

Original Article

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Machine Learning-Based Clusters of Vital Signs and Lactate Levels Predict Vasopressor Use in Sepsis

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ABSTRACT

Objective: Sepsis remains a major clinical challenge because of its complex, heterogeneous, and multidimensional clustering patterns. This study aimed to investigate the association between vasopressor administration and machine learning–derived clusters based on initial vital signs and lactate measurements obtained in emergency department (ED) and intensive care unit (ICU) settings.

Methods: A retrospective cohort analysis was performed using data from the Korean Shock Society Septic Shock (KOSS) Registry (septic shock in the ED) and the Marketplace for Medical Information in Intensive Care (MIMIC)-IV database (ICU patients with suspected infection). To derive clusters, k-means clustering was applied to six initial vital signs and serum lactate measurements. The primary outcome was vasopressor administration.

Secondary outcomes included second vasopressor administration and 28-day mortality.

Results: A total of 17,500 patients were included in the analysis (KOSS cohort, n=7,130; MIMIC-IV cohort, n=10,370). K-means clustering identified three distinct clusters in each cohort. In the KOSS cohort, Cluster 3 was characterized by the lowest mean arterial pressure (MAP) (62 mmHg [IQR, 53–71]) and the highest diastolic shock index (DSI) (2.6 [2.3–3.0]). This cluster was associated with the highest rates of vasopressor administration (93.9%), second vasopressor administration (33.5%), and 28-day mortality (25.3%) (all $p < 0.001$).

Comparable physiological and clinical patterns were observed in the MIMIC-IV cohort, in which Cluster 3 likewise demonstrated the lowest MAP (68 mmHg [60–76]) and highest DSI (2.0 [1.8–2.3]). This group similarly exhibited the poorest outcomes, including vasopressor administration (41.0%), second vasopressor administration (16.7%), and 28-day mortality (29.0%).

Conclusion: Machine learning–derived clusters based on initial vital signs and serum lactate levels demonstrated different patterns of vasopressor use and mortality. The clinical utility of

this approach for guiding timely or targeted vasopressor therapy requires prospective validation.

Keywords: Sepsis; Septic shock; Emergency department; Intensive care units; Cluster analysis

Pre-proofs

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Despite advances in critical care, sepsis continues to pose a substantial clinical challenge, with reported mortality rates reaching 24% [2,3]. Recently, the World Health Organization declared sepsis a global health priority, highlighting its considerable burden on healthcare systems and its persistently high mortality worldwide [4].

The complex and multidimensional nature of sepsis, together with the lack of a unified classification framework, remains a major obstacle to effective treatment and accurate prognostication [5]. In recognition of this heterogeneity, numerous studies have sought to identify phenotypic subgroups of sepsis using data-driven approaches [6]. Among available machine learning models for classification, k-means clustering has emerged as one of the most frequently applied unsupervised learning techniques in sepsis research [7–9]. This method assigns patients to k distinct clusters by quantifying similarities across multidimensional clinical features.

Previous studies have suggested that cluster-based stratification may facilitate precision medicine approaches in sepsis management [10,11]. These clusters were intended to capture underlying clinical and biological characteristics that may be overlooked by conventional diagnostic criteria. However, many of the variables used in prior models, including laboratory parameters and organ dysfunction scores, are not readily available during the earliest phases of clinical management, thereby limiting their applicability in time-sensitive decision-making.

In this study, machine learning was applied to initial vital signs and serum lactate levels obtained at emergency department (ED) arrival in patients with septic shock and at intensive care unit (ICU) admission in patients with suspected infection. The objectives were

to identify distinct clusters and to evaluate their associations with vasopressor use and 28-day mortality.

METHODS

Study design, data source, and population

A retrospective cohort analysis was conducted using data from two sources: the Korean Shock Society Septic Shock (KOSS) Registry and the Marketplace for Medical Information in Intensive Care (MIMIC)-IV database.

The KOSS registry is an ongoing prospective multicenter study that includes 14 EDs in South Korea [12,13]. The registry includes patients who met the following criteria within 6 hours of ED arrival: (1) age >18 years; (2) refractory hypotension or hyperlactatemia; and (3) suspected or confirmed infection. Refractory hypotension was defined as persistent hypotension, including systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <70 mmHg, or a decrease in SBP >40 mmHg from baseline, despite the administration of a fluid bolus (20–30 mL/kg or at least 1 L of crystalloid solution administered over 30 min) [14,15]. Hyperlactatemia was defined as a serum lactate level ≥ 4 mmol/L [16]. For the KOSS cohort, we further excluded patients who met any of the following criteria: (1) transfer from another hospital; (2) missing survival outcome data; and (3) missing initial vital signs (SBP, diastolic blood pressure [DBP], MAP, heart rate [HR], respiratory rate [RR], body temperature [BT]) or missing serum lactate level.

The MIMIC-IV database contains de-identified, comprehensive clinical information on patients who presented to the ED or were admitted to the ICU at Beth Israel Deaconess Medical Center, a tertiary academic medical center in Boston, Massachusetts, United States, between 2008 and 2019 [17]. After finalizing a data use agreement and completing the “Protection of Human Subjects” training, researchers can access the MIMIC-IV database via

<https://mimic.physionet.org>. Investigators who completed the Collaborative Institutional Training Initiative (CITI) program extracted data using PostgreSQL tools version 10.16 (PostgreSQL Global Development Group, Berkeley, CA, USA) and Python version 3.7. Authorization to access the MIMIC-IV database was obtained on October 27, 2021, and data codes used for the analyses were obtained from the MIMIC Code Repository [18]. Patients aged 18 years or older with suspected or confirmed infection on the first day of ICU admission were included. Suspected infection was defined by the presence of at least one of the following: (1) a microbiological culture obtained within the first 24 hours after antibiotic prescription or on the first day of ICU admission; and/or (2) antibiotic administration within the first 72 hours after a microbiological culture or on the first day of ICU admission [1]. Patients were excluded if they met any of the following criteria: (1) missing survival outcome data; (2) missing initial vital signs or serum lactate measurements; and (3) vasopressor administration before the initial ICU vital sign measurements.

In both the KOSS and MIMIC-IV cohorts, vasopressor administration was defined as initiation of a vasopressor within 24 hours after shock diagnosis. The “time to vasopressor administration” variable was calculated as the elapsed time from the documented shock diagnosis to vasopressor initiation.

Outcomes and selected variables for clustering

The primary outcome was vasopressor administration. Secondary outcomes included second vasopressor administration and 28-day mortality.

Variables for k-means clustering were selected based on prior evidence and clinical relevance and included initial vital signs (SBP, DBP, HR, RR, BT, diastolic shock index [DSI]) and serum lactate levels [19–22]. Clustering variables were restricted to measurements that can be obtained very early in the clinical course to ensure the practical applicability of

the model for real-time decision-making. The DSI is a composite metric reflecting the loss of vascular tone characteristic of vasodilatory septic shock. Previous studies have demonstrated that patients presenting with a higher DSI experience poorer outcomes and that delayed vasopressor initiation in this subgroup is associated with increased mortality [21,23,24]. Lactate was included because, although sometimes nonspecific, it remains the most widely used bedside indicator of tissue hypoperfusion and is strongly associated with sepsis severity and the likelihood of vasopressor support [25].

Statistical methods

K-means cluster analysis was used to derive patient clusters. Analyses were performed independently for each cohort, generating separate models for the KOSS and MIMIC-IV datasets. Before clustering, all variables were standardized using z-score normalization to account for differences in measurement scales. K-means clustering was performed using the Euclidean distance metric. Because the k-means algorithm minimizes the within-cluster sum of squares (WCSS), it effectively groups observations by minimizing squared Euclidean distances within clusters. The optimal number of clusters was determined using the elbow method based on WCSS. In both cohorts, a clear inflection point was observed at $k=3$, supporting the selection of a three-cluster solution (Supplementary Figure 1).

Categorical variables are presented as frequencies and percentages, whereas continuous variables are reported as means (standard deviations, SD) or medians (interquartile ranges [IQR]), as appropriate. Differences in categorical variables were assessed using the chi-square test, and differences in continuous variables were evaluated using Kruskal–Wallis test. Survival differences among phenotypes were assessed using the

log-rank test, and adjustments for multiple comparisons were performed using the Benjamini–Hochberg (BH) method.

Statistical significance was defined as $p < 0.05$. All analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Study approval

This study was approved by the Institutional Review Board of Samsung Medical Center (2024-02-270). Given the retrospective design and use of anonymized patient data, the requirement for informed consent was waived. All procedures were conducted in accordance with relevant guidelines and regulations.

RESULTS

Baseline characteristics

In total, 10,328 patients were included in the KOSS registry. After excluding patients because of missing survival outcome data, missing initial vital sign measurements, or vasopressor administration delayed beyond 24 hours after ED arrival, 7,130 patients were included in the final KOSS cohort (Figure 1). The median patient age was 70 years (IQR, 61–78), and 58.3% were male. The median Sequential Organ Failure Assessment (SOFA) score was 6 (IQR, 4–8), and the median serum lactate level was 3.6 mmol/L (IQR, 2.1–5.8). Septic shock was identified in 57.3% of patients. Overall, 90.3% of patients received vasopressors, and 25.8% received multiple vasopressors. The median time to first vasopressor administration was 2.6 hours (IQR, 1.5–4.3). The 28-day mortality rate was 23.4%.

The MIMIC-IV cohort comprised 10,370 patients with suspected infection who were admitted to medical ICUs. The median age was 65 years (IQR, 53–77), and 53.3% were male. The median SOFA score was 5 (IQR, 3–8), and the median serum lactate level was 1.8

mmol/L (IQR, 1.3–2.6). Septic shock was present in 16.5% of patients. Overall, 31.0% of patients received vasopressors, and 9.3% received a second vasopressor. The median time to first vasopressor administration was 0.6 hours (IQR, 0.2–3.7). The 28-day mortality rate was 22.1%. Detailed baseline characteristics are presented in Table 1.

Characteristics of clusters

In the KOSS cohort, k-means clustering identified three distinct clusters (Cluster 1, Cluster 2, and Cluster 3). The median ages of patients in Cluster 1, Cluster 2, and Cluster 3 were 70 years (IQR, 62–79), 72 years (63–79), and 67 years (58–76), respectively. Median serum lactate levels were 2.7 mmol/L (1.7–4.7), 4.3 mmol/L (2.4–6.5), and 4.1 mmol/L (2.5–6.3) in Cluster 1, Cluster 2, and Cluster 3, respectively. The prevalence of septic shock was 51.5% in Cluster 1, 55.6% in Cluster 2, and 66.3% in Cluster 3. Cluster 1 demonstrated the lowest HR (94.5 beats/min; IQR, 80–105), RR (20 breaths/min; 18–22), and BT (36.9°C; 36.2–37.9). Cluster 2 exhibited the highest MAP (95 mmHg; 87–107.3) and the lowest DSI (1.5; 1.2–1.7). In contrast, Cluster 3 exhibited the lowest MAP (62 mmHg; 53–71) and the highest DSI (2.6; 2.3–3.0).

In the MIMIC-IV cohort, the median ages of patients in Cluster 1, Cluster 2, and Cluster 3 were 66 years (IQR, 55–78), 63 years (51–76), and 64 years (52–76), respectively. Median serum lactate levels were 1.6 mmol/L (1.2–2.2), 1.8 mmol/L (1.3–2.6), and 2.1 mmol/L (1.5–3.4) in Cluster 1, Cluster 2, and Cluster 3, respectively. The incidence of septic shock was 13.0% in Cluster 1, 11.2% in Cluster 2, and 27.1% in Cluster 3. Cluster 1 demonstrated intermediate SBP (111 mmHg; 100–123), DBP (61 mmHg; 54–69), the lowest HR (82 beats/min; 72–90), RR (18 breaths/min; 15–21), and BT (36.7°C; 36.4–37.1). Cluster 3 exhibited the highest SOFA score (6.0; 3.0–9.0) and DSI (2.0; 1.7–2.2), as well as the

lowest MAP (68 mmHg; 60.0–76.0). The characteristics of the three clusters are summarized in Table 2 and Figure 2.

Clusters and clinical outcomes

In the KOSS cohort, Cluster 3 showed the highest incidence of vasopressor administration at 93.9% (n=2,108), followed by Cluster 1 at 93.2% (n=2,691) and Cluster 2 at 82.1% (n=1,642) ($p<0.001$). Secondary outcomes, including second vasopressor administration and 28-day mortality, were also most frequent in Cluster 3 (33.5% and 25.3%, respectively), followed by Cluster 2 (22.6% and 23.1%) and Cluster 1 (22.2% and 22.1%) (Table 3).

In the MIMIC-IV cohort, Cluster 3 demonstrated the highest incidence of vasopressor administration (41.0%; n=1,207), followed by Cluster 1 (31.5%; n=1,381) and Cluster 2 (20.7%; n=631). Second vasopressor administration was also most frequent in Cluster 3 (16.7%; n=491), followed by Cluster 1 (6.8%; n=298) and Cluster 2 (5.8%; n=178). The 28-day mortality rate was highest in Cluster 3 (29.0%; n=854), followed by Cluster 2 (20.2%; n=615) and Cluster 1 (18.7%; n=821) (Table 3).

Figure 3 illustrates the cumulative incidence of the primary outcome across the three clusters. The cumulative incidence of first vasopressor administration differed significantly among clusters in both cohorts (all $p<0.001$). Cluster 3 demonstrated the earliest and steepest increase in cumulative incidence, indicating a higher likelihood of early vasopressor initiation within the first 12 hours, whereas Cluster 2 exhibited the lowest incidence during this period. The cumulative incidence of second vasopressor administration was likewise highest in Cluster 3 compared with the other clusters (all $p<0.001$) (Figure 4A and 4B). The cumulative incidence of 28-day mortality was highest in Cluster 3 (KOSS cohort: Cluster 1 vs. Cluster 3,

p=0.02; Cluster 2 vs. Cluster 3, p=0.16; MIMIC-IV cohort: all p<0.001) (Figure 4C and Figure 4D).

DISCUSSION

In this study, we applied unsupervised machine learning to early clinical data, including initial vital signs and serum lactate levels, collected from two independent cohorts: patients with septic shock presenting to the ED (the KOSS cohort) and patients admitted to the ICU with suspected infection (the MIMIC-IV cohort). In both cohorts, k-means clustering identified three distinct clusters with differing physiological profiles and clinical outcomes, including vasopressor administration and 28-day mortality.

The three clusters demonstrated clinical differences in circulatory status and tissue perfusion. Cluster 1 was characterized by a distinct hemodynamic profile featuring significant hypotension (the second lowest MAP) accompanied by the lowest serum lactate levels, in contrast to the overt shock observed in Cluster 3. Although this group exhibited the lowest HR, RR, and BT, the substantial requirement for vasopressors—ranking second in both cohorts—was likely driven by the need to correct hypotension. However, the relative absence of hyperlactatemia suggests that tissue hypoperfusion or metabolic dysfunction was less severe compared with the other clusters. This phenotype may therefore represent a stage of “hypotension without severe tissue hypoperfusion,” in which the overall severity of shock is relatively lower. In contrast, Cluster 2 demonstrated relatively preserved blood pressure despite elevated lactate levels, consistent with occult hypoperfusion. Although not overtly hypotensive, these patients may have experienced microcirculatory or metabolic dysfunction that was not adequately captured by MAP alone [26]. Vasopressor administration was lowest in this group; however, the 28-day mortality rate was intermediate, raising the possibility that this phenotype may be less readily recognized early. While clearly observed in the KOSS

cohort, this pattern was less distinct in the MIMIC-IV cohort, where lactate elevation was mild. Cluster 3 represented a state of profound vasoplegia or overt circulatory shock, characterized by the highest DSI, lowest MAP, and elevated serum lactate levels. This group had the highest rates of vasopressor administration and 28-day mortality in both cohorts, indicating a strong association between physiological severity and adverse outcomes. The early and steep increase in vasopressor use in this cluster suggests that more aggressive and urgent treatment approaches may be required.

Patients requiring vasopressor support typically represent the more severe end of the sepsis spectrum and may therefore be candidates for earlier targeted interventions. Although the optimal timing of vasopressor initiation remains controversial, prompt therapy may shorten the duration of deleterious hypotension and facilitate faster hemodynamic stabilization [27–29]. Our findings indicate that simple, readily available clinical parameters can distinguish patient subgroups with differing physiological risk profiles. With adequate validation, incorporating cluster-based information into clinical workflows may assist early clinical assessment and support clinician recognition of patients with divergent risk trajectories. Because its application remains exploratory, with further validation, this framework warrants investigation as part of an automated clinical decision support system or bedside monitoring tool.

Unsupervised cluster analysis was used to identify patient subgroups with heterogeneous characteristics [30–32]. Prior studies have proposed sepsis cluster classifications using clinical variables, biomarkers, or transcriptomic data [10,11,33–35]. Seymour et al. suggested that clustering could help elucidate heterogeneity in treatment effects by deriving four sepsis phenotypes associated with host-response patterns and 28-day and 365-day mortality outcomes [10]. Zhou et al. identified sepsis phenotypes using readily available clinical parameters and demonstrated improved performance in predicting 28-day

mortality compared with traditional non-clustering methods [34]. However, many of these approaches rely on complex or delayed variables, which limits their applicability in early care settings. In contrast, our approach relied exclusively on variables available at ED arrival or ICU admission. This distinction highlights the feasibility of implementing early clustering models in time-sensitive environments such as emergency and critical care.

This study has several limitations. First, the retrospective design limits causal inference. To improve generalizability, we applied the same clustering framework to two large independent cohorts drawn from distinct clinical settings. While this strategy enhanced external validity, it may also have introduced heterogeneity related to patient characteristics and clinical practice patterns. Second, the KOSS and MIMIC-IV cohorts originated from different healthcare environments, which may have contributed additional variability. However, applying a consistent clustering methodology across both datasets helped mitigate this concern and supported the reproducibility of observed patterns. Third, the use of a limited set of early clinical variables—initial vital signs and serum lactate levels—may not fully capture the underlying complexity of sepsis. In addition, unmeasured confounders, including infection source, comorbidities, and fluid resuscitation practices, may have influenced the results. Fourth, k-means clustering was selected to prioritize model transparency and reproducibility over algorithmic complexity. Although deep learning approaches are powerful, their black-box nature limits clinical interpretability. In contrast, k-means clustering yielded intuitive and reproducible centroids that represent average patient profiles and are well suited to structured clinical data [36–38]. Finally, clustering patterns were largely consistent across cohorts, but some variations were observed. Therefore, prospective validation and iterative model refinement are required to confirm the robustness and clinical applicability of these findings.

Machine learning–derived clusters based on initial vital signs and serum lactate levels demonstrated distinct patterns of vasopressor use, including second vasopressor administration, and 28-day mortality in an ED septic shock cohort and an ICU suspected infection cohort. These findings suggest that clustering using readily available clinical parameters may aid early risk stratification; however, prospective validation is required before such approaches can be used to inform vasopressor initiation decisions in clinical practice.

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Ethical approval: This study was approved by the Institutional Review Board of Samsung Medical Center (2024-02-270). Given the retrospective nature of the study and use of anonymized patient data, the requirement for informed consent was waived. All studies were performed in accordance with the relevant guidelines and regulations.

Conflicts of Interest: None of the authors have any competing interests to declare.

Contributors: DJ, MC, and HY conceptualized and designed the study, collected the data, performed data analysis, drafted the initial manuscript, and reviewed and revised the final manuscript. SJM, JEP, GTL, SYH, SPC, and THL participated in the drafting and review of the final manuscript. TGS provided guidance and supervision throughout the study, reviewed study results, and participated in the drafting and review of the final manuscript.

Pre-proofs

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Pre-proofs

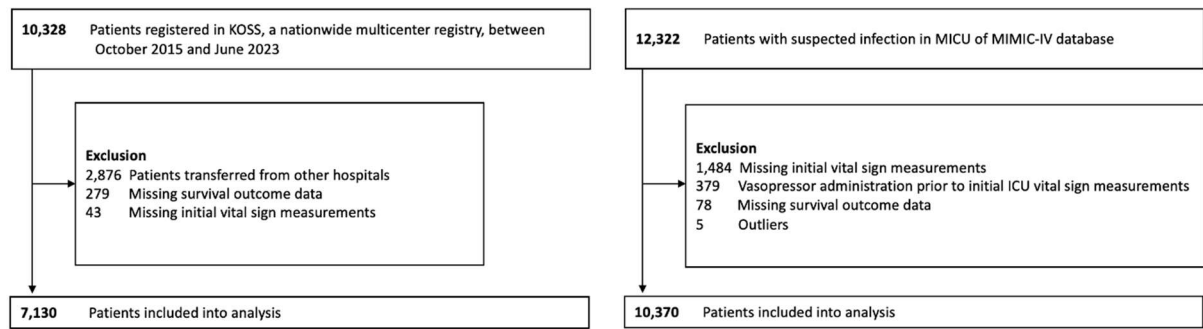


Figure 1. Study flow.

KOSS, Korean Shock Society; ED, emergency department; ICU, intensive care unit; MIMIC, Marketplace for Medical Information in Intensive Care Unit.

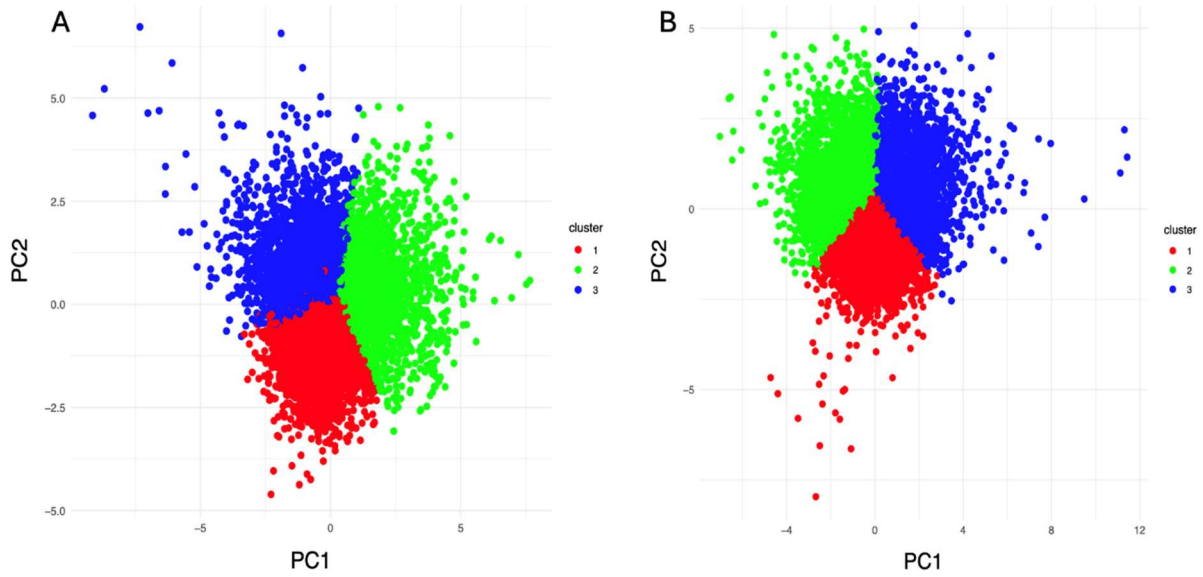


Figure 2. Identified clusters using k-means clustering.

Panels A and B show k-means clustering applied to the KOSS and MIMIC-IV cohorts, respectively, visualized using the first two PCs derived from the initial clinical variables: serum lactate, SBP, DBP, DSI, HR, RR, and BT.

$$PC1 = (0.02 \times \text{lactate}) + (0.588 \times \text{SBP}) - (0.511 \times \text{DSI}) + (0.610 \times \text{DBP}) - (0.014 \times \text{HR}) + (0.097 \times \text{RR}) + (0.102 \times \text{BT})$$

$$PC2 = (0.248 \times \text{lactate}) + (0.130 \times \text{SBP}) + (0.400 \times \text{DSI}) + (0.089 \times \text{DBP}) + (0.665 \times \text{HR}) + (0.416 \times \text{RR}) + (0.372 \times \text{BT})$$

Each point represents a patient, and the color indicates the cluster assignment identified through unsupervised learning. Red, green, and blue denote Clusters 1, 2, and 3, respectively. Because clustering and PCA were performed independently in each cohort, the cluster labels were derived separately, and the PCA axis directions may differ due to the inherent sign indeterminacy of PCs.

KOSS, Korean Shock Society; MIMIC, Medical Information Market for Intensive Care; PC, principal component; PCA, principal component analysis; SBP, systolic blood pressure;

DBP, diastolic blood pressure; DSI, diastolic shock index; HR, heart rate; RR, respiratory rate; BT, body temperature

Pre-proofs

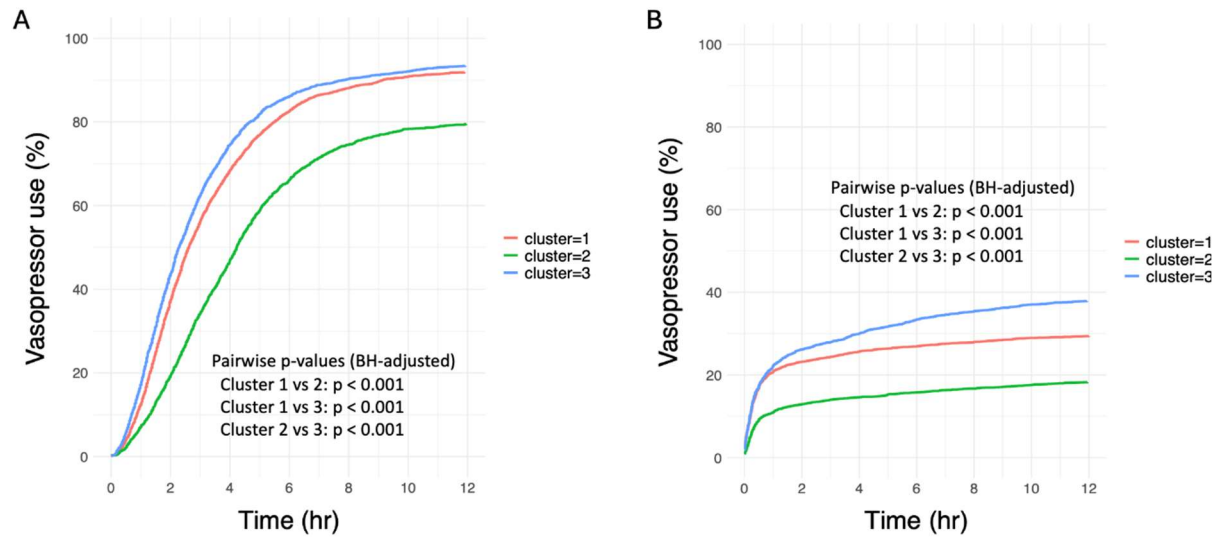


Figure 3. Cumulative incidence of the primary outcome.

Panel A shows the cumulative incidence of vasopressor administration in the KOSS cohort.

Panel B shows the corresponding outcomes for the MIMIC-IV cohort. The red line represents Cluster 1, the green line denotes Cluster 2, and the blue line represents Cluster 3.

KOSS, Korean Shock Society; MIMIC, Marketplace for Medical Information in Intensive Care; h, hours

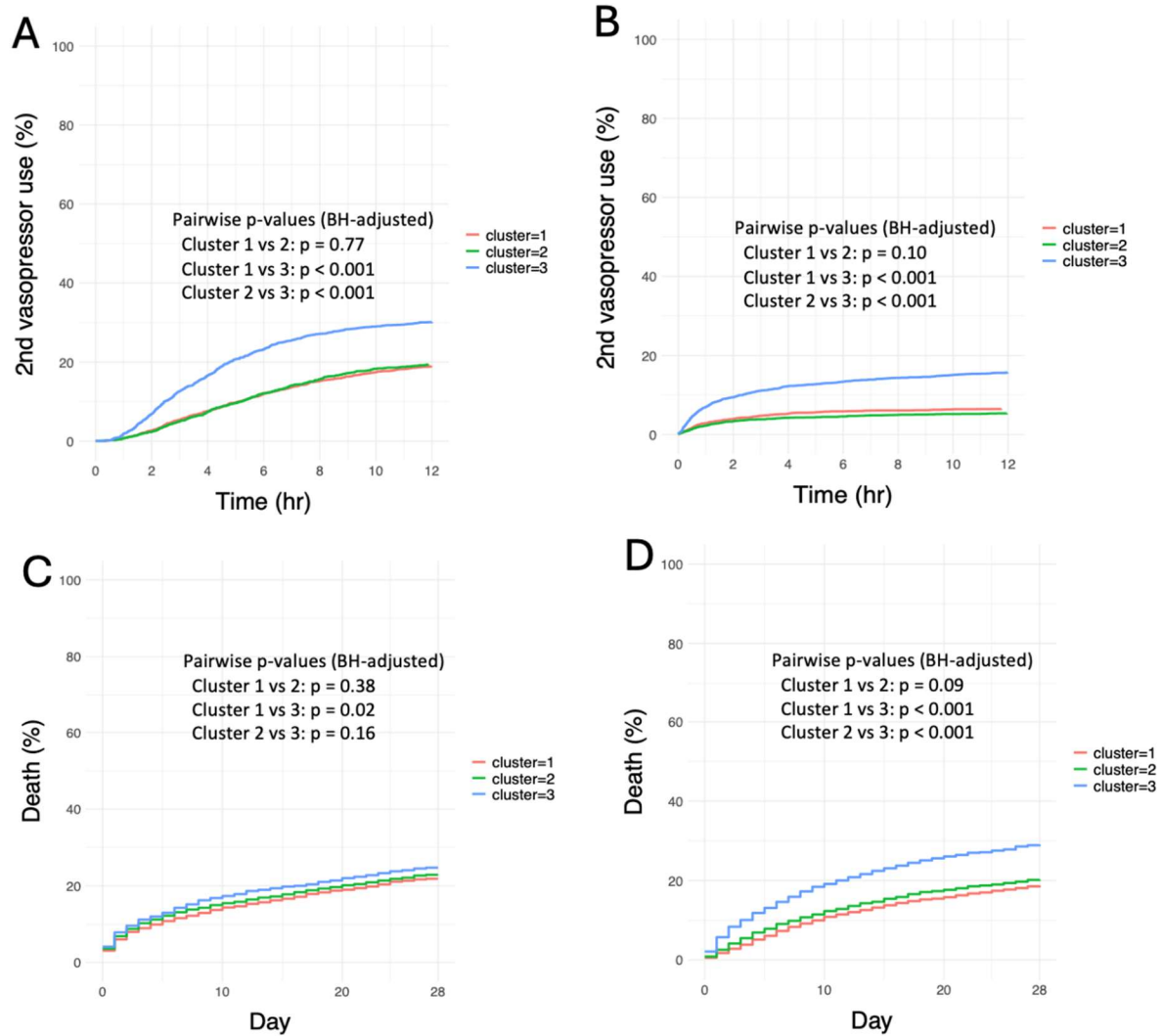


Figure 4. Cumulative incidence of the secondary outcomes.

Panels A and B illustrate the cumulative incidence of second vasopressor administration in the KOSS and MIMIC cohorts, respectively. Panels C and D present the cumulative incidence of 28-day mortality in the KOSS and MIMIC cohorts, respectively. The red line represents Cluster 1, the green line denotes Cluster 2, and the blue line represents Cluster 3. KOSS, Korean Shock Society; MIMIC, Marketplace for Medical Information in Intensive Care; h, hours

Table 1. Baseline characteristics

	KOSS Cohort	MIMIC-IV Cohort
	N=7,130	N=10,370
Age (median [IQR]), y	70 (61-78)	65 (53-77)
Male sex, N (%)	4,160 (58.3)	5,526 (53.3)
SBP (median [IQR]), mmHg	93 (78-115)	117 (102-135)
DBP (median [IQR]), mmHg	57 (48-69)	65 (55-78)
MAP (median [IQR]), mmHg	69.3 (58-84)	78 (67-91)
RR (median [IQR]), breaths per minute	20 (18-24)	20 (17-25)
HR (median [IQR]), beats per minute	111.5 (94-129)	95 (81-109)
BT (median [IQR]), °C	37.8 (36.7-38.8)	36.8 (36.5-37.2)
DSI (median [IQR])	1.9 (1.5-2.4)	1.4 (1.2-1.8)
Lactate (median [IQR]), mmol/L	3.6 (2.1-5.8)	1.8 (1.3-2.6)
Total SOFA score (median [IQR])	6 (4-8)	5 (3-8)
Septic shock*	4,087 (57.3)	1,707 (16.5)
Time to vasopressor administration (median [IQR]), hours	2.6 (1.5-4.3)	0.6 (0.2-3.7)
Norepinephrine use, N (%)	6,428 (90.2)	2,776 (26.8)
Vasopressin use, N (%)	1,693 (23.7)	601 (5.8)
Dopamine use, N (%)	82 (1.2)	203 (2)
Epinephrine use, N (%)	80 (1.1)	103 (1)
Vasopressor administration, N (%)	6,441 (90.3)	3,219 (31.0)
Second vasopressor administration, N (%)	1,842 (25.8)	967 (9.3)

28-day mortality, N (%)	1,668 (23.4)	2,290 (22.1)
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*Septic shock that meets the criteria defined by the Sepsis-3. KOSS, Korean Shock Society;

MIMIC, Marketplace for Medical Information in Intensive Care; IQR, interquartile range;

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure;

RR, respiratory rate; HR, heart rate; BT, body temperature; DSI, diastolic shock index;

SOFA, Sequential Organ Failure Assessment

Pre-proofs

Table 2. Characteristics of clusters

	KOSS cohort				MIMIC-IV cohort			
	Cluster 1	Cluster 2	Cluster 3	p-value	Cluster 1	Cluster 2	Cluster 3	p-value
	N=2,886	N=1,999	N=2,245		N=4,384	N=3,045	N=2,941	
Age (median [IQR]), y	70 (62–79)	72 (63–79)	67 (58–76)	0.001	66 (55–78)	63 (51–76)	64 (52–76)	0.001
Male sex, N (%)	1,687 (58.5)	1,140 (57.0)	1,333 (59.4)	0.30	2,408 (54.9)	1,659 (54.5)	1,459 (49.6)	0.001
SBP (median [IQR]), mmHg	85 (74–97)	131 (117–148)	84 (71–96)	0.001	111 (100–123)	142 (131–155)	104 (93–117)	0.001
DBP (median [IQR]), mmHg	53 (46–60)	78 (70–89)	51 (43–58)	0.001	61 (54–69)	86 (77–96)	57 (49–64)	0.001
MAP (median [IQR]), mmHg	63.7 (56–71.7)	95 (87–107.3)	62.3 (53–70.7)	0.001	74 (67–81)	98 (91–108)	68 (60–76)	0.001
RR (median [IQR]), breaths per minute	20 (18–22)	22 (20–28)	22 (20–26)	0.001	18 (15–21)	22 (18–27)	23 (19–28)	0.001
HR (median [IQR]), beats per minute	94.5 (80–105)	116 (101–131)	130 (119–141)	0.001	82 (72–90)	102 (89–114)	110 (100–121)	0.001

	36.9	38.3	38.4		36.7	36.9	36.9	
BT (median [IQR]), °C	(36.2–37.9)	(37.1–39.2)	(37.5–39.2)	0.001	(36.4–37.1)	(36.6–37.3)	(36.6–37.6)	0.001
DSI (median [IQR])	1.8 (1.5–2.1)	1.5 (1.2–1.7)	2.6 (2.3–3)	0.001	1.4 (1.2–1.6)	1.2 (1–1.4)	2.0 (1.7–2.2)	0.001
Lactate (median [IQR]), mmol/L	2.7 (1.7–4.7)	4.3 (2.4–6.5)	4.1 (2.5–6.3)	0.001	1.6 (1.2–2.2)	1.8 (1.3–2.6)	2.1 (1.5–3.4)	0.001
Total SOFA score (median [IQR])	6 (4–8)	5 (3–8)	6 (4–9)	0.001	5 (3–8)	5 (3–7)	6 (3–9)	0.001
Septic shock*	1,486 (51.5)	1,112 (55.6)	1,489 (66.3)	0.001	569 (13.0)	340 (11.2)	798 (27.1)	0.001
Time to vasopressor administration (median [IQR]), hour	2.4 (1.4–4.2)	3.6 (2.1–5.3)	2.1 (1.2–3.6)	0.001	0.4 (0.1–2.4)	0.8 (0.2–5.4)	0.8 (0.2–4.3)	0.001
Norepinephrine use, N (%)	2,686 (93.1)	1,637 (81.9)	2,105 (93.8)	0.001	1,177 (26.8)	545 (17.9)	1,054 (35.8)	0.001
Vasopressin use, N (%)	575 (19.9)	415 (20.8)	703 (31.3)	0.001	152 (3.5)	104 (3.4)	345 (11.7)	0.001
Dopamine use, N (%)	39 (1.4)	22 (1.1)	21 (0.9)	0.37	107 (2.4)	38 (1.2)	58 (2)	0.001
Epinephrine use, N (%)	31 (1.1)	19 (1)	30 (1.3)	0.47	19 (0.4)	21 (0.7)	63 (2.1)	0.001

*Septic shock that meets the criteria defined by the Sepsis-3. KOSS, Korean Shock Society;

MIMIC, Marketplace for Medical Information in Intensive Care; IQR, interquartile range;

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Pre-proofs

	KOSS cohort				MIMIC-IV cohort			
	Cluster 1	Cluster 2	Cluster 3	p-value	Cluster 1	Cluster 2	Cluster 3	p-value
	N=2,886	N=1,999	N=2,245		N=4,384	N=3,045	N=2,941	
Vasopressor administration, N (%)	2,691 (93.2)	1,642 (82.1)	2,108 (93.9)	0.001	1,381 (31.5)	631 (20.7)	1,207 (41.0)	0.001
Second vasopressor administration, N (%)	640 (22.2)	451 (22.6)	751 (33.5)	0.001	298 (6.8)	178 (5.8)	491 (16.7)	0.001
28-day mortality, N (%)	639 (22.1)	462 (23.1)	567 (25.3)	0.001	821 (18.7)	615 (20.2)	854 (29.0)	0.001

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