Research Square

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A New SOFA Score Calculation to Improve the Predictive Performance for Mortality

Makoto Arakawa (arakawa@nihon-pharm.co.jp)
Department of Emergency and Disaster Medicine, Juntendo University Graduate School of Medicine
https://orcid.org/0000-0003-0600-3192

Jerrold H Levy
Duke University School of Medicine

Kenta Kondo
Juntendo University Graduate School of Medicine

Toshiaki Iba
Juntendo University Graduate School of Medicine

Research

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Abstract

Background: The sequential organ failure assessment (SOFA) is one of the most commonly used scoring systems to evaluate organ failure in sepsis. The trajectory of the SOFA score, a delta-SOFA ($SOFA_{\Delta}$), is proposed as a better indicator for predicting mortality, and potentially as an endpoint in exploratory clinical trials. However, there are some concerns about the use of $SOFA_{\Delta}$. For example, $SOFA_{\Delta}$ represents only the changes in the score, and the potential value of the absolute SOFA score has not been considered. Therefore, we hypothesized that the addition of the absolute SOFA score to the $SOFA_{\Delta}$ would improve the predictive performance for patient outcomes. Based on this theory, a new indicator, $SOFA_{Comb}$ calculated by $SOFA_{\Delta}$ + absolute SOFA score, was examined in this study.

Methods: Data obtained from 297 patients in multiinstitutional post-marketing surveys performed during June 2014, and May 2016 were retrospectively analyzed. All patients were diagnosed as having sepsis-associated disseminated intravascular coagulopathy (DIC) and treated with antithrombin concentrate. The $SOFA_{Comb}$ and $SOFA_{\Delta}$ were calculated on days 2, 4, and 7, and the performance was analyzed in terms of predictive ability for 28-day mortality.

Results: Of the 297 patients included in the analysis, 214 patients survived (72.1%), while 83 patients (27.9%) died. The area under the receiver operating curve (AUC) of SOFA at baseline for predicting 28-mortality was 0.679. The AUCs of $SOFA_{\Delta}$ on day 2, 4, 7 were 0.662, 0.769, 0.815, respectively, and those of $SOFA_{Comb}$ on day 2, 4, 7 were 0.765, 0.830, 0.866, respectively. The AUCs of $SOFA_{Comb}$ were significantly greater at all time points compared to $SOFA_{\Delta}$ (day 2: P <0.001, day 4: P =0.002, day 7: P <0.001). In addition, the accuracy of $SOFA_{Comb}$ was better than that of $SOFA_{\Delta}$ (day 2: P <0.001, day 4: P =0.067, day 7: P =0.049).

Conclusions: $SOFA_{Comb}$ is simple to calculate and provides better predictive performance compared to $SOFA_{\Delta}$ for predicting mortality. Additional studies are needed to confirm these findings.

Background

Sequential Organ Failure Assessment (SOFA) score is one of the most commonly used scoring systems to evaluate the severity of sepsis that is routinely monitored in the intensive care unit (ICU). The SOFA score was first established in the 1990s to determine the morbidity of the sepsis population [1]. In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) was updated and described infection-induced organ dysfunction as determined by an increase in the SOFA score of two points or more [2]. Since then, the utilization of the SOFA score, using the changes in SOFA score ($SOFA_{\Delta}$), has increasingly been adopted by clinicians and researchers in critical care. Currently, an absolute SOFA score is commonly applied to determine patient severity in the ICU, and $SOFA_{\Delta}$ have been calculated to determine treatment effects and the prediction of patient outcomes [3–5].

In clinical studies, the SOFA score was initially used to assess patient severity and quantitatively examine clinical study cohorts. Subsequently, an absolute SOFA score is used to evaluate the treatment effect [6]. Recently, the European Medicines Agency (EMA) adopted the evaluation of organ dysfunction by organ failure assessment scores, including SOFA as the endpoint of the therapeutic efficacy in both exploratory studies and randomized controlled trials (RCTs) [7]. de Grooth et al. [8] validated the predictive performance of fix-day SOFA (the SOFA score on a fixed day after randomization), $SOFA_{\Delta}$ (fix-day SOFA minus baseline SOFA score), and other SOFA derivatives and concluded that $SOFA_{\Delta}$ was superior to detect the therapeutic effect and recommended using $SOFA_{\Delta}$ as an endpoint of RCTs. Other reports also supported the idea that $SOFA_{\Delta}$ was more suitable as an alternative endpoint of mortality than the absolute SOFA score accordingly [9]. However, using $SOFA_{\Delta}$ as an endpoint has potential limitations since $SOFA_{\Delta}$ only represents changes in patient severity and not disease severity at a specific timing [10]. Because $SOFA_{\Delta}$ is determined regardless of the baseline severity, $SOFA_{\Delta}$ may not properly evaluate the treatment effect unless the trial targets the specific baseline SOFA score. Due to these limitations, we hypothesized that combining the $SOFA_{\Delta}$ with the SOFA score on a fixed day may result in an improved predictive performance. As a result, we developed a novel scoring system, $SOFA_{Comb}$, that is calculated by absolute SOFA + $SOFA_{\Delta}$, and compared its performance with $SOFA_{\Delta}$ in sepsis-associated DIC patients.

Methods

Data Collection

Data from a multiinstitutional, post-marketing survey performed between June 2014 and May 2016 by Nihon Pharmaceutical were used in our analysis. A total of 297 suspected sepsis-associated disseminated intravascular coagulation (DIC) patients with decreased antithrombin activity who were treated with antithrombin concentrate (Nihon Pharmaceutical Co. Ltd, Tokyo, Japan) were included in the analysis. Patients received an antithrombin dose of 30 to 60 IU/kg/day for up to 3 consecutive days, or treatment was stopped for any justifiable reason. Other treatments for sepsis and DIC were performed based on individual physician's decisions.

Laboratory measurements and diagnostic criteria

The platelet count and other coagulation markers were measured at local laboratories. DIC was diagnosed according to the Japanese Association for Acute Medicine (JAAM) DIC diagnostic criteria, which were composed of four items (i.e. platelet count, prothrombin time (PT), fibrinogen/fibrin degradation product (FDP), and Systemic Inflammatory Response Score [SIRS] score) [11]. SOFA score was composed of six items (i.e. respiratory, coagulation, hepatic, circulation, nervous system, and renal scores), and calculated on Day 1 (baseline) and Day 2, Day 4, Day 7. The patients' outcomes on day 28 were also recorded.

Ethics approval, patient consent, and study permissions, and consent to publish

The survey was conducted in accordance with the Declaration of Helsinki and Good Vigilance Practice and Good Post-marketing surveillance Practice. Although there was no need to obtain since the data were collected anonymously from participated institutes, the patients' agreement and consent were obtained based on a pre-defined process when required by the ethics committee of each hospital.

Calculation of SOFA derivatives and other parameters

The fix-day SOFA was calculated as a sum of each organ's score on a fixed day. Combined SOFA ($SOFA_{Comb}$) was calculated from $SOFA_{\Delta}$ (changes from the previous score to the score on a designated timing) plus absolute SOFA score on a designated timing, for example, $SOFA_{Comb}$ on day 7 was calculated as (day 7 SOFA score − baseline SOFA score) + day 7 SOFA score. Patients who died on day 4 or day 7 by death were managed by using the last observed value [6]. Patients with missing values not due to death were excluded from the analysis. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the areas under the curve (AUCs) of SOFA derivatives. The predictive mortality rate was calculated as a predictive probability by logistic regression model. The optimal cutoff-point offering the best sensitivity and specificity to predict 28-day mortality was calculated, so that distance between ROC plot and top left was minimized.

Statistical Analysis

The numerical values in the text and tables represent the median and interquartile range (IQR). Univariate associations were evaluated using the Fisher exact test and the unpaired Wilcoxon rank-sum test (Mann-Whitney U test). ROC curve analysis was performed to evaluate AUCs of SOFA derivatives to compare their performance for the prediction of 28-day mortality. Accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the optimal cut-point were calculated. Predictive probability for mortality was calculated by logistic regression model and the overall effect explained by the model was quantified by Nagelkerke's R^2. A P-value < 0.05 was considered statistically significant, and all P-values were two-sided. The above-mentioned analyses were performed using R version 4.0.2.

Results

Of the 297 patients included in the analysis, 214 patients survived (72.1%) for 28 days, while 83 patients (27.9%) died. Table 1 summarizes the baseline characteristics of the survivors and non-survivors. The median age of the survivors was 74 years, while that of the non-survivors was 79 years (P < 0.001). The gender distribution did not differ between survivors and non-survivors. The Body Mass Index did not differ between the groups.

Regarding the coagulation profiles, the differences of antithrombin activity, PT-INR, and FDP were significantly different between the survivors and non-survivor (P = 0.012, 0.009, and 0.039, respectively). In contrast, the platelet count, fibrinogen, and JAAM DIC score were not different between the groups. The

baseline SOFA score of survivors was 11, and that of non-survivors was 13, and the difference was significant ($P < 0.001$).

Table 1
Background of patients

	Non-survivors (n = 83)	Survivors (n = 214)	*P*-value
Age	79.0 [70.5, 85.0]	74.0 [65.0, 80.0]	<0.001
Sex/male (%)	57 (69%)	136 (64%)	0.420
BMI	20.9 [18.7, 23.1]	22.0 [19.0, 24.3]	0.260
Antithrombin (%)	44.0 [33.0, 51.0]	47.0 [39.0, 56.9]	0.012
Platelet count (/mm^3)	6.5 [4.4, 12.0]	7.3 [4.8, 10.4]	0.350
PT-INR	1.56 [1.27, 1.90]	1.38 [1.24, 1.62]	0.009
FDP (μg/mL)	34.9 [20.5, 69.3]	27.6 [15.3, 50.9]	0.039
Fibrinogen (g/L)	317 [208, 507]	353.0 [251, 496]	0.187
JAAM DIC score	6.0 [5.0, 7.0]	6.0 [5.0, 7.0]	0.102
SOFA score	13.0 [10.0, 16.0]	11.0 [8.0, 13.0]	<0.001
BMI: body mass index, PT-INR: prothrombin time-international normalized ratio			
FDP: fibrin/ fibrinogen degradation product, JAAM: Japanese Association for Acute Medicine			
DIC: disseminated intravascular coagulation, SOFA: Sequential Organ Failure Assessment			

The distribution of SOFA scores among the patients is shown in Figure 1. There was no bias in the distribution, and it was widely distributed from minimum value 2 to maximum value 22. The mortality increased as with SOFA scoring, and the rate was 16.2% based on SOFA score 1–8, 29.0% based on 9–16, and 51.6% for a total SOFA > 17.

Figure 2 shows the ROCs of SOFA derivatives for the prediction of 28-day mortality. The AUC of SOFA score at baseline was 0.679, and that of $SOFA_{\Delta}$ on day 7 was 0.815, which was significantly larger than the baseline SOFA, however, the AUCs of $SOFA_{\Delta}$ on day 2 and day 4 were not significantly higher than those of SOFA score. On the other hand, AUC of $SOFA_{Comb}$ on day 2 (0.765) was significantly larger than baseline SOFA, and the AUCs became greater on day 4 or 7 (0.830, 0.866, respectively). In addition, compared with $SOFA_{\Delta}$, the AUCs of $SOFA_{Comb}$ were significantly larger at all time points ($P < 0.001$, = 0.002, < 0.001, respectively).

The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value are summarized in Table 2. The accuracies of $SOFA_{Comb}$ were better than those of $SOFA_{\Delta}$ on day2, 4, 7 ($P <$ 0.001, 0.067, 0.049, respectively).

Table 2
Discriminating values of $SOFA_{\Delta}$ and $SOFA_{Comb}$

	Sensitivity	Specificity	PPV	NPV	Accuracy
Baseline SOFA score	63.9%	70.1%	45.3%	83.3%	68.4%
$SOFA_{\Delta}$ on day 2	74.7%	47.7%	35.6%	82.9%	55.2%
$SOFA_{Comb}$ on day 2	72.3%	69.2%	47.6%	86.5%	70.0%
$SOFA_{\Delta}$ on day 4	73.5%	66.8%	46.2%	86.7%	68.7%
$SOFA_{Comb}$ on day 4	79.5%	74.3%	54.5%	90.3%	75.8%
$SOFA_{\Delta}$ on day 7	73.5%	74.3%	52.6%	87.8%	74.1%
$SOFA_{Comb}$ on day 7	74.7%	83.6%	63.9%	89.5%	81.1%
best cutoff point $SOFA_{\Delta}$ on day 2: -0.5, $SOFA_{\Delta}$ on day 4: -0.5, $SOFA_{\Delta}$ on day 7: -1.5,					
$SOFA_{Comb}$ on day 2: 12.5, $SOFA_{Comb}$ on day 4: 10.5, $SOFA_{Comb}$7: 9.5					
P-value when accuracy is compared, $SOFA_{\Delta}$ on day 2 vs. $SOFA_{Comb}$ on day 2: $P < 0.001$, $SOFA_{\Delta}$ on day 4 vs. $SOFA_{Comb}$ on day 4: $P = 0.067$, $SOFA_{\Delta}$ on day 7 vs. $SOFA_{Comb}$ on day 7: $P = 0.049$ PPV: positive predictive value, NPV: negative predictive value					

Figure 3 shows the correlation of predictive probability of mortality in $SOFA_{\Delta}$ (left) and $SOFA_{Comb}$ (right). The logistic regression curve ± standard error of $SOFA_{\Delta}$ on day 4 and 7 which predicts 50% mortality were 2.4 (1.8-3.0) and 1.1 (0.6-1.7), respectively, and those of $SOFA_{Comb}$ on days 4 and 7 were 15.6 (14.7-16.5) and 13.1 (12.1-14.1), respectively.

Discussion

Sepsis-associated DIC is a serious life-threatening complication with a reported mortality rate that ranges from 30–60% [12], due to inflammation, coagulopathy, that cause tissue injury and multiorgan failure [13–14]. Anticoagulant therapy in septic DIC patients may have important effects in inhibiting

thromboinflammation to improve potential outcomes [15–20]. In septic patients who develop DIC, a timely and accurate evaluation of the severity and prediction of outcomes is important for clinicians.

In the current study, we evaluated the predictive performance for 28-day mortality using a new scoring system, the $SOFA_{Comb}$, calculated by $SOFA_{\Delta}$ + absolute SOFA score, and validated its potential applicability using a sepsis-associated DIC patient database. We previously reported the superiority of $SOFA_{\Delta}$ compared to DIC scores [21], and our goal was to improve the performance of $SOFA_{\Delta}$ in the present study. The performance of $SOFA_{\Delta}$ has been repeatedly validated for predicting the prognosis in sepsis patients, but the results are inconsistent.

Minne et. al. reported the predictive performance of $SOFA_{\Delta}$ for the mortality, but the AUCs varies widely from 0.510 to 0.828 in their systemic review [5]. This inconsistency may be due to the consideration that $SOFA_{\Delta}$ represents only the changes of the SOFA score and ignores the absolute SOFA score. Indeed, among the patients with the same $SOFA_{\Delta}$, the mortality should be different depending on the absolute SOFA score. For instance, the significance of a -2 point in $SOFA_{\Delta}$ should be different between from two to 0 and from 24 to 22 point. However, de Grooth et. al. [8] validated the treatment effects, and mortality evaluated by $SOFA_{\Delta}$ and reported $SOFA_{\Delta}$ reflected the efficacy more accurately than the absolute SOFA score on a fixed day after randomization. They also reported the association between $SOFA_{\Delta}$ and mortality did not change even after the adjustment by SOFA score on admission. Karakike et al. [22] reported SOFA score changes evaluated by a percentage of the initial score on day 7 or later was a better predictor of mortality, and the 25% decrease of initial SOFA was the best cut-off value. In our study, $SOFA_{\Delta}$ on day 7 did not exhibit a better predictive value over the SOFA score on day 7, but the $SOFA_{Comb}$ on day 2 and later had a better predictivity than baseline SOFA, and the performance increased over time. Based on the timing of evaluation, $SOFA_{\Delta}$ cannot detect the status change or the treatment effect at an early timing since there should be a time lag until the SOFA score improves. The absolute SOFA score included in $SOFA_{Comb}$ may help to reduce this drawback. In fact, $SOFA_{Comb}$ demonstrated a better performance than $SOFA_{\Delta}$ at early timing in the present study since $SOFA_{Comb}$ reflects both the time-trend of disease status and real-time severity. The early detection of the status change or treatment effect is particularly helpful for clinicians to reconsider their therapeutic strategy.

For designing $SOFA_{Comb}$, we did not use a multivariable logistic regression model because its predictive value did not improve the performance, and the day 7 AUC was 0.866, and identical to the value calculated by our proposed method. As a result, we selected a simple method using absolute SOFA score plus $SOFA_{\Delta}$ to calculate $SOFA_{Comb}$.

A logistic regression curve revealed the relationship between the scores and the estimated mortality as shown in Fig. 3. Both curves showed similar sigmoid shape, with standard error, implying that the performance of both $SOFA_{\Delta}$ and $SOFA_{Comb}$ was able to predict 28-day mortality over the entire range of the scores. However, the R^2 calculated from the logistic regression curve analysis for $SOFA_{Comb}$ on day 7

was 44.0% and higher than that of $SOFA_{\Delta}$ (32.0%), which are consistent with the superior performance of $SOFA_{Comb}$ shown by the higher accuracy, sensitivity, and specificity.

The present study has some limitations. First, the performance of $SOFA_{Comb}$ was developed using the data from a post-marketing survey, and the timing of the evaluation was pre-specified on day 1 (before the treatment), 2, 4 (after the treatment), and 7. In addition, all patients received antithrombin supplementation. It is uncertain whether the results obtained in this study are generalizable and need additional validation. Second, in the post-marketing database used, missing data was present, and patients were excluded from the analysis. Because this data is a retrospective analysis, the results need to be confirmed in a prospective study.

Conclusions

$SOFA_{Comb}$ is simple to calculate and provides better predictive performance compared to $SOFA_{\Delta}$ for predicting mortality. Additional studies are needed to confirm our findings.

Abbreviations

SOFA, sequential organ failure assessment; DIC, disseminated intravascular coagulation; JAAM, Japanese Association for Acute Medicine; PT, prothrombin time; FDP, fibrinogen/fibrin degradation product; SIRS, Systemic Inflammatory Response Score;

Declarations

Ethics approval and consent to participate

There was no need to obtain the patients' agreement and consent since the data were collected anonymously from participated institutes. However, those were obtained based on a pre-defined process when required by the ethics committee of each hospital.

Consent for publication

Not applicable

Availability of data and material

Not applicable

Competing interests

TI has received a research grant from Japan Blood Products Organization and JIMRO. JHL serves on the Steering Committees for Instrumentation Laboratories, Octapharma, Leading Biosciences, and Merck. The other authors state that they have no conflicts of interest.

Funding

Not applicable

Authors' contributions

MA and TI wrote the draft. JHL reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figures

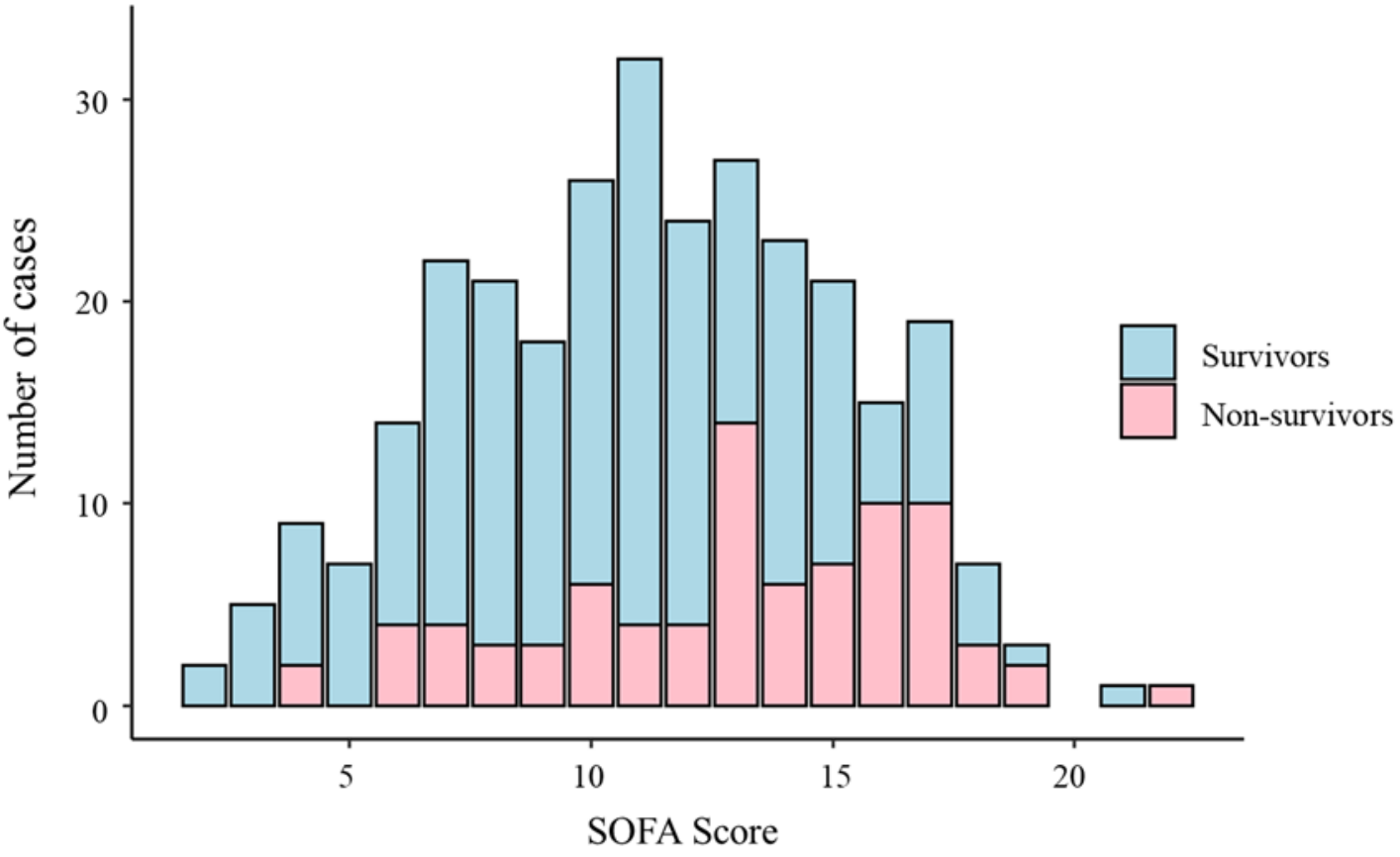

Figure 1

The histogram of distribution of SOFA score at baseline The blue part of the bars represents the number of survivors and red part represents the number of non-survivors. Minimum SOFA score was two and maximum SOFA score is 22. There is no bias in the distribution and the mortality rate is higher according to the score increasing. SOFA, Sequential Organ Failure Assessment

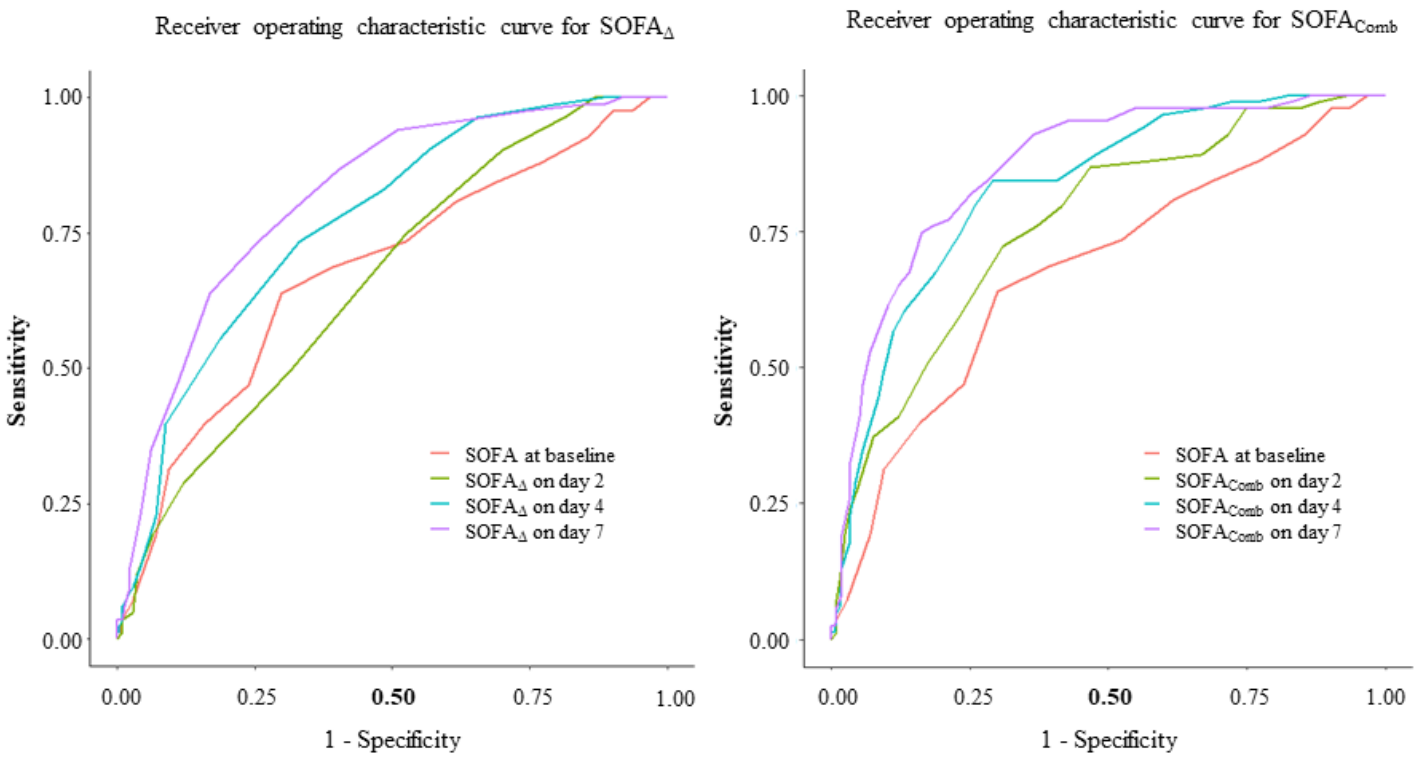

Figure 2

Receiver operating characteristic curve of SOFAΔ and SOFAComb for the prediction of 28-day mortality Each line represents the receiver operating characteristic (ROC) curve for the prediction of mortality either at baseline, day 2, day 4, or day 7. Though the area under the curve (AUC) of SOFAΔ on day 7 is significantly larger than that of baseline SOFA, the AUCs of SOFAΔ on day 2 and day 4 are not different from AUC of baseline SOFA (left). On the other hand, the AUCs of SOFAComb on either day 2, day 4, or day 7 is significantly larger than that of baseline SOFA (right). The AUCs of SOFAComb are significantly larger than those of SOFAΔ at each time point. SOFA, Sequential Organ Failure Assessment

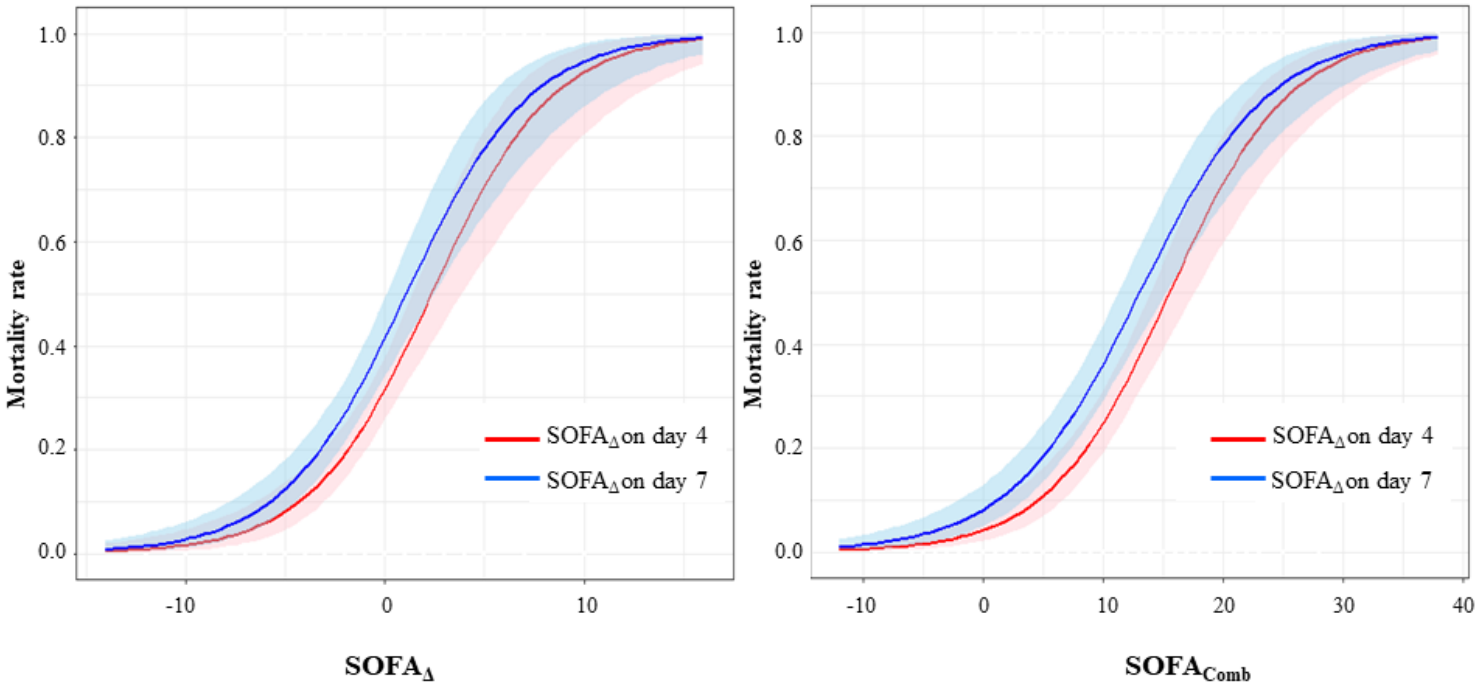

Figure 3

Logistic regression curves about predictive mortality rate of SOFAΔ and SOFAComb Lines indicate predictive mortality rate, and bands indicate the standard error (SE). The logistic regression curves are both sigmoid shape in both SOFAΔ (left) and SOFAComb (right). However, the R2, which represents explanatory power of model, for SOFAComb on day 7 is 44.0% and was higher than that of SOFAΔ (32.0%).