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Analysis of the heterogeneous treatment effect of vasoactive drug dosage and time on hospital mortality across different sepsis phenotypes: a retrospective cohort study

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Abstract

Background The heterogeneity of sepsis poses challenges for the individualized treatment of vasoactive drugs.

Methods This study used data from ICUs in MIMIC-IV (2008–2019) and eICU (2014–2015) databases, identified sepsis by sepsis-3 criteria, and stratified sepsis into phenotypes by consensus K-means. The norepinephrine equivalence (NEE) formula balance treatment of different vasoactive drugs, with NEE captured hourly for up to 72 h to record both time of use and dosage. The logistic regression model, including phenotype–dosage–time interactions, examined heterogeneous treatment effects on hospital mortality. To address confounding, three models were fitted: Model 1 unadjusted, Model 2 adjusted for age and sex, and Model 3 additionally included 7 clinical variables identified via machine learning and directed acyclic graph. Nonlinear dosage was further analyzed based on restricted cubic splines. *P* values and *P* for interaction were Bonferroni-adjusted.

Results A total of 54,673 sepsis patients were included for phenotype identification, and 8,803 patients were further analyzed to evaluate heterogeneous treatment effect of vasoactive drugs. Four sepsis phenotypes were identified: A, B, C and D. Phenotype D was the most severe subgroup, followed by phenotype C, while phenotypes A and B were mild subgroups. In Model 3, each 0.05 μg/kg/min increase in NEE dosage was linked to higher hospital mortality (OR 1.328, 95% CI 1.314–1.342; $p < 0.001$). Longer NEE time of use also significantly increased mortality risk (OR 1.006, 95% CI 1.005–1.007; $p < 0.001$). In addition, these associations varied significantly by phenotype (*P* for interaction < 0.001). In RCS model, phenotype A consistently showed higher mortality than the other phenotypes at NEE dosages of 0.1–0.5 μg/kg/min, with this gap increasing over time, showing a clear dosage–time dependence. Phenotype B displayed lower overall mortality but the steepest relative risk of hospital mortality increased as dosage and time (OR of dosage: 1.309; OR of time: 1.005) in Model 3. Phenotype C reached the highest mortality risk when dosages exceeded 0.5 μg/kg/min, which was dosage dependence. Finally, phenotype D followed a U-shaped curve in RCS model, and minimum mortality was around 20% at 0.03–0.05 μg/kg/min.

Conclusions Sepsis phenotypes differ significantly in their treatment effects of vasoactive drug dosage and time of use, indicating the need for phenotype-specific treatment strategies to improve outcomes.

Keywords Sepsis, Phenotypes, Vasoactive drugs, Norepinephrine equivalence, Critical care

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Introduction

Sepsis is a syndrome of organ dysfunction caused by infection [1] and the leading cause of death among critically ill patients worldwide [2, 3]. Currently, sepsis bundle management has significantly reduced the mortality of sepsis [4]. Since sepsis is widely considered to have strong heterogeneity [5–7], an increasing number of researchers have suggested that the one-size-fits-all treatment should not be used [8–11]. Therefore, in the clinical treatment, doctors should classify sepsis phenotypes and implement individualized treatment based on the sepsis characteristics of each phenotype, so that the treatment effect can be maximized and the patient prognosis improved.

In previous studies, the sources of sepsis heterogeneity have been explored from multiple perspectives, including clinical data, immune inflammation, and gene expression. For example, K-means clustering was used to identify four sepsis phenotypes based on clinical characteristics [12]; SRS1 and SRS2 phenotypes were established based on the transcriptome of peripheral blood leukocytes [13] and the whole genome blood gene expression spectrum was used to identify the MASK1-4 phenotypes of sepsis using consensus K-means [14]. In the above studies, unsupervised clustering methods have not only been widely used in the study of sepsis heterogeneity, but have also demonstrated their scientificity and effectiveness in the identification of subtypes in various diseases [15–17]. These methods do not require predefined classification criteria and can reveal potential phenotypic characteristics from high-dimensional complex data [18], providing researchers with new perspectives. Unsupervised learning methods, such as K-means clustering, gaussian mixture models (GMM), and hierarchical clustering, are widely used for data analysis and pattern recognition. While K-means clustering is a popular choice due to its simplicity and efficiency, it has limitations in handling complex data structures, such as non-spherical or overlapping clusters [19]. GMM, on the other hand, provide a probabilistic framework that can model more intricate data distributions, making them suitable for scenarios, where clusters are not well-separated [20]. Hierarchical clustering offers a different approach by constructing a tree-like structure (dendrogram) that reveals the hierarchical relationships within the data and identifies clusters of complex shapes, not just spherical clusters [21]. In this study, we primarily employ the K-means clustering to perform phenotype identification of sepsis based on clinical characteristics, which is compared with other methods in the following text, but other clustering methods are also viable extensions for future research.

Sepsis phenotyping can inform treatment decisions, such as fluid therapy and immunotherapy. Previous studies have shown that certain phenotypes (based on vital–sign trajectories) respond differently to balanced saline solutions than to normal saline [22], and that sepsis phenotypes vary in their fluid resuscitation outcomes [23]. SRS2 phenotypes may be more susceptible to increased mortality when receiving hydrocortisone [13]. However, compared with fluid therapy and immunotherapy, the research between application of vasoactive drugs and sepsis heterogeneity is relatively lacking [24]. As an important part of sepsis treatment, optimizing the use of vasoactive drugs can improve the rationality and effectiveness of sepsis treatment, as well as improve patient outcomes and achieve precision treatment [5]. Therefore, we will explore the response of different sepsis phenotypes to vasoactive drugs to provide new perspectives for sepsis treatment.

Our research aims to systematically investigate the treatment effect between vasoactive drugs and sepsis phenotype. The sepsis phenotype is identified using an unsupervised clustering method, and we seek to obtain a more detailed understanding of the effect of the sepsis phenotype on the dosage and duration of use of vasoactive drugs.

Methods

The overall workflow chart is illustrated in Fig. 1.

Databases and participants

Two publicly available critical care databases were utilized: (1) the training cohort comprised data from the Medical Information Mart for Intensive Care IV v2.2 (MIMIC) [25] and (2) the validation cohort consisted of data from the eICU Collaborative Research Database (eICU) [26].

All ICU patients admitted with a diagnosis of sepsis were eligible for inclusion in the study, with sepsis defined as the presence of infection and a Sequential Organ Failure Assessment (SOFA) score of ≥ 2 [1]. For the analysis of sepsis phenotypes, the only exclusion criterion was age < 18 years. Subsequently, to evaluate the treatment effects between vasoactive drugs and different sepsis phenotypes, we further excluded patients with conditions that could significantly interfere with the action of vasoactive drugs (such as myocardial infarction, neurological diseases, tumors, and AIDS) and selected sepsis patients who had received vasoactive drugs from the MIMIC cohort.

Depending on the source of the first ICU, we considered sepsis patients from Surgical Intensive Care Unit (SICU), Trauma SICU, Neuro SICU, Cardiac SICU as surgical sepsis, and for sepsis patients from comprehensive ICU or medical ICU as non-surgical sepsis. In addition, we categorized the types of sepsis patients into community-acquired and hospital-acquired sepsis based

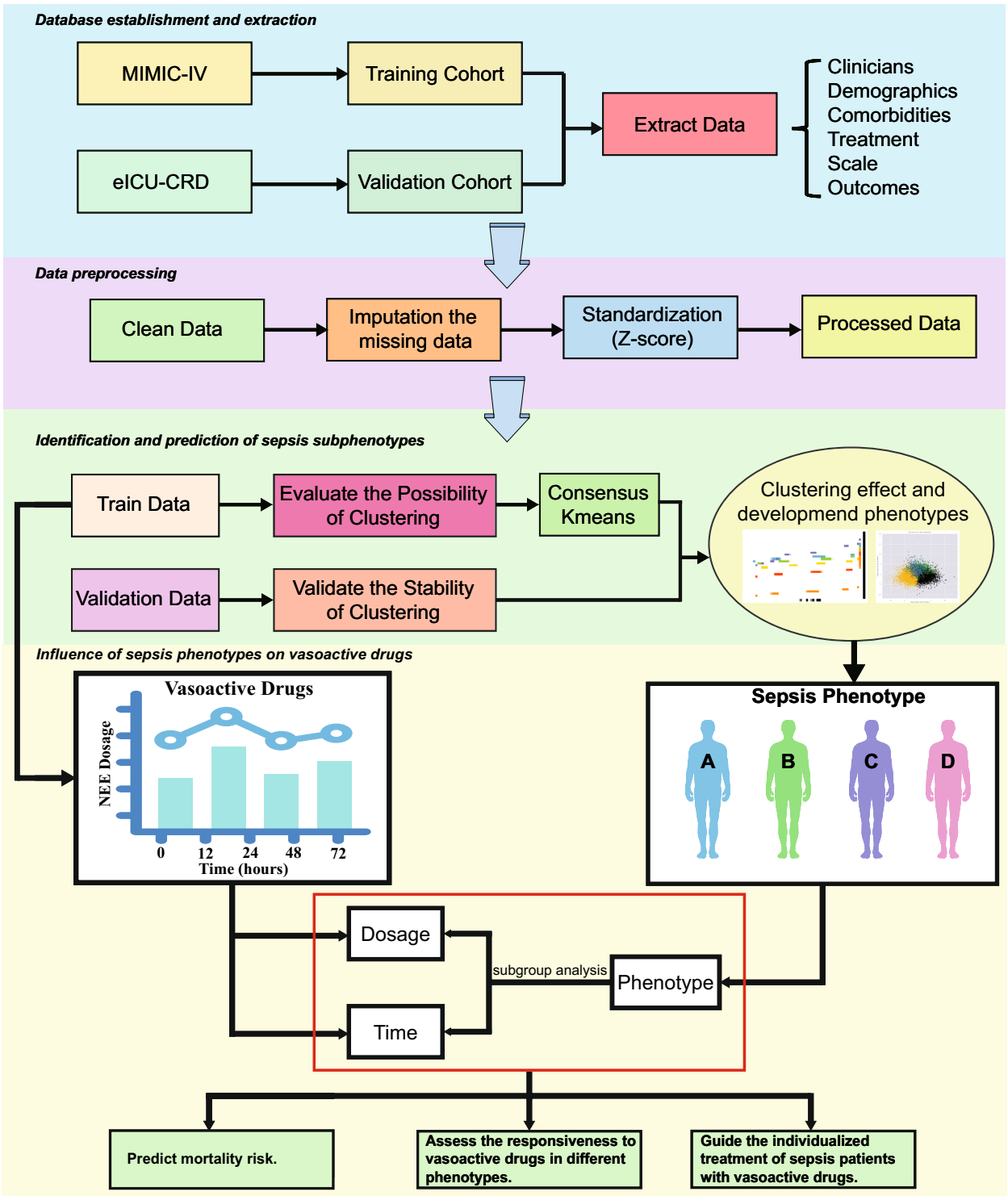

Fig. 1 Workflow chart of the research. Initially, the MIMIC cohort was designated as the training data, while the eICU cohort served as the validation data. Relevant data of sepsis patients, including clinical variables, demographic variables, comorbidity variables, treatment variables, scales variables, and observed outcomes, were extracted from both cohorts. Subsequently, the extracted data set underwent data cleansing, including the removal of highly correlated variables, interpolation of missing values, and standardization. In the next step, the training cohort underwent consensus K-means clustering to identify sepsis subphenotypes, and the stability and generalizability of the clustering results were validated using the validation cohort. Finally, we filtered the data on vasoactive drugs in the training cohort to extract a flow of hourly vasoactive drug dosages. Using the dosage and time of use of vasoactive drugs, we analyzed the mortality risk in different phenotypes of sepsis to examine the influence of sepsis heterogeneity on the efficacy of vasoactive drugs

on the time of diagnosis of sepsis. Community-acquired sepsis was defined as sepsis presenting at the time of admission or within 48 h of hospitalization, whereas hospital-acquired sepsis was defined as sepsis presenting 48 h or more after admission [27].

Preprocessing of data

Clinical variables were extracted from the data set for the 3 days preceding admission, and for each variable, the maximum, minimum, and mean values were obtained. Based on the training cohort, variables with over 50% missing values or Pearson correlation coefficient ≥ 0.8 were eliminated (When multiple variables exhibit high pairwise correlations, we retained the variable with the highest number of correlations to other variables, as it is likely to capture the most shared information; When the two variables are consistent, the choice is based on clinical experience.), resulting in 61 variables for interpolating data and further analysis (see supplementary material: data preprocessing, pages 1–3 for details).

In the treatment of sepsis, especially septic shock, there is no doubt that the position of norepinephrine is a first-line vasoactive drug. However, due to the complex and dynamic clinical conditions of patients, both monotherapy and combination therapy with vasoactive drugs are commonly used. Hence, this study considered six drugs: norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine and dobutamine. To quantify the dosage of treatment with different vasoactive drugs (monotherapy or combination therapy), we employed the Norepinephrine Equivalence formula to obtain the dosage equivalent to norepinephrine [28]. We extracted the data flow of vasoactive drug dosages used from the start of use and within 3 days (1-hourly data streams), and replaced outliers with 3 standard deviations.

Definition of NEE time of use and dosage

We tracked NEE use in 1-h intervals for up to 72 h (or until discontinuation), creating a two-dimensional record: the time of use dimension (hour 0, defined as the time of initial vasoactive drug use, to hour 72) and the dosage dimension (the amount of NEE administered during each hour). This structure allows us to analyze both how long NEE was administered and the specific dosage given at each hour.

Identification and validation of sepsis phenotypes

Clustering was employed to identify distinct sepsis phenotypes. We employed K-means clustering as our primary clustering method. While K-means assumes that data are distributed in spherical clusters, which may not always hold true for real-world clinical data, it remains one of the most efficient and computationally cost-effective methods, particularly for large databases. To address the potential limitations of this assumption and ensure the robustness of our results, we conducted a comprehensive comparative analysis of several unsupervised clustering algorithms, including K-mean clustering, hierarchical clustering, OPTICS clustering, GMM clustering, SOM clustering, and Birch Clustering (supplementary material: Supplementary Table 1). Besides, Hopkins statistic and reachability plot were used to analyze the suitability of data for K-means clustering [29, 30]. In addition, to mitigate the sensitivity of K-means to extreme values and variable scaling, we standardized all variables prior to clustering (Z-score). Furthermore, we evaluated the effect of distance metrics on K-means clustering by comparing Euclidean distance and Mahalanobis distance (supplementary material: Supplementary Table 1). Based on this analysis, K-means clustering (Euclidean distance) demonstrated superior performance in capturing the underlying structure of our databases, justifying its reasonability and effectiveness for identification of sepsis phenotypes.

Optimal clustering (K) was determined by evaluating the flatness of the consensus cumulative density function (CDF) curve and identifying the elbow point of the relative change in the area under the CDF curve [31] (see supplementary material: clustering of sepsis patients, pages 5–8 for details). The sepsis phenotypic attribution was determined by calculating the Euclidean distances between their clinical characteristics and the individual clusters, and the cluster corresponding to the smallest Euclidean distance was used as the sepsis phenotype. Finally, the consensus K-means clustering outcomes were externally validated using the validation cohort.

Model construction

To investigate the heterogeneous treatment effect between the sepsis phenotype and vasoactive drugs, a logistic regression model was established, with the NEE dosage and time of use as treatment factors, treatment factors by sepsis phenotype interaction terms as independent variables, and hospital mortality as the outcome. Since the treatment of vasoactive drugs often depend on both dosage and time of use, the interaction term between NEE dosage and time of use was also included in the model. The regression equation incorporates pairwise interactions:

$$\begin{aligned}\text{Hospital mortality} \sim\ & \beta_0 + \beta_1 \text{dosage} + \beta_2 \text{time} \\ & + \beta_3 \text{phenotype} + \beta_4 \text{dosage} \times \text{phenotype} + \beta_5 \text{time} \\ & \times \text{phenotype} + \beta_6 \text{dosage} \times \text{time} + \varepsilon\end{aligned}$$

where in the formula, the dosage was represented by the NEE dosage, the time referred to the NEE time of use, and the phenotype referred to the sepsis phenotype, with β denoting the coefficient and ε representing the residual.

For adjustment of confounding factors, three models constructed for sensitivity analysis. Model 1 did not adjust for confounding factors. Model 2 adjusted only for age and sex. Model 3 adjusted for confounding factors screened using machine learning and directed acyclic graph (DAG) (see supplementary material: confounding factors, pages 9–12 for details). To investigate the nonlinear influence of the NEE dosage, we further optimized the model using Restricted Cubic Spline (RCS).

Statistical analysis

Continuous variables were assessed for normal distribution utilizing the Kolmogorov–Smirnov test, and subsequently expressed as mean (standard deviation) or median (interquartile range, IQR). Categorical variables were presented as numbers (percentages). Differences between subgroups were compared using the Wilcoxon test for continuous data and the chi-square test for categorical data. Analysis of variance (ANOVA) was used to understand if there was a significant interaction between sepsis phenotypes and NEE treatment. Due to the inflating effect of multiple comparisons on the Type I error, both the *P* values and the P for the interaction have been Bonferroni adjusted. A two-sided *P* value <0.05 was considered statistically significant.

Results

Patients and study cohorts

In this study, a total of 54,673 patients were diagnosed with sepsis to identify sepsis phenotypes, with 33,177 patients in the MIMIC cohort, and 21,496 patients in the eICU cohort. After excluding myocardial infarction, neurological diseases, tumors, and AIDS, we screened 8,803 sepsis patients who had used vasoactive drugs from the MIMIC cohort (supplementary material: Supplementary Fig. 1). In addition, the missing values of the clinical data for sepsis patients, the correlations between clinical data, and the results of data interpolation were detailed in supplementary material: Supplementary Figs. 2–4.

Comparison of sepsis phenotype characteristics and outcomes

Consensus clustering identified four distinct sepsis phenotypes: A, B, C, and D (Fig. 2). The parameters required to specifically define the sepsis phenotype are detailed in the supplementary material: Supplementary Table 2. Phenotypes A and B represented milder cases, with lower adverse event rates. Phenotype A included the youngest patients with stable blood pressure and high hemoglobin levels. Phenotype B, the largest number of subgroup, had stable respiratory and circulatory systems, higher nutritional status, and lower creatinine and anion gap levels, along with the lowest WBC counts, indicating a mild inflammatory response. Phenotype C showed features, such as carbon dioxide retention, hypochlorhydria, and hypercalcemia. Phenotype D exhibited the most severe multi-organ dysfunction, including renal insufficiency, anemia, hemodynamic instability, coagulation abnormalities, and acidosis, with the highest infection severity and the worst nutritional status. In MIMIC cohort, compared with community-acquired sepsis, hospital-acquired sepsis accounted for a smaller proportion at 9.45%. Furthermore, as the severity of sepsis phenotypes increases, the proportion of hospital-acquired sepsis gradually decreases, with only 5.43% in phenotype D. Approximately 2.1% of sepsis patients undergo organ transplantation, with the highest proportion being phenotype D patients, at 3.6%. Approximately 26.98% of patients received immunosuppressive therapy during hospitalization, with the highest proportion observed in phenotype C (36.74%) and the lowest in phenotype B (18.71%). This group had the highest rates of hospital mortality (34.51%), longest hospital stay (10.53 [5.52, 19.87] days), and ICU stay (3.66 [1.92, 7.56] days). Kaplan–Meier curves showed lower cumulative risks at 28 and 90 days

(See figure on next page.)

Fig. 2 Results of clustering sepsis patients in the MIMIC cohort. **A** Hopkins statistic, depicted in the left plot, evaluates the clusterability of the data. A value greater than 0.7 suggests that the data are clusterable, while a value around 0.5 indicates random data, and a value close to 0 suggests uniformly distributed data. The reachability plot, shown on the right, demonstrates the smooth increase in reachability distances, indicating the suitability of ensemble clustering (e.g., consensus K-means clustering). **B** Consensus cumulative distribution function (CDF) plot, depicted in the top plot, displays the stability of clustering with varying numbers of clusters (k). The elbow point at k = 4 in the bottom plot indicates the optimal number of clusters. **C** Top 20 important clustering features are presented. **D** Silhouette coefficient, shown in the left plot, assesses the quality of clustering, with values close to 1 indicating reasonable clustering and values close to −1 suggesting incorrect cluster assignments. The right plot displays the distribution of consensus K-means clustering results projected onto a two-dimensional plane using principal component analysis (PCA). **E** Chordal graph illustrates the relationship of subphenotypes to features (vital signs, blood gas analysis, blood routine, biochemistry, coagulation). **F** Subplots compare the features of different sepsis subphenotypes after Z-score standardization: (variable–mean)/standard deviation. **G** Radar charts display the relationships and comparisons between individual subphenotypes and comorbidities. **H** Radar charts demonstrate the relationships and comparisons between individual subphenotypes and scales. **I** Radar charts exhibit the relationships and comparisons between individual subphenotypes and the use of vasoactive drugs. **J** Cumulative risk curves for death within 28 days of hospitalization for each MIMIC sepsis subphenotype. **K** Cumulative risk curves for death within 90 days of hospitalization for each MIMIC sepsis subphenotype

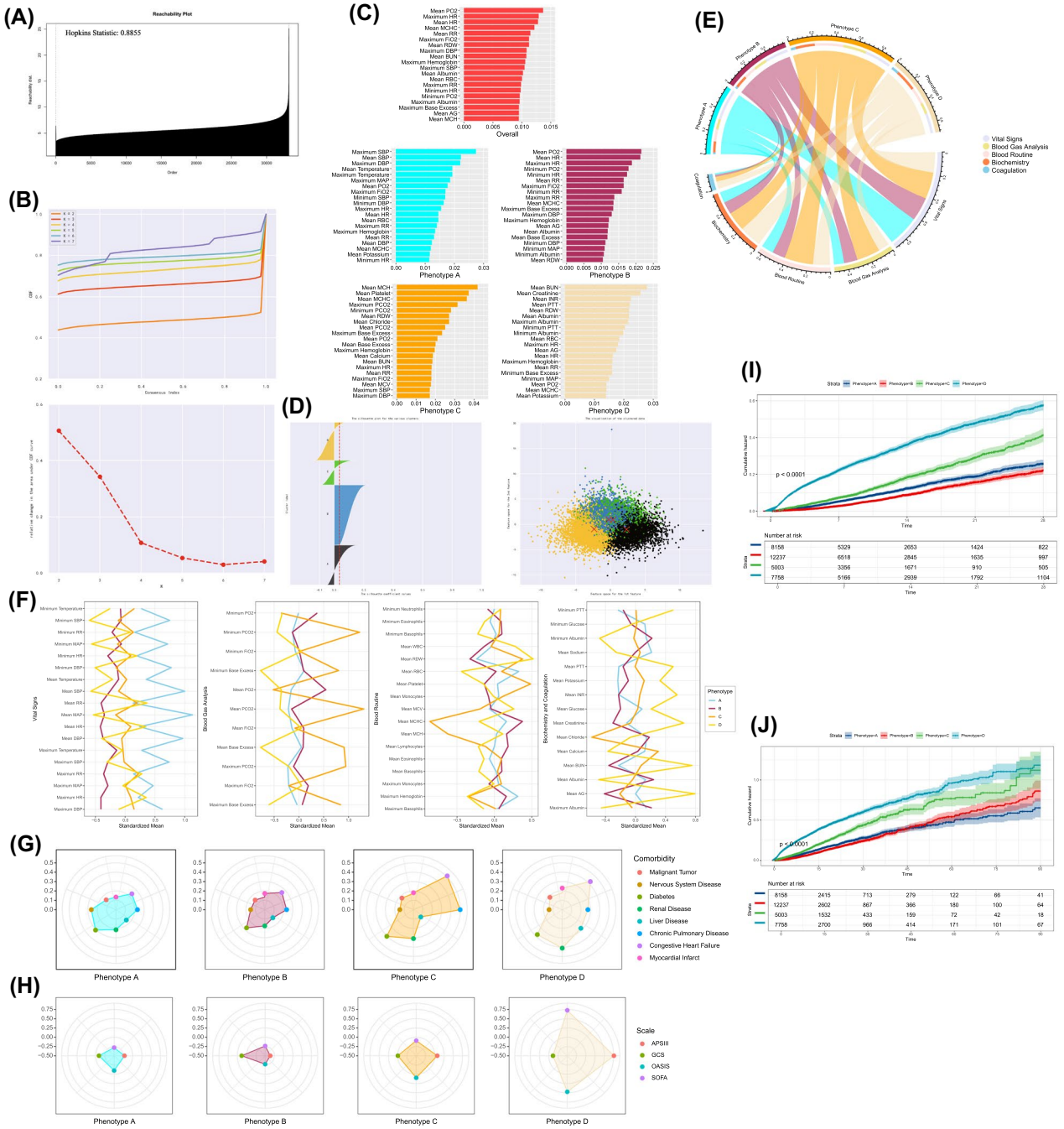

Fig. 2 (See legend on previous page.)

for phenotypes A and B compared to C and D. External validation using the eICU cohort confirmed the generalizability and stability of these phenotypes (supplementary material: Supplementary Fig. 5). For detailed baseline characteristics of different sepsis phenotypes, see supplementary material: Supplementary Tables 3 and 4.

Treatment effect between vasoactive drugs and sepsis phenotypes

In Table 1, the dosage and time of use of NEE were significantly affected by sepsis phenotype. Through machine learning and DAG, the confusing variables were screened out: age, sex, anemia (including Mean RDW and Mean MCV), congestive heart failure, infection (including Mean WBC), RR (including Mean RR), and renal

Table 1 Phenotype influence on dosage and time of vasoactive drugs

Variable		Model 1			Model 2			Model 3		
		OR (95%CI)	*P* value	*P* for interaction	OR (95%CI)	*P* value	*P* for interaction	OR (95%CI)	*P* value	*P* for interaction
Dosage	Overall	1.346 (1.332–1.360)	< 0.001		1.359 (1.344–1.373)	< 0.001		1.328 (1.314–1.342)	< 0.001	
	Phenotype			< 0.001			< 0.001			< 0.001
	A	1.227 (1.208–1.247)	< 0.001		1.226 (1.207–1.246)	< 0.001		1.196 (1.177–1.216)	< 0.001	
	B	1.341 (1.324–1.359)	< 0.001		1.349 (1.331–1.366)	< 0.001		1.309 (1.292–1.326)	< 0.001	
	C	1.152 (1.136–1.169)	< 0.001		1.170 (1.154–1.187)	< 0.001		1.156 (1.139–1.173)	< 0.001	
	D	1.112 (1.106–1.118)	< 0.001		1.117 (1.111–1.123)	< 0.001		1.111 (1.105–1.117)	< 0.001	
Time	Overall	1.006 (1.005–1.007)	< 0.001	< 0.001	1.007 (1.006–1.008)	< 0.001	< 0.001	1.006 (1.005–1.007)	< 0.001	< 0.001
	Phenotype									
	A	1.003 (1.002–1.004)	< 0.001		1.003 (1.002–1.004)	< 0.001		1.003 (1.002–1.004)	< 0.001	
	B	1.005 (1.004–1.006)	< 0.001		1.005 (1.004–1.006)	< 0.001		1.005 (1.004–1.005)	< 0.001	
	C	1.002 (1.001–1.003)	0.002		1.002 (1.001–1.003)	0.001		1.002 (1.001–1.003)	0.013	
	D	1.004 (1.004–1.005)	< 0.001		1.005 (1.004–1.005)	< 0.001		1.004 (1.004–1.005)	< 0.001	

[*] Model 1 did not adjust for confounding factors. Model 2 adjusted only for age and sex. Model 3 adjusted for age, sex, anemia (including Mean RDW and Mean MCV), congestive heart failure, infection (including Mean WBC), RR (including Mean RR), and renal function (including Mean Creatinine and Mean BUN) by machine learning and directed acyclic graph

[*] *P* value and *P* for interaction were Bonferroni-adjusted

function (including Mean Creatinine and Mean BUN) (supplementary material: Supplementary Figs. 6–8). In the Model 3 adjusting for the above confusing factors, the OR for NEE dosage was 1.328 (95% confidence interval, CI 1.314–1.342; p < 0.001) per 0.05 μg/kg/min and the OR for NEE time of use was 1.006 (95% CI 1.005–1.007; p < 0.001) per 1 h. All of them were affected by the sepsis phenotype, and the P for interaction was less than 0.001. It is noteworthy that phenotype B was most affected by the NEE dosage, and the OR was 1.309 (95% CI 1.292–1.326; p < 0.001). Besides, phenotype B was the most dependent on the NEE time of use (OR 1.005, 95% CI 1.004–1.005; p < 0.001).

Dosage–time mortality risk curve

Figure 3 shows the relationship between NEE dosage and hospital mortality in different sepsis phenotypes at different times of use (0, 6, 12, 24, 48 and 72 h) by RCS. The dosage response in phenotype A was significantly dosage-dependent and time-dependent. At a dosage of 0.05 μg/kg/min, the hospital mortality risk of phenotype A was consistent with phenotype D. As the dosage was continuously increased, the dosage–mortality risk curve for phenotype A increased significantly faster than that for phenotype D. When the drug was administered for 12 h at a dosage of 0.05 μg/kg/min, the difference in mortality risk between phenotype A and phenotype D was 0.045 (95% CI −0.009–0.099). However, when the drug was administered for 24 h at the same dosage, the difference in mortality risk was 0.173 (95% CI 0.121–0.234), indicating that mortality risk would rise rapidly. This showed a very significant time-dependent effect, with becoming more pronounced at 48 and 72 h. The dosage–mortality risk curve in phenotype B was more stable. Compared to phenotype D, the mortality risk was higher only at high NEE dosages (≥ 0.5 μg/kg/min). However, phenotype B still needs to pay attention to the NEE time of use and dosage, because in Model 3, ORs regarding the NEE time of use and dosage were the highest compared with other phenotypes. This means that the use of NEE causes the most significant increase in the relative risk of hospital mortality in phenotype B. The dosage–mortality risk curve of phenotype C mainly changed dramatically at high NEE dosages, which was greatly influenced by the dosage-dependent effect. When the dosage exceeded 0.5 μg/kg/min, the dosage–mortality risk curve for phenotype C rapidly increased, gradually becoming the highest mortality risk. The dosage–mortality risk curve for phenotype D was U-shaped, with the minimum mortality (about 20%) occurring at a dosage of 0.03–0.05 μg/kg/min. In addition, in the high NEE dosage range, the mortality risk was relatively the lowest among other phenotypes.

Sensitivity analysis of restricted cubic spline

In the sensitivity analysis, we compared the effect of different numbers of RCS nodes (3, 4, 5, 6) on the model fitting effect (supplementary material: Supplementary Table 5). The results showed that as the number of nodes increased, the AIC and BIC values of the model gradually decreased, indicating an improvement in the fitting degree. Compared with a model with 3 nodes, the AIC and BIC values of a model with 4 nodes was significantly lower (AIC decreased by about 936 and BIC decreased by about 879), and the log likelihood value is higher. Although the AIC and BIC of the models with 5 and 6 nodes decreased slightly further, the effect was weakened, especially as the BIC changed less (only decreased by about 240 to 440). Therefore, considering the fitting effect and model complexity, the RCS model with 4 nodes was the optimal choice.

Subgroup analyses

To further investigate the heterogeneous treatment effects of vasoactive drug therapy, we employed interaction terms between treatment factors and four factors: blood glucose, age, immunosuppressants, and type of sepsis. A blood glucose level of 108–180 mg/dL was used as the threshold. The subgroups were defined as low, goal, and high glucose. Figure 4 shows the NEE dosage–mortality risk curve for different blood glucose groups at the 24-h timepoint of vasoactive drug administration. The results showed that the mortality risk in the goal glucose group was significantly lower than that in the other glucose groups, which was particularly pronounced in phenotype D. In addition, compared to other glucose groups, the risk of hyperglycemia was higher when low NEE dosages were used. The risk in older patients was significantly higher than young patients, based on the age cutoff of 60 years, and was an independent factor affecting hospital mortality in sepsis patients. It was notable that in older patients, the mortality risk for phenotype D appeared to be significantly higher than in other phenotypes. In low and medium dosages of NEE, sepsis patients who used immunosuppressants had a higher risk of mortality compared to those who do not. However, in high-dosage NEE, the mortality risk was similar in both. Hospital-acquired sepsis had a consistent overall trend compared with community-acquired sepsis, and there was little difference in the mortality risk in phenotypes A, B, and C. Hospital-acquired sepsis might have a higher risk of mortality only in patients with phenotype D using low-dosage NEE.

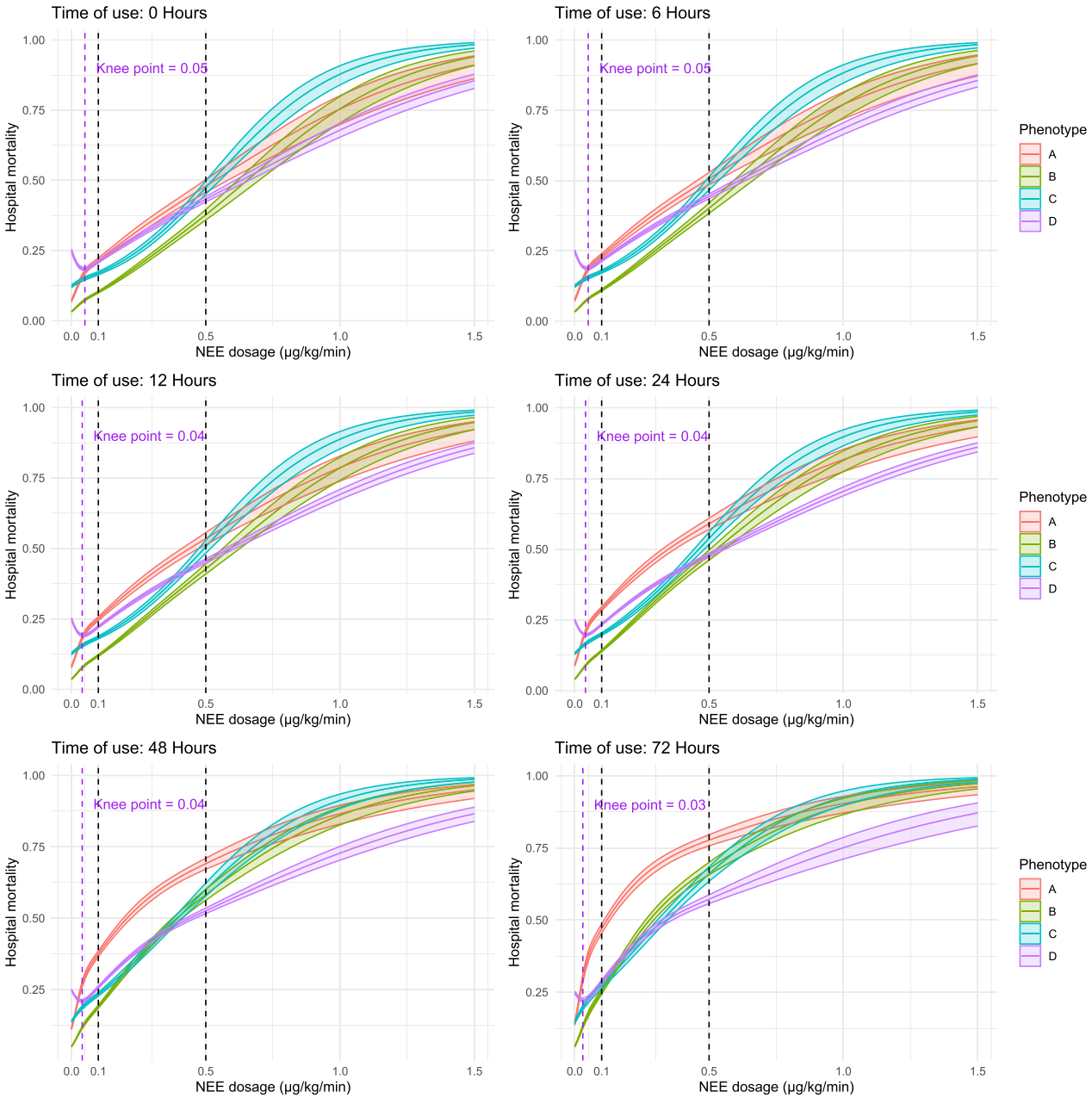

Fig. 3 Influence of the sepsis phenotype on the treatment of vasoactive drugs. The six subplots above represent 0, 6, 12, 24, 48, and 72 h of drug use, respectively. The *x*-axis represents the norepinephrine equivalence (NEE) dosage, and the *y*-axis represents the mortality risk. The purple dotted line represents the inflection point of the mortality risk curve for phenotype D. The two black lines divide the dosages into low, medium, and high dosages

Discussion

This study first reported the effect of the sepsis phenotype on the treatment of vasoactive drugs. Specifically, we observed that phenotype A was highly sensitive to dosage and time of NEE; phenotype B showed high relative risk of hospital mortality and low-dosage safety; phenotype C was primarily dosage-dependent; and phenotype D was characterized by severe multi-organ failure and hemodynamic instability, and NEE dosage–mortality risk curve was U-shaped and dangerous.

Previous studies have investigated the effect of vasoactive drug dosage on mortality in sepsis [32–34]. It is undeniable that there is a strong positive correlation between dosage and mortality. It is important to also

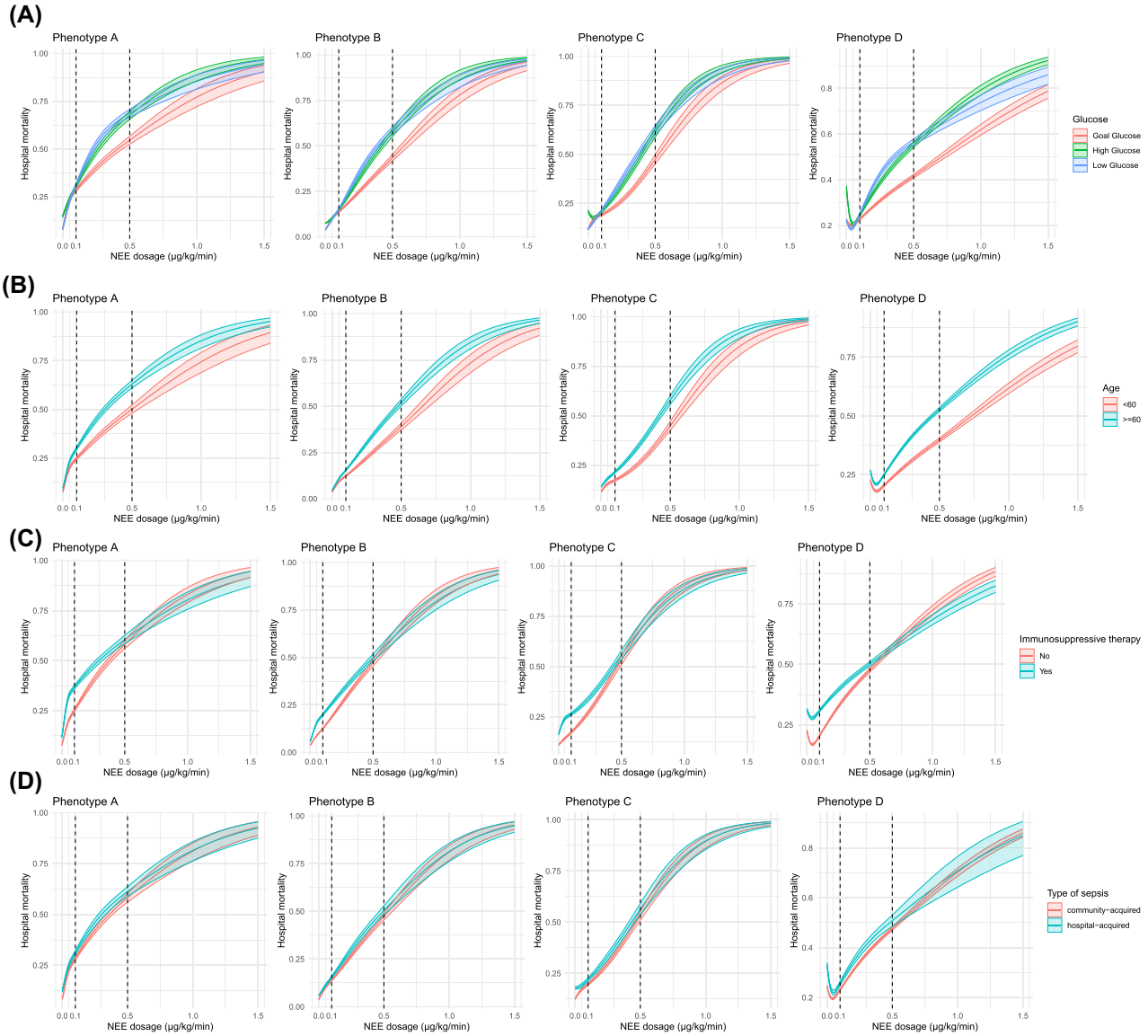

Fig. 4 Subgroup analysis of blood glucose and age on mortality in sepsis patients. **A** represents a subgroup analysis of blood glucose. **B** represents a subgroup analysis of age. **C** represents a subgroup analysis of immunosuppressive therapy. **D** represents a subgroup analysis of community-acquired and hospital-acquired sepsis

pay attention to other aspects of time, the formulation and the type of drug. Recent studies have shown that the way drugs'formulation can also affect mortality [35]. However, studies on time of vasoactive drug use are limited and its role in drug efficacy and safety should not be overlooked. Prolonged use of vasoactive drugs may lead to drug resistance, cumulative drug side effects, and exacerbation of immunoparalysis [36], especially in complex and heterogeneous diseases. This effect may aggravate the condition and even increase the patient's mortality risk. In addition, sepsis is highly heterogeneous, with significant differences in pathophysiological mechanisms, inflammatory responses, and degrees of organ function impairment between patients [10, 37, 38]. This heterogeneity makes it difficult to apply a uniform treatment regimen to all patients. Consequently, we sought to explore the effect of vasoactive drug dosage and time on sepsis mortality while considering the heterogeneity of sepsis and revealing differences in sepsis phenotypes.

Most patients were treated with norepinephrine (58.92%), followed by phenylephrine (54.27%). Epinephrine and vasopressin are often used in combination with other drugs. The use of dopamine and dobutamine

accounts for an extremely small proportion (less than 1%). However, as shown in supplementary material: Supplementary Fig. 9, phenylephrine alone was the first choice (32.73%). This may be due to the fact that phenylephrine has a low cardiac load and avoids the transmission of arrhythmias. When combined with other vasoactive drugs, the norepinephrine dosage was 0.2 [0.1, 0.35] μg/kg/min, which was similar to the dosage recommended in the guidelines [8]. We defined an NEE dosage ≤ 0.1 as a low dosage, and the dosage was low-mortality risk. An NEE dosage ≥ 0.5 was considered a high dosage and was expected to result in a mortality rate of more than 50%. Most of the phenotypes showed an S-shaped relationship between dosage and mortality risk, with only phenotype D showing a U-shaped relationship. In phenotype A, mortality risk increases rapidly with dosage and time, and even at low dosage, the mortality risk is similar to phenotype D. A possible explanation is that phenotype A have more normal vascular function and organ compensation, leading to their increased sensitivity to vasoactive drug therapy and lower thresholds for dosage and time. Prolonged or excessive treatment resulted in complications, such as impaired visceral organs and microcirculation. Based on the mortality risk of patients, we need to be alert to the following situations: first, for phenotype A patients, we need to be alert when the NEE dosage exceeds 0.05 μg/kg/min and/or is used for more than 12 h. Second, for phenotype B patients, it is essential to closely monitor the use of vasoactive drugs, avoiding prolonged administration or excessive dosages. Third, for phenotype C patients, we should be vigilant when the NEE dosage exceeds 0.5 μg/kg/min. Finally, it is important to pay specific attention to patients with phenotype D due to their markedly high hospital mortality.

We analyzed the differences in the dosages of NEE in the sepsis phenotypes from six perspectives: hypotension, hypoxemia, hypercapnia, metabolic acidosis, hyperinflammatory response, and renal insufficiency (supplementary material: Supplementary Table 6). Metabolic acidosis and renal insufficiency are closely related to the use of high NEE dosages. This may be due to the fact that a decrease in pH affects the sensitivity of vascular smooth muscle cells to catecholamine [39], and higher NEE dosages are required to maintain blood pressure. In addition, high dosages reduce blood perfusion to the kidneys, further exacerbating the deterioration of renal function, leading to an accumulation of acidic metabolic products and creating a vicious cycle. In phenotype B, a high dosage is associated with a high proportion of hypoxemia. This is similar with previous research, which found that hypoxemia requires higher vasoactive drug dosages to maintain [40]. In phenotype C, which received high dosages, hypercapnia was prevalent (62.83%), and this was closely associated with reduced vascular sensitivity to catecholamines in the hypercapnic state. Phenotype D with high dosages, exhibited stubborn hypotension (66.94%), which was also a major factor in the poor prognosis. In most cases, a hyperinflammatory response is associated with a high dosage of NEE. However, in phenotype B, compared with other levels of NEE dosages, the elevated proportion of patients with WBC counts $>10 \times 10^9$/L was observed with a low dosage of NEE. This might be attributed to the patient's immune function is still relatively good and the functions of various organs are intact, which permit the use of a minimal dosage of vasoactive drugs to maintain hemodynamic stability.

In the subgroup analysis, we explore the independent effects of blood glucose, age, immunosuppressive therapy and type of sepsis (community-acquired vs. hospital-acquired) on hospital mortality. The sepsis patient is in a state of stress and has a higher energy cost. Patients with blood glucose levels of 108–180 mg/dL are more likely to maintain an adequate energy supply and avoid hypoglycemia as much as possible [41]. Hyperglycemia exacerbates inflammation and oxidative stress [42], leading to organ dysfunction and suppressing immune system function, increasing the risk of infection. Hypoglycemia also negatively affects multiple organ systems, especially brain tissue, which may lead to acute brain dysfunction and long-term neurological damage [43]. In addition, hypoglycemia can exacerbate liver and heart failure and lead to hemodynamic instability [44]. Therefore, it is crucial to control the blood glucose of patients with sepsis within the range of 108–180 mg/dL. Age is an independent risk factor for the prognosis of sepsis. Older patients are more susceptible to changes in the condition and have a poorer prognosis due to immune senescence, chronic diseases, and reduced organ reserve capacity. In addition, older patients often require long-term use of multiple drugs, which increases the complexity and risk of treatment. Therefore, it is necessary to consider age-related risk factors when managing older patients with sepsis, and individualized treatment plans should be formulated to improve the prognosis. Immunosuppressive therapy is one of the key treatments for sepsis. Sepsis patients undergoing immunosuppressive therapy often face cytokine storms, which also indicate poor prognosis. In patients receiving high dosages NEE, where the baseline mortality risk is already high, the use of immunosuppressive therapy has little effect on the mortality risk. Finally, compared with community-acquired sepsis, hospital-acquired sepsis has a higher risk of mortality, which may be related to differences in the causative pathogens. In addition, hospital-acquired sepsis is often associated with

severe underlying conditions, leading to a higher baseline mortality risk.

Certainly, this study has several limitations that warrant acknowledgment. First, this study used the NEE to simplify the analysis of the combined effects of vasoactive drugs, without delving into the potential effect of specific combinations of each drug. Therefore, further research is needed in the future to clarify the specific effects of different vasoactive drug combinations. In addition, this study only included six vasoactive drugs and did not observe or analyze other vasoactive drugs that could be used for sepsis treatment. Second, the data used in our analysis were extracted from electronic health records of routine clinical practice, which may limit the availability of variables for phenotyping, particularly regarding sepsis-related immune indicators. In addition, the presence of misreporting and missing values might compromise the reliability of our results. Third, there is the significant time difference between the MIMIC-IV (2008–2019) training cohort and the eICU (2014–2015) validation cohort. Due to clinical practices, treatment protocols, and available medical technologies can evolve substantially over time, this discrepancy may influence the generalizability of our model when assessing the treatment of vasoactive drugs. Finally, due to the retrospective nature of this study, there may be unmeasured confounders influencing analysis of vasoactive drug effects on hospital mortality. Nevertheless, our analysis of the different phenotypes of vasoactive drugs offers a framework for individualized use of vasoactive drugs in sepsis patients.

Conclusion

Sepsis is remarkably heterogeneous, and sepsis phenotypes exhibit different characteristics and mortality risks. The dosage and time of use of vasoactive drugs are independently associated with hospital mortality and are significantly affected by the sepsis phenotype. We recommend particular caution in the following situations: (1) phenotype A patients receiving NEE dosage > 0.05 μg/kg/min or treatment > 12 h; (2) phenotype B patients with using vasoactive drugs; (3) phenotype C patients receiving NEE dosage > 0.5 μg/kg/min; and (4) all patients with phenotype D. Early identification of sepsis phenotypes, risk stratification, and vigilance in high-risk situations are essential to optimize and individualize vasoactive drug use.

Abbreviations

NEE	Norepinephrine equivalence
CDF	Cumulative density function
RCS	Restricted cubic spline
DAG	Directed acyclic graph
AIC	Akaike information criterion
BIC	Bayesian information criterion
GMM	Gaussian mixture models

Supplementary Information

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Supplementary material 1: The methods used in paper are described in detail in the supplementary information, including data preprocessing, missing data interpolation, consensus K-means clustering, machine learning, and DAG. Meanwhile, it also contains a series of required supplementary figures and tables.

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Author contributions

JCS and LL conceived and designed the study. JCS and KF analyzed and interpreted the data. JCS prepared figures and wrote the initial manuscript. JCS and LL contributed to the discussion. JCS and LL critically examined the manuscript and reviewed the work. JCS and LL agree to be responsible for all aspects of the work and ensure that issues relating to the accuracy or integrity of any part of the work are properly investigated and resolved. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

Please contact corresponding author if you need refined data, under reasonable request. Raw data are available from the following web resources: MIMIC-IV (https://mimic.physionet.org/) and eICU-CRD (https://physionet.org/content/eicu-crd/2.0/).

Declarations

Ethics approval and consent to participate

The establishment of the database used in this study was approved by the Massachusetts Institute of Technology (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA). One author (Jiacheng Shen) obtained access to the database and was responsible for data extraction (certification number 55253289). Therefore, ethical approval and informed consent were waived for this manuscript.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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