

Development of New Equations Predicting the Mortality Risk of Patients on Continuous RRT

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Key Points

- Predicting the risk of mortality in patients with CRRT is important for appropriate management, but is challenging.
- We developed equations for predicting the mortality risk of patients with CRRT, using patients' clinical data.
- The newly developed equations showed superior performance to SOFA and APACHE II scores.

Abstract

Background Predicting the risk of death in patients admitted to the critical care unit facilitates appropriate management. In particular, among patients who are critically ill, patients with continuous RRT (CRRT) have high mortality, and predicting the mortality risk of these patients is difficult. The purpose of this study was to develop models for predicting the mortality risk of patients on CRRT and to validate the models externally.

Methods A total of 699 adult patients with CRRT who participated in the VolumE maNagement Under body composition monitoring in critically ill patientS on CRRT (VENUS) trial and 1515 adult patients with CRRT in Seoul National University Hospital were selected as the development and validation cohorts, respectively. Using 11 predictor variables selected by the Cox proportional hazards model and clinical importance, equations predicting mortality within 7, 14, and 28 days were developed with development cohort data.

Results The equation using 11 variables had area under the time-dependent receiver operating characteristic curve (AUROC) values of 0.75, 0.74, and 0.73 for predicting 7-, 14-, and 28-day mortality, respectively. All equations had significantly higher AUROCs than the Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. The 11-variable equation was superior to the SOFA and APACHE II scores in the integrated discrimination index and net reclassification improvement analyses.

Conclusions The newly developed equations for predicting CRRT patient mortality showed superior performance to the previous scoring systems, and they can help physicians manage patients.

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Introduction

Predicting prognosis and outcomes is helpful in the management of patients. Especially in intensive care, it is necessary to select patients who are salvageable and have reversible medical conditions, and provide them with more active treatment (1). Patients and families in the intensive care unit are often concerned about the risk of death, and accurate prognostic information can help reduce anxiety and avoid potentially futile therapy. Therefore, predicting the outcomes of patients who are critically ill is important, and various

scoring systems have been developed for this purpose. The Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores are representative predictive scoring systems for critical care populations and have been widely used (2–5).

Patients who are critically ill, especially those undergoing continuous RRT (CRRT), are at a particularly high risk for death (6,7). In addition, patients undergoing CRRT have many comorbidities, and it is difficult to predict the mortality of these patients

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because of their complex clinical situations and the rapid changes in their condition (8,9). Because the SOFA and APACHE II scores were developed for all patients who are critically ill, there may be limitations in their application to specific patient subgroups, such as those with CRRT. The purpose of this study is to develop and validate equations that predict the mortality of patients undergoing CRRT, and to compare them with the existing scoring systems, SOFA and APACHE II.

Materials and Methods

Study Population

We studied patients on CRRT admitted to eight hospitals in Korea who participated in the VENUS (VolumE management Under body composition monitoring in critically ill patients on CRRT) trial from March 24, 2017, to October 31, 2019, and Seoul National University Hospital from June 24, 2010, to December 29, 2016 (10). We excluded patients who were younger than 18 years, or had missing mortality data. Patients with missing data on variables needed for developing equations were excluded. All procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients who participated in the VENUS trial provided written informed consent at the time of their enrollment. Approval to perform the study was obtained from the Institutional Review Board of each center (Institutional Review Board of the Seoul National University Hospital, Bundang Seoul National University Hospital, Seoul National University Boramae Medical Center, Ewha Womans University Seoul Hospital, Pusan National University Hospital, Kyungpook National University Hospital, Korea University Guro Hospital, and Hallym University Dongtan Sacred Heart Hospital). The study population data of VENUS trial were used as a development cohort to develop the equations. Patient data from Seoul National University Hospital were used as a validation cohort to validate the equations developed from the development cohort (Figure 1).

Variables and Development of Equations for Predicting Mortality

To select variables for use as predictor variables in the equation, we collected the demographic data, comorbidities,

laboratory data, and vital signs of patients. All predictor variables were obtained at baseline of starting CRRT. The laboratory value was the latest test result within 24 hours of CRRT initiation. Comorbid conditions were categorized as present or absent at the time of starting CRRT. Using univariate Cox proportional hazards regression models, we selected the variables that had a statistically significant association with all-cause mortality at a *P* value threshold of 0.05. Even if the variables did not have a statistically significant association with mortality in the Cox proportional model, those that were identified to be clinically associated with mortality were selected as predictor variables.

Using the survival rate, Cox regression coefficients, and mean values of the variables, we made equations for calculating the probability of death within specific days (11). The equations were developed with the development cohort, which includes patient data from VENUS trial. Equations using many predictor variables could have good prediction performance. However, they have a disadvantage in being difficult to apply to patients with limited data. Therefore, among the selected predictor variables, variables that had a higher correlation with mortality in the Cox proportional hazard models or were identified to be highly associated with mortality were selected to develop equations with fewer predictor variables. The outcome was all-cause mortality within 7, 14, and 28 days.

Validation of the Equations

In both the development and validation cohorts, time-dependent receiver operating characteristic (ROC) curves for predicting 7-, 14-, and 28-day mortality were analyzed for the developed equations and SOFA and APACHE II scores. Then, the areas under the time-dependent ROC (AUROCs) curve of the developed equations were analyzed and compared with the AUROCs of the SOFA and APACHE II scores. To compare the equations and conventional scoring systems, such as SOFA and APACHE II, and identify the equation with the best performance among the developed equations, integrated discrimination improvement (IDI) and continuous net reclassification improvement (NRI) analyses were performed with validation cohort data (12–14).

To identify the calibration performance of the developed equations, calibration plots were analyzed, and the Brier scores of the equations were calculated and compared with

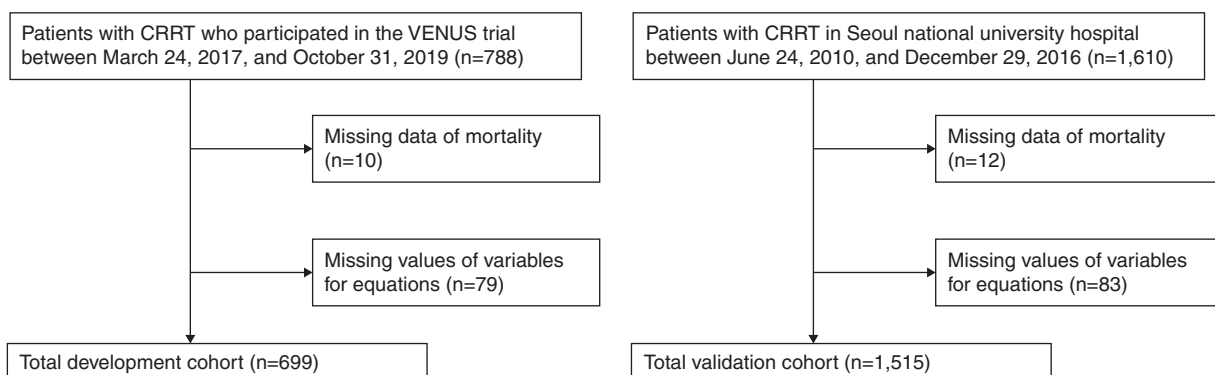


Figure 1. | Diagram showing the study population.

Table 1. Baseline characteristics

Characteristics	Development Cohort	Validation Cohort	P Value
Age, yr	67.86±14.02	63.33±15.20	<0.001
Mean arterial pressure, mm Hg	79.86±16.59	81.01±17.14	0.140
Heart rate, /min	99.72±24.94	105.10±25.53	<0.001
Respiratory rate, /min	22.11±6.62	23.9±8.01	<0.001
Platelet, ×10 ³ /ul	134.70±101.61	99.88±80.79	<0.001
Creatinine, mg/dl	3.47±2.71	2.74±1.78	<0.001
Total bilirubin, mg/dl	2.95±5.14	4.99±7.81	<0.001
Albumin, g/dl	2.76±0.55	2.74±0.62	0.58
pH	7.33±0.12	7.32±0.13	0.05
Glasgow coma scale	8.20±4.68	8.45±4.52	0.24
Malignancy, %	26.18	36.44	<0.001

each other. Statistical analyses were performed using R software (Version 4.0.3. R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: <https://www.R-project.org/>). *P* values <0.05 were considered significant.

Results

Study Population and Baseline Characteristics

A total of 699 patients in the development cohort and 1515 patients in the validation cohort were included in the analysis (Figure 1). The mean follow-up duration was 135.6 days in the development cohort and 32.2 days in the validation cohort. The baseline characteristics, excluding mean arterial pressure, albumin, pH, and Glasgow coma scale, differed between the development cohort and validation cohort (Table 1).

Development of Equations

As a result of univariate Cox proportional hazards regression analysis in the development cohort data, 10 variables were significantly associated with mortality: presence of malignancy, mean arterial pressure, heart rate, respiratory rate, platelet count, creatinine level, total bilirubin level, albumin level, pH, and Glasgow coma scale. Although age did not show a significant association with mortality in the univariate Cox proportional hazards regression analysis, because elderly patients have high mortality in general, age was selected as a predictor variable. We performed multivariate Cox proportional hazards regression analysis using the 11 predictor variables described above and analyzed the survival

rates at 7, 14, and 28 days, and Cox regression coefficients of the predictor variables were calculated. In multivariate Cox proportional hazards regression analysis using the 11 predictor variables, seven variables with the strongest association that were clinically considered to be more associated with mortality were selected: age, heart rate, creatinine level, total bilirubin level, albumin level, pH, and Glasgow coma scale. Among the seven variables, four variables were selected in the same way, and the equations were developed in the same way using seven and four variables. As a result, we developed nine equations, which were 11-, seven-, and four-variable equations that predict mortality within 7, 14, and 28 days: VENUS scores (Supplemental Table 1).

Prediction Model Discrimination in the Development Cohort

In the development cohort, the 11-variable equation had time-dependent AUROC values of 0.73, 0.73, and 0.74 for predicting 7-, 14-, and 28-day mortality, respectively (Supplemental Table 2). Among the developed equations, the 11-variable equation had the highest AUROC values, followed by the seven-variable equation and the four-variable equation (Supplemental Table 2, Supplemental Figure 1). All developed equations had AUROC values significantly higher than those of SOFA and APACHE II.

Prediction Model Discrimination in the Validation Cohort

In the validation cohort, the 11-variable equation had time-dependent AUROC values of 0.75, 0.74, and 0.73 for predicting 7-, 14-, and 28-day mortality, respectively (Table 2). As in

Table 2. The areas under the time-dependent receiver operating characteristic curve of conventional scoring systems and equations predicting 7-, 14-, and 28-day mortality in validation cohort

Models	Outcomes								
	7-day Mortality	<i>P</i> ^a	<i>P</i> ^b	14-day Mortality	<i>P</i> ^a	<i>P</i> ^b	28-day Mortality	<i>P</i> ^a	<i>P</i> ^b
SOFA	0.66 (0.63–0.69)			0.64 (0.61–0.67)			0.62 (0.59–0.66)		
APACHE II	0.65 (0.62–0.67)			0.63 (0.61–0.66)			0.62 (0.58–0.65)		
Four-variable	0.69 (0.66–0.71)	0.12	0.03	0.66 (0.62–0.69)	0.16	0.10	0.65 (0.62–0.68)	0.18	0.10
Seven-variable	0.73 (0.71–0.76)	<0.001	<0.001	0.73 (0.70–0.75)	<0.001	<0.001	0.71 (0.68–0.74)	<0.001	<0.001
11-variable	0.75 (0.72–0.77)	<0.001	<0.001	0.74 (0.72–0.77)	<0.001	<0.001	0.73 (0.70–0.76)	<0.001	<0.001

SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

^aCompared with the SOFA II model.

^bCompared with the APACHE model.

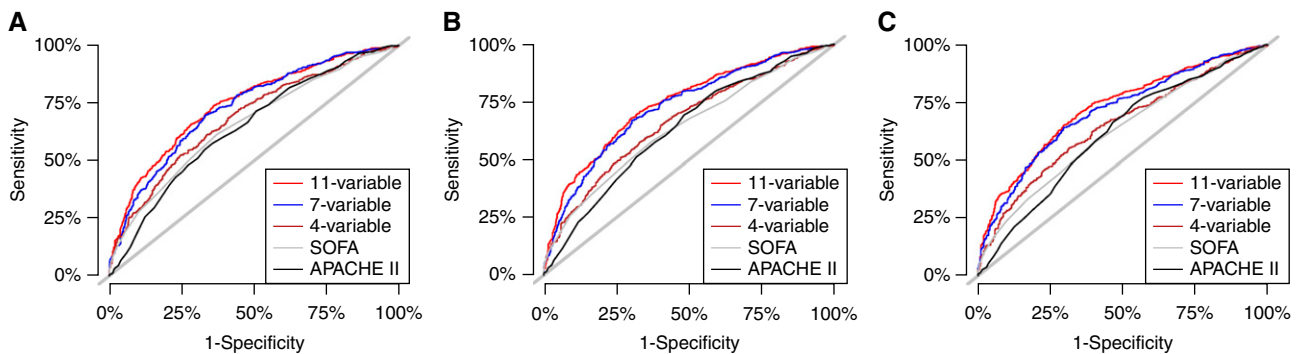


Figure 2. | Time-dependent receiver operating characteristic curves of SOFA, APACHE II, four-, seven-, 11-variable equations in validation cohort. (A) The 7-day mortality prediction. (B) The 14-day mortality prediction. (C) The 21-day mortality prediction. SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

the development cohort, 11-variable equation had the highest AUROC value, followed by the seven-variable equation and the four-variable equation (Table 2, Figure 2). Additionally, all developed equations had AUROC values significantly higher than those of SOFA and APACHE II. As a result of IDI and NRI, the 11- and seven-variable equations showed statistically superior performance compared with SOFA and APACHE II. However, the four-variable equation had superior performance compared with APACHE II alone, not SOFA (Table 3).

Calibration and Reclassification Analyses

Figure 3 shows the calibration plot, and all of the equations showed good calibration. The calibration plot showed the tendency of the equations to overestimate the risk of patients with a high mortality risk, but overall calibration was good, with all three equations approximating the diagonal line.

For the Brier scores, among the developed equations, the 11-variable equation had the lowest Brier score for all outcomes at 7, 14, and 28 days. However, there was no statistically significant difference when comparing Brier scores among the developed equations (Table 4).

When comparing the discrimination slopes (IDI) or net reclassification, the 11-variable equation was superior to both the seven-variable and four-variable equations, and the seven-variable equation was superior to the four-variable equation (Table 3).

Discussion

In this study, the newly developed equations, VENUS scores, for predicting the mortality of patients with CRRT had better discrimination and calibration than the SOFA and APACHE II scores. Among the equations, the 11-variable equation, which contains the most variables, showed the best performance.

Patients undergoing CRRT have a high risk of mortality, and previous studies have reported in-hospital mortality ranging from 37% to 79% (7,15–18). There are various reasons for the high mortality of patients on CRRT, including the many comorbidities of patients with CRRT and severe clinical situations such as septic shock. Therefore, high mortality and many situations must be considered for

predicting the mortality of patients on CRRT. Previous studies showed that the SOFA and APACHE II scores have limitations in predicting the mortality of patients on CRRT (19–21). Several studies have predicted the mortality of patients on CRRT. However, in previous studies, the study population was limited to patients who underwent CRRT due to AKI (19–21). According to previous studies, the in-hospital mortality of patients on CRRT due to AKI was similar to that of patients with underlying ESKD. Therefore, in this study, prediction equations were developed with data from patients on CRRT, including not only patients with AKI, but also those with underlying ESKD (15). In addition, this study developed equations not only for short-term mortality within 7 days, but also for mortality within 14 days and within 28 days. Additionally, the evaluations of the prediction models were analyzed considering time variables using time-dependent ROC, NRI, IDI, calibration plot, and Brier score for time-to-event data (22–24).

We developed mortality prediction equations using a total of 11 variables: age, presence of malignancy, mean arterial pressure, heart rate, respiratory rate, platelet count, creatinine level, total bilirubin level, albumin level, pH, and Glasgow coma scale. Patients who are critically ill with metabolic acidosis and patients on CRRT with low pH have high mortality (8,25,26). In patients undergoing CRRT, baseline thrombocytopenia, hyperbilirubinemia, and hypoalbuminemia were also associated with high mortality (27–30). As a result of multivariate Cox regression analysis, malignancy was the only variable that was statistically significant among the underlying comorbidities. Therefore, we used malignancy as a predictor variable in the Supplemental Equation. In addition, previous studies showed that patients who are critically ill with low creatinine levels were associated with high mortality, and in this study, low creatinine levels were related to mortality (31,32). Tachycardia is associated with high mortality in patients on CRRT (9). Respiratory rate, body temperature, and Glasgow coma scale are related to the mortality of patients who are critically ill and have been used as indicators in many mortality scoring systems (5,33–36).

The AUROCs of the seven-variable and 11-variable equations were significantly greater than the AUROCs of the SOFA and APACHE II scores in the development

Table 3. Comparing the equations and conventional scoring systems for predicting 7-, 14-, and 28-day mortality using integrated discrimination improvement and continuous net reclassification improvement in validation cohort

Models	IDI (95% Confidence Interval)	P	Continuous Net Reclassification Improvement (95% Confidence Interval)	P
7-day mortality				
Four-variable versus SOFA	0.03 (0.00 to 0.06)	0.06	0.05 (−0.03 to 0.13)	0.24
Four-variable versus APACHE II	0.05 (0.02 to 0.08)	<0.01	0.13 (0.05 to 0.21)	<0.01
Seven-variable versus SOFA	0.08 (0.06 to 0.11)	<0.01	0.21 (0.14 to 0.28)	<0.01
Seven-variable versus APACHE II	0.10 (0.08 to 0.13)	<0.01	0.24 (0.17 to 0.29)	<0.01
11-variable versus SOFA	0.10 (0.07 to 0.13)	<0.01	0.27 (0.19 to 0.33)	<0.01
11-variable versus APACHE II	0.13 (0.09 to 0.15)	<0.01	0.27 (0.21 to 0.33)	<0.01
Seven-variable versus four-variable	0.05 (0.03 to 0.08)	<0.01	0.17 (0.07 to 0.26)	<0.01
11-variable versus four-variable	0.08 (0.05 to 0.10)	<0.01	0.23 (0.15 to 0.29)	<0.01
11-variable versus seven-variable	0.02 (0.01 to 0.04)	<0.01	0.17 (0.07 to 0.25)	<0.01
14-day mortality				
Four-variable versus SOFA	0.02 (0.00 to 0.05)	0.12	0.03 (−0.04 to 0.12)	0.28
Four-variable versus APACHE II	0.04 (0.02 to 0.07)	<0.01	0.11 (0.02 to 0.18)	0.02
Seven-variable versus SOFA	0.09 (0.06 to 0.11)	<0.01	0.22 (0.14 to 0.30)	<0.01
Seven-variable versus APACHE II	0.11 (0.08 to 0.13)	<0.01	0.25 (0.19 to 0.30)	<0.01
11-variable versus SOFA	0.11 (0.08 to 0.14)	<0.01	0.29 (0.21 to 0.34)	<0.01
11-variable versus APACHE II	0.14 (0.09 to 0.17)	<0.01	0.30 (0.22 to 0.36)	<0.01
Seven-variable versus four-variable	0.07 (0.04 to 0.09)	<0.01	0.20 (0.10 to 0.27)	<0.01
11-variable versus four-variable	0.09 (0.05 to 0.12)	<0.01	0.27 (0.15 to 0.33)	<0.01
11-variable versus seven-variable	0.03 (0.01 to 0.04)	<0.01	0.20 (0.11 to 0.27)	<0.01
28-day mortality				
Four-variable versus SOFA	0.02 (−0.01 to 0.04)	0.26	0.01 (−0.07 to 0.09)	0.61
Four-variable versus APACHE II	0.04 (0.01 to 0.07)	0.02	0.09 (0.00 to 0.18)	0.02
Seven-variable versus SOFA	0.08 (0.06 to 0.11)	<0.01	0.24 (0.16 to 0.31)	<0.01
Seven-variable versus APACHE II	0.10 (0.08 to 0.13)	<0.01	0.22 (0.15 to 0.30)	<0.01
11-variable versus SOFA	0.10 (0.07 to 0.13)	<0.01	0.27 (0.20 to 0.34)	<0.01
11-variable versus APACHE II	0.12 (0.09 to 0.15)	<0.01	0.28 (0.21 to 0.33)	<0.01
Seven-variable versus four-variable	0.07 (0.05 to 0.09)	<0.01	0.18 (0.11 to 0.29)	<0.01
11-variable versus four-variable	0.09 (0.05 to 0.12)	<0.01	0.26 (0.17 to 0.33)	<0.01
11-variable versus seven-variable	0.02 (0.01 to 0.03)	<0.01	0.17 (0.05 to 0.25)	<0.01

SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

cohort and validation cohort. In addition, the seven-variable and 11-variable equations were statistically significantly superior to the SOFA and APACHE II scores as a result of IDI and NRI analyses in the validation cohort. However, the four-variable equation showed no statistically significant difference in AUROCs with SOFA and APACHE II scores. As a result of the IDI

and NRI analyses, the four-variable equation showed superiority to only APACHE II and not to SOFA. The seven-variable and 11-variable equations showed a generally good calibration and had a tendency for overestimation in patients with a high mortality risk in the calibration plot. The results of IDI and NRI analyses in the validation cohort showed that the 11-variable

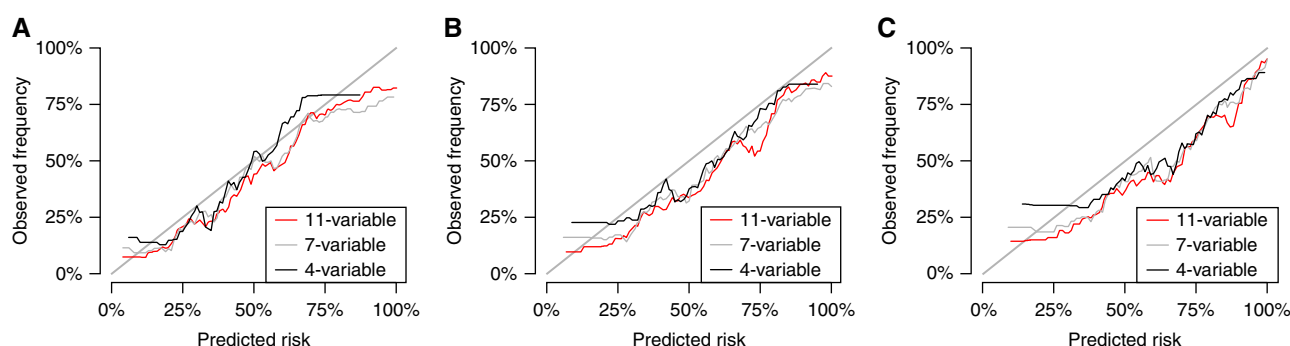


Figure 3. | Calibration plots of four-, seven-, and 11-variable equations in validation cohort. (A) The 7-day mortality prediction. (B) The 14-day mortality prediction. (C) The 21-day mortality prediction.

Table 4. Comparing the equations and conventional scoring systems for predicting 7-, 14-, and 28-day mortality using Brier scores in validation cohort

Model	Brier score (95% Confidence Interval)	Model Comparison	P Value
7-day mortality			
Four-variable	0.22 (0.12 to 0.31)	Seven-variable versus four-variable	0.16
Seven-variable	0.21 (0.13 to 0.28)	11-variable versus four-variable	0.18
11-variable	0.20 (0.13 to 0.28)	11-variable versus seven-variable	0.37
14-day mortality			
Four-variable	0.24 (0.18 to 0.30)	Seven-variable versus four-variable	0.008
Seven-variable	0.22 (0.17 to 0.28)	11-variable versus four-variable	0.03
11-variable	0.22 (0.17 to 0.27)	11-variable versus seven-variable	0.44
28-day mortality			
Four-variable	0.24 (0.18 to 0.31)	Seven-variable versus four-variable	0.005
Seven-variable	0.23 (0.17 to 0.29)	11-variable versus four-variable	0.02
11-variable	0.23 (0.17 to 0.33)	11-variable versus seven-variable	0.81

equation had significantly better performance than the four- and seven-variable equations. Although the 11-variable equation requires many variables, the 11 necessary variables consist of variables that are almost always measured in patients in the intensive care unit. Therefore, we recommended using the 11-variable equation for mortality prediction. If patient data are insufficient, the seven-variable equation can be used, but the seven-variable equation is not recommended.

This study had several limitations. Although the equations were developed in a multicenter study, the equations were validated in a cohort on the basis of only one center. Additional validation is needed using data from patients on CRRT from other centers before widespread use. The best equations also require seven or 11 variables collected within 24 hours of CRRT initiation, whether these variables predict prognosis at different time frames after CRRT, or when contemplating CRRT initiation is unknown. Finally, the models can help identify deciles of patients where mortality risk may approach 80%–90% in the 28-day period. However, it is unknown whether CRRT or other treatments would be futile in these subgroups, because medical futility often requires a higher burden of evidence and is also modified by patient values and preferences regarding death and discontinuation of therapy.

The newly developed VENUS score equations, which used seven or 11 predictor variables, can be used to accurately predict the mortality within 7, 14, and 21 days, showing adequate discriminations and calibrations. These equations showed superior performance to the previously known scoring systems, and they can help physicians prognosticate more accurately in patients using CRRT.

Disclosures

C. Lim reports having an advisory or leadership role as the President Elect, Korean Society of Nephrology. J. Lee reports having an advisory or leadership role with the Kidney Research and Clinical Practice. N. Tangri reports having consultancy agreements with Marizyme, Mesentech Inc., PulseData Inc., Renibus, and Tricida Inc.; reports having an ownership interest in Clinpredict, Klinrisk, Marizyme, Mesentech Inc., PulseData Inc., Quanta, Renibus, and Tricida Inc.; reports receiving research funding from

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Author Contributions

S. Han, M. Kang, S. Kwon, J.P. Lee, and N. Tangri conceptualized the study; J. An, S. Han, M. Kang, D. Kim, S. Kim, Y. Kim, S. Kwon, H. Lee, J. Lee, J.P. Lee, L. Li, C. Lim, and the VENUS trial investigators were responsible for the data curation; J. An, S. Han, M. Kang, D. Kim, S. Kim, Y. Kim, S. Kwon, J. Lee, J. P. Lee, C. Lim, N. Tangri, and VENUS trial investigators were responsible for the formal analysis; M. Kang and J.P. Lee were responsible for the funding acquisition; J. An, M. Kang, D. Kim, S. Kim, Y. Kim, S. Kwon, J. Lee, J.P. Lee, C. Lim, N. Tangri, and VENUS trial investigators were responsible for the methodology; M. Kang, S. Kwon, and J.P. Lee provided supervision; M. Kang, J. P. Lee, and N. Tangri were responsible for the visualization; M. Kang, J.P. Lee, and N. Tangri wrote the original draft; all of the authors read and approved the final manuscript.

Data Sharing Statement

All data is included in the manuscript and/or supporting information.

Supplemental Material

This article contains the following supplemental material online at <http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0000862022/-/DCSupplemental>

Supplemental Equation. Applying equations to individual patient.

Supplemental Table 1. VENUS score equations for 7-, 14-, and 28-day mortality prediction

Supplemental Table 2. The areas under the time-dependent receiver operating characteristic curve of conventional scoring systems and equations predicting 7-, 14-, and 28-day mortality in development cohort.

Supplemental Figure 1. Time-dependent receiver operating characteristic curves of SOFA, APACHE II, four-, seven-, 11-variable equations in development cohort. (A) The 7-day mortality prediction. (B) The 14-day mortality prediction. (C) The 21-day mortality prediction.

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