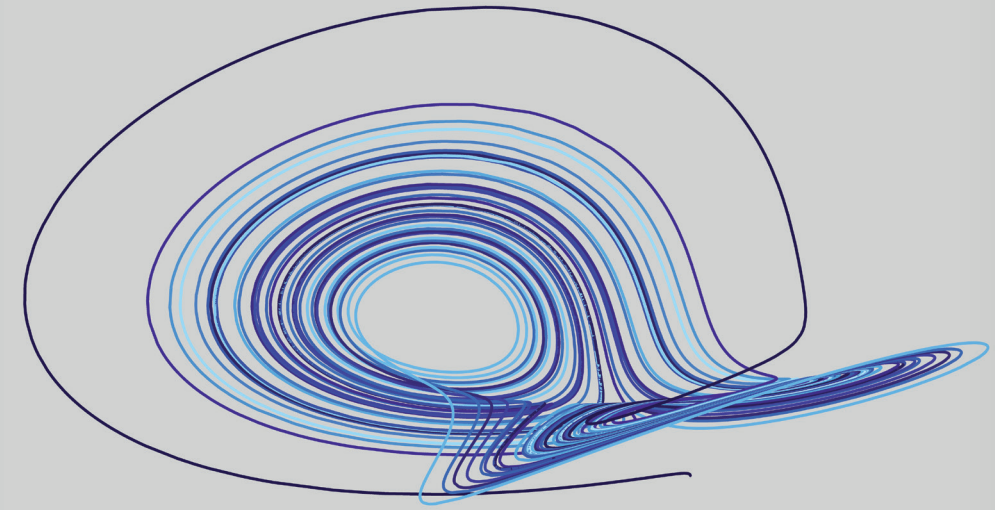

CHAPTER **6**

Mortality prediction by SOFA score in ICU-patients after cardiac surgery; comparison with traditional prognostic–models

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Abstract

Background: There are many prognostic models and scoring systems in use to predict mortality in ICU patients. The only general ICU scoring system developed and validated for patients after cardiac surgery is the APACHE-IV model. This is, however, a labor-intensive scoring system requiring a lot of data and could therefore be prone to error. The SOFA score on the other hand is a simpler system, has been widely used in ICUs and could be a good alternative. The goal of the study was to compare the SOFA score with the APACHE-IV and other ICU prediction models.

Methods: We investigated, in a large cohort of cardiac surgery patients admitted to Dutch ICUs, how well the SOFA score from the first 24 hours after admission, predict hospital and ICU mortality in comparison with other recalibrated general ICU scoring systems. Measures of discrimination, accuracy, and calibration (area under the receiver operating characteristic curve (AUC), Brier score, R2, and Ĉ-statistic) were calculated using bootstrapping. The cohort consisted of 36,632 Patients from the Dutch National Intensive Care Evaluation (NICE) registry having had a cardiac surgery procedure for which ICU admission was necessary between January 1st, 2006 and June 31st, 2018.

Results: Discrimination of the SOFA-, APACHE-IV-, APACHE-II-, SAPS-II-, MPM24-II - models to predict hospital mortality was good with an AUC of respectively: 0.809, 0.851, 0.830, 0.850, 0.801. Discrimination of the SOFA-, APACHE-IV-, APACHE-II-, SAPS-II-, MPM24-II - models to predict ICU mortality was slightly better with AUCs of respectively: 0.809, 0.906, 0.892, 0.919, 0.862. Calibration of the models was generally poor.

Conclusion: Although the SOFA score had a good discriminatory power for hospital- and ICU mortality the discriminatory power of the APACHE-IV and SAPS-II was better. The SOFA score should not be preferred as mortality prediction model above traditional prognostic ICU-models.

Background

Prediction models and scoring systems are widely used in Intensive Care medicine for prognosis, quality measures, comparison between Intensive Care Units (ICU's) or scientific reasons. The Simplified Acute Physiology Score-II (SAPS-II) (1), Mortality Probability Model after 24 hours-II (MPM_{24}-II) (2), Acute Physiology and Chronic Health Evaluation–II (APACHE-II) (3) and Sequential Organ Failure Assessment (SOFA) score (4) were developed for such purposes but excluded cardiac surgery patients. Nevertheless, some of these scoring systems are also used in the cardiac surgery population admitted to the ICU (5) (6). The only general ICU-scoring system developed to include cardiac surgery patients is the Acute Physiology and Chronic Health Evaluation–IV model (APACHE-IV), which was published in 2006 (7).

The SOFA score was initially developed as a tool to learn from the evolution of organ failure in sepsis and to assess the effects of therapies like mechanical ventilation and vasopressors on the course of organ dysfunction. It scores 1-4 points for each of the six organ systems (respiratory, circulation, renal, neurologic, hepatogenic, coagulation) (4). The importance of the SOFA score is growing and it has been incorporated in the latest surviving sepsis campaign as a tool to describe and detect sepsis (8). Although the SOFA score was initially not developed to predict mortality, several studies showed that SOFA has been used to predict morbidity and mortality and has been validated for that purpose in several ICU populations (9) (10). It would be interesting to know if the SOFA score could predict mortality in the cardiac surgery population as well.

The SOFA score is much simpler compared to general ICU prediction models such as the APACHE-IV model, which requires a lot of data and lays a heavy burden on precise data acquisition. If mortality prediction could be achieved with the SOFA score as accurately as with the APACHE-IV model, use of the SOFA score would be preferable for that purpose.

The aim of the current study is to investigate, in a large retrospective cohort derived from the Dutch National Intensive Care Evaluation (NICE) registry (11) (12), how well the SOFA score on day one predicts ICU and hospital mortality in comparison to the general ICU mortality prediction models, i.e. SAPS-II, MPM_{24}-II, APACHE-II, and APACHE-IV. Secondly, we wanted to investigate the contribution of the different components of the SOFA to its predictive value.

Methods

Data

The NICE registry collects demographic, physiological, clinical, and organizational data from all 84 Dutch ICUs (12). To ensure that the data are of a high quality, ICU employees are trained how to score patients, the data are checked before being included into the database, and data quality audits are carried out (11, 13).

We used data from cardiac surgery centers in the NICE SOFA database with an APACHE-IV admission diagnosis related to open heart surgery (see Supplement 2) between January 1st, 2007 and June 31st, 2018. Patients were included if they were 18 years or older and all of the following scoring systems were available: SOFA score on day one and its six individual organ scores, APACHE-IV, APACHE-II, MPM_{24}-II, and SAPS-II. All readmissions within the same hospital admission were excluded from analyses.

Severity of illness scores

Demographic data as well as all data needed to calculate the scoring systems were collected in the hospital in which the patient was admitted and were securely uploaded to the NICE registry (12). All scoring systems were calculated according to the standards in the international literature (1) (2) (3) (4) (7). A summary of the different scoring system is included in Supplement 1 and 4. We used only the SOFA score on day one because the general ICU prediction models included only data collected from the first 24 hours of admission. To account for organ replacement devices that were not in common use at the time the SOFA score was developed, minor adaptations were made to the original SOFA score (4). Consequently, we gave the maximum number of points for the renal category if the patient received continuous renal replacement therapy (CRRT) or other forms of renal replacement therapy. We gave the maximum number of points for the cardiovascular category if the patient had a left ventricular- or right ventricular assist device, an intra-aortic balloon pump (IABP) or was on veno-arterial extra corporeal membrane oxygenation (VA-ECMO). We gave the maximum number of points for the respiratory category if the patient was on veno-venous extra corporeal membrane oxygenation (VV-ECMO) or had special forms of ventilation (Nitric Oxygen (NO)-ventilation, Differential lung ventilation, Partial liquid ventilation but not prone position ventilation).

Statistical analyses

Categorical variables are presented as percentages, and continuous variables are presented as mean and SD or as median and interquartile range (IQR) depending on the data distribution. Demographics are also provided for sub-populations based on quartiles of the SOFA score. To assess differences in distribution of continuous variables between the sub-populations based on quartiles of the SOFA score, independent t-test was used when

the data was distributed normally or Mann-Whitney U test when de data was distributed not normally. Normality was tested using graphical methods. All statistical analyses were performed using R version 3.6.0. A p value of less than 0.05 was applied as level of significance.

Prediction models

Hospital mortality

The SOFA score was initially developed to quantify organ dysfunction and not to predict mortality. In order to predict hospital mortality based on SOFA score and its sub-scores, we used logistic regression modelling. To keep these models as simple as possible but also to give it a fair chance to achieve a good prognostic performance compared to the general ICU prediction models, gender and age were added to the model as covariates.

The general ICU prediction models, i.e. APACHE-IV, APACHE-II, MPM_{24}-II, and SAPS-II, are logistic regression models that use different predictor variables to predict hospital mortality. These models are not stable over time (14). To make the mortality predictions comparable to the newly defined mortality prediction models based on SOFA score, the original models were calibrated using first-level customization (14). To this end, for each model, a logistic regression model was fitted with observed in-hospital death as the dependent variable and the logit-transformed original predictions as the independent variable.

ICU mortality

In order to predict ICU mortality based on SOFA score and its sub-scores, we again used logistic regression modelling. Gender and age were added to the models as covariates. The general ICU prediction models are developed to predict hospital mortality. To predict ICU mortality, logistic regression modelling was used with observed ICU mortality as the dependent variable and the logit-transformed predictions based on the original model as the independent variable.

Performance assessment of the models

The area under the receiver operating characteristic curve (AUC) was used to describe the discrimination of the models (15). An AUC of 0.5 indicates that the model has no discriminative power and an AUC of 1.0 indicates perfect discriminative power (15). To compare the calibration of the models, the Hosmer-Lemeshow Ĉ-statistic was used (16). The Hosmer-Lemeshow Ĉ-statistic assesses whether or not the observed mortality rates match the expected mortality rates in the sub-populations of the total model population (16). The Ĉ-statistic is a χ^2 statistic in which a p value of > 0.05 is considered good calibration, i.e. the difference between predicted and actual outcomes in de subgroups is low and not significantly different (16).

The Brier score was used to assess the overall accuracy of the models (17). The Brier score is the mean squared difference between the observed and predicted outcome, which includes both discrimination and calibration aspects. The smaller the difference between observed and predicted mortalities, the lower the score, the better the model.

The performance of the models was assessed using the ordinary bootstrap method with a sample of 500 bootstraps (18). In each sample, the performance measures were calculated and exported to a separate table. For each model, the median and 95% confidence intervals for each performance measure was defined using the 2.5th, 50th and 97.5th percentiles of the bootstrap distribution. A difference in performance measure between the models was considered statistically significant in case the median was different and the related confidence intervals did not overlap. First-level customization does not change the influence of individual covariates included in the model but calibrates their joint influence on the observed mortality (14). Note that therefore, for the APACHE-IV, APACHE-II, MPM_{24}-II, and SAPS-II models the AUC for each bootstrap sample should be the same because the order of the probabilities will not change, only the absolute magnitude of the probabilities will differ.

Ethics

Data are encrypted such that all patient-identifying information are untraceable. The need for ethical committee approval was waived by the Central Committee on Research Involving Human Subjects, because the study was purely retrospective and used de-identified patient data (reference number W17_297 # 17.349; Medical Ethics Review Committee of the Academic Medical Center, University of Amsterdam).

Results

We included 36,632 cardiac surgery patients from 12 cardiac surgery centers participating in the NICE SOFA module of whom 70.7% were men. Figure 1 shows a flowchart of the data inclusion process. Mean age was 66.8 years, 1.3 % died during their ICU admission and 2.2% died in hospital. In table 1 baseline characteristics, procedures and outcome are described, categorized by quartiles of the SOFA score (Table 1). It was not possible to distribute the number of patients evenly over the different quartiles because the data was skewed. The incidence of ICU mortality and hospital mortality is highest in the quartile with the highest SOFA scores. In these patients more emergency surgery and complex surgery is prevalent compared to the other quartiles, while the number CABG's is lower. All patient characteristics showed unequal distribution among the sub-populations based on quartiles of SOFA score (P<0.001).

Table 1. Demographics for all patients and stratified according to quartiles of the SOFA score

Demographics, Procedures, models & outcome	All patients	Q1 [SOFA 0-4]	Q2 [SOFA 5-6]	Q3 [SOFA 7-8]	Q4 [SOFA 9-22]
N	36,632	13,039	5486	11,848	6259
Age (mean; sd)	66.6 (11.4)	65.6 (11.9)	65.9 (11.1)	67.3 (10.7)	68.2 (11.3)
Male (%)	70,7	70,3	71	71	71
BMI (mean; sd)	27.2 (4.5)	27.2 (4.6)	27.4 (4.5)	27.1 (4.3)	26.8 (4.5)
Renal Insufficiency (%)	3.2	1.8	2	2.5	8.7
Emergency Surgery (%)	5.3	4.3	4.9	4.8	8.8
CABG (%)	51.6	56.1	58.3	51.1	37.3
Valve surgery Only (%)	24.9	24.5	22.7	25.3	26.9
Valve surgery and CABG (%)	11.9	7.6	9.2	14.1	18.9
Aorta surgery Only (%)	4.4	4.9	3.9	3.7	5.2
Myocardial surgery only (%)	1.4	1.8	0.9	1.2	1.5
Combination surgery (%)	5.8	5.2	5	4.6	10.3
Apache IV model predicted mortality (%)	3	1.6	2.0	2.6	7.9
Apache III[a] score (mean; sd)	47 (16.9)	41 (13.4)	44.8 (13.6)	47.6 (14.6)	60.4 (21.8)
Apache II model predicted mortality (%)	7.6	5.5	6.6	7.6	13
Apache II score (mean; sd)	14 (4.6)	12.2 (3.7)	13.5 (3.8)	14.5 (4.0)	17.3 (5.8)
SAPS II model predicted probability (%)	12.8	8.5	10.8	12.9	23.1
SAPS II score (mean; sd)	29.4 (9.3)	25.7 (7.0)	28.2 (7.5)	30.1 (7.9)	36.7 (12.5)
MPM_{24}-II score (mean; sd)	13.5 (8.9)	11.4 (7.5)	11.4 (7.1)	14.2 (7.4)	18.7 (12.5)
Death in ICU (%)	1.3	0.1	0.2	1	5.4
Death in Hospital (%)	2.2	0.6	0.8	1.8	7.6

All patiënt characteristics showed unequal distribution among the subgroups based on SOFA quartiles (P < 0.001). [a]The APACHE III score is a part of the APACHE-IV model

Performance assessment of the models

Table 2 and 3 describe the performance of the models for predicting hospital mortality and ICU mortality respectively. Measured by the AUC, the SOFA model on day one had a significantly lower discriminative power for hospital mortality compared to the APACHE-IV, APACHE-II and SAPS-II models. Also, the discriminative power of the SOFA model for ICU mortality was worse than that of the APACHE-IV, APACHE-II and SAPS-II models. The MPM_{24}-II model had a significantly worse discriminative power compared to the SOFA model for both hospital mortality and ICU mortality.

Based on the Hosmer and Lemeshow goodness-of-fit Ĉ-statistic and related confidence intervals, the SOFA model had comparable calibration with the APACHE IV, SAPS II and MPM_{24}-II models for predicting hospital mortality. APACHE II model had a significantly better calibration compared to the SOFA model (i.e. Ĉ-statistic 16.3 (12.6 – 24.8) versus 43.7 (31.5-61.1)). As for ICU mortality, the SOFA model showed significantly better calibration compared to the APACHE IV model (i.e. 16.4 (12.9 – 25.1) versus 38.5 (30.2 – 54.8)).

Overall, the models showed good accuracy according to the Brier score (18). The accuracy was comparable between the models for both hospital mortality (Brier score ranging between 0.019 and 0.020) and for ICU mortality (Brier score ranging between 0.011 and 0.012).

Performance measures were also calculated for the prediction models based on the six individual organ components of the SOFA model for both hospital and ICU mortality (table 4 and table 5). For all performance measures, the overall SOFA model performed significantly better than the individual organ component models. There was no significant difference between the calibration and accuracy of the models based on individual SOFA components, however discriminative power did differ. The renal component had a significantly better discrimination compared to all other components (Renal AUC 0.771 (0.763 – 0.777) for ICU mortality and 0.741 (0.736 – 0.745) for hospital mortality). The respiratory component had a significantly poor discrimination compared to all other components.

Table 2. Performance of the models for predicting hospital mortality; N = 36,632 patients

Models	AUC (CI 95%)*	Brier score (CI 95%)	Ĉ-statistic (CI)*	Ĉ-statistic p-value
APACHE IV – model	0.851 (0.851- 0.851)	0.019 (0.019-0.019)	27.0 (24.1-36.4)	< 0.0001
APACHE II – model	0.830 (0.830 – 0.830)	0.020 (0.19 – 0.20)	16.3 (12.6 – 24.8)	0.0308
SOFA	0.809 (0.808-0.810)	0.020 (0.019-0.20)	43.7 (31.5-61.1)	< 0.0001
SAPS-II model	0.850 (0.850 – 0.850)	0.019 (0.019 – 0.019)	19.4 (11.0 – 33.5)	0.009
MPM_{24}-II	0.801 (0.801 – 0.801)	0.020 (0.20 – 0.020)	30.3 (28.7 – 37.6)	< 0.0001

* AUC: area under the receiver operating characteristic curve; Ĉ-statistic: Hosmer and Lemeshow goodness-of-fit Ĉ-statistic; CI: 95% confidence interval

Table 3. Performance of the models for predicting ICU mortality; N = 36,632patients

Models	AUC (CI 95%)*	Brier score (CI 95%)	Ĉ-statistic (CI)*	Ĉ-statistic p-value
APACHE IV – model	0.906 (0.904 – 0.906)	0.011 (0.011 – 0.011)	38.5 (30.2 – 54.8)	< 0.001
APACHE II – model	0.892 (0.891 – 0.893)	0.011 (0.011 - 0.011)	27.1 (14.1 – 35.4)	0.001
SOFA	0.865 (0.864 – 0.866)	0.012 (0.012 – 0.012)	16.4 (12.9 – 25.1)	0.030
SAPS-II model	0.919 (0.917 – 0.919)	0.011 (0.011 – 0.012)	9.7 (5.7 – 21.3)	0.215
MPM_{24}-II	0.862 (0.860 – 0.863)	0.012 (0.012 – 0.012)	7.2 (2.8 – 15.3)	0.462

* AUC: area under the receiver operating characteristic curve; Ĉ-statistic: Hosmer and Lemeshow goodness-of-fit Ĉ-statistic; CI: 95% confidence interval

Table 4. Performance of the SOFA score and its components in predicting hospital mortality; N = 36,632patients

SOFA components	AUC (CI 95%) *	Brier score (CI 95%)	Ĉ-statistic (CI)*	Ĉ-statistic p-value
SOFA – total	0.809 (0.808-0.810)	0.020 (0.019-0.20)	43.7 (31.5-61.1)	< 0.001
SOFA – Respiratory	0.654 (0.651 – 0.656)	0.022 (0.022 – 0.022)	10.7 (5.1 – 22.0)	0.170
SOFA – Coagulation	0.707 (0.702 – 0.709)	0.021 (0.021 – 0.021)	8.8 (4.0 – 21.1)	0.283
SOFA – Hepatogenic	0.706 (0.704 – 0.707)	0.021 (0.021 – 0.021)	9.5 (4.8 – 19.6)	0.267
SOFA – Circulation	0.718 (0.715 – 0.719)	0.021 (0.021 – 0.021)	16.3 (7.16 – 33.7)	0.021
SOFA – Renal	0.741 (0.736 – 0.745)	0.021 (0.021 – 0.021)	31.0 (19.0 – 44.9)	< 0.001
SOFA - Neurology	0.691 (0.689 – 0.692)	0.021 (0.021 – 0.021)	10.1 (4.3 – 19.3)	0.245

* AUC: area under the receiver operating characteristic curve; Ĉ-statistic: Hosmer and Lemeshow goodness-of-fit Ĉ-statistic; CI: 95% confidence interval

Table 5. Performance of the SOFA score and its components in predicting ICU mortality; N = 36,632patients

SOFA components	AUC (CI 95%) *	Brier score (CI 95%)	Ĉ-statistic (CI)*	Ĉ-statistic p-value
SOFA – total	0.865 (0.864 – 0.866)	0.012 (0.012 – 0.012)	16.4 (12.9 – 25.1)	0.030
SOFA – Respiratory	0.634 (0.630 - 0.637)	0.013 (0.013 – 0.013)	9.7 (3.1 – 19.9)	0.253
SOFA – Coagulation	0.728 (0.726 – 0.730)	0.013 (0.013 – 0.013)	37.6 (13.1 – 61.4)	< 0.001
SOFA – Hepatogenic	0.721 (0.719 – 0.722)	0.013 (0.013 – 0.013)	14.2 (8.1 – 23.7)	0.066
SOFA – Circulation	0.733 (0.730-0.734)	0.013 (0.013 – 0.013)	81.3 (33.4 – 134.8)	< 0.001
SOFA – Renal	0.771 (0.763 – 0.777)	0.013 (0.013 – 0.013)	40.0 (27.5 – 54.1)	< 0.011
SOFA - Neurology	0.668 (0.663 – 0.671)	0.013 (0.013 – 0.013)	18.7 (8.7 – 32.9)	0.014

* AUC: area under the receiver operating characteristic curve; Ĉ-statistic: Hosmer and Lemeshow goodness-of-fit Ĉ-statistic; CI: 95% confidence interval

Discussion

Our main finding is that the SOFA score used as a prediction model underperforms in predicting ICU- and hospital mortality among cardiac surgery patients compared to the APACHE-IV, APACHE-II and SAPS-II models. Calibration of all models was poor for the outcome hospital mortality. From the recalibration curves (supplement 3) it is clear that most models perform badly in patients with high risk, which influences the Hosmer-Lemeshow Ĉ-statistic (19). Only the SAPS-II model and the MPM_{24}-II model had good calibration for the outcome measure ICU mortality.

This study is not the first study investigating ICU prediction models in cardiac surgery patients, but it is the first study comparing these different models in a cohort of more than 36.000 patients.

Doerr et al. (5) have shown in a previous study in 2801 patients that the SOFA score and the SAPS-II had a good discriminative power for hospital mortality with an AUC of 0.85 (CI 95%: 0.81 – 0.88) for the SOFA score and 0.83 (0.79 – 0.86) for the SAPS-II model, which is different compared to our findings. Pätilä et al. (20) studied the SOFA score in 857 patients and found that the maximum SOFA score on day one predicted 30-day mortality with an AUC of 0.78 (CI 95%; 0.64 – 0.92) which was comparable with our finding but with a broader confidence interval, which can be explained by the low number of cases. Ceriani et al. tested the SOFA score for mortality prediction in 218 cardiac surgery patients who stayed in the ICU for > 96 h (21). The AUC for the prediction of hospital mortality of the SOFA score on day 1 was 0.71 (CI 95%; ± 0.08).

We scored the SOFA score a little different than in the original article (4) because we included items such as (CRRT) and patients on (ECMO) giving them the maximum score possible within the respective SOFA component. It could be that other study groups treated the SOFA score differently in these patients leading to some discrepancy. We believe that the discrepancy cannot be large because it is unlikely that many patients started on day one with CRRT or ECMO. Giving patients on CRRT or ECMO the highest score within the respective SOFA component is, in our view, logical because these patients have the most severe deterioration of organ function.

From our data it is clear that most patients who died are found in the group with a SOFA score in the highest quartile. It is notable that in the last quartile surgery is of a more complex nature and has a more emergent character, while the percentage of CABG was lower, explaining the rise in mortality in this group of patients.

From the SOFA components, the renal component had the highest discriminative power followed by the circulation component. From these data we can conclude that renal insufficiency is an important determinant of mortality in cardiac surgery patients. Ceriani et al. also tested the importance of the SOFA components on day 1 and found that the cardiac component predicted mortality the best, followed by the neurologic-component and liver-component (21). Their findings may have differed from ours because they only included patients who were admitted for more than 96 hours while the median length of stay in our population was 1.8 days.

It is surprising that the SAPS-II model performed similar to the APACHE-IV model in predicting hospital mortality and was even better in predicting ICU mortality. SAPS-II does not include specific cardiac-surgical diagnostic categories and is generated from much less variables than APACHE-IV. In fact, the original SAPS-II model excluded cardiac surgery patients. The same observation has been made by Brinkman et al. (22) in the complete ICU population (i.e. all general, surgical and thoracic surgery patients).

Our data does not support the use of the SOFA score as a mortality prediction model in cardiac surgery patients. Nevertheless, we think that the SOFA score is still a valuable tool in other settings such as in the detection of sepsis (8) and the evolution of the condition of the patient (10) (4).

Conclusion

The SOFA score has important potential advantages when compared with the APACHE-IV model being simpler and less labor intensive. However, we must conclude that in this large cohort of cardiac surgery patients the SOFA score used as a mortality prediction model underperformed compared to the APACHE-IV and SAPS-II model in predicting hospital- and ICU mortality.

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Supplement

Supplement 1. Table with different items scored per ICU score

Item/score	APACHE-IV	APACHE-II	MPM_{24}-II	SAPS-II	SOFA
age	X	X	X	X	
temperature	X	X		X	
Mean arterial pressure	X	X			
Systolic blood pressure				X	
Blood pressure status MAP combined with vasopressors					X
Use of vasopressors			X		
Heart rate	X	X		X	
Respiratory rate	X	X			
Mechanical ventilation	X		X	X	
FiO_2	X	X			
pO_2	X	X	X		
pO_2/FiO_2 ratio combined with or without mechanical ventilation					X
pCO_2	X				
Arterial pH	X	X			
Na^+	X	X		X	
Potassium		X		X	
Bicarbonate				X	
Urine output	X		X	X	
Creatinine	X	X	X		X
Urea	X			X	
Blood sugar level	X				
Bilirubin	X				X
Hematocrit	X	X			
White blood cell count	X	X			
Total leucocyte count				X	
Platelets					X
Glascow coma score	X	X			X
GCS 3-5			X		
Albumin	X				
Prothrombin time			X		

Supplement 1. Table with different items scored per ICU score *Continued*

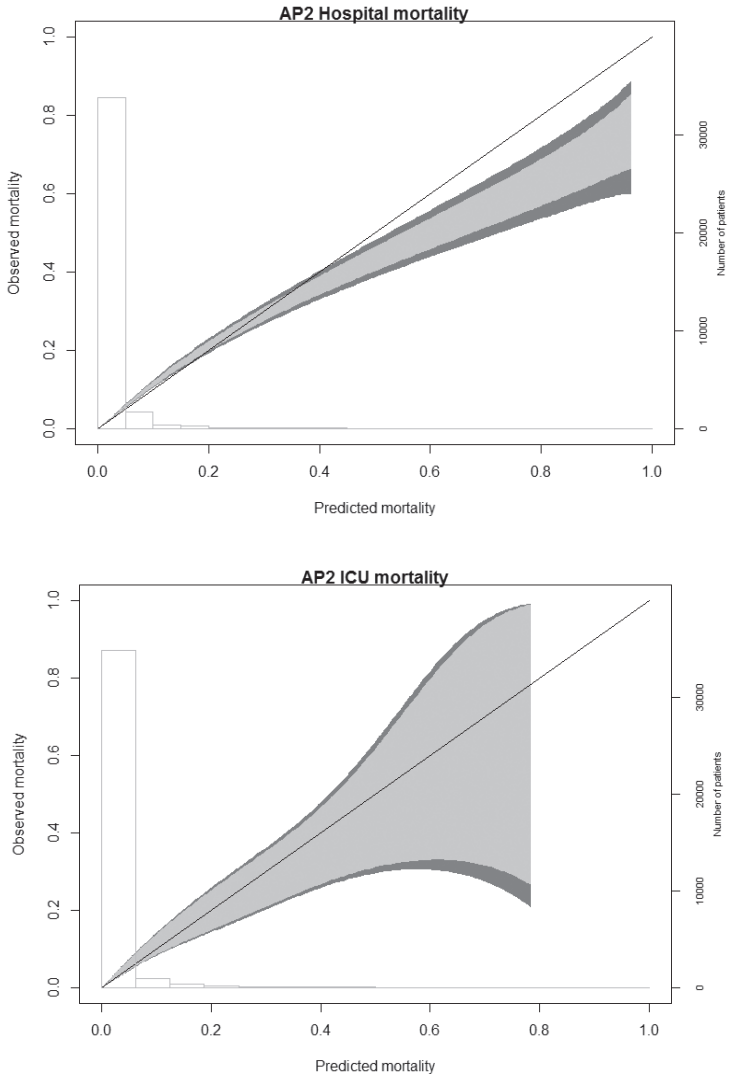
Item/score	APACHE-IV	APACHE-II	MPM_{24}-II	SAPS-II	SOFA
Chronic diseases:					
Chronic renal failure	X	X			
Cirrhosis	X	X	X		
Hepatic failure	X	X			
COPD		X			
Cardiovascular		X			
Metastatic carcinoma	X		X	X	
Lymphoma	X				
Leukemia/Myeloma	X			X	
Immunosupression	X	X			
AIDS	X			X	
Admission specifics					
Pre-ICU Length of stay	X				
Origin of patient	X				
Readmission	X				
Medical	X	X	X	X	
Emergency surgery	X	X	X	X	
Surgery	X	X		X	
Admission diagnosis	X				
Thrombolysis	X				
Confirmed infection			X		
Intracranial mass effect			X		

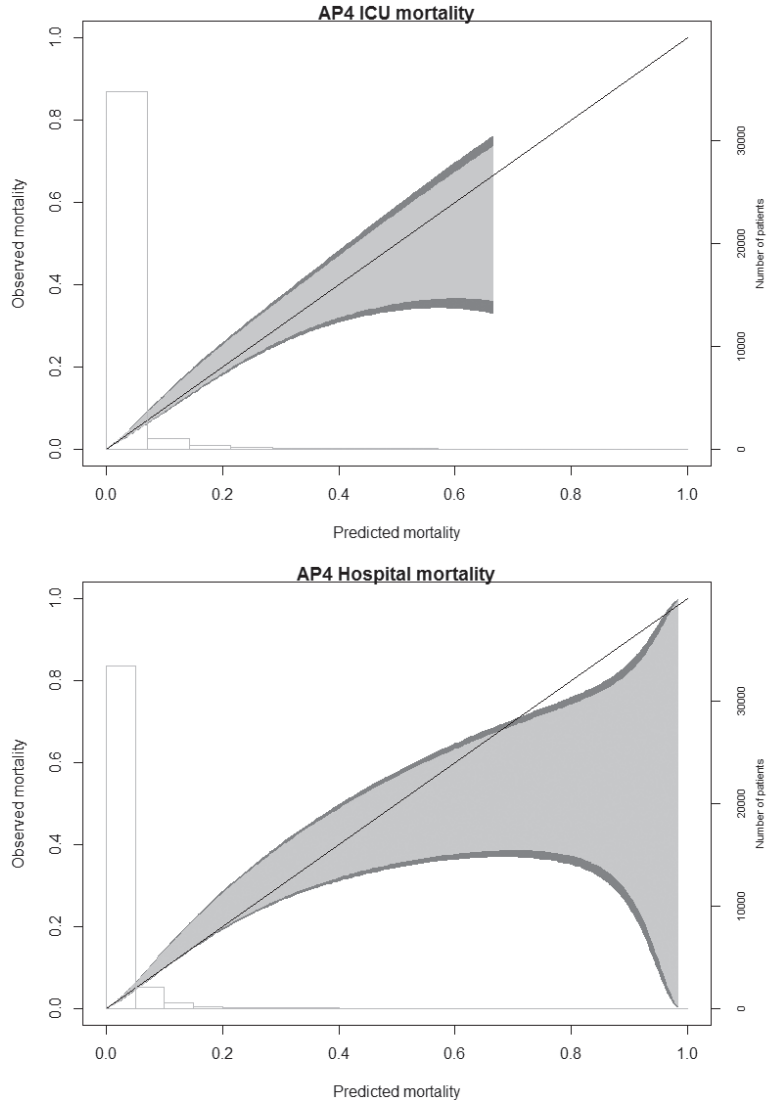
Supplement 2. APACHE-IV diagnoses used in study

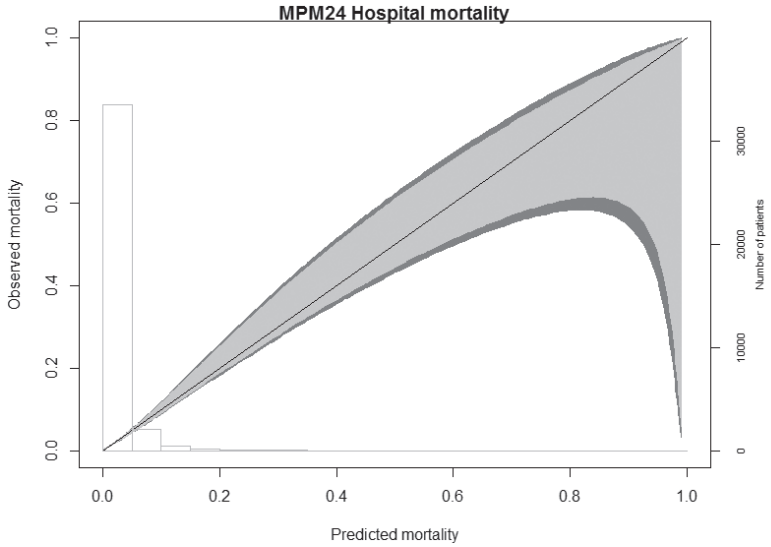
Aneurysm repair, ventricular
Aneurysm, thoracic aortic
Aneurysms, repair of other (except ventricular)
Aortic and Mitral valve replacement
Aortic valve replacement (isolated)
Atrial Septal Defect (ASD) Repair
CABG alone, coronary artery bypass grafting
CABG alone, redo
CABG redo with other operation
CABG redo with valve repair/replacement
CABG with aortic valve replacement
CABG with double valve repair/replacement
CABG with mitral valve repair
CABG with mitral valve replacement
CABG with other operation
CABG with pulmonic or tricuspid valve repair or replacement ONLY.
CABG, Minimally invasive; Mid-CABG
Mitral valve repair
Mitral valve replacement
Pericardiectomy (total/subtotal)
Pulmonary valve surgery
Tricuspid valve surgery
Tumor removal, intracardiac
Ventricular Septal Defect (VSD) Repair

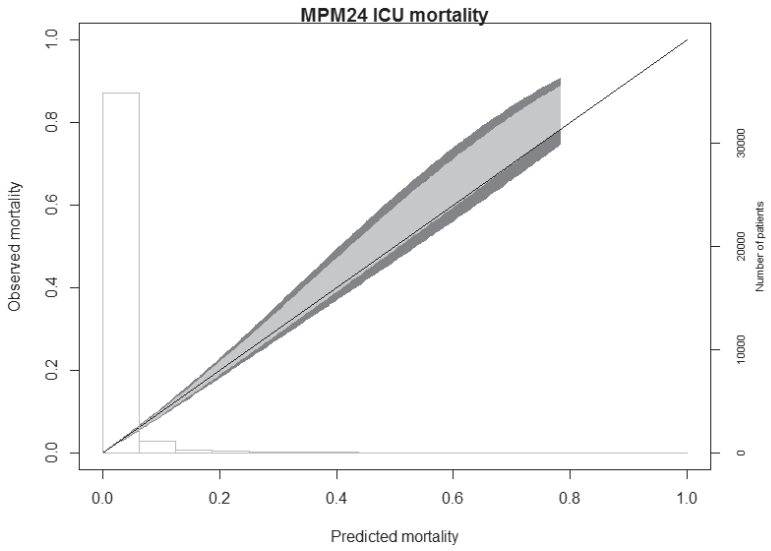
Supplement 3. Callibration graphs of different Models with different outcomes.

Left y-axis is observed outcome. X-axis is the predicted outcome. The histogram represents the number of patients corresponding with the right y-axis.
The light-gray area of the plume is 1 sd and the dark gray area is 2 sd.
Perfect Calibration would coincide with the 45° line with a small area of the plume.
AP2 is APACHE II. AP4 is APACHE IV.






MPM24 Hospital mortality
Observed mortality
Predicted mortality
Number of patients
0.0
0.2
0.4
0.6
0.8
1.0
0
10000
20000
30000


MPM24 ICU mortality
Observed mortality
Predicted mortality
Number of patients
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1.0
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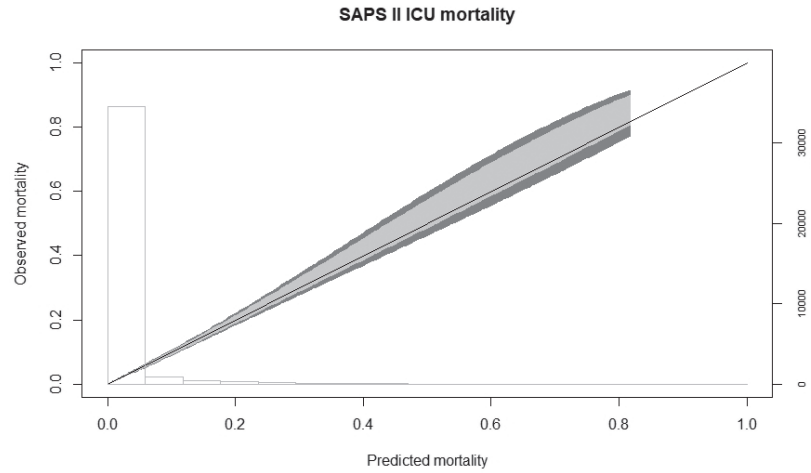
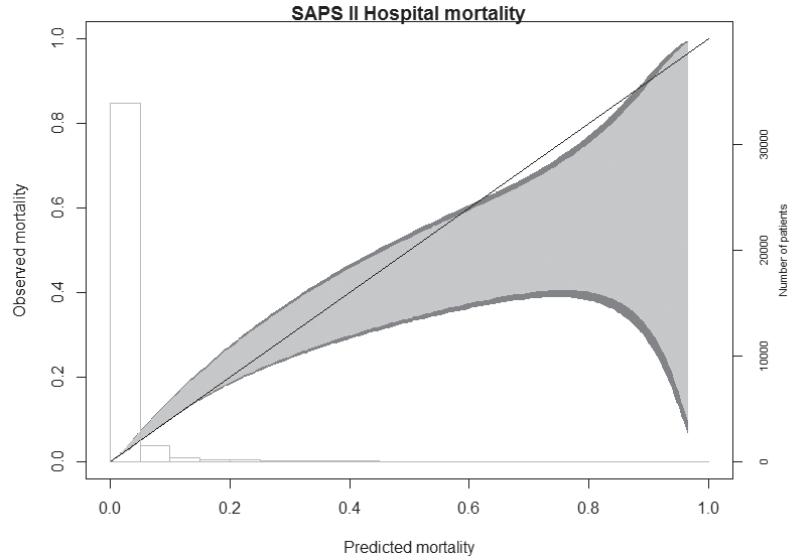
20000
30000


SAPS II ICU mortality
Observed mortality
Predicted mortality
0.0
0.2
0.4
0.6
0.8
1.0
0
10000
20000
30000


SAPS II Hospital mortality
Observed mortality
Predicted mortality
Number of patients
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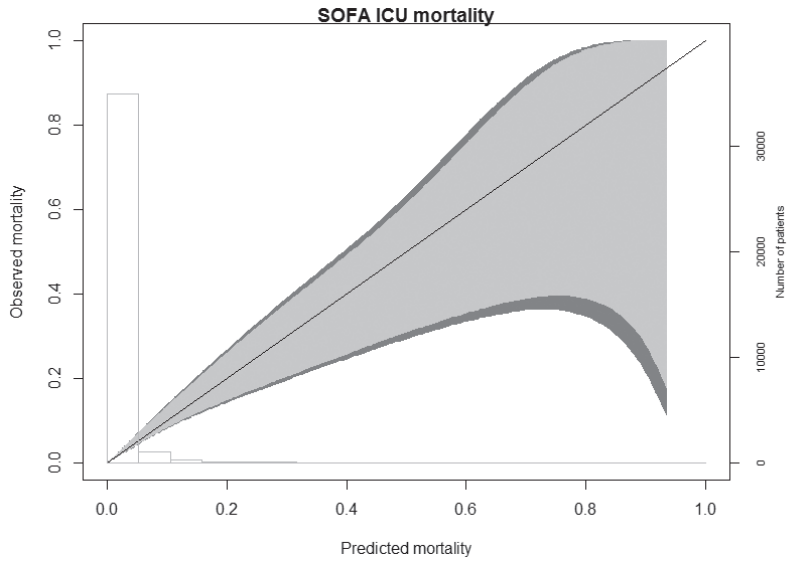

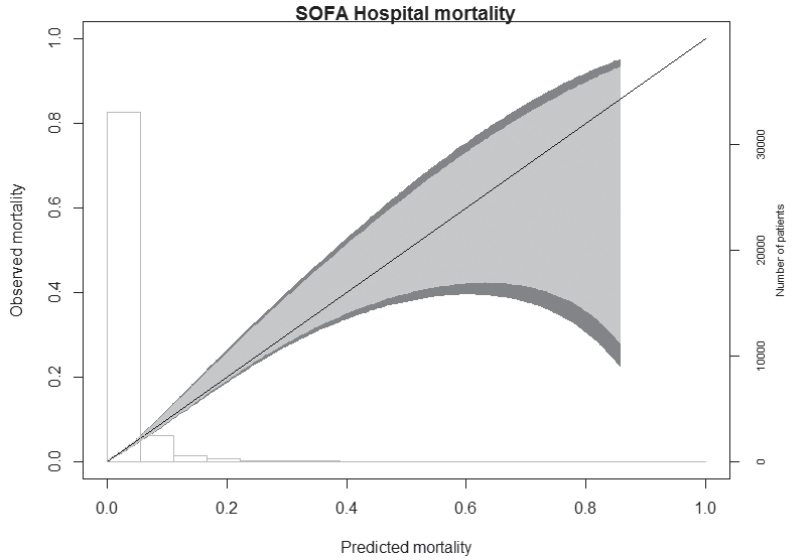

Supplement 4 Additional information of the Prediction Models.

The text below gives a short description of the different prediction models used. Because this is not a concise review, we do encourage the reader to read the original papers and additional references to get a more complete picture. Furthermore, it is good to know that hospitals and ICU's have to make use of third parties, such as the NICE registry, who calculate predictions, Standard mortality ratios (SMR's), keep the models up to date (recalibration etc.) or adapt the models to the local health environment where the models were not developed (see further under the heading APACHE-IV model). Although prediction models were developed initially so that individual ICU's could predict mortality of patients in a minimum of time - almost at the bedside - the use, views and further development of prediction models necessitated the cooperation with third parties.

APACHE-II model

The APACHE-II (Acute Physiology And Chronic Health Evaluation) is a prognostic model with hospital mortality as outcome measure. It consists of three parts, an acute physiological score with 12 variables with different weights collected from the first 24 hours of ICU admission, age points and chronic health points, leading to a total score. This score, together with a distinct coefficient for every diagnostic category (like pneumonia or abdominal surgery due to perforation), and the variable emergency surgery or not, calculates an individual probability of mortality (1). The probability of death in a group can be calculated by taking the sum of the individual probabilities divided by the number of patients. From this the SMR can be calculated by dividing the actual mortality of the group by the predicted mortality of that group; a SMR larger than 1 says that the actual mortality is higher than the predicted and vice versa. The SMR can be used for comparison with other different ICU's from other countries although recalibration needs to be done when using models in other health care environments (2). The advantage of the APACHE-II score is that it consists of relatively few variables and is relatively easy to calculate. However, for mortality prediction the admission diagnosis is needed. Which is to say that the same score can lead to different mortality prediction depending on the admission diagnosis.

APACHE-IV model

The APACHE-IV score and model has been developed form the APACHE III model (3). It used the acute physiology score of the APACHE III model with a few variables added. The number of patients used to develop and validate the model was more than 110 000. The APACHE IV score is the total of the acute physiology score (APS – 18 variables), chronic health condition (6 variables), admission information (several variables) and admission diagnosis (116 in the original article by Zimmermann but ever expanding). The calculation of mortality and length of stay depends on the APS, the APACHE IV score and the admission diagnosis (3). The advantage of the model is that it allows comparison over a vast range of admission diagnoses including cardiac surgery. But this comes at a price. The model

requires extensive high-quality data acquisition and is labor and time consuming. It also requires a third party, either commercial or non-commercial, for software development and aid in data collection. The third party is obliged to recalibrate the model, or models if they offer multiple models, for use in their own country and to update the model, which is a constant process. Even to allow decent comparison, a third party is necessary so it is clear that everyone uses the right coefficients and the data processing is not in the hands of the data owners, which could, inadvertently or not, lead to bias.

SAPS II

The SAPS model has been developed by Le Gall et al. in 1984(4) and a second version in 1993 also by Le Gall and coworkers (5). In the first version they used 14 variables with analog weights to the APACHE system. Simplicity was their aim as the APACHE system was too complex at that time. In the second version was made up of 17 variables: 12 physiological variables, age, type of admission and three variables related to underlying disease. They included 13152 patients from 137 adult ICUs (medical and/or surgical) from 12 countries (10 European countries and 2 countries from North America) and divided these patients randomly into a developmental (65%) and validation (35%) cohort. Cardiac surgery patients were excluded. They used statistical techniques to come the weights of the different variables – LOWESS (locally weighted least series smoothing (6)) and multiple logistic regression. From this score they calculated a probability of mortality. Goodness-of-fit analysis was done using the method described by Hosmer and Lemeshow (7). The authors presented the SAPS II as a simple system for the user, estimating that it would take less than 5 minutes per patient to calculate mortality. One of the goals of the modeling process was to maintain a pure physiology-based system. However, by including three underlying chronical clinical conditions, discrimination and calibration were considerably improved. Missing values were treated as if they were within normal limits, an assumption which has been made often in model developing in the 20th century for practical reasons but also an assumption which does not hold.

MPM_0 II and MPM_{24} II

The second version of the Mortality Prediction Model included 19 124 ICU patients (8). Cardiac surgery patients, coronary care patients and burn victims were excluded. Patients were randomly assigned to the development cohort (12 610) or the validation cohort (6514). Patients from 137 ICU's form 12 countries (2 form North America, 10 from Europe), were included. The MPM consists of an admission model MPM_0 and a model at 24 hours MPM_{24}. The admission model contains 15 readily obtainable variables. The 24-hour model was developed on 10 357 patients still in the ICU at 24 hours, contains five of the admission variables and eight additional variables easily ascertained at 24 hours. Multiple logistic regression with backward elimination was used to derive the set of variables. Calibration was assessed using the Hosmer-Lemeshow goodness-of fit test (7). Variables

whose elimination improved calibration while not significantly affecting discrimination, were considered for exclusion to further reduce the number of variables in the model. The Area under the curve for the MPM_0 was 0.837 in the developmental set and 0.824 in the validation set. Calibration was also good with p = 0.632 in the developmental set and p = 0.327 in the validation set (a high p-value indicating good calibration).

The MPM_{24} developmental set existed of 10 357 patients, 2253 patients had either died or been discharged alive from the ICU prior to 24 hours. Model development proceeded in the same manner as for the MPM_0 model. Calibration was good in both developmental database and validation database. Discrimination was good with an AUC-ROC of 0.844 in the development database and 0.836 in the validation database.

The MPM_0 -II and MPM_{24} -II are included in the NICE registry.

The SOFA-score

The SOFA-score was initially developed as a tool to learn from the evolution of organ failure in sepsis and to assess the effects of therapies like mechanical ventilation and vasopressors on the course of organ dysfunction. It scores 1-4 points for each of the six organ systems (9) (table 1.). The importance of the SOFA score is growing and it has been incorporated in the latest surviving sepsis campaign as a tool to describe and detect sepsis (10). Although the SOFA score was initially not developed to predict mortality, several studies showed that SOFA has been extensively used to predict morbidity and mortality and has been validated for that purpose in several ICU populations and among cardiac surgery patients (11) (Minne et al., 2008, #41574).

SOFA score table 1. Adapted from reference 9

Organ system		Score				
	Variable	0	1	2	3	4
Pulmonary	Lowest PaO2 (Torr)/FiO2 (%)	>400	<400	<300	< 200+respiratory support	< 100+respiratory support
Coagulation	Lowest platelet (1 OVmm3)	>150	<150	<100	<50	<20
Hepatic	Highest bilirubin (µmol/L)	<20	20-32	33-101	102-204	>204
Circulatory	Blood pressure status	Mean arterial pressure (mmHg) >70	Mean arterial pressure (mmHg) <70	Dopamine* dose <5 or dobutamine any dose	Dopamine dose>5 or epinephrine<0.1 or norepinephrine <0.1	Dopamine dose> 15 or epinephrine>0.1 or norepinephrine >0.1
Neurologic	GCS	15	13-14	10-12	6-9	<6
Renal	Highest creatinine level (/L/mol/L)	<110	110-170	171-299	300-440	>440
	Total urine output (mL/24 h)				<500	<200
Score	0-6	7-9	10-12	13-14	15	15-24
Score %	<10	15-20	15-20	50-60	>80	>90

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