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# A new SOFA score calculation to improve the predictive performance for mortality in sepsis-associated disseminated intravascular coagulopathy patients

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## ABSTRACT

**Purpose:** The change in the sequential organ failure assessment (SOFA) score from the entry day, a delta-SOFA (SOFA<sub>Δ</sub>), has been proposed as a better indicator for predicting mortality, and potentially as an endpoint in clinical trials. However, there are some concerns that the value of the absolute SOFA score has not been considered. The purpose of the study is to examine whether the addition of an absolute SOFA score can increase the predictive performance of SOFA<sub>Δ</sub>.

**Materials and methods:** Data obtained from 297 patients with sepsis-associated disseminated intravascular coagulopathy (DIC) in multiinstitutional post-marketing surveys were analyzed retrospectively. The SOFA<sub>Comb</sub> (SOFA<sub>Δ</sub> score + absolute SOFA score) and SOFA<sub>Δ</sub> were calculated, and the performance of each indicator was analyzed in terms of predictive ability for 28-day mortality.

**Results:** The area under the receiver operating curve (AUC) for the mortality of SOFA<sub>Comb</sub> on day 2, 4, 7 were significantly greater compared to those of SOFA<sub>Δ</sub> ( $P < 0.001$ ,  $= 0.002$ ,  $< 0.001$ , respectively). In addition, the accuracy [(True positive + True negative) / total number at the best cutoff points] of SOFA<sub>Comb</sub> was better than that of SOFA<sub>Δ</sub>.

**Conclusions:** SOFA<sub>Comb</sub> is simple to calculate and provides better predictive performance compared to SOFA<sub>Δ</sub> for predicting mortality.

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## 1. Introduction

Although multiple strategies for patient management in sepsis have been reported, most of the therapies either have failed or do not have strong evidence for efficacy despite large clinical trials with all of the associated issues that include costs, need for patient consent. Further, clinical trials for anticoagulants in sepsis often did not specifically target coagulopathic patients [1]. As a result, the ‘choosing wisely campaign’ (<https://abimfoundation.org/what-we-do/choosing-wisely>) has highlighted the relationship between physicians and patients, and achieving correct knowledges about the association among disease condition,

**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.

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treatment and prognosis are a fundamental consideration for ICU physicians. Therefore, our intention was to establish a modality to evaluate the patients' illness severity and prognosis after the start of treatment for sepsis using a readily available SOFA score. 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 [2]. 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 [3]. Since then, the utilization of the SOFA score, including the changes in SOFA score (SOFA<sub>Δ</sub>), has increasingly been adopted by clinicians and researchers in critical care. Currently, an absolute SOFA score is commonly applied to determine patients' illness severity in the ICU, and SOFA<sub>Δ</sub> have been calculated to determine disease improvement or deterioration and the prediction of patient outcomes [4–6].

In clinical studies, the SOFA score was initially used to assess patients' illness severity and quantitatively examine clinical study cohorts. Subsequently, an absolute SOFA score was also used to evaluate the treatment

effect by comparing the score of the intervention group and that of the control group after the treatment [7]. 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) [8]. de Grooth et al. [9] validated the performance of fixed-day SOFA (the SOFA score on a fixed day after randomization),  $SOFA_{\Delta}$  (fixed-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 surrogate for mortality than the absolute SOFA score accordingly [10]. However, using  $SOFA_{\Delta}$  as an endpoint has potential limitations since  $SOFA_{\Delta}$  only represents changes in patients' illness severity and not disease severity at a specific timing [11]. Because  $SOFA_{\Delta}$  is determined regardless of the baseline severity,  $SOFA_{\Delta}$  may not properly evaluate the prognosis 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 improved prediction of 28-day mortality. 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.

## 2. Material and methods

### 2.1. Data collection

Data from a multiinstitutional, post-marketing survey performed between June 2014 and May 2016 by Nihon Pharmaceutical (unpublished data) 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.

### 2.2. 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) [12]. SOFA score was composed of six items (i.e. respiratory, coagulation, hepatic, circulation, nervous system, and renal scores), and calculated on day 1 (baseline) that was 24 h period before intervention of original survey (antithrombin supplementation), and day 2, day 4, day 7. The Glasgow Coma Scale (GCS) was evaluated by each doctor and the SOFA score included the assumed GCS to evaluate neurologic function, i.e., the score the patient would have in the absence of any sedation. The patients' outcomes on day 28 were also recorded prospectively in the original survey.

### 2.3. 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.

### 2.4. Calculation of SOFA derivatives and other parameters

The fixed-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 baseline 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 with missing values due to death before day 4 or day 7 were managed by using the last observed value [7]. 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.

### 2.5. 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. To calibrate the model, calibration curve was drawn. Bootstrap validation was performed to correct for over-fitting. Accuracy [(True positive + True negative) / total number of cases], sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at the best cutoff point with the ROC curve closest to the point (0,1) were calculated. Predictive probability for mortality was calculated by logistic regression model and the overall power of estimation 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.

## 3. Results

Fig. 1 is a study flow chart. The record of patients with suspected sepsis-associated DIC patient was 635 cases. 12 cases were excluded

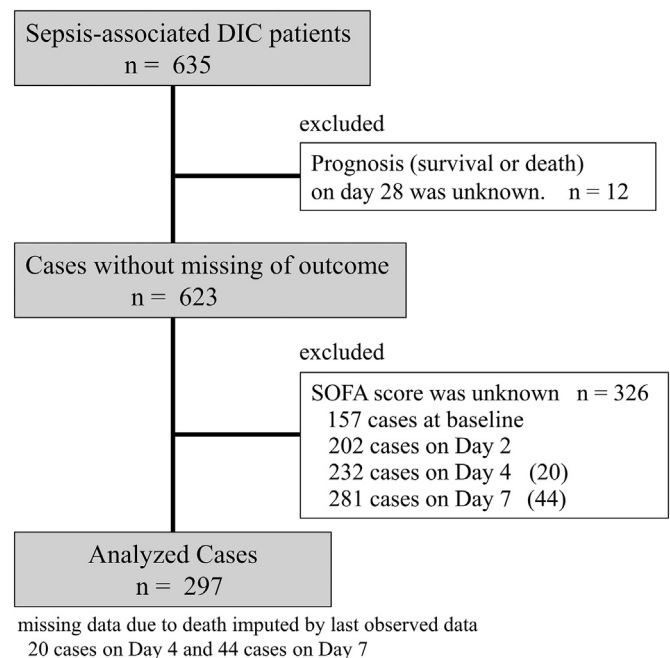


Fig. 1. The study flowchart. 297 patients were analyzed about SOFA score in total 635 patients with sepsis-associated DIC.

**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 <sup>3</sup> )	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

for undetermined outcome, and 326 cases were excluded for missing of SOFA score. Finally, 297 cases were used as the analysis dataset. Of the 297 patients included in the analysis, 214 patients (72.1%) survived 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 ( $P < 0.001$ ).

The distribution of SOFA scores among the patients is shown in Fig. 2. 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.

Fig. 3 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<sub>Δ</sub> on day 7 was 0.815, which was significantly larger than the baseline SOFA, however, the AUCs of SOFA<sub>Δ</sub> on day 2 (0.662) and day 4 (0.769) were not significantly higher than that of baseline SOFA score. On the other hand, AUC of SOFA<sub>Comb</sub> 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<sub>Δ</sub>, the AUCs of SOFA<sub>Comb</sub> were significantly larger at all time points ( $P < 0.001$ ,  $= 0.002$ ,  $< 0.001$ , respectively). On the other hand, the AUC of absolute SOFA are 0.756 on day 2, 0.816 on day 4, 0.857 on day 7, and the differences between AUCs of SOFA<sub>Comb</sub> and those of absolute SOFA were not statistically significant.

To correct for over-fitting, bootstrap validation with 1000 replications were performed. The difference of AUC between original and bootstrap sample were less than 0.01 on all time points in SOFA<sub>Comb</sub> and SOFA<sub>Δ</sub>, and the result indicate our logistic regression model was not over-fitted.

Fig. 4 is the calibration curve. A good calibration was showed in less than 0.5 of observed mortality. However, in higher mortality, deviation from the actual mortality was observed, especially on early time points.

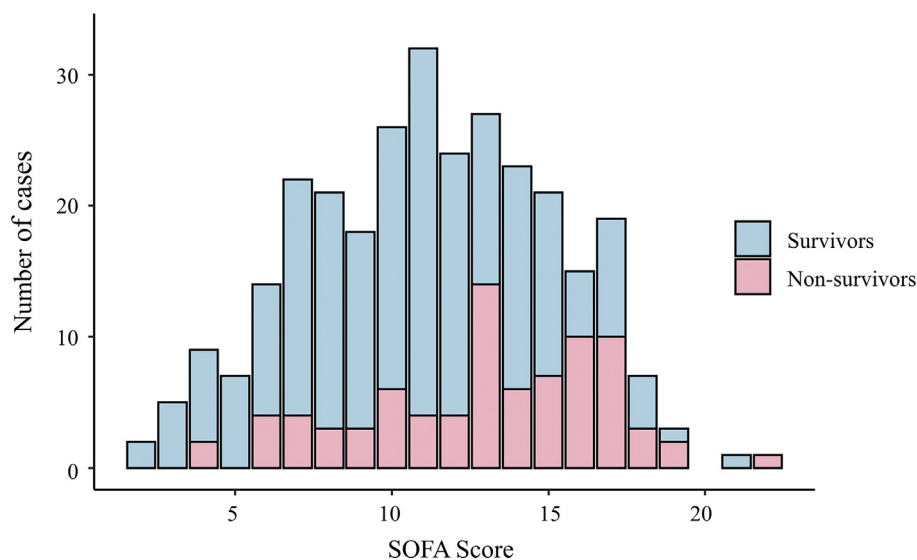
The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value are summarized in Table 2. The accuracies of SOFA<sub>Comb</sub> were better than those of SOFA<sub>Δ</sub> on day2, 4, 7 ( $P < 0.001$ , 0.067, 0.049, respectively).

Fig. 5 shows the correlation of predictive probability of mortality in SOFA<sub>Δ</sub> (left) and SOFA<sub>Comb</sub> (right). The logistic regression curve  $\pm$  standard error of SOFA<sub>Δ</sub> 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<sub>Comb</sub> on days 4 and 7 were 15.6 (14.7–16.5) and 13.1 (12.1–14.1), respectively.

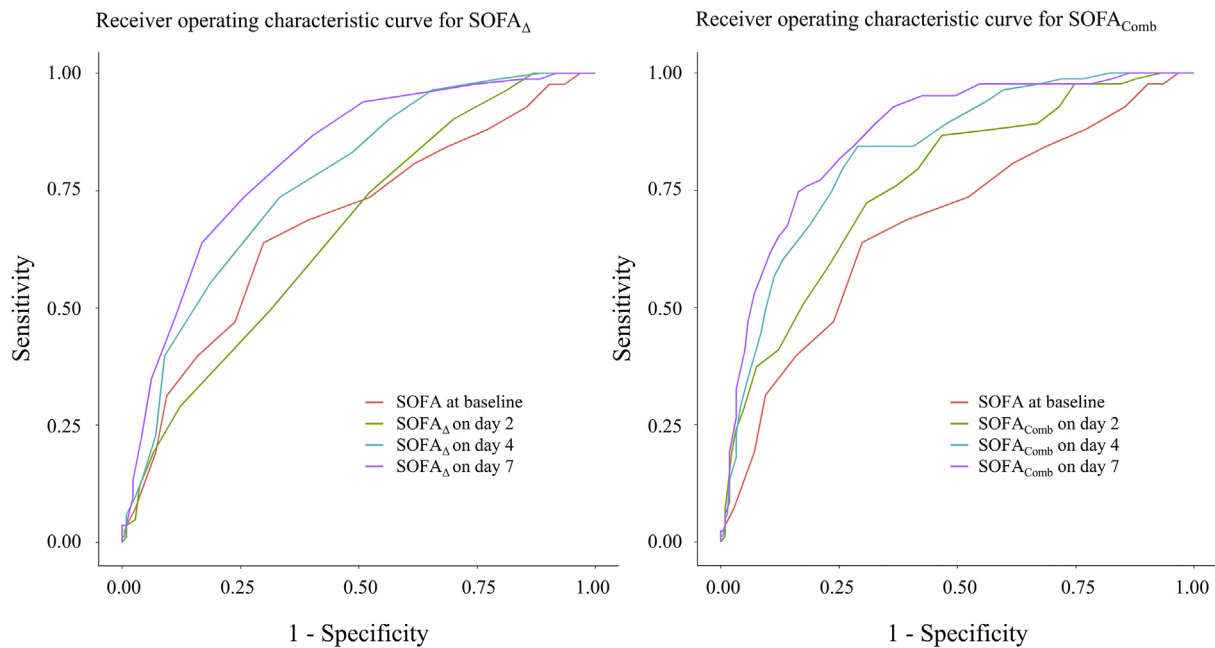
#### 4. Discussion

Sepsis-associated DIC is a serious life-threatening complication with a reported mortality rate that ranges from 30 to 60% [13], due to inflammation and coagulopathy that cause tissue injury and multiorgan failure [14,15]. Anticoagulant therapy in septic DIC patients may have important effects in inhibiting thromboinflammation to improve potential outcomes [16–21]. In septic patients who develop DIC, a timely and accurate evaluation of the severity and prediction of outcomes is important for clinicians.

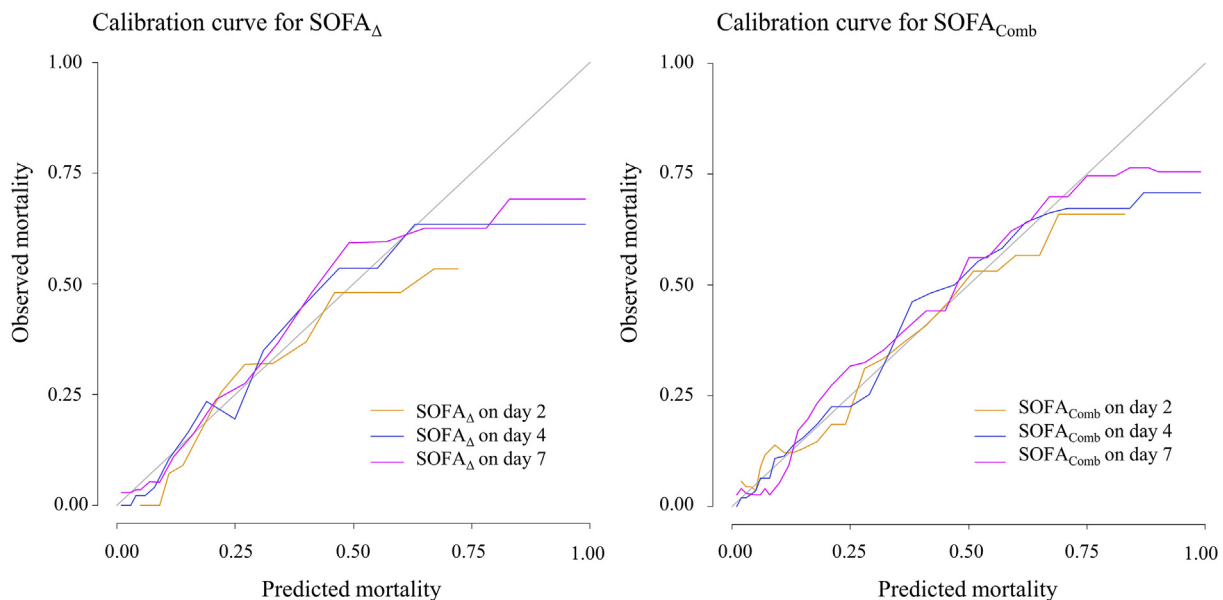
In the current study, we evaluated the predictive performance for 28-day mortality using a new scoring system, the SOFA<sub>Comb</sub>, calculated



**Fig. 2.** 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. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)



**Fig. 3.** Receiver operating characteristic curve of  $SOFA_{\Delta}$  and  $SOFA_{Comb}$  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  $SOFA_{\Delta}$  on day 7 (0.815) is significantly larger than that of baseline SOFA (0.679), the AUCs of  $SOFA_{\Delta}$  on day 2 (0.662) and day 4 (0.769) are not different from AUC of baseline SOFA (left). On the other hand, the AUCs of  $SOFA_{Comb}$  on either day 2, day 4, or day 7 (0.765, 0.830, 0.866, respectively) is significantly larger than that of baseline SOFA (right). The AUCs of  $SOFA_{Comb}$  are significantly larger than those of  $SOFA_{\Delta}$  at each time point. SOFA, Sequential Organ Failure Assessment.



**Fig. 4.** Calibration curves of predicted and observed mortality. The curve shows the correlation between predicted and observed mortality of  $SOFA_{\Delta}$  (left) or  $SOFA_{Comb}$  (right) on day 2, day 4, and day 7. The curve fits relatively at a low mortality rate. On the other hand, the predicted mortality rate was overestimated more than about 60% of the observed mortality rate.

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 [22], 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 mortality, but the AUCs vary widely from 0.510 to 0.828 in their systemic review [6]. 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. [9] 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

**Table 2**  
Discriminating values of SOFA $_{\Delta}$  and SOFA $_{\text{Comb}}$ .

	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 $_{\text{Comb}}$ 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 $_{\text{Comb}}$ 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 $_{\text{Comb}}$ 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 $_{\text{Comb}}$  on day 2: 12.5, SOFA $_{\text{Comb}}$  on day 4: 10.5, SOFA $_{\text{Comb}}$  on day 7: 9.5  
 $P$ -value when accuracy is compared,  
 SOFA $_{\Delta}$  on day 2 vs. SOFA $_{\text{Comb}}$  on day 2:  $P < 0.001$ , SOFA $_{\Delta}$  on day 4 vs. SOFA $_{\text{Comb}}$  on day 4:  $P = 0.067$ ,  
 SOFA $_{\Delta}$  on day 7 vs. SOFA $_{\text{Comb}}$  on day 7:  $P = 0.049$   
 PPV: positive predictive value, NPV: negative predictive value

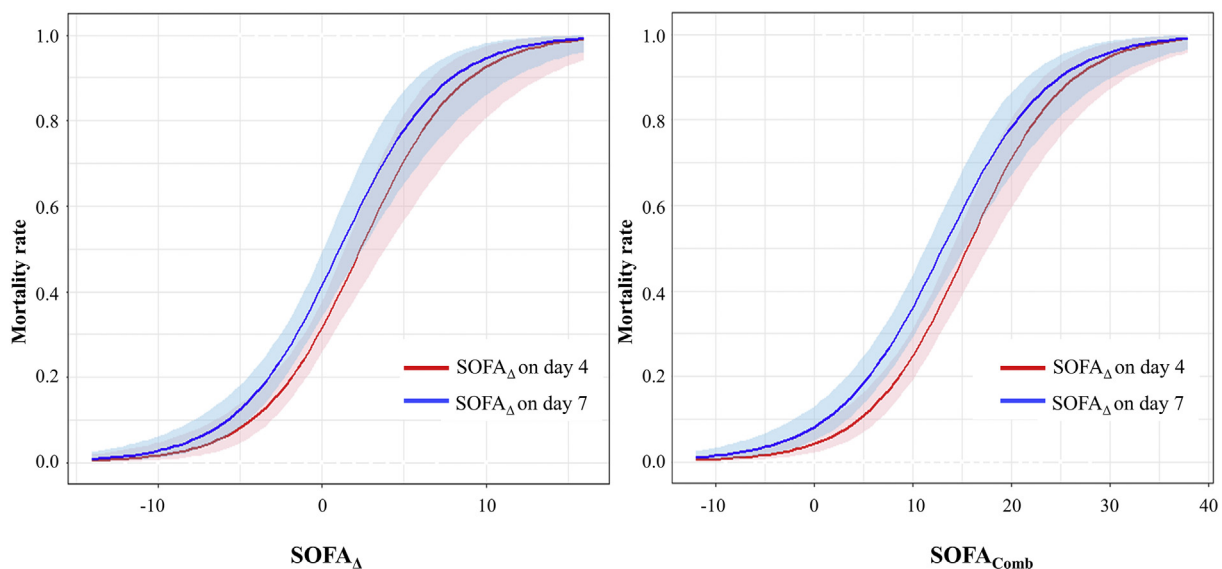
even after the adjustment by SOFA score on admission. Karakike et al. [23] reported SOFA score changes evaluated by a percentage of the initial score on day 7 or later was a better predictor of mortality, and the 25% decrease of initial SOFA was the best cut-off value. In our study, SOFA $_{\Delta}$  on day 7 exhibited a better predictive value over the baseline SOFA score, but the SOFA $_{\text{Comb}}$  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 $_{\text{Comb}}$  may help to reduce this drawback. In fact, SOFA $_{\text{Comb}}$  demonstrated a better performance than SOFA $_{\Delta}$  at early timing in the present study since SOFA $_{\text{Comb}}$  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 $_{\text{Comb}}$ , we did not use a multivariable logistic regression model. First, we evaluated multivariable logistic regression model (SOFA $_{\Delta}$  and absolute SOFA) with or without interaction term as well as simple addition model. However, the results were not largely different each other in discrimination (AUC, SOFA $_{\text{Comb}}$ : 0.866, multivariable with interaction term: 0.868, without: 0.866) and calibration

(Akaike's Information Criterion (AIC), SOFA $_{\text{Comb}}$ : 268.7, multivariable with interaction term: 270.7, without: 269.6). In terms of historical knowledge, we also performed multivariate logistic regression analysis with SOFA $_{\text{Comb}}$  and well-known confounder; age, sex, neoplasm, major focus of infection (respiratory, digestive, renal, liver) that caused septic DIC and chronic disease burden [24]. In fact, the predictive performance improved (AUC: 0.874 on day 4 and 0.891 on day 7, AIC: 252.8 on day 4 and 238.9 on day 7). However, when calibrated by bootstrap method, corrected AUC was 0.853 on day 4 and 0.872 on day 7, and the difference became considerably smaller from AUC of SOFA $_{\text{Comb}}$  (0.830 on day 4, 0.866 on day 7). The cohort size in this research was not enough large and external validation was not performed. And the primary objective of this study was to improve the performance of SOFA as severity marker by combining absolute and delta scores, we decided to adopt the simple calculation method using absolute SOFA score plus SOFA $_{\Delta}$  to calculate SOFA $_{\text{Comb}}$ . However, false correlations based on mathematical coupling [25] exist between baseline SOFA and SOFA $_{\Delta}$  or SOFA $_{\text{Comb}}$ . If the baseline and absolute score were independent, the erroneous inverse correlation occurs (e.g. correlation coefficients in day 7: baseline SOFA vs SOFA $_{\Delta}$ :  $-0.58$ , se: 0.06, and baseline SOFA vs SOFA $_{\text{Comb}}$ :  $-0.34$ , se: 0.05). Although the enough analysis was not conducted, we have considered the correlation may affect the accuracy of the prediction in this research.

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 $_{\text{Comb}}$  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 $_{\text{Comb}}$  on day 7 was 44.0% and higher than that of SOFA $_{\Delta}$  (32.0%), which are consistent with the superior performance of SOFA $_{\text{Comb}}$  shown by the higher accuracy, sensitivity, and specificity.

The present study has some limitations. First, the performance of SOFA $_{\text{Comb}}$  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 and 7 (after the treatment). In addition, because all patients received antithrombin supplementation for sepsis-associated DIC, this may make generalizability difficult. As a result, it is uncertain whether the results are applicable to the septic patients without DIC or sepsis-associated DIC treated with other agents. Second, many



**Fig. 5.** Logistic regression curves about predictive mortality rate of SOFA $_{\Delta}$  and SOFA $_{\text{Comb}}$ . Lines indicate predictive mortality rate, and bands indicate the standard error (SE). The logistic regression curves are both sigmoid shape in both SOFA $_{\Delta}$  (left) and SOFA $_{\text{Comb}}$  (right). However, the  $R^2$ , which represents explanatory power of model, for SOFA $_{\text{Comb}}$  on day 7 is 44.0% and was higher than that of SOFA $_{\Delta}$  (32.0%).

cases with missing days and data of SOFA score were present, because initial recording of the SOFA score was not mandatory in the survey. Therefore, dataset for analysis was incomplete and insufficient for the validation. Additionally, there would be risk of bias represented by selection bias due to missing data. Third, in patients with higher SOFA scores, the predicted risk was overestimated compared with observed risk. While we considered this overestimate was acceptable in comparatively high-risk patients, the mismatch should be calibrated in the future study. Fourth, we adopted the univariable analysis instead of multivariable analysis with confounders. It was because the primary objective of this study was to examine the usefulness of combining absolute and delta scores. Furthermore, we thought that all the possible confounders might not be collected in clinical practice and SOFA<sub>Δ</sub> included in SOFA<sub>Comb</sub> may partly act as an intermediate factor for unmeasured variables. Finally, because this data is a retrospective analysis, the results need to be confirmed in a prospective study.

## 5. Conclusions

SOFA<sub>Comb</sub> is simple to calculate and provides better predictive performance compared to SOFA<sub>Δ</sub> for predicting mortality. Additional studies are needed to confirm our findings.

## Competing interests

MA is an employee of Nihon Pharmaceutical Co. Ltd. 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.

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## Authors' contributions

MA and TI wrote the draft. KF advised on statistical description. JHL reviewed and revised the manuscript. All authors read and approved the final manuscript.

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