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Original Article

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Prediction of vasopressor requirement among hypotensive patients with suspected infection: usefulness of diastolic shock index and lactate

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Objective We evaluated the performance of diastolic shock index (DSI) and lactate in predicting vasopressor requirement among hypotensive patients with suspected infection in an emergency department.

Methods This was a single-center, retrospective observational study for adult patients with suspected infection and hypotension in the emergency department from 2018 to 2019. The study population was split into derivation and validation cohorts (70/30). We derived a simple risk score to predict vasopressor requirement using DSI and lactate cutoff values determined by Youden index. We tested the score by the area under the receiver operating characteristic curve (AUC). We performed a multivariable regression analysis to evaluate the association between the timing of vasopressor treatment and 28-day mortality.

Results A total of 1,917 patients were included. We developed a score, assigning 1 point each for the high DSI (≥2.0) and high lactate (≥2.5 mmol/L) criteria. The AUCs of the score were 0.741 (95% confidence interval [CI], 0.715–0.768) at hypotension and 0.736 (95% CI, 0.708–0.763) after initial fluid challenge in the derivation cohort and 0.676 (95% CI, 0.631–0.719) at hypotension and 0.688 (95% CI, 0.642–0.733) after initial fluid challenge in the validation cohort, respectively. In patients with scores of 2 points, early vasopressor therapy initiation was significantly associated with decreased 28-day mortality (adjusted odds ratio, 0.37; 95% CI, 0.14–0.94).

Conclusion A prediction model with DSI and lactate levels might be useful to identify patients who are more likely to need vasopressor administration among hypotensive patients with suspected infection.

Keywords Septic shock; Sepsis; Diastolic shock index; Lactic acid; Vasopressors

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Capsule Summary

What is already known

Early initiation of a vasopressor for septic shock might be beneficial in terms of more quickly correcting hypotension, maintaining organ perfusion, and limiting the amount of fluid administration. However, some controversial results have been reported; therefore, a predictive tool might help to identify patients who would benefit from vasopressor administration, rather than a "one-size-fits-all" approach to all hypotensive septic patients.

What is new in the current study

In this study, we demonstrated that the diastolic shock index and lactate levels could be used for predicting vasopressor requirement in hypotensive patients with suspected infection. We developed a simple risk assessment model using both values with fair discriminating performance. The prediction model might be helpful for identifying patients who are more likely to need vasopressor administration before or during initial fluid resuscitation. Notably, associations between the timing of vasopressor administration and 28-day mortality varied according to prediction score.

INTRODUCTION

Sepsis is a life-threatening problem defined as dysregulated host responses to an infection that causes organ dysfunction, and the overall hospital mortality rate of affected patients is > 10%.[1-4] Septic shock, which is a subtype of sepsis involving circulatory, cellular, and metabolic abnormalities, remains a critical illness associated with a hospital mortality rate of about 40%.[1,5,6] Systemic vasodilatation is a key pathophysiologic process in septic shock, and fluid resuscitation and vasopressor administration are the main treatment modalities.[7,8]

The Surviving Sepsis Campaign (SSC) guidelines recommend using norepinephrine (NE) as a first-line vasopressor, and this medication is included in the 1-hour treatment bundle.[7] Early initiation of NE for septic shock might be beneficial in terms of more quickly correcting hypotension, maintaining organ perfusion and limiting the amount of fluid administration.[9-12] However, some controversial results have been reported.[13,14] In addition, there is no clear consensus on the appropriate time to initiate vasopressors during initial fluid resuscitation, and it has not been determined which index can be used to select patients who require vasopressors early.[15] Therefore, a predictive tool might be helpful to identify patients who need NE urgently in a personalized context rather than adopting a "one-size-fits-all" approach to all hypotensive septic patients.

Measuring the diastolic arterial pressure (DAP) may be a simple way to identify patients who need NE administration because a low DAP is mainly due to reduced vascular tone.[8,16] On the other hand, the diastolic shock index (DSI), which is defined as the ratio between heart rate (HR) and DAP, has been proposed as an early predictor for identifying high-risk patients with septic shock.[17] In this study, neither isolated low DAP nor high HR showed prognostic value, but the DSI value calculated before or at the start of vasopressor treatment showed similar performance to initial lactate levels and the Sequential Organ Failure Assessment (SOFA) score in predicting mortality. Importantly, early initiation of vasopressors within 1 hour showed a survival benefit only in the higher DSI quintile group. The results suggested that a higher DSI might be a trigger for early vasopressor treatment.

Lactate has been widely used as a biomarker for tissue perfusion, a screening tool for sepsis and part of the septic shock definition.[5,7] In an observational study, hyperlactatemia ≥ 4 mmol/L was also associated with a phenotype refractory to fluid resuscitation.[18] Given these results, DSI and lactate, as widely available indices that can easily be measured, might be used to identify patients who need vasopressor treatment.

In this study, we evaluated the performance of the DSI and initial lactate levels for predicting vasopressor requirement among hypotensive patients with suspected infection in an emergency department (ED), and we developed a risk assessment scoring protocol for vasopressor use.

METHODS

Study design, setting, and population

This was a single-center, retrospective, observational study performed at Samsung Medical Center, a 1,960-bed, university-affiliated, tertiary care referral hospital in Seoul, Korea. The study period was from January 2018 to December 2019. This study was approved by the Institutional Review Board of Samsung Medical Center (No. 2022-03-070); the need for informed consent was waived because this study was retrospective and observational in nature, and patients' data were anonymized.

We included patients aged ≥ 18 years with suspected infection

and hypotension who presented to the ED. A suspected infection was defined as a case in which blood culture and antibiotic administration were conducted in the ED.[1] Hypotension was defined as systolic blood pressure of <90 mmHg. We excluded patients who had limitations on invasive care (e.g., patients who had terminal malignancy or who had previously signed a do-not-resuscitate order), who presented with cardiac arrest, who were transferred from or to another hospital, who had obviously noninfectious conditions such as trauma or bleeding, who showed hypotension 6 hours after ED arrival and who had inadequate data due to an inability to access electronic medical records.

Data collection and outcomes

Eligible cases were electronically identified based on the definition of suspected infection and hypotension. The following data were extracted from the hospital database: age, sex, comorbidities, vital signs, mental status, suspected infection focus, initial laboratory tests, vasopressor use, mechanical ventilation, ED disposition, and survival data.

DSI was defined as the quotient between HR and DAP.[17] We calculated the DSI at the time of initial hypotensive events and immediately after a rapid infusion of 300 to 1,000 mL. DSI values after vasopressor administration were not used. We used arterial blood pressure values first, but noninvasive measurements were used if an arterial line was not inserted. The SOFA score was calculated using maximum variables recorded at 24 hours from ED arrival. Missed variables for the SOFA components were considered as normal values. Septic shock was defined according to the Sepsis-3 criteria.[5] The primary study outcome was vasopressor requirement. NE was used as the first vasopressor, and the target mean arterial pressure was ≥ 65 mmHg. General ED management for sepsis was conducted according to the SSC guidelines.[7]

Statistical analysis

The study population was split randomly into derivation and validation cohorts (70/30). The results were expressed as mean ± standard deviation values or median with interquartile range (IQR) values for continuous variables and as the number of patients with percentages for categorical data. Continuous variables were analyzed using Wilcoxon rank-sum tests, while categorical variables were analyzed using chi-squared tests. For the derivation and validation cohorts, we categorized patients according to the quintile of the DSI values and initial lactate levels, and we evaluated P-value for trends with the incidence of vasopressor use. The accuracy of prediction for vasopressor requirement was assessed using the area under the receiver operating characteristic curve (AUC), sensitivity, specificity, and their corresponding 95% confidence intervals (CIs). Optimal cutoff values of the DSI and lactate levels were calculated using Youden index. We derived a simple risk scoring system to predict vasopressor requirement using the DSI and lactate cutoff values in the derivation cohort. We used regression coefficients of the DSI and lactate level for vasopressor use to derive a score in multivariable linear regression models. We converted the coefficient into a single-integer risk score.

Afterwards, the final risk model was assessed by multivariable logistic regression analysis with variables showing differences in baseline characteristics, the AUC, and calibration plots. For sensitivity analysis, we evaluated the predictive validity of a model in which missing values of the DSI and lactate level were replaced with normal values. In addition, we investigated whether the timing of vasopressor administration was associated with the 28-day mortality rate according to the developed score obtained by multivariable logistic regression modeling. We calculated adjusted odds ratios (aORs) with predefined variables, including age, infection focus, lactate levels, and SOFA score. A two-tailed P-value of less than 0.05 was considered statistically significant. All analyses were performed using R ver. 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) and Stata ver. 17.0 (StataCorp., College Station, TX, USA).

RESULTS

Study population

We assessed the eligibility of 17,736 adult patients who underwent blood cultures and antibiotic administration in the ED from January 2018 through December 2019. Patients who were transferred from or to another hospital, who had limitations on invasive care, who did not have an infection, who presented with cardiac arrest and/or who had inadequate data were excluded (n = 2,827). We also excluded patients without hypotension or with hypotension after 6 hours from ED arrival (n = 12,992). A total of 1,917 patients with suspected infection with hypotension within 6 hours from ED arrival were included in the analysis. We randomly split the data with 1,342 patients (70%) included in the derivation cohort and 575 patients (30%) included in the validation cohort (Fig. 1).

Baseline characteristics

The baseline characteristics of the overall population, the derivation, and validation cohorts are presented in Table 1. The median age was 65 years (IQR, 56–74 years), and 1,052 study participants (54.9%) were male. The 28-day mortality rate was 12.4% (n = 237). The median DSI value was 1.9 (IQR, 1.6–2.3) at the time of hypotension and 1.8 (IQR, 1.5–2.2) after fluid challenge. The

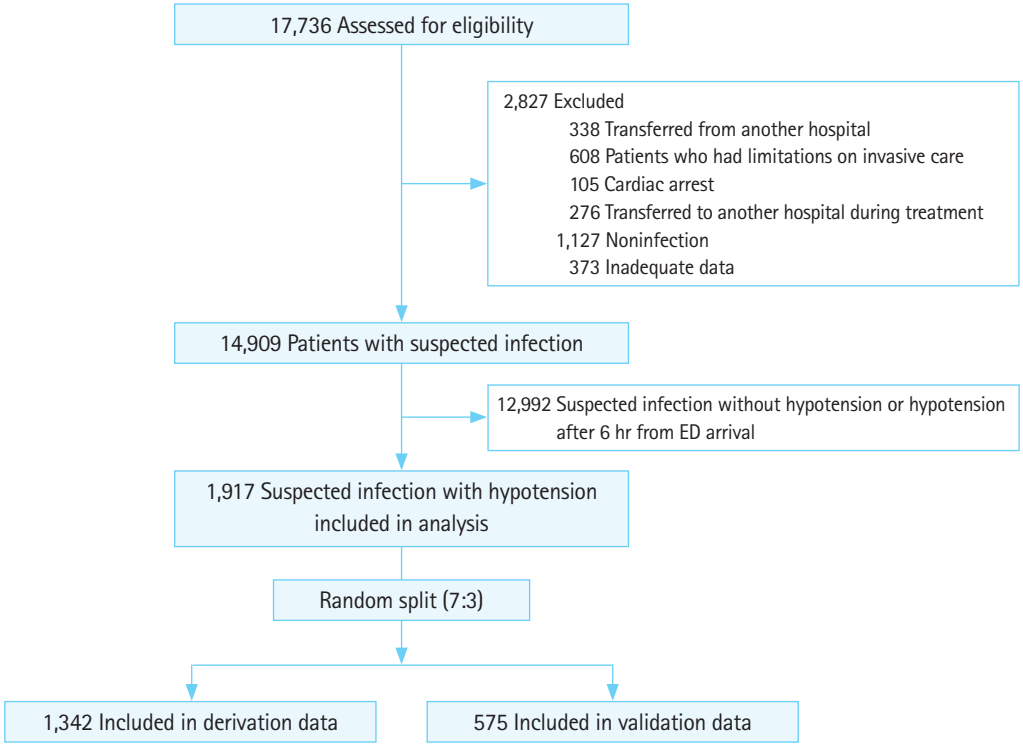

Fig. 1. Study population. ED, emergency department.

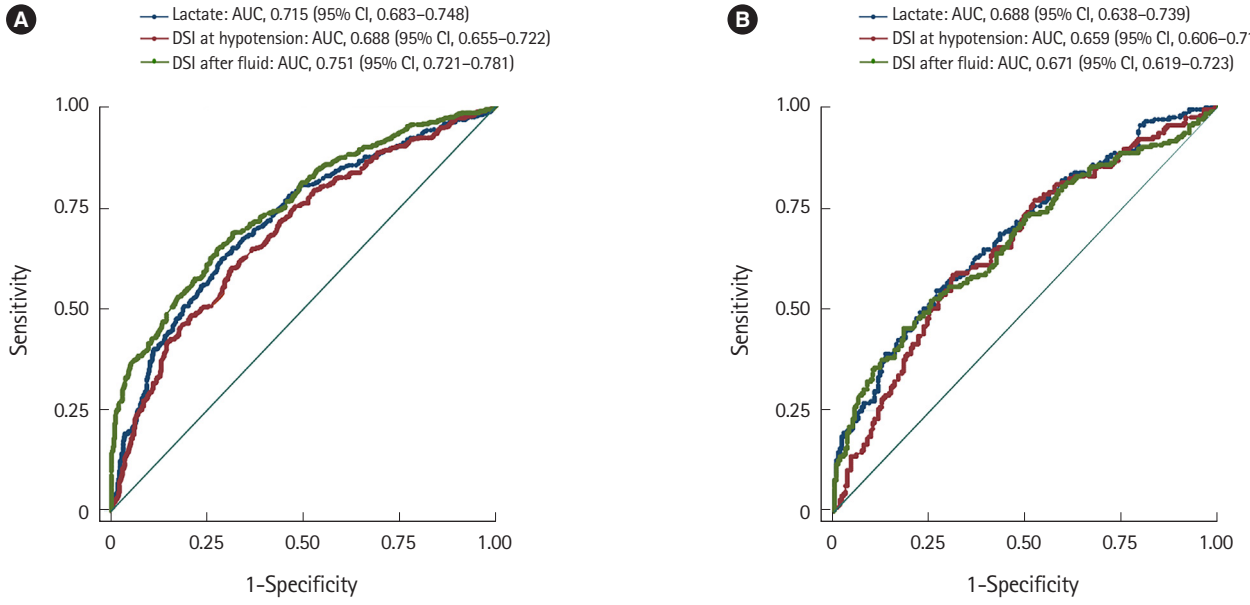

Fig. 2. Area under the receiver operating characteristic curves (AUCs) of the diastolic shock index (DSI) at the time of hypotension and after fluid challenge and initial lactate levels for predicting vasopressor requirement in (A) the derivation cohort and (B) the validation cohort. The AUC of the DSI after fluid was significantly higher than that of the DSI at hypotension (P<0.01). There was no significant difference in other post hoc comparisons. CI, confidence interval.

mean volume of initial fluid before vital sign follow-up was 838.0±261.8 mL. The median lactate level was 2.3 (IQR, 1.5–3.6), and the SOFA score on the 1st day was 5.0 (IQR, 3.0–8.0). The overall vasopressor requirement was 45.7% (n=876), with 620 patients (46.2%) included in the derivation cohort and 256 patients (44.5%) included in the validation cohort.

Table 1. Baseline characteristics of the derivation and validation cohorts

Characteristic	Overall (n = 1,917)	Derivation (n = 1,342)	Validation (n = 575)
Age (yr)	65 (56–74)	65 (55–74)	65 (56–74)
Male sex	1,052 (54.9)	734 (54.7)	318 (55.3)
Comorbidity			
Hypertension	581 (30.3)	403 (30.0)	178 (31.0)
Diabetes	459 (23.9)	307 (22.9)	152 (26.4)
Cardiac disease	333 (17.4)	234 (17.4)	99 (17.2)
Cerebrovascular disease	197 (10.3)	145 (10.8)	52 (9.0)
Chronic lung disease	170 (8.9)	117 (8.7)	53 (9.2)
Chronic liver disease	192 (10.0)	135 (10.1)	57 (9.9)
Solid cancer	1,041 (54.3)	700 (52.2)	341 (59.3)
Suspected infection source			
Respiratory infection	392 (20.5)	269 (20.0)	123 (21.4)
Intraabdominal infection	504 (26.3)	357 (26.6)	147 (25.6)
Urinary tract infection	271 (14.1)	187 (13.9)	84 (14.6)
Other or unknown	750 (39.1)	529 (39.4)	221 (38.4)
Positive blood culture	442 (23.1)	333 (24.8)	109 (19.0)
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	83 (78–87)	83 (78–87)	83 (79–87)
Diastolic pressure (mmHg)	52 (47–56)	52 (47–56)	52 (47–56)
Respiratory rate (/min)	20 (18–22)	20 (18–22)	20 (18–22)
Heart rate (/min)	101 (86–117)	101 (86–118)	99 (85–116)
Vital sign after fluid challenge			
Systolic pressure (mmHg)	93 (85–103)	93 (85–103)	93.5 (85–104)
Diastolic pressure (mmHg)	55 (48–62)	54 (47–61)	55 (48–62)
Respiratory rate (/min)	20 (17–23)	20 (18–23)	19 (17–22)
Heart rate (/min)	98 (85–112)	98 (85–112)	97.5 (85–111)
Diastolic shock index			
At the time of hypotension (n = 1,768)	1.9 (1.6–2.3)	1.9 (1.6–2.3)	1.9 (1.6–2.3)
After fluid challenge (n = 1,531)	1.8 (1.5–2.2)	1.8 (1.5–2.1)	1.8 (1.5–2.2)
Lactate (mmol/L) (n = 1,865)	2.3 (1.5–3.6)	2.3 (1.5–3.6)	2.2 (1.5–3.6)
SOFA score on the 1st day	5.0 (3.0–8.0)	5.0 (3.0–8.0)	5.0 (3.0–8.0)
Vasopressor requirement	876 (45.7)	620 (46.2)	256 (44.5)
Septic shock (Sepsis-3)[a]	649 (33.9)	471 (35.1)	178 (31.0)
Time to hypotension from ED arrival (min)	56 (5–171)	52 (5–172)	32.5 (6–171)
Time to vasopressor use from ED arrival (min)	188 (94–318)	184 (89–309)	196 (100–327)
Vasopressor duration (hr)	20.8 (9.4–40.2)	20.4 (9.2–40.6)	21.6 (10.3–43.2)
Mechanical ventilation	203 (10.6)	146 (10.9)	57 (9.9)
Intensive care unit admission	469 (24.5)	326 (24.3)	143 (24.9)
28-Day mortality	237 (12.4)	169 (12.6)	68 (11.8)

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment; ED, emergency department.
[a]Patients who met septic shock criteria according to the new Sepsis-3 definition, which are persistent hypotension requiring vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg and a serum lactate level of > 2 mmol/L despite adequate volume resuscitation.

The comparison of clinical characteristics and outcomes according to vasopressor requirement in the derivation cohort is shown in Supplementary Table 1. Both DSI values and lactate levels were significantly higher in the vasopressor use group than the nonvasopressor use group (DSI at hypotension, 2.2 [IQR, 1.8–2.6] vs. 1.8 [IQR, 1.5–2.1]; DSI after fluid, 2.0 [IQR, 1.7–2.4] vs. 1.6 [IQR, 1.4–1.9]; lactate, 3.2 mmol/L [IQR, 2.0–4.9] vs. 1.8 mmol/L [IQR, 1.3–2.6]; P < 0.001 for all comparisons). The results were similar in the validation cohort (Supplementary Table 2).

Prognostic performance for vasopressor requirement according to DSI and lactate level

The AUC in predicting vasopressor use was 0.715 (95% CI, 0.683–0.748) for lactate, 0.688 (95% CI, 0.655–0.722) for DSI at hypo-

tension, and 0.751 (95% CI, 0.721–0.781) for DSI after fluid challenge (Fig. 2). The optimal cutoff values of the DSI at hypotension (2.06), DSI after fluid (1.77), and lactate (2.36 mmol/L), calculated by the Youden index, were simplified to 2.0 for both DSI at hypotension and a after fluid challenge, and 2.5 mmol/L for lactate, as rounded to the nearest 0.5 interval value. The prognostic performance of the cutoff values of DSI and lactate levels are presented in Supplementary Table 3.

Development and validation of a prediction score model

The vasopressor requirement prediction score was developed using the DSI and lactate (Table 2) and ranged from 0 to 2 points, with 1 point each assigned for the high DSI and high lactate criteria because the regression coefficients of the DSI and lactate values for vasopressor requirement were similar (model 1 in Supplementary Table 4). The prediction score was significantly associated with vasopressor requirement after adjusting confounding variables, including age, sex, hypertension, diabetes, infection source, bacteremia, SOFA score, and respiratory rate (aOR at hypotension, 1.66; 95% CI, 1.34–2.05; P<0.001; aOR after fluid challenge, 1.71; 95% CI, 1.39–2.10; P<0.001).

Table 2. Vasopressor requirement prediction score for hypotensive patients

No. of positive criteria[a]	Risk
0	Low
1	Intermediate
2	High

DSI, diastolic shock index.
[a]DSI ≥2.0 or lactate ≥2.5 mmol/L.

The proportions of vasopressor use significantly increased as the prediction score increased, both at the time of hypotension (20.6%, 44.7%, and 79.1% for scores of 0, 1, and 2 points, respectively) and after fluid challenge (29.1%, 57.1%, and 85.8% for scores of 0, 1, and 2 points, respectively) (Fig. 3), with a similar tendency present in the validation cohort (Supplementary Fig. 1).

Table 3. Multivariable logistic regression for the effect of the timing of vasopressor administration from initial hypotension on 28-day mortality according to the prediction score

Score	Adjusted OR[a]	95% CI	P-value
0 Points			
Hourly delay of vasopressor administration	0.92	0.78–1.09	0.346
Timing of vasopressor administration (min)			
>60	Reference		
30–60	4.76	1.07–21.14	0.040
<30	7.28	1.43–37.10	0.017
1 Point			
Hourly delay of vasopressor administration	1.07	0.98–1.15	0.113
Timing of vasopressor administration (min)			
>60	Reference		
30–60	0.61	0.24–1.57	0.306
<30	0.33	0.10–1.14	0.079
2 Points			
Hourly delay of vasopressor administration	1.06	1.01–1.11	0.021
Timing of vasopressor administration (min)			
>60	Reference		
30–60	0.71	0.30–1.71	0.451
<30	0.37	0.14–0.94	0.038

OR, odds ratio; CI, confidence interval.
[a]Adjusted variables were age, infection source, initial lactate levels, and Sequential Organ Failure Assessment score.

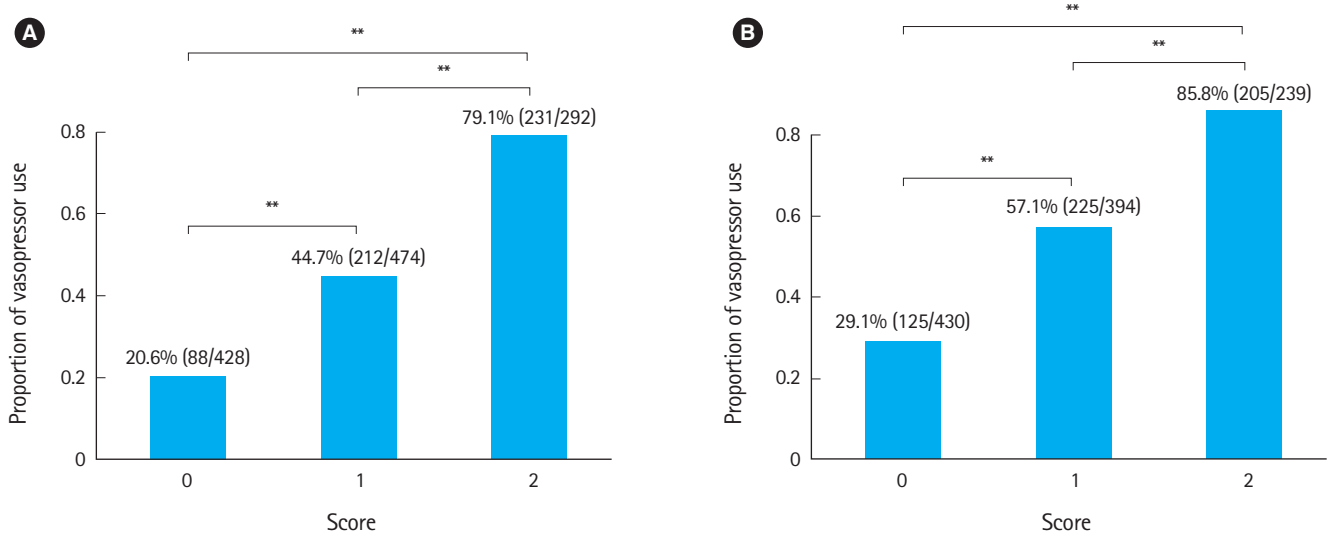

Fig. 3. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort and (B) after fluid challenge in the derivation cohort. **P<0.001.

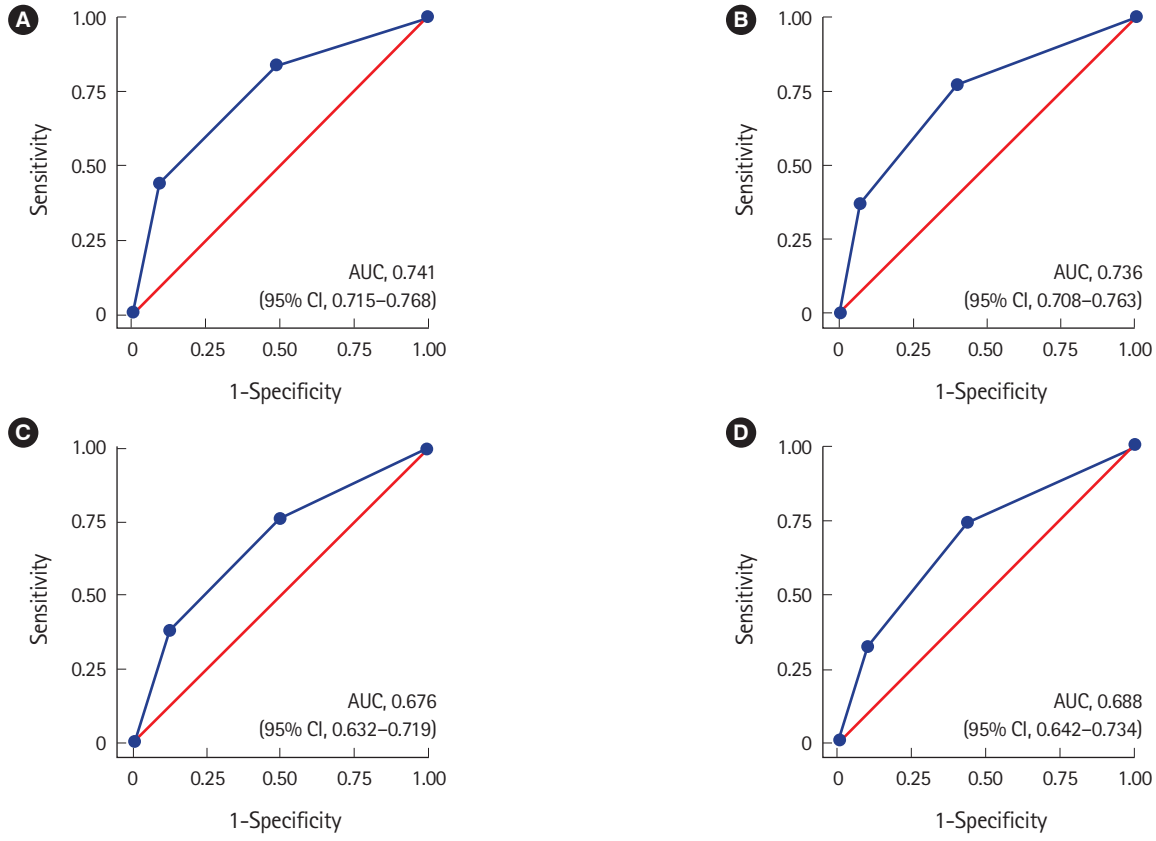

Fig. 4. Area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after fluid challenge in the validation cohort. CI, confidence interval.

The prognostic performance of the prediction score was fair, with an AUC of 0.741 (95% CI, 0.715–0.768) at hypotension or 0.736 (95% CI, 0.708–0.763) after fluid challenge in the derivation cohort and 0.679 (95% CI, 0.631–0.719) at hypotension or 0.688 (95% CI, 0.642–0.734) in the validation cohort, respectively, as well as during calibration (Figs. 4, 5).

The 28-day mortality was also increased along with the prediction score both at the time of hypotension (5.1%, 11.8%, and 17.8% for scores of 0, 1, and 2 points, respectively) and after a fluid challenge (5.9%, 16.0%, and 21.8% for scores of 0, 1, and 2 points, respectively) in the derivation and validation cohorts (Supplementary Fig. 2). In the sensitivity analysis using missing value imputation, the prognostic accuracy was similar (Supplementary Fig. 3).

The effect of the timing of vasopressor administration from initial hypotension on 28-day mortality according to the prediction score is shown in Table 3. With a score of 0 points, an hourly delay of vasopressor administration was not associated with 28-day mortality, but an early start of vasopressor administration (<30 minutes or 30–60 minutes) was significantly associated with increased 28-day mortality (aOR, 7.28; 95% CI, 1.43–37.10; P=0.017 or aOR, 4.76; 95% CI, 1.07–21.14; P=0.040). On the contrary, with a score of 2 points, both an hourly delay of vasopressor administration (aOR, 1.06; 95% CI, 1.01–1.11; P=0.021) and early start (<30 minutes) of vasopressor administration (aOR, 0.37; 95% CI, 0.14–0.94; P=0.038) were significantly associated with 28-day mortality.

DISCUSSION

In this study, we demonstrated that the DSI and lactate levels could be used for predicting vasopressor requirement in hypotensive patients with suspected infection. We developed a simple risk assessment model using both values with fair discriminating performance. The prediction model might help to identify patients earlier who are more likely to need vasopressor administration before or during initial fluid resuscitation. Notably, the associations between the timing of vasopressor administration and 28-day mortality were different according to the prediction score. The results suggest that early vasopressor use might show more benefit for improving survival in high-risk patients (DSI ≥2.0 and lactate ≥2.5 mmol/L) than in low-risk patients (DSI <2.0 and

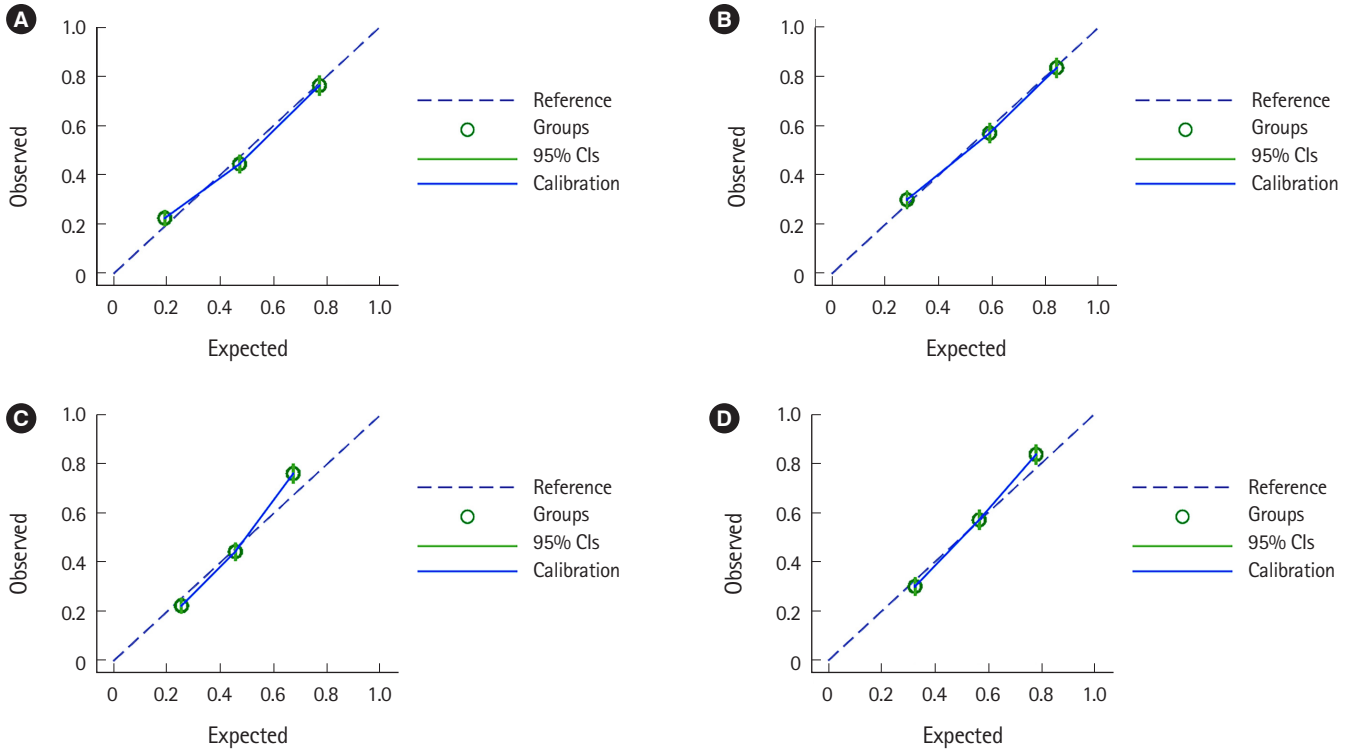

Fig. 5. Calibration plots of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. CI, confidence interval.

lactate < 2.5 mmol/L).

Sepsis-induced hypotension may be associated with various hemodynamic changes, including severe vasodilatation, decreased preload and cardiac dysfunction.[19] Fluid resuscitation is the initial step of emergency management, but a significant number of hypotensive patients need vasopressor administration to maintain blood pressure.[13,20] Although vasopressor administration is included in the sepsis 1-hour bundle as the first-line intervention,[7,15] vasopressors are commonly used after fluid resuscitation fails, resulting in prolonged duration of hypotension.[17,20,21] Previous studies have suggested the potential benefits of early vasopressor use,[8-12,22,23] but there is no precise index for the timing of vasopressor administration during initial sepsis management. Moreover, we could not conclude that prompt vasopressor use would improve outcomes in all hypotensive patients with suspected sepsis.[14]

The diastolic pressure might be a marker of arterial tone and the perfusion pressure for the left ventricle.[24] The previous 2012 version of the SSC guidelines recommended that administering vasopressors early as an emergency measure in patients with severe shock is often necessary, such as when diastolic blood pressure is too low (e.g., DAP < 40 mmHg).[25] Compared with the systolic or mean arterial pressure, the DAP might remain constant in the peripheral circulation, and differences in invasive and noninvasive measurements of the DAP are usually smaller than those for systolic pressure.[26,27] Despite some advantages of diastolic pressure measurement in septic shock patients, isolated DAP might not be a significant prognostic factor.[17] Rather than a single index, the DSI value could reflect the severity of cardiovascular dysfunction in septic shock, which is a combination of the DAP and HR, because tachycardia might be a compensating or maladaptive process for acute hypotension.

The effect of early vasopressor use on the clinical outcome according to sepsis severity is uncertain and could vary depending on the physiologic status of an individual patient. Unfortunately, we could not clearly explain why an early start of vasopressor therapy was associated with decreased 28-day mortality in high-risk patients and increased mortality in low-risk patients. Theoretically, high-risk patients with higher DSI and lactate levels might have lower vascular tone and more impaired tissue perfusion. Early vasopressor use might allow faster achievement of the mean arterial pressure target. However, there are also traditional concerns regarding the impact of early vasopressor use.[14,28] Vasopressors may have potentially harmful effects in masking inadequate fluid resuscitation, and vasoconstriction may induce tissue hypoperfusion and organ dysfunction.[14] These might be explanations for the

study findings, but further investigation will be needed.

We incorporated lactate values in our predictive scoring. In sepsis, lactate is a strong biomarker for predicting mortality, although it could be increased by various mechanisms such as inadequate oxygen delivery, impaired oxygen extraction, decreased lactate clearance, and glycolytic flux by β_2-stimulation.[29] Our results might be consistent with the prognostic value of lactate and findings of the previous study showing that lactate elevation was a factor in predicting vasopressor use.[18]

There are some limitations to this study. First, this was a single-center study conducted in the ED. External validation studies from multiple centers in different settings will be needed for generalizability. Second, there were some missing lactate level and DSI values, although the proportion of such was not too large. DSI values after a fluid challenge were not available when NE was administered during fluid challenge, and vital signs were not measured. Third, the amounts of fluid were not consistent when the vital signs were followed up on. Due to the study's retrospective nature, we could not control the volume of fluid challenge. However, it is notable that the DSI after fluid challenge was measured before reaching the fluid amount (30 mL/kg of crystalloids) recommended by the SSC guidelines.[7] We used the DSI value after crystalloid administration of about 5 to 15 mL/kg. In a future study, serial DSI values should be tested at fixed doses. Fourth, the AUCs in the validation cohort were relatively lower than those in the derivation cohort. This finding might be due to the smaller sample size of the validation cohort or overfitting in the derivation cohort. Further validation and modification of the model are needed. Fifth, we used only the initial lactate value. However, it would not be practical to wait for repeated values when deciding to administer a vasopressor early since it takes time for the lactate levels to change and to be reported. Sixth, considering the number of variables and incidence of outcome, the sample size might be insufficient in the multivariable models for the subgroups, although the C-statistics of the models were acceptable. The findings should be confirmed in larger cohorts. Seventh, we focused on hypotensive patients with suspected infection, so further study is needed to evaluate whether the score could be used in patients without hypotension for early screening of high-risk sepsis patients.

In conclusion, in this study of a single ED, the DSI and lactate levels showed fair diagnostic accuracy in predicting vasopressor requirement in hypotensive patients with suspected infection. The prediction model using DSI and lactate levels could identify patients who are more likely to need vasopressor administration during initial resuscitation in the ED. External validation and clinical trials for early vasopressor use in high-risk patients are required.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Comparisons by vasopressor requirement in the derivation cohort

Supplementary Table 2. Comparisons by vasopressor requirement in the validation cohort

Supplementary Table 3. Diagnostic performance of the cutoff values of the DSI and lactate levels for predicting vasopressor requirement

Supplementary Table 4. Multivariable linear regression analysis of the DSI and lactate values for vasopressor requirement in the derivation cohort

Supplementary Fig. 1. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the validation cohort and (B) after a fluid challenge in the validation cohort.

Supplementary Fig. 2. 28-Day mortality according to the prediction score for vasopressor requirement using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort.

Supplementary Fig. 3. Sensitivity analysis of area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. CI, confidence interval.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Comparisons by vasopressor requirement in the derivation cohort

Variable	Vasopressor use (n = 620, 46.2%)	No vasopressor use (n = 722, 53.8%)	P-value
Age (yr)	67 (59–76)	63 (53–72)	< 0.001
Male sex	366 (59.0)	368 (51.0)	0.003
Comorbidity			
Hypertension	220 (35.5)	183 (25.3)	< 0.001
Diabetes	167 (26.9)	140 (19.4)	0.001
Cardiac disease	118 (19.0)	116 (16.1)	0.153
Cerebrovascular disease	76 (12.3)	69 (9.6)	0.112
Chronic lung disease	56 (9.0)	61 (8.4)	0.706
Chronic liver disease	67 (10.8)	68 (9.4)	0.399
Solid cancer	316 (51.0)	384 (53.2)	0.417
Suspected infection source			0.012
Respiratory infection	115 (18.5)	154 (21.3)	< 0.001
Intraabdominal infection	145 (23.4)	212 (29.4)	< 0.001
Urinary tract infection	90 (14.5)	97 (13.4)	< 0.001
Other or unknown	270 (43.5)	259 (35.9)	< 0.001
Blood culture-positive	225 (36.3)	108 (15.0)	< 0.001
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	81 (74–85)	85 (82–88)	< 0.001
Diastolic pressure (mmHg)	49 (43–54)	53 (49–57)	< 0.001
Respiratory rate (/min)	20 (18–23)	18 (18–20)	< 0.001
Heart rate (/min)	109 (93–125)	96 (82–111)	< 0.001
Vital sign after fluid challenge			
Systolic pressure (mmHg)	89 (80–102)	96 (89–105)	< 0.001
Diastolic pressure (mmHg)	51 (44–57)	57 (52–64)	< 0.001
Respiratory rate (/min)	20 (18–25)	19 (17–21)	< 0.001
Heart rate (/min)	104 (91–118)	92 (81–104)	< 0.001
Diastolic shock index			
At the time of hypotension (n = 1,231)	2.2 (1.8–2.6)	1.8 (1.5–2.1)	< 0.001
After fluid challenge (n = 1,081)	2.0 (1.7–2.4)	1.6 (1.4–1.9)	< 0.001
Lactate (mmol/L) (n = 1,304)	3.2 (2.0–4.9)	1.8 (1.3–2.6)	< 0.001
SOFA score on the 1st day	8.0 (7.0–11.0)	3.0 (2.0–5.0)	< 0.001
Mechanical ventilation	131 (21.1)	15 (2.1)	< 0.001
Intensive care unit admission	296 (47.7)	30 (4.2)	< 0.001
28-Day mortality	115 (18.5)	54 (7.5)	< 0.001

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment.

Supplementary Table 2. Comparisons by vasopressor requirement in the validation cohort

Variable	Vasopressor use (n = 256, 44.5%)	No vasopressor use (n = 319, 55.5%)	P-value
Age (yr)	67 (58.5–75.0)	63 (54.0–71.0)	< 0.003
Male sex	164 (64.1)	154 (48.3)	< 0.001
Comorbidity			
Hypertension	103 (40.2)	75 (23.5)	< 0.001
Diabetes	85 (33.2)	67 (21.0)	0.001
Cardiac disease	56 (21.9)	43 (13.5)	0.008
Cerebrovascular disease	32 (12.5)	20 (6.3)	0.010
Chronic lung disease	27 (10.5)	26 (8.2)	0.324
Chronic liver disease	34 (13.3)	23 (7.2)	0.015
Solid cancer	143 (55.9)	198 (62.1)	0.132
Suspected infection source			0.272
Respiratory infection	52 (20.3)	71 (22.3)	0.966
Intraabdominal infection	71 (27.7)	76 (23.8)	0.831
Urinary tract infection	43 (16.8)	41 (12.9)	0.136
Other or unknown	90 (35.2)	131 (41.1)	0.102
Blood culture-positive	76 (29.7)	33 (10.3)	< 0.001
Vital sign at the time of hypotension			
Systolic pressure (mmHg)	81 (75–85)	85 (81–87)	< 0.001
Diastolic pressure (mmHg)	50 (44–54)	53 (49–58)	< 0.001
Respiratory rate (/min)	20 (18–24)	18 (18–20)	0.001
Heart rate (/min)	104 (89–120)	96 (84–111)	< 0.001
Vital sign after fluid challenge			
Systolic pressure (mmHg)	92 (83–102)	95 (89–105)	0.001
Diastolic pressure (mmHg)	52 (45–59)	57 (52–64)	< 0.001
Respiratory rate (/min)	20 (18–23)	18 (17–21)	0.001
Heart rate (/min)	100 (89–115)	94 (83–109)	0.001
Diastolic shock index			
At the time of hypotension (n = 537)	2.1 (1.8–2.4)	1.8 (1.5–2.1)	< 0.001
After fluid challenge (n = 450)	2.0 (1.6–2.3)	1.6 (1.4–1.9)	< 0.001
Lactate (mmol/L) (n = 561)	2.8 (1.8–5.0)	1.9 (1.3–2.7)	< 0.001
SOFA score on the 1st day	8.0 (6.0–11.0)	3.0 (2.0–5.0)	< 0.001
Mechanical ventilation	52 (20.3)	5 (1.6)	< 0.001
Intensive care unit admission	121 (47.3)	22 (6.9)	< 0.001
28-Day mortality	48 (18.8)	20 (6.3)	< 0.001

Values are presented as median (interquartile range) or number (%).
SOFA, Sequential Organ Failure Assessment.

Supplementary Table 3. Diagnostic performance of the cutoff values of the DSI and lactate levels for predicting vasopressor requirement

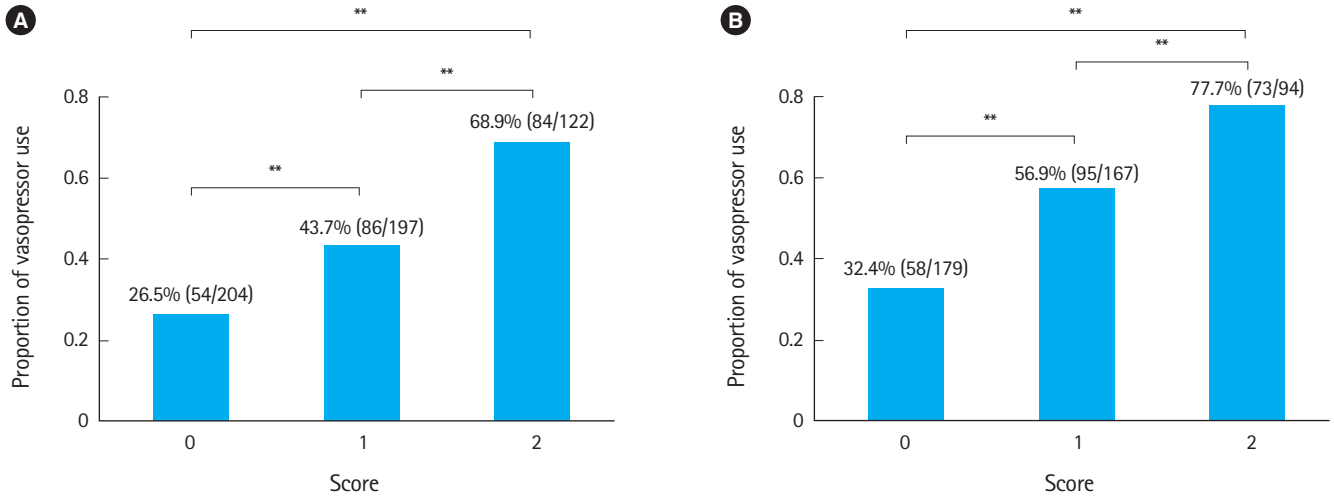
Variable	DSI ≥ 2.0 (initial hypotension)	DSI ≥ 2.0 (after fluid challenge)	Lactate ≥ 2.5 mmol/L
Derivation cohort			
Sensitivity (%)	64.5 (60.3–68.6)	52.1 (47.8–56.3)	63.3 (59.3–67.1)
Specificity (%)	67.8 (64.2–71.2)	83.2 (79.7–86.3)	73.2 (69.7–76.5)
Predictive value			
Positive	60.5 (56.3–64.5)	72.1 (76.7–80.9)	68.0 (64.0–71.8)
Negative	67.8 (71.5–74.9)	58.3 (62.0–65.6)	68.9 (65.4–72.2)
AUC	0.662 (0.635–0.689)	0.676 (0.650–0.703)	0.682 (0.657–0.708)
Validation cohort			
Sensitivity (%)	57.6 (50.8–64.1)	49.6 (42.9–56.3)	56.3 (49.9–62.4)
Specificity (%)	67.1 (61.6–72.3)	79.0 (73.1–84.2)	70.5 (65.0–75.6)
Predictive value			
Positive	55.6 (49.0–62.1)	70.4 (62.7–77.4)	61.5 (55.0–67.8)
Negative	68.9 (63.0–74.0)	55.0 (60.8–66.5)	65.7 (60.3–70.9)
AUC	0.623 (0.582–0.665)	0.643 (0.601–0.685)	0.634 (0.594–0.674)

Values are presented as percentages or AUC (95% confidence interval).
DSI, diastolic shock index; AUC, area under the receiver operating characteristic curve.

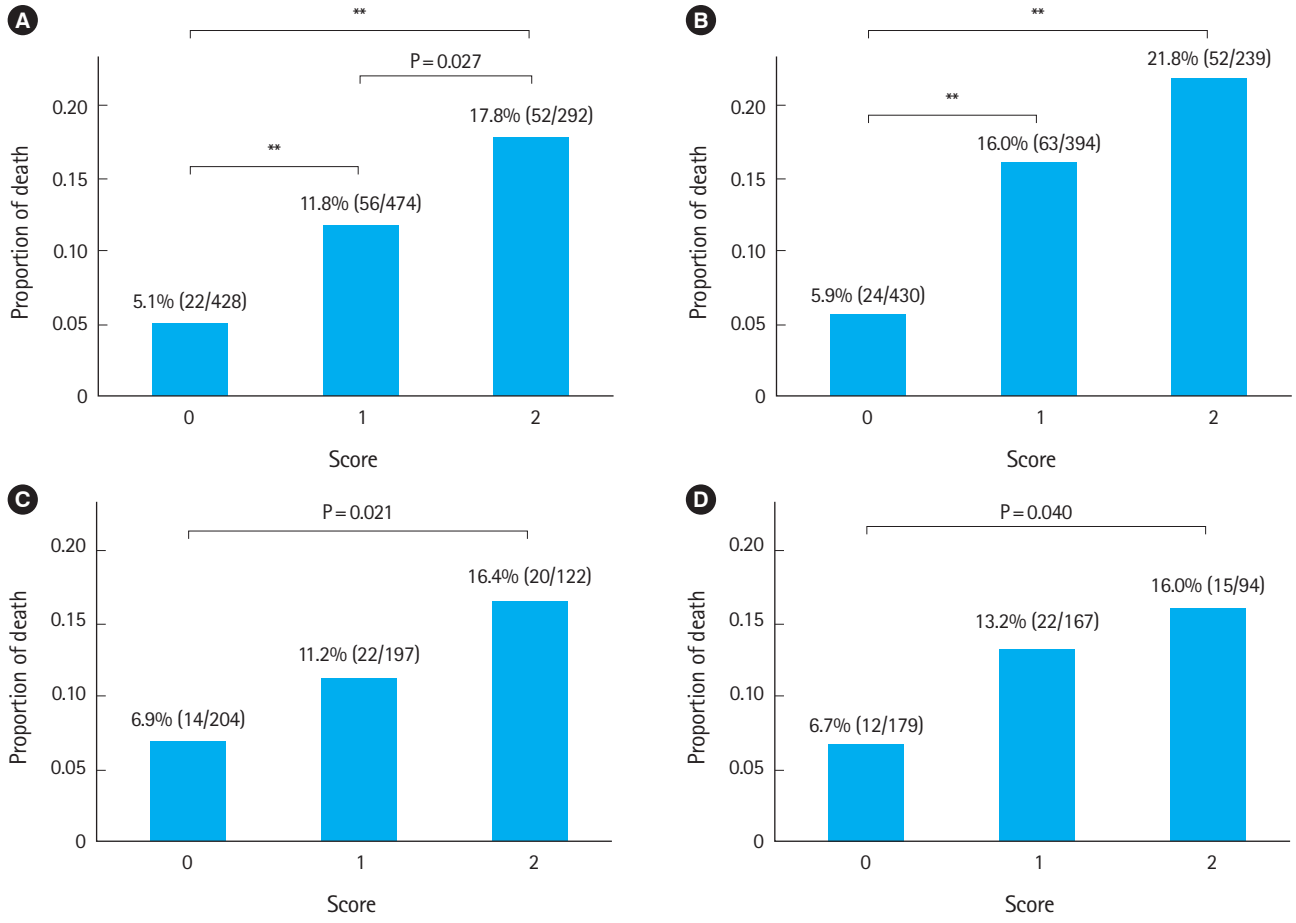
Supplementary Table 4. Multivariable linear regression analysis of the DSI and lactate values for vasopressor requirement in the derivation cohort

Variable	Coefficient (95% CI)	Standard error	P-value
Model 1[a]			
DSI at hypotension	0.300 (0.248 to 0.352)	0.026	<0.001
Lactate	0.264 (0.212 to 0.315)	0.026	<0.001
DSI after fluid	0.243 (0.186 to 0.301)	0.023	<0.001
Lactate	0.323 (0.265 to 0.382)	0.023	<0.001
Model 2[b]			
DSI at hypotension	0.123 (0.087 to 0.160)	0.019	<0.001
Lactate	0.053 (0.015 to 0.092)	0.020	0.006
DSI after fluid	0.140 (0.098 to 0.183)	0.022	<0.001
Lactate	0.039 (-0.043 to 0.082)	0.022	0.078

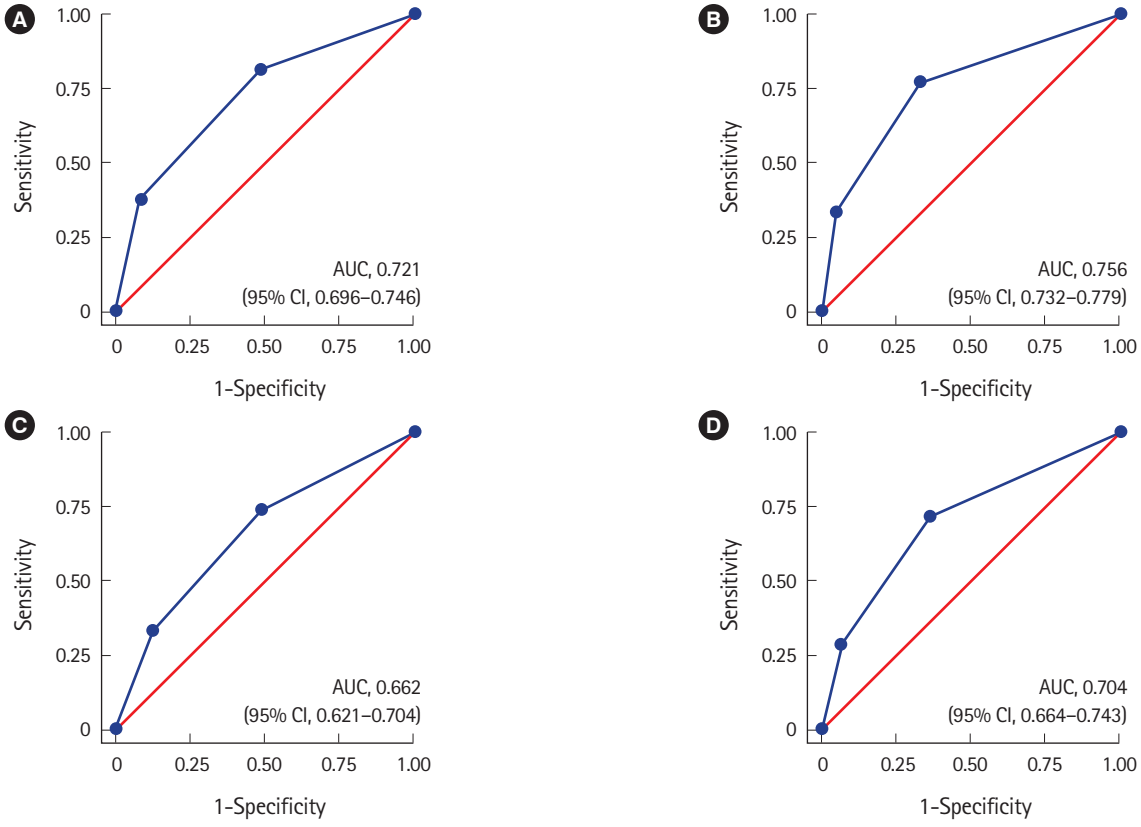
DSI, diastolic shock index; CI, confidence interval.
[a]Model 1 included the DSI and lactate value. [b]Age, sex, hypertension, diabetes, infection focus, bacteremia, Sequential Organ Failure Assessment score, and respiratory rate were adjusted in model 2.



Supplementary Fig. 1. Vasopressor requirement according to the prediction score using the diastolic shock index and lactate levels (A) at the time of hypotension in the validation cohort and (B) after a fluid challenge in the validation cohort. **P<0.001



Supplementary Fig. 2. The 28-day mortality according to the prediction score for vasopressor requirement using the diastolic shock index and lactate levels (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort. **P<0.001



Supplementary Fig. 3. Sensitivity analysis of area under the receiver operating characteristic curves (AUCs) of the prediction score for vasopressor requirement (A) at the time of hypotension in the derivation cohort, (B) after a fluid challenge in the derivation cohort, (C) at the time of hypotension in the validation cohort, and (D) after a fluid challenge in the validation cohort.