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Address for Correspondence:

Kyuseok Kim, MD, PhD
Department of Emergency Medicine, CHA Bundang Medical Center, CHA University, 59 Yatap-ro, Bundang-gu, Seongnam 13496, Republic of Korea.
Email: dremkks@cha.ac.kr
        dreinstein70@gmail.com

Tae Gun Shin, MD, PhD
Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea.
Email: taegunshin@skku.edu
        drshin88@gmail.com

*These authors equally contributed to this work.

†Current affiliation: Department of Emergency Medicine Sejong General Hospital, Bucheon, Korea

ORCID iDs
Byuk Sung Ko
https://orcid.org/0000-0002-4212-2255

Modified Cardiovascular Sequential Organ Failure Assessment Score in Sepsis: External Validation in Intensive Care Unit Patients

Byuk Sung Ko [1*] Seung Mok Ryoo [2*] Eunah Han [3*] Hyunglan Chang [4*] Chang June Yune [5*†] Hui Jai Lee [6,7*] Gil Joon Suh [7] Sung-Hyuk Choi [8] Sung Phil Chung [3] Tae Ho Lim [1] Won Young Kim [2] Jang Won Sohn [9] Mi Ae Jeong [10] Sung Yeon Hwang [11] Tae Gun Shin [11] Kyuseok Kim [4] and on behalf of Korean Shock Society

[1]Department of Emergency Medicine, College of Medicine, Hanyang University, Seoul, Korea
[2]Department of Emergency Medicine, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea
[3]Department of Emergency Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[4]Department of Emergency Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea
[5]Department of Critical Care Medicine, Anyang Sam Hospital, Anyang, Korea
[6]Department of Emergency Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea
[7]Department of Emergency Medicine, Seoul National University College of Medicine, Seoul, Korea
[8]Department of Emergency Medicine, College of Medicine, Korea University, Seoul, Korea
[9]Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, Korea
[10]Department of Anesthesiology and Pain Medicine, Hanyang University Medical Center, Hanyang University College of Medicine, Seoul, Korea
[11]Department of Emergency Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Background: There is a need to update the cardiovascular (CV) Sequential Organ Failure Assessment (SOFA) score to reflect the current practice in sepsis. We previously proposed the modified CV SOFA score from data on blood pressure, norepinephrine equivalent dose, and lactate as gathered from emergency departments. In this study, we externally validated the modified CV SOFA score in multicenter intensive care unit (ICU) patients.

Methods: A multicenter retrospective observational study was conducted on ICU patients at six hospitals in Korea. We included adult patients with sepsis who were admitted to ICUs. We compared the prognostic performance of the modified CV/total SOFA score and the original CV/total SOFA score in predicting 28-day mortality. Discrimination and calibration were evaluated using the area under the receiver operating characteristic curve (AUROC) and the calibration curve, respectively.

Results: We analyzed 1,015 ICU patients with sepsis. In overall patients, the 28-day mortality rate was 31.2%. The predictive validity of the modified CV SOFA (AUROC, 0.712; 95% confidence interval [CI], 0.677–0.746; $P < 0.001$) was significantly higher than that of the original CV SOFA (AUROC, 0.644; 95% CI, 0.611–0.677). The predictive validity of modified total SOFA score for 28-day mortality was significantly higher than that of the original total SOFA (AUROC, 0.747 vs. 0.730; 95% CI, 0.715–0.779; $P = 0.002$). The calibration curve of the

Seung Mok Ryoo
https://orcid.org/0000-0002-2436-3311

Eunah Han
https://orcid.org/0000-0001-7928-3901

Hyunglan Chang
https://orcid.org/0000-0003-4829-8902

Chang June Yune
https://orcid.org/0000-0002-2848-0021

Hui Jai Lee
https://orcid.org/0000-0002-9064-4680

Gil Joon Suh
https://orcid.org/0000-0001-5163-2217

Sung-Hyuk Choi
https://orcid.org/0000-0002-6686-6937

Sung Phil Chung
https://orcid.org/0000-0002-3074-011X

Tae Ho Lim
https://orcid.org/0000-0003-1045-413X

Won Young Kim
https://orcid.org/0000-0002-6904-5966

Jang Won Sohn
https://orcid.org/0000-0001-7132-2988

Mi Ae Jeong
https://orcid.org/0000-0001-8560-0838

Sung Yeon Hwang
https://orcid.org/0000-0002-1352-3009

Tae Gun Shin
https://orcid.org/0000-0001-9657-1040

Kyuseok Kim
https://orcid.org/0000-0002-7991-9428

original CV SOFA for 28-day mortality showed poor calibration. In contrast, the calibration curve of the modified CV SOFA for 28-day mortality showed good calibration.
Conclusion: In patients with sepsis in the ICU, the modified SOFA score performed better than the original SOFA score in predicting 28-day mortality.

Keywords: Sepsis; Mortality; Organ Dysfunction Scores; Severity of Illness Index

INTRODUCTION

The Sequential Organ Failure Assessment (SOFA) score was created in 1994 at a Consensus Conference of the Working Group of the European Society of Intensive Care Medicine.[1] The primary objective of the SOFA score was to describe objectively and grade organ dysfunction of the six essential organ systems—respiratory, coagulation, hepatic, cardiovascular (CV), renal, and central nervous system function.[2,3] It was originally designed to be easy to use with a minimal number of variables and to assess the change in the degree of organ failure. Now it is one of the most widely used scoring systems in clinical practice and in research on adult critical care.[3-9]

In 2016, the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) proposed clinical criteria using the SOFA score as a main measurement of organ dysfunction reflecting the sepsis definition of a life-threatening organ dysfunction caused by a dysregulated host response to infection.[10] Since then, the SOFA score has been adopted as a means of identifying sepsis among patients with suspected infection with the criteria of an acute change in total SOFA score of two points or more consequent to the infection; the metric was derived by mortality-based analyses in multiple large cohorts.[7] Regarding septic shock, a lactate criterion of > 2 mmol/L despite adequate volume resuscitation was introduced to reflect circulatory dysfunction and cellular metabolic abnormality with persisting hypotension requiring vasopressors to maintain mean arterial pressure (MAP) ≥ 65 mmHg.[11]

Despite the widespread use and advantages of the SOFA score, there is a need to update the SOFA score to reflect the current practice particularly in sepsis because management strategies have evolved since the SOFA score was developed.[2] Among the components of the SOFA, the CV SOFA has a critical limitation.[12] The Surviving Sepsis Campaign (SSC) guidelines currently recommend using norepinephrine as the first-line vasopressor instead of dopamine and have done so since 2008, and other vasopressors including vasopressin and epinephrine have been commonly used as second-line vasopressors.[13] Therefore, recent studies showed that there were few cases with CV SOFA score of 2 depending on the use of dopamine or dobutamine and the mortality rate of each CV SOFA score did not show incremental tendency.[6,9,12,14-16] In addition, considering the diagnostic importance of lactate level in sepsis patients and the current septic shock definition, lactate criteria can be incorporated but has not been fully evaluated.[2,13,17-19]

With this background, we proposed the modified CV SOFA score using MAP, norepinephrine equivalent (NEq) dose (**Supplementary Table 1**), and lactate in the previous multi-center, emergency department (ED) based study using suspected infection, sepsis, and septic shock cohorts.[20] We found that the modified CV/total SOFA score had better discrimination for 28-day mortality than the SOFA score and identified more patients at risk of septic mortality. In the present study, we externally validated the modified CV SOFA score in multi-center intensive care unit (ICU) patients with sepsis.

WY, Sohn JW, Jeong MA, Hwang SY, Shin TG, Kim K. Methodology: Shin TG, Kim K. Project administration: Kim WY, Hwang SY, Shin TG, Kim K. Resources: Suh GJ, Choi SH, Chung SP, Lim TH, Kim WY, Hwang SY, Shin TG, Kim K. Supervision: Suh GJ, Choi SH, Chung SP, Lim TH, Shin TG, Kim K. Validation: Kim WY, Hwang SY, Shin TG, Kim K. Visualization: Ko BS, Ryoo SM, Han E, Chang H, Yune CJ, Lee HJ, Sohn JW, Jeong MA, Shin TG. Writing - original draft: Ko BS, Ryoo SM, Han E, Chang H, Yune CJ, Lee HJ,Shin TG, Kim K. Writing - review & editing: Ko BS, Ryoo SM, Han E, Chang H, Yune CJ, Lee HJ, Suh GJ, Choi SH, Chung SP, Lim TH, Kim WY, Sohn JW, Jeong MA, Hwang SY, Shin TG, Kim K.

METHODS

Study design, setting, and population

This was a multi-center, retrospective, observational study of ICU patients from six hospitals in Korea. We included adult patients (age ≥ 18 years) with sepsis who were admitted to medical or surgical ICUs. Sepsis cases were defined as cases with suspected infection and an acute change in total SOFA score of two points or more according to the sepsis-3 definition.[10] The study period varied by location and occurred over the range of years from 2015 to 2021.

Data collection and outcome

The data were retrospectively collected by board-certified emergency medicine physicians or trained research coordinators of participating hospitals. We extracted data from the hospitals' clinical data warehouses and reviewed the electronic medical record. We collected general patient characteristics, including age, gender, comorbidities, vital signs, infection focus on final diagnosis, laboratory tests, therapeutic interventions including vasopressor, mechanical ventilation use and renal replacement therapy, and survival data from the hospital database. The SOFA score was calculated as described in the previous study using the worst value obtained during the 24 hours after ICU admission.[20] If variables were missing, including lactate and SOFA components, we imputed a normal value. The primary outcome was 28-day mortality after ICU admission. The secondary outcomes were in-hospital mortality and ICU mortality.

Modified cardiovascular SOFA score

The modified CV SOFA scores in our previous study and the original CV SOFA scores are shown in **Table 1**. The modified CV SOFA score was developed and validated by testing multiple candidate models combining hypotension (MAP < 70 mmHg), dose of vasopressor, and lactate levels in the ED cohorts of suspected infection, sepsis, and septic shock (**Supplementary Table 2**). We used a NEq dose converted from each dose of vasopressor (dopamine, epinephrine, and vasopressin) and peak equivalent doses administered for at least one hour during the 24-hour period from ICU admission.[3] In cases with MAP < 70 mmHg or use of low NEq dose (< 0.2 µg/kg/min), the modified CV SOFA score is 1 point, corresponding to MAP < 70 mmHg in the original CV SOFA. Modified cut-offs (0.2 and 0.5 µg/kg/min) of vasopressor dose were incorporated from score 1 to 4. If the serum lactate level is above 2 mmol/L in cases of CV SOFA score of 0 to 3 points, one point is added to the modified CV SOFA.

Table 1. Original and modified cardiovascular SOFA scores

Score	Original cardiovascular SOFA	Modified cardiovascular SOFA
0	MAP ≥ 70 mmHg	MAP ≥ 70 mmHg Add 1 point if lactate ≥ 2 mmol/L
1	MAP < 70 mmHg	MAP < 70 mmHg or NEq ≤ 0.2 Add 1 point if lactate ≥ 2 mmol/L
2	Dopamine ≤ 5 Dobutamine (any dose)	0.2 < NEq ≤ 0.5 Add 1 point if lactate ≥ 2 mmol/L
3	Dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	NEq > 0.5 Add 1 point if lactate ≥ 2 mmol/L
4	Dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1	NEq > 0.5 *AND* Lactate ≥ 2 mmol/L

Vasopressor doses are given as µg/kg/min at least 1 hour.
SOFA = Sequential Organ Failure Assessment, MAP = mean arterial pressure, NEq = norepinephrine equivalent dose.

Statistics

Continuous data are presented as mean (standard deviation, SD) or median (interquartile range, IQR) values, as appropriate. Categorical data are presented as numbers with percentages. For comparison, continuous variables were analyzed using Student's *t*-test, while categorical variables were analyzed using χ^2 tests. We compared predictive accuracy with the area under the receiver operating characteristic curves (AUROCs) of the original CV/total SOFA and the modified CV/total SOFA score using a non-parametric approach. We evaluated calibration plots of predicted and observed probability. Predicted mortality in calibration and 95% confidence interval (CI) were estimated by the bootstrap method.

We performed sensitivity analysis using a dataset with the last observation carried forward (LOCF) imputation and a complete data set without missing values. If there are missing values by the LOCF method, we imputed each mean value of 28-day survivors and non-survivors. A two-tailed *P* value < 0.05 was considered statistically significant. All analyses were performed using the R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and STATA version 17.0 (STATA Corporation, College Station, TX, USA).

Ethics statement

This study was approved by the Institutional Review Boards (IRB) of the six hospitals (Seoul Metropolitan Government–Seoul National University Boramae Medical Center [No. 30-2021-139], Asan Medical Center [No.2022-0203], Gangnam Severance Hospital [No. 3-2021-0506], Hanyang University Medical Center [No. 2022-01-019], Anyang Sam Hospital [No. 2022007], and CHA Bundang Medical Center [No.2022-07-070]). Informed consent was waived or obtained depending on cohort or hospital requirements.

RESULTS

Study population and characteristics of cohorts

We analyzed 1,015 ICU patients with sepsis. In overall patients, the 28-day mortality was 31.2% (n = 317) (**Supplementary Fig. 1**, **Table 2**). The mean age was 70.9 years, and the number of males was 582 (57.3%). Among included patients, 832 (82.0%) patients were admitted to the medical ICU and 208 (65.6%) patients were admitted to the ICU through the ED. The proportion of a lung source of infection in non-survivors was significantly higher than in survivors (47.6% vs. 40.3%, *P* = 0.028). The mean levels of lactate among survivors and non-survivors were 2.8 and 5.8 mmol/L (*P* < 0.001), respectively. The mean value of the SOFA score of the non-survivors was significantly higher than that of the survivors (11.0 vs. 7.7, *P* < 0.001). Other baseline characteristics of the study population are summarized in **Table 2**. The characteristics of the patients from the six hospitals participating in the study are described in **Supplementary Table 3**. The 28-day mortality rate by hospital varied from 23.5% to 59.4% (Hospital D). Number of cases used in analysis and missing values are outlined in **Supplementary Table 4**.

Incidence and 28-day mortality of original vs. modified CV SOFA score

We analyzed the 28-day mortality of the original CV SOFA score and modified CV SOFA score (**Fig. 1**, **Supplementary Table 5**). There were only 2 patients with an original CV SOFA score of 2, and the 28-day mortality of patients with a CV SOFA score of 2 was lower than that of patients with an original CV SOFA score of 0 or 1 (16.9%, 21.5%, and 0.0% respectively in 0, 1, and 2 original CV SOFA score). The 28-day mortality increased as the modified CV SOFA

Table 2. Baseline characteristics

Variables	All patients (N = 1,015)	Survivors (n = 698, 68.8%)	28-day death (n = 317, 31.2%)	P
Age, yr	70.9 ± 14.2	69.6 ± 14.9	73.7 ± 12.3	< 0.001
Male sex	582 (57.3)	394 (56.4)	188 (59.3)	0.393
Intensive care unit				0.403
Medical	832 (82)	565 (80.9)	267 (84.2)	
Surgical	97 (9.6)	72 (10.3)	25 (7.9)	
Mixed	86 (8.5)	61 (8.7)	25 (7.9)	
Route of admission				0.002
Emergency department	708 (69.8)	500 (71.6)	208 (65.6)	
General ward	230 (22.7)	139 (19.9)	91 (28.7)	
Operating room	31 (3.1)	27 (3.9)	4 (1.3)	
Transfer from other hospitals	17 (1.7)	9 (1.3)	8 (2.5)	
Others	29 (2.9)	23 (3.3)	6 (1.9)	
Comorbidities				
Hypertension	559 (55.1)	367 (52.6)	192 (60.6)	0.018
Diabetes mellitus	371 (36.6)	240 (34.4)	131 (41.3)	0.033
Cardiac disease	214 (21.1)	125 (17.9)	89 (28.1)	< 0.001
Cerebrovascular disease	148 (14.6)	100 (14.3)	48 (15.1)	0.733
Chronic lung disease	127 (12.5)	83 (11.9)	44 (13.9)	0.375
Metastatic cancer	82 (8.1)	45 (6.4)	37 (11.7)	0.005
Chronic kidney disease	159 (15.7)	102 (14.6)	57 (18.0)	0.171
Chronic liver disease	92 (9.1)	55 (7.9)	37 (11.7)	0.051
Source of infection				
Lung	432 (42.6)	281 (40.3)	151 (47.6)	0.028
Gastrointestinal	169 (16.7)	111 (15.9)	58 (18.3)	0.343
Hepatobiliary	82 (8.1)	49 (7.0)	33 (10.4)	0.066
Urinary tract infection	214 (21.1)	160 (22.9)	54 (17.0)	0.033
Septic shock (Sepsis-3)	412 (40.6)	216 (30.9)	196 (61.8)	< 0.001
MAP[a], mmHg	60.8 ± 16.1	63.4 ± 13.9	55 ± 18.9	< 0.001
GCS score[a]	11.2 ± 4.3	11.8 ± 3.9	9.7 ± 4.7	< 0.001
Laboratory findings[a]				
WBC, 10^9/L	12.2 ± 25.7	12.1 ± 29.7	12.6 ± 13.2	0.758
Hb, g/dL	10.5 ± 4.7	10.6 ± 2.4	10.2 ± 7.6	0.232
Platelet, 10^9/L	96.5 ± 121	103.8 ± 124.4	80.4 ± 111.8	0.004
Bilirubin, mg/dL	2.1 ± 7.7	2.0 ± 9.2	2.4 ± 2.1	0.001
Creatinine, mg/dL	1.7 ± 3.2	1.5 ± 2.5	2.2 ± 4.4	0.447
Lactate, mmol/L	3.8 ± 3.7	2.8 ± 2.4	5.8 ± 4.9	< 0.001
Vasopressor use				
Norepinephrine	609 (60.0)	372 (53.3)	237 (74.8)	< 0.001
Epinephrine	61 (6.0)	22 (3.2)	39 (12.3)	< 0.001
Dopamine	73 (7.2)	28 (4)	45 (14.2)	< 0.001
Vasopressin	137 (13.5)	67 (9.6)	70 (22.1)	< 0.001
Norepinephrine equivalent dose[a,b], µg/kg/min	0.27 ± 1.01	0.16 ± 0.29	0.51 ± 1.73	< 0.001
SOFA score[a]	8.7 ± 4.1	7.7 ± 3.7	11.0 ± 3.9	< 0.001
Mechanical ventilation	553 (54.6)	326 (46.8)	227 (72.1)	< 0.001
Renal replacement therapy	215 (21.2)	89 (12.8)	126 (39.9)	< 0.001
ICU LOS, day	11.5 ± 21.6	13.2 ± 25.3	7.7 ± 8.2	< 0.001

Values are presented as mean ± standard deviation or number (%).
MAP = mean arterial pressure, GCS = Glasgow Coma Scale, WBC = white blood cell, Hb = hemoglobin, SOFA = Sequential Organ Failure Assessment, ICU = intensive care unit, LOS = length of stay.
[a]The worst value and intervention on the first day of intensive care unit admission were extracted.
[b]Norepinephrine equivalent doses are given as µg/kg/min at least 1 hour.

score increased (15.0%, 16.6%, and 30.4% respectively in 0, 1, and 2 modified CV SOFA score). The incidence and 28-day mortality of the original total SOFA score and modified total SOFA score were shown in **Fig. 1**. The 28-day mortality tended to increase as either the original total SOFA score or the modified total SOFA score increased.
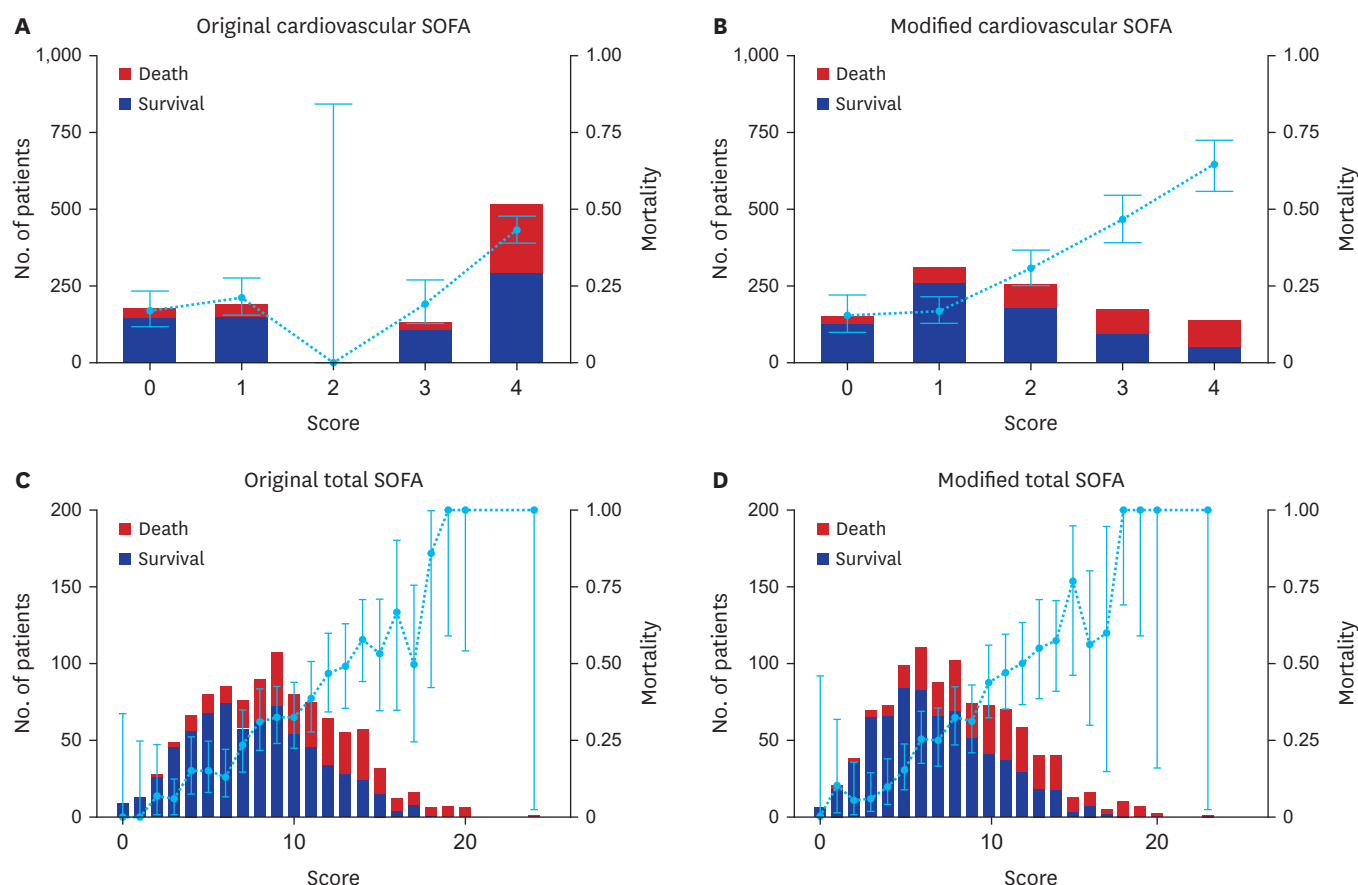
Fig. 1. Distribution and 28-day mortality according to original and modified cardiovascular/total SOFA scores. Bar graphs represent the number of patients, and points with error bars indicate 28-day mortality with 95% confidence intervals.
SOFA = Sequential Organ Failure Assessment.

The discrimination and calibration of original vs. modified CV SOFA score

The AUROC of the original CV SOFA for predicting 28-day mortality was 0.644 (95% CI, 0.611–0.677; **Fig. 2**). The AUROC of the modified CV SOFA (AUROC, 0.712; 95% CI, 0.677–0.746; $P < 0.001$) was significantly higher than that of the original CV SOFA.

The predictive validity of modified total SOFA score for 28-day mortality was significantly higher than that of the original total SOFA (AUROC, 0.747 vs. 0.730; 95% CI, 0.715–0.779; $P = 0.002$) (**Fig. 2**).

Calibration was evaluated with calibration plots of predicted and observed probability. The calibration curve of the original CV SOFA for 28-day mortality showed poor calibration (**Fig. 3**). In contrast, the calibration curve of the modified CV SOFA for 28-day mortality showed good calibration. The calibration curve of the original total SOFA and modified total SOFA for 28-day mortality showed good calibration.

AUROC for predicting 28-day mortality of the original CV/total SOFA and all candidate models are presented in **Supplementary Table 6**. Calibration plots for 28-day mortality of the candidate CV/total SOFA models are presented in Supplementary **Fig. 2**. AUROC for predicting in-hospital mortality in the original and modified CV SOFA were 0.643 and 0.702, respectively ($P < 0.001$) (**Supplementary Table 7**). AUROC of modified total SOFA was
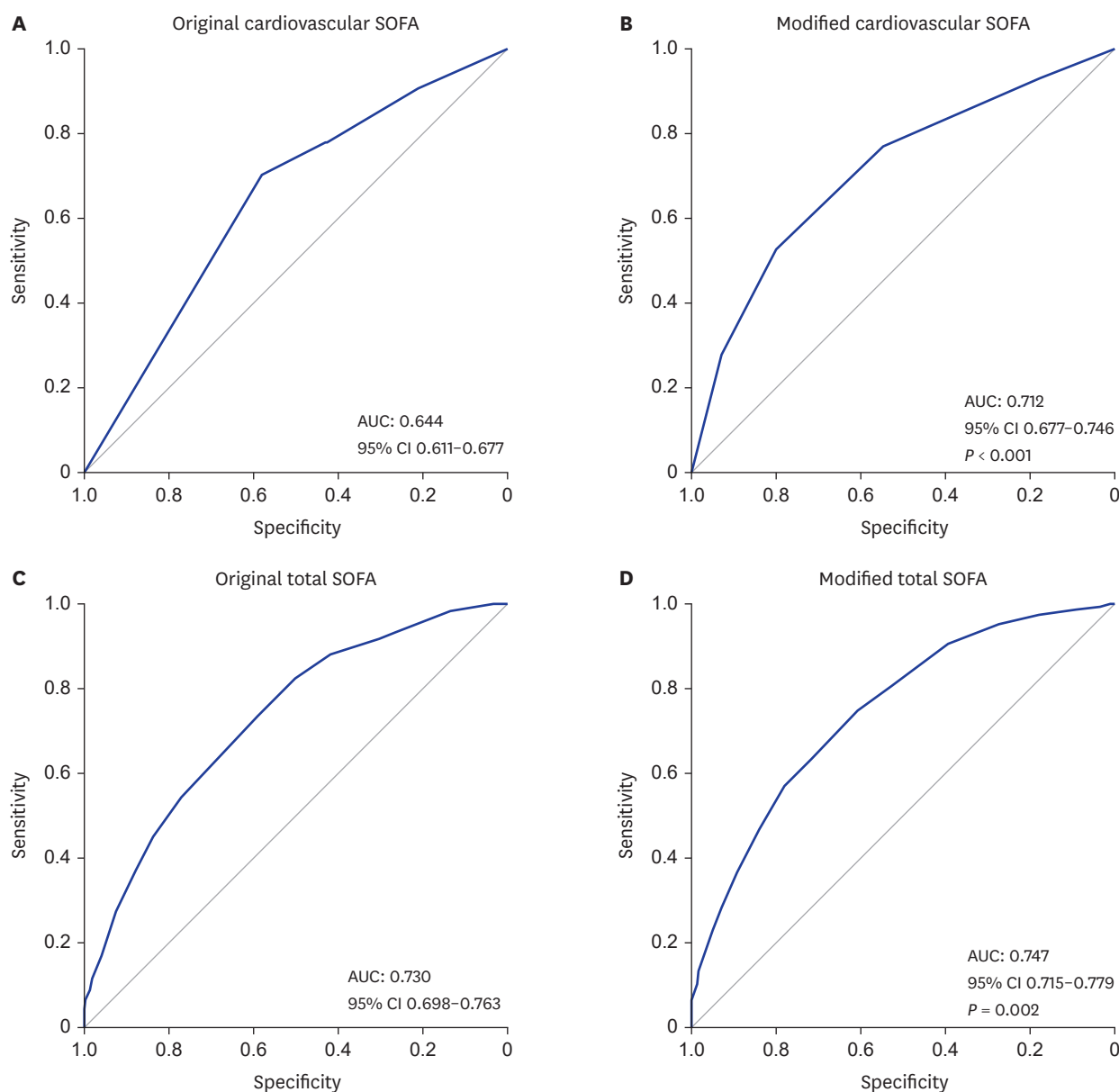
Fig. 2. Receiver operating characteristic curves for predicting 28-day mortality in the original and modified cardiovascular/total SOFA.
SOFA = Sequential Organ Failure Assessment, AUC = area under the curve, CI = confidence interval.

significantly higher than that of the original total SOFA (0.748 vs. 0.731; *P* = 0.002). AUROC for predicting ICU mortality of modified total CV/original total SOFA were also significantly higher than that of the original CV/total SOFA.

In the LOCF dataset, the AUROC of the modified CV SOFA (AUROC, 0.713; 95% CI, 0.679–0.746; *P* < 0.001) and the modified total SOFA score (AUROC, 0.745; 95% CI, 0.714–0.777; *P* = 0.003) for predicting 28-day mortality was significantly higher than that of the original SOFA (**Table 3**). AUROC of modified CV/total SOFA using the LOCF dataset without Hospital D which had the highest mortality and the complete data set were also higher than that of the original CV/total SOFA. Further results of the sensitivity analyses for in-hospital and ICU mortality are shown in **Supplementary Table 8**.
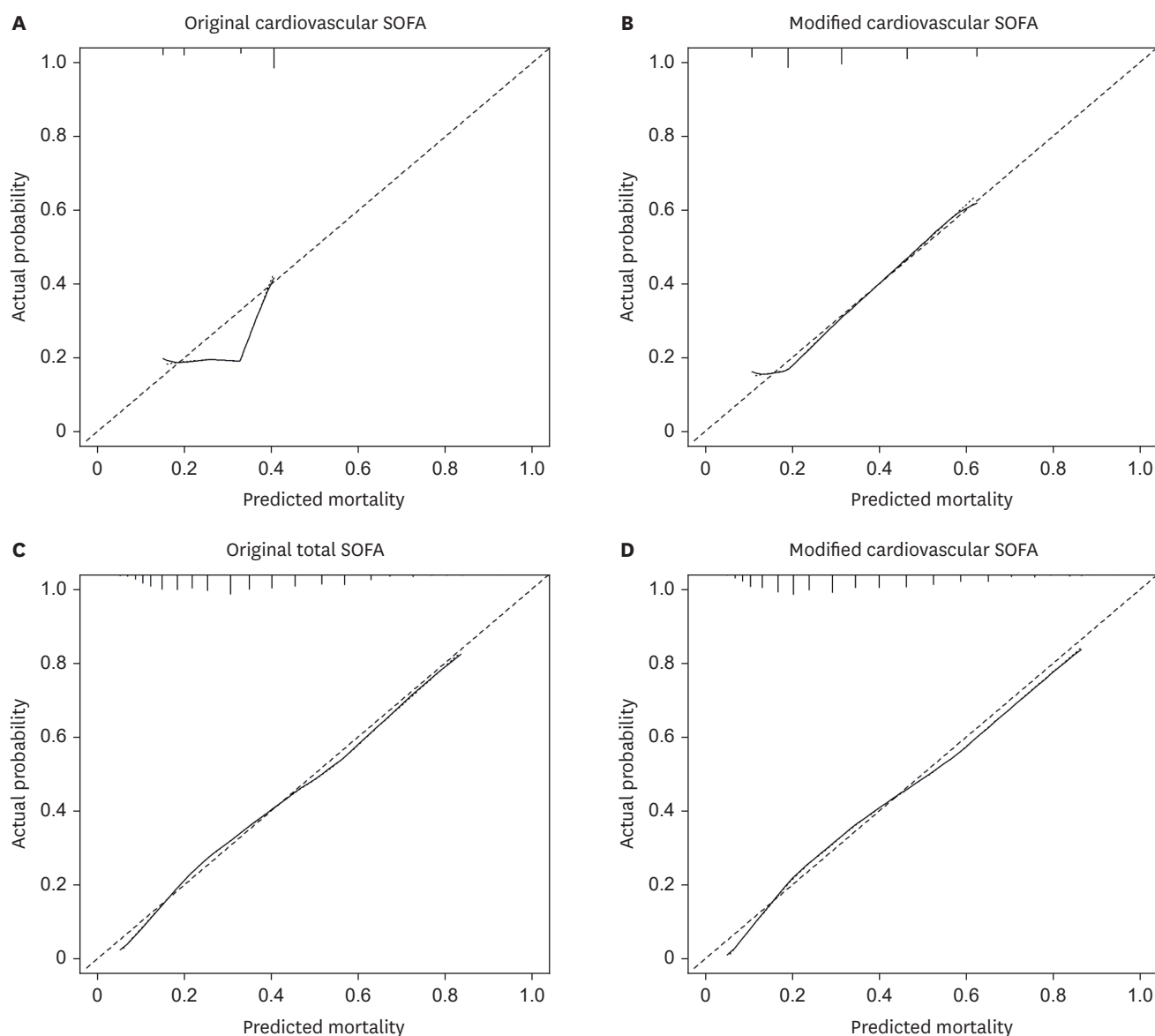
Fig. 3. Calibration plots for 28-day mortality between the original and modified cardiovascular/total SOFA.
SOFA = Sequential Organ Failure Assessment.

Table 3. Sensitivity analysis of AUROC for predicting 28-day mortality in the original and modified CV/total SOFA

Model	CV SOFA	P	Total SOFA	P
	AUROC (95% CI)		AUROC (95% CI)	
LOCF dataset				
Original SOFA	0.644 (0.611–0.677)	Reference	0.730 (0.697–0.762)	Reference
Modified SOFA	0.713 (0.679–0.746)	< 0.001	0.745 (0.714–0.777)	0.003
LOCF dataset (without Hospital D)				
Original SOFA	0.652 (0.618–0.687)	Reference	0.735 (0.700–0.770)	Reference
Modified SOFA	0.714 (0.677–0.750)	< 0.001	0.747 (0.713–0.782)	0.033
Complete dataset				
Original SOFA	0.642 (0.608–0.676)	Reference	0.732 (0.697–0.766)	Reference
Modified SOFA	0.715 (0.680–0.751)	< 0.001	0.749 (0.715–0.782)	0.004

AUROC = area under the receiver operating characteristic curve, CV = cardiovascular, SOFA = Sequential Organ Failure Assessment, CI = confidence interval, LOCF = last observation carried forward.

DISCUSSION

In the previous study, we demonstrated that newly developed modified CV/total SOFA score had higher predictive validity and calibration in ED patients with suspected infection, sepsis, and septic shock.[20] In this study, the same concept was applied to ICU patients, and the prognostic performance of modified CV/total SOFA score is better than that of the original scoring system, consistent with previous study.

When developing and validating a scoring system, the generalizability issue is important. To make accommodation for this issue, we used a multi-institution/mixed type ICU cohort. The baseline characteristics such as age, gender, shock status, the dose of vasopressor used, SOFA score, and mortality rate were different in the different participating ICUs. We proved the better performance of modified SOFA scoring system in sepsis under these various cases, which is the merit of this study. As in previous ED study, we also used multiple and various cohorts for the external validation, implying the modest generalizability of this modified SOFA score. However, a more extensive study to include multiple nationalities and more varied ICU type/ward/ED data should be performed to update the SOFA score.

The SOFA score has been widely used since it was developed by Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine in 1996.[1] The SOFA score was adopted as sepsis definition in Sepsis-3 definition.[10] However, it needs updating since the clinical practice has changed with the times. Recently, multinational groups started to develop the SOFA 2.0 score, which would definitely be helpful for the management of sepsis patients.[2] We think our findings might be referenced with SOFA 2.0.

In this study, patients with an original CV SOFA score of 2 were rare, and the 28-day mortality rate among them was lower than among patients with original CV SOFA scores of 0 and 1. These findings support the need for modified SOFA score, and with the modified CV/total SOFA score, such problems were solved.

Sepsis is managed at the emergency department, ICU, and sub-ICU/ward.[10,21] We validated the modified SOFA score in ED and ICU; data from other types of ICU, sub-ICUs or other wards might be needed for more extensive validation.

There are several limitations with this study. First, the data of this study drew from ICUs at 6 different centers, but all from within a single country. It needs multi-national validation. Hospital D had a little different baseline characteristic, but sensitivity analysis excluding Hospital D showed similar performance. Therefore, heterogeneity of baseline characteristics of participating hospitals could be an advantage of this study. Second, because this is a retrospective analysis, there are concerns about data completeness and missing values. There are a few missing variables to calculate the SOFA score. We used normal imputation and last observation carried forward approach.[22] The results of two imputation methods are similar. In addition, the results of complete analysis drawn from patients without missing data were nearly identical to those with some missing variables, implying minimal effects of missing data on the primary analysis. However, the missing lactate values are one of limitations of this study. Third, the SOFA score has not been developed to predict mortality. Many prior studies have, however, evaluated the performance of the SOFA score to predict mortality, and in the definition of Sepsis-3, the SOFA score's discriminatory power was evaluated to predict in-hospital mortality.[5,15,23-25] Lastly, the predictive validity of the modified SOFA score

may differ depending on the route of admission to the ICU; however, additional analysis according to the route of admission (general ward, other location) was not performed.

In patients with sepsis in the ICU, the modified SOFA score performed better than the original SOFA score in predicting 28-day mortality.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Conversion table of norepinephrine equivalent dose

Click here to view

Supplementary Table 2
Candidate models for modified cardiovascular SOFA score

Click here to view

Supplementary Table 3
Baseline characteristics according to participating hospitals

Click here to view

Supplementary Table 4
Number of cases used in analysis and missing values

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Supplementary Table 5
Distribution and 28-day mortality according to original SOFA score components

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Supplementary Table 6
AUROC for predicting 28-day mortality using the original CV/total SOFA and candidate models

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Supplementary Table 7
AUROC for predicting in-hospital and intensive care unit mortality in the original and modified CV/total SOFA

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Supplementary Table 8
Sensitivity analysis of AUROC for predicting in-hospital and intensive care unit mortality in the original and modified CV/total SOFA

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Supplementary Fig. 1
Study population.

Click here to view

Supplementary Fig. 2
Calibration plots for 28-day mortality of the candidate cardiovascular/total SOFA models.

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