Supplementary Material

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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Detailed dataset information

The two electronic health record (EHR) datasets in this study were derived from data from large public critical care databases:

the Medical Information Mart for Intensive Care IV (MIMIC-IV v2.2), data collected from the Beth Israel Deaconess Medical Center in Boston, Massachusetts, US, collected between 2008 and 2019, defined as a training cohort [1].

the eICU Collaborative Research Database, data collected from 208 hospitals across the US, collected between 2014 and 2015, defined as the validation cohort (US) [2].

Data preprocessing

Prior to the analysis, we first dealt with missing data and outliers. Highly missing variables (≥50% missing data, Supplementary Figure 2) were excluded using the MIMIC cohort as the criteria database. Considering individual variability, extreme values of variables may have practical significance, so instead of removing extreme values, we replaced these extreme values with the mean ± 3 standard deviation. For missing values interpolation was performed by multiple imputation based on random forest. A Pearson correlation test was then performed to exclude variables with correlation coefficients ≥ 0.8 (Supplementary Figure 3). Specific exclusion criteria: 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. For example, if variable A is highly correlated with both variables B and C, but B and C are not correlated with each other, we retained variable A. If the number of correlations is the same among variables, we prioritized retaining variables based on clinical relevance.

More detailed information on missing value interpolation is listed below.

Missing value interpolation

In our data imputation process, we employed a method implemented in the open-source Python library "Miceforest." This library provides a random forest-based imputation approach within the Multiple Imputation by Chained Equations (MICE) framework (also known as full conditional specification). This method—hereafter abbreviated as MF—leverages random forest modeling to capture nonlinear relationships and interactions among variables, reducing imputation bias [3]. Compared with the single interpolation method, MF can produce different fill values for the missing value, which allows the model to take into account the uncertainty and multiple possibilities of missing values and reduce the bias of the data. In addition, it can generate several different datasets from which the parameters closest to the original dataset can be selected [4]. Specific steps for MF [3]:

Step1: Perform simple interpolation for each missing value in the dataset, e.g. randomly populated by similar data.

Step2: Select one variable as the dependent variable and the other variables as the independent variables to be predicted by the random forest counterpart, and repeat the process until all variables are predicted.

Step3: Fill in the missing data with the predicted values of the random forest and compare the effect of the true value prediction (e.g., goodness-of-fit R-squared and accuracy) with the distribution of the data.

Step4: Repeat Step2 & Step3 for multiple cycles and update the interpolation in each cycle until the data distribution is not changing or reaching the expected values, and finally output the resampling results.

Step5: We compare these multiple interpolation outputs, compare the difference in data means before and after interpolation, and select the interpolation result for each column variable that best matches the data distribution to ensure the stability of the interpolation results, and visualize them using kernel density plots (Supplementary Figure 4).

Missing values for comorbidity data were interpolated as "0" to indicate that the patient did not have the comorbidity, and missing values for treatment data were interpolated as "0" to indicate that the patient did not have the treatment measure. Data from the scales were interpolated by taking the most normal value for the scale. For example, if the GCS score was in the range of 0-15, the missing value was interpolated with "15".

Inclusion of features

Variables were extracted from the dataset 3 days prior to admission, and maximum, minimum, and mean values were extracted for each variable. In the MIMIC cohort, a total of 111 clinical variables were obtained from the raw data (a total of 37 variables, with maximum, minimum, and mean values extracted for each variable); in the eICU cohort, a total of 108 clinical variables were obtained from the raw data (a total of 36 variables, with maximum, minimum, and mean values extracted for each variable). The proportion of missing values for each variable was calculated, based on the missing values of the training cohort, and after removing more than 50% of the variables that were missing, there were still 108 variables to be further analyzed. Then by analyzing the Pearson correlation coefficients between variables, based on the correlation of the training cohort, after removing highly correlated (Pearson correlation coefficients ≥ 0.8) variables, there were still 61 variables (recorded as base features) to be

further analyzed. These variables included vital signs: heart rate (HR: maximum, minimum, and mean), systolic blood pressure (SBP: maximum, minimum, and mean), diastolic blood pressure (DBP: maximum, minimum, and mean), mean arterial pressure (MAP: maximum, minimum, and mean), respiratory rate (RR: maximum, minimum, and mean), temperature (maximum, minimum, and mean); blood gas analysis: oxygen partial pressure (PO_2: minimum and mean), partial pressure of carbon dioxide (PCO_2: maximum, minimum, and mean), fraction of inspiration oxygen (FiO_2: maximum, minimum, and mean), base excess (maximum, minimum, and mean); blood routine: red blood cell count (RBC: mean), hemoglobin (maximum), red distribution width (RDW: mean), mean corpuscular hemoglobin (MCV: mean), mean corpuscular volume (MCH: mean), mean corpuscular hemoglobin concentration (MCHC: mean), platelet count (mean), white blood cell count (WBC: mean), percentage of basophils (maximum, minimum, and mean), percentage of eosinophils (minimum and mean), percentage of lymphocytes (mean), percentage of monocytes (maximum and mean), percentage of neutrophils (mean); biochemical indicators: albumin (maximum, minimum, and mean), anion gap (AG: mean), urea nitrogen (BUN: mean), calcium (mean), chloride (mean), sodium (mean), potassium (mean), blood glucose (minimum and mean), creatinine (mean); coagulation: international normalized ratio (INR: mean), partial thromboplastin time (PTT: minimum and mean). We also counted demographic information: sex, age; comorbidities information: cardiac infarction, chronic heart failure, chronic pulmonary disease, liver disease, renal disease, diabetes, nervous system disease, and malignancy; scales information : the sequential organ failure assessment (SOFA) score, the acute physiology score III (APSIII) score, the oxford acute severity of illness score (OASIS), and the glasgow coma scale (GCS) score; and treatment information: vasoactive drugs (norepinephrine, epinephrine, phenylephrine, vasopressin, dopamine,

dobutamine).

Clustering of sepsis patients

Hopkins statistical values

To determine the heterogeneity of sepsis, we used unsupervised clustering to analyze the sepsis population. If the data are random, then the results of clustering are meaningless. Therefore, we use Hopkins statistic value to analyze whether there is a clusterable non-random structure in the data distribution of sepsis patients [5]. Hopkins statistic values close to 1 indicate that the data are highly clustered, and generally when the Hopkins statistic value is in the range of 0.7-0.9 the data can be considered to have a strong tendency to cluster, and when the Hopkins statistic value is close to 0.5, the data are considered to be generated by randomization, and uniformly distributed data tends to produce values close to 0 [6].

Selecting the best clustering algorithm by reachability distance

Clustering algorithms can be broadly divided into two categories: agglomerative clustering and ensemble clustering. Among them, ensemble clustering includes the following types of clustering: prototype clustering (e.g., K-means), density clustering (e.g., DBSCAN), grid clustering (e.g., STING), graph clustering (e.g., MST), and neural network clustering (e.g., SOM). The reachability plot can be used to compare which is more appropriate as a clustering algorithm for this dataset, hierarchical clustering or ensemble clustering. In general, a smooth rise in reachability distance indicates that ensemble clustering is more appropriate, while a jagged curve in reachability distance indicates that clustering methods such as agglomerative clustering are more appropriate. From Supplementary Figure 2, it was clear that the

sepsis patient dataset is more suitable for ensemble clustering. Density clustering is not considered for the time being since it may cause a curse of dimensionality when clustering high dimensional data. Since grid clustering is more or less related to prototype clustering and density clustering, grid clustering is not considered for the time being. Graph clustering selection of the initial place clustering center has a great impact on the whole clustering purity, it is difficult to find the optimal solution of the graph division, the number of clusters to choose for the whole clustering results have a great impact on the clustering of the clustering of the stability of the clusters is low, so also not considered for the time being the method. Specifically, both STING and MST clustering are unsuitable for our big medical data due to STING's exponential grid complexity in high dimensions and MST's prohibitive memory and computational costs. For K-means clustering and SOM clustering, we consider that the applied clustering model should be as simple and convenient as possible. In addition, we conducted a comprehensive comparative analysis of multiple clustering methods, including K-means (Euclidean distance), K-means (Mahalanobis distance) clustering, hierarchical clustering, OPTICS clustering, GMM clustering, SOM clustering, and Birch clustering. Clustering performance was rigorously evaluated using standard metrics such as the Silhouette Score, Calinski-Harabasz Index, Davies-Bouldin Index, and Dunn Index (detailed results are provided in Supplementary Table 1). In summary, we selected K-means clustering (Euclidean distance) as the best clustering algorithm for sepsis phenotype identification.

Consensus K-means clustering

Consensus Clustering is not a specific clustering method, but rather an indicator for the chosen clustering algorithm regarding the stability of the clusters and the choice of parameters (e.g., the number of clusters). Selecting clusters for K-means clustering through consensus clustering enhances the stability and

generalizability of the clustering model. The specific steps of consensus clustering are described in the following [7]:

Step1: Create a consensus matrix (M) of size $(N \times N)$, where (N) is the number of sepsis patients.

Step2: Take some samples as the training set for K-means clustering and predict the clustering of the whole dataset. For each pair of samples, determine whether each pair of sample clustering is clustered in the same cluster, i.e., formula (1):

$$M^{(h)}(i,j) = \begin{cases} 1 & \text{if samples } i \text{ and } j \text{ belong to the same cluster} \\ 0 & \text{otherwise} \end{cases} \quad (1)$$

Step 3: Repeat Step 2 until (H) times, and calculate the proportion of each pair of samples being clustered into the same cluster, i.e. formula (2):

$$M(i,j) = \frac{\sum_{h=1}^{H} M^{(h)}(i,j)}{H} \quad (2)$$

Step4: Repeat Steps 1-3 for different clustered clusters (K) and compute the consensus cumulative density function (CDF) for the and the area under the curve of the CDF (A), see formulas (3) and (4):

$$CDF^{(K)}(c) = \frac{\sum_{i<j} 1\{M(i,j) \leq c\}}{N(N-1)/2} \quad (3)$$

$$A(K) = \int_0^1 \frac{dCDF^{(K)}}{dc} \quad (4)$$

where in formulas (3) and (4), c is the consensus index, ranging from 0 to 1, which serves as a cutoff to determine the stability of the clustering algorithm. The larger the area under the CDF curve ($A \geq 0.8$ means that it can be considered to have a high degree of consistency) [8], indicates the greater the stability and generalizability of the clustering algorithm at that number of clusters (K). To determine the optimal clusters for K-means clustering, we evaluate it by performing consensus clustering for K = 2 to 7. We utilize the elbow method to determine the optimal clustering cluster by comparing the amount of change

in the area under the CDF curve. In this study, the elbow point in the amount of change in the area under the CDF curve was located at $K = 4$, which implies that the phenotypes of sepsis patients can be roughly categorized into 4 groups.

Feature Importance of K-means Clustering

We used the results of culling individual features and using the remaining features to determine the sepsis phenotype after clustering. The importance of features for K-means clustering is judged by comparing how many patients' phenotypes changed before and after culling. The specific steps are shown below:

Step1: Select a single feature (Z), cull the individual features, and use the remaining features to calculate the Euclidean distance from feature (X) to each cluster (C) for each sepsis population, see formula (5).

$$D(i,j) = \sum_{z=1}^{61}\big(X(i,z) - C(j,z)\big)^2 \quad z \neq Z \tag{5}$$

where i is the patient with sepsis $i \subseteq \{1,2,3,4, \cdots, N\}$, j is the clustered cluster $j \subseteq \{1,2, \cdots, K\}$, and z is the feature of the cluster.

Step2: The cluster with the closest Euclidean distance for each sepsis patient was calculated and used as a new phenotype prediction (L'), see formula (6).

$$L'(i) = J, if\ D(i,J) = min\big(D(i,j)\big) \tag{6}$$

Step3: Compare the original phenotype prediction results with the new results and calculate the error rate (P), see formula (7).

$$P(z) = \frac{\sum_i 1, if\ L'(i) \neq L(i)}{N} \tag{7}$$

Step4: Repeat Step1 to Step3 for each feature (Z). Calculate the phenotype error rate of the clustering prediction after excluding each feature. After eliminating the features, the larger error rate represents the more important the feature is to the clustering model, thus ranking the importance of K-means clustering features.

Confounding Factors

Machine Learning Models

In this thesis, backpropagation neural network (BPNN), eXtreme gradient boosting (XGBoost), support vector machine (SVM), and random forest (RF) were selected as models for phenotype prediction.

Neural networks are shining in this era of artificial intelligence and big data [9, 10], and have a very prominent flashpoint in the medical field, especially in medical imaging, medical pathology, epidemiology, and so on. This shows that the potential of neural networks is huge. However, we do not want to use a deep and complex network construction in order to avoid overfitting the model due to its overwhelming learning ability [11], which greatly reduces its generalizability. Therefore, we build a neural network with only 1-2 hidden layers (16 neurons) and a sigmoid function (i.e., a logistic function) as the activation function.

XGBoost is a machine learning model based on decision tree integration [12], which is one of the most widely used machine learning algorithms. It is a model based on the idea of boosting integration and introduces techniques such as regularization terms and parallel computing, which improves the generalization ability and computational efficiency of the model. It has the advantages of high accuracy,

strong interpretability, and high computational efficiency. However, it also has the disadvantages of complex parameter fitting, easy overfitting, and sensitivity to outliers. To avoid overfitting in XGBoost, we set “max_depth” to 5.

SVM is a popular supervised learning algorithm. Its main idea is to find an optimal hyperplane that separates samples of different classes [13]. When the data is linearly divisible, the support vector machine looks for a hyperplane that completely separates the samples of different classes, which is called hard spacing. When the data is linearly indistinguishable, soft spacing allows some sample points to appear on the wrong side of the hyperplane, and allows some misclassification by introducing a slack variable, thus increasing the robustness and generalization ability of the model.

Random forest algorithm is also an integrated algorithm based on decision tree; the core idea is to integrate multiple weak classifiers with voting for better results [14]. It used in many different domains like banking, stock market, medicine and e-commerce. It is highly interpretable like XGBoost. While it is theoretically true that if there are enough trees in the forest, the classifier won't overfit the model, it is also true that if the tree model is too deep, it can also lead to overfitting, so we also set “max_depth” to 5.

SHAP plots to explain the model

The SHAP plots, which uses the classical Shapley value from game theory and related extensions to link optimal credit allocation to local explanations, is a method for explaining individual predictions based on the game-theoretically optimal Shapley value [15]. From a game-theoretic perspective, treating each feature variable in a data set as a player and using that data set to train a model to obtain a prediction can

be viewed as the gains from many players cooperating to complete a project. The Shapley value distributes the gains from cooperation fairly by taking into account the contributions of individual players. To gain a better understanding of the factors predicted for the different sepsis phenotypes, we used SHAP plots for features explanation of the neural network model. Due to the large samples of MIMIC and eICU databases, it was too slow to run the SHAP plots, we used the resampling method to extract 1000 samples for the MIMIC cohort and the eICU cohort, respectively, to be used as baseline and validation samples for the parsing of the model features of the SHAP plots, and we repeated the above sampling for 100 times, and compared the mean and the variance of the SHAP values of the different features.

Causal Inference for Directed Acyclic Graphs (DAGs)

Directed Acyclic Graphs (DAGs) have unique advantages in controlling confounders, mainly in the following aspects: Firstly, identification of confounders: with DAGs, it is clear which variables are confounders. For example, a variable is a confounder if it is an antecedent of both the independent and dependent variables. Secondly, adjustment strategy: The DAG helps identify the set of variables that need to be adjusted to eliminate the effects of confounders. For example, through the d-separation (d-separation) theory, a set of conditional variables can be found, so that after controlling these variables, the independent variable and the dependent variable are no longer affected by confounding factors. Finally, the minimum adjustment set: DAG helps to find the minimum adjustment set (minimal adjustment set), that is, in the control of a minimum number of variables, the maximum number of variables to eliminate the influence of confounding factors [16,17]. Recently, there were many papers that use this method to control confounding factors [18-21].

Clinical Features

The top 20 important variables were obtained based on the importance of sepsis phenotype clustering. The top 20 important variables, in descending order, were: mean PO_2, maximum HR, mean HR, mean MCHC, mean RR, maximum FiO_2, mean RDW, maximum DBP, mean BUN, maximum hemoglobin, maximum SBP, mean albumin, mean RBC, maximum RR, minimum PO_2, maximum albumin, maximum base excess, mean AG, mean MCH. The MIMIC cohort was used as a training set and the eICU cohort was used as a validation set to evaluate the model. We plotted ROC curves for different numbers of variables and calculated AUC to evaluate the optimum sepsis phenotype prediction model Supplementary Figure 6 and Supplementary Figure 7). The AUC curves indicated that the model stroked a balance between acceptable predictive power and model complexity when using BPNN and retaining the 11 most important variables. Therefore, we retained these 11 variables with the highest importance of model output features (mean PO_2, maximum HR, mean HR, mean MCHC, mean RR, maximum FiO_2, mean RDW, maximum DBP, mean BUN, maximum hemoglobin, maximum SBP). Based on clinical experience, these 11 variables reflected hemodynamic alterations, oxygen metabolism, anemia, and renal metabolic problems in patients with sepsis, and were salient features that could reflect the four phenotypes.

Finial Confounding Factor

Combining these with age, sex, and comorbidities, we created DAG plots using DAGitty (Supplementary Figure 8). The minimum sufficient adjustment set, included the following covariates: age, anemia (including Mean RDW and Mean MCV), Congestive Heart Failure, infection (including Mean WBC), RR (including Mean RR), renal function (including Mean Creatinine and Mean BUN).

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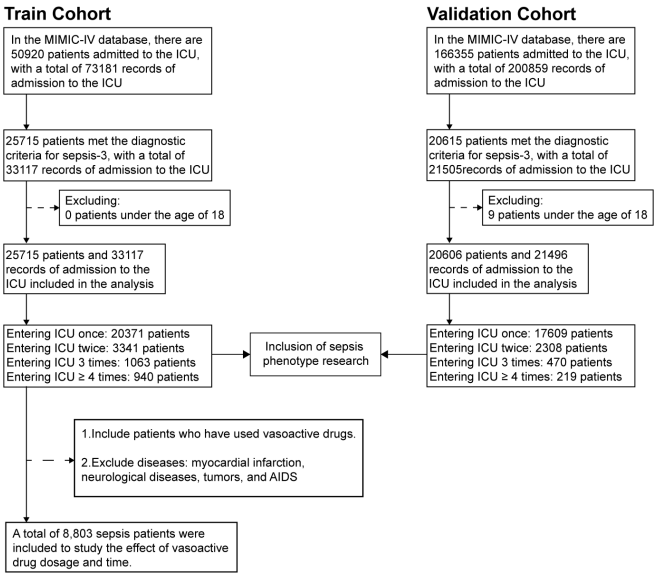
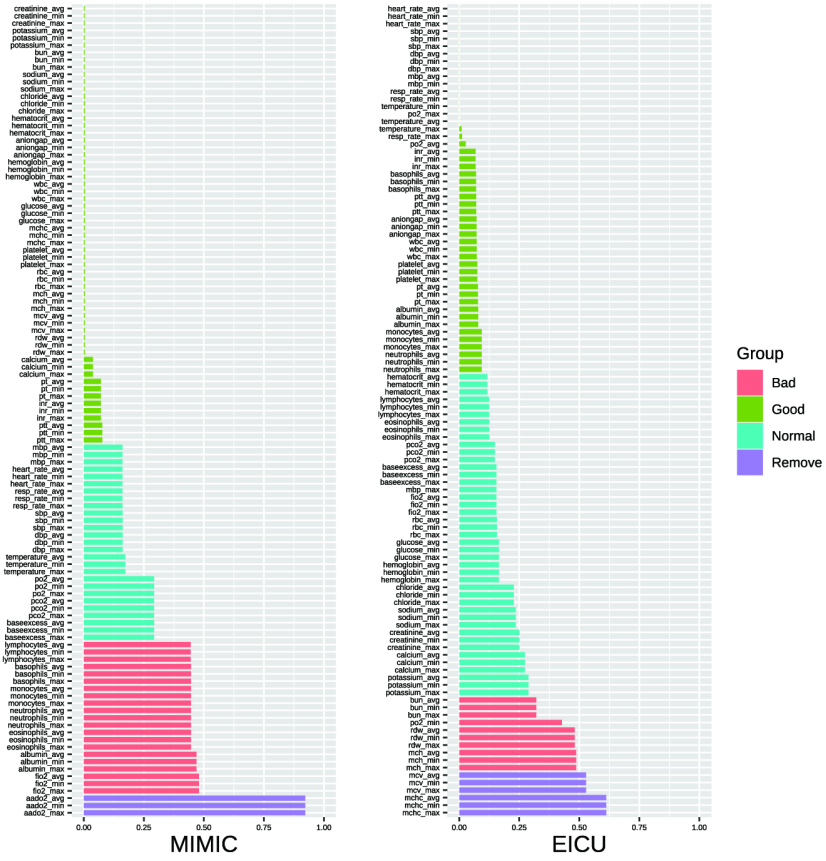
Supplementary Figure



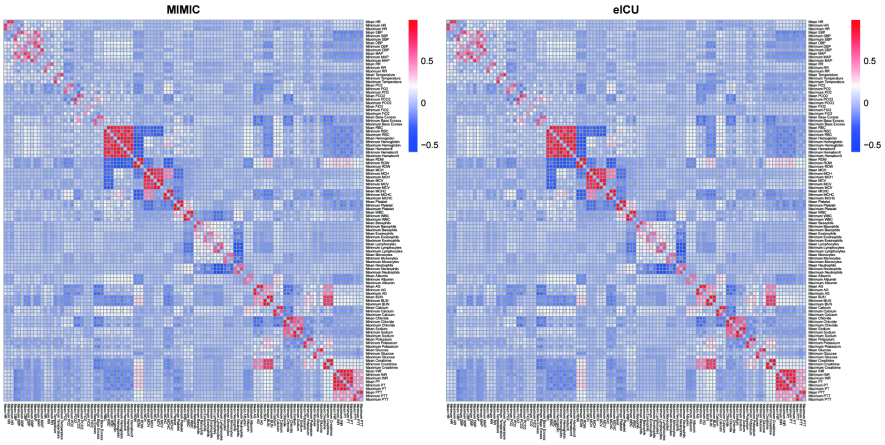
Supplementary Figure 1 Sepsis population included in the study.



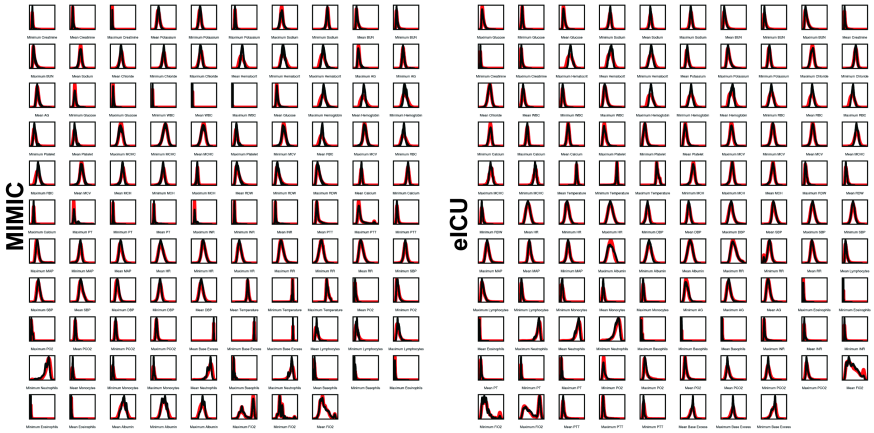
Supplementary Figure 2 Missing value proportion of raw data. We define four levels of quality for variables based on their missing values as good (<10%), normal (10%-30%), bad (30%-50%) and remove (>50%). variables with level remove are removed based on the MIMIC cohort.

* HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial

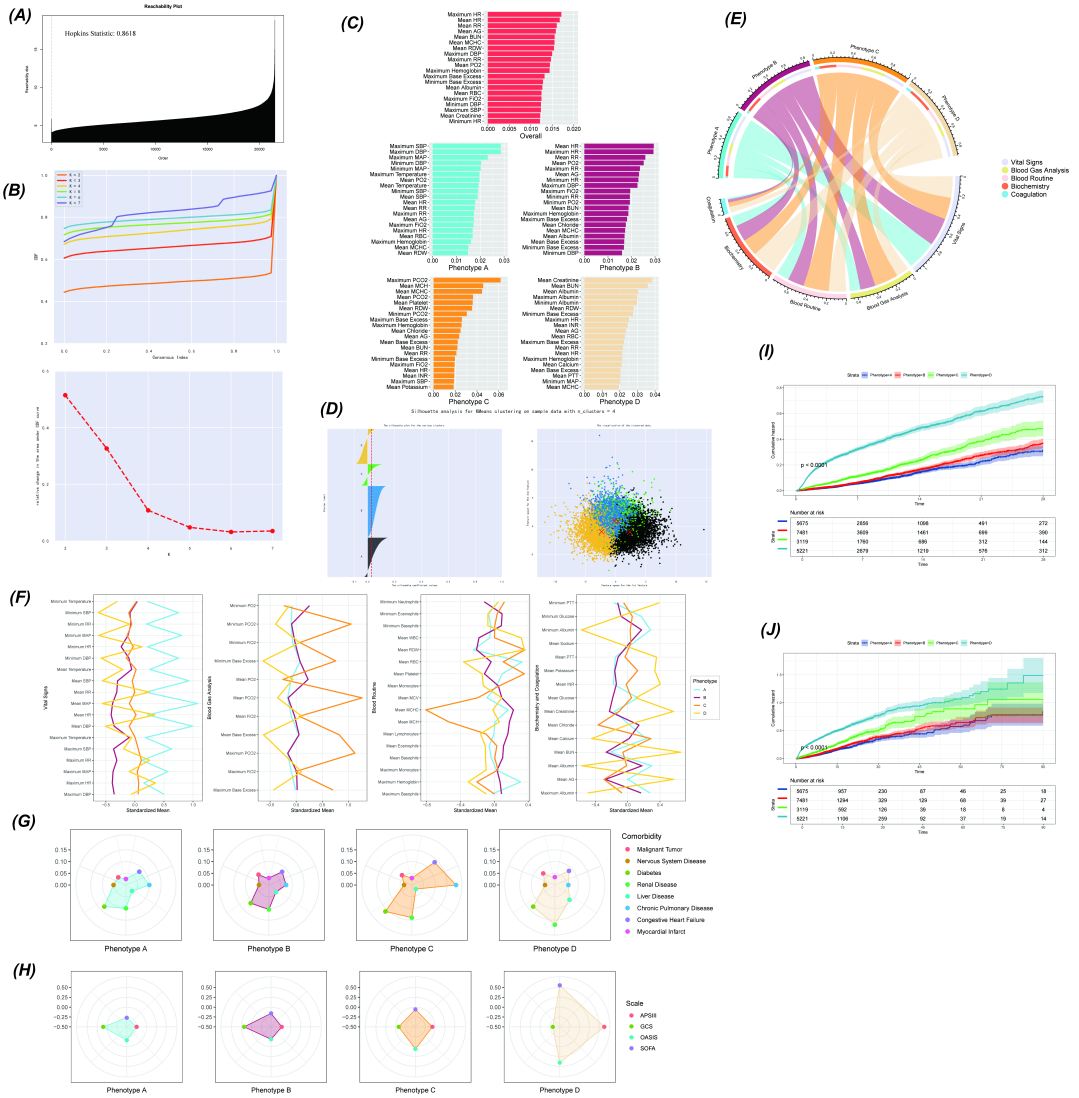
pressure; RR: respiratory rate; PO_2: oxygen partial pressure; PCO_2: partial pressure of carbon dioxide; FiO_2: fraction of inspiration oxygen; $AaDO_2$: Alveolar-arterial difference of oxygen partial pressure; RBC: red blood cell count; RDW: red distribution width; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; Platelet: platelet count; WBC: white blood cell count; Basophils : percentage of basophils; Eosinophils: percentage of eosinophils; Lymphocytes: percentage of lymphocytes; Monocytes: percentage of monocytes; Neutrophils: percentage of neutrophils; AG: anion gap; BUN: urea nitrogen; Glucose: blood glucose; INR: international normalized ratio; PTT: partial thromboplastin time.



Supplementary Figure 3 The heat map of Pearson Correlation. The larger the absolute value of the Pearson correlation coefficient of a pair of variables, the higher the correlation between the two variables. In the heat map representation, it is dark red or dark blue.

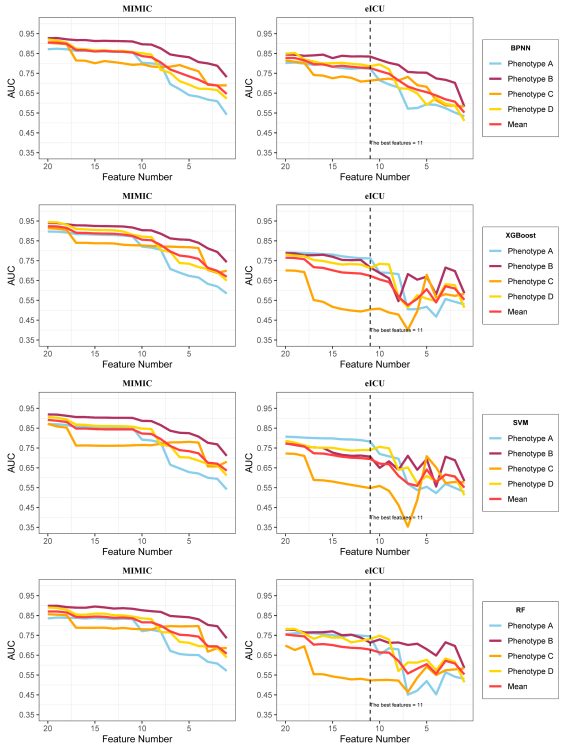


Supplementary Figure 4 Imputation missing data by miceforest. Displayed the distribution of data before and after using miceforest Imputation method. The more the red and black lines overlap, the more reliable the imputation results of the variables.

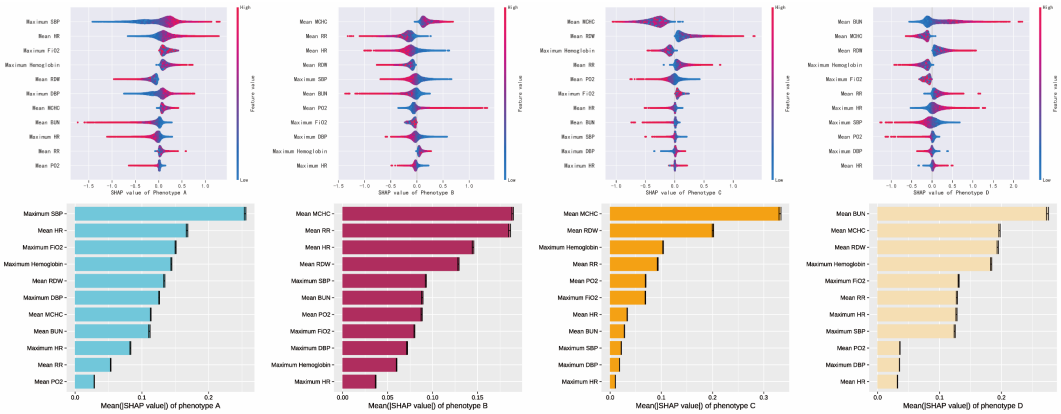


Supplementary Figure 5 Results of clustering sepsis patients in the eICU cohort. (A) The Hopkins statistic, depicted in the left plot, evaluates the clusterability of the data. A value greater than 0.7 suggests that the data is clusterable, while a value around 0.5 indicates random data, and a value 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) The 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) The top 20 important clustering features are presented. (D) The 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 2-dimensional plane using Principal Component Analysis (PCA). (E) The chordal graph illustrates the relationship of phenotypes to features (vital signs, blood gas analysis, blood routine, biochemistry, coagulation). (F) Subplots compare the features of different sepsis phenotypes after Z-score standardization. (G) Radar charts display the relationships and comparisons between individual phenotypes and

comorbidities. (H) Radar charts demonstrate the relationships and comparisons between individual phenotypes and scales. (I) Cumulative risk curves for death within 28 days of hospitalization for each eICU sepsis phenotype. (J) Cumulative risk curves for death within 90 days of hospitalization for each eICU sepsis phenotype.

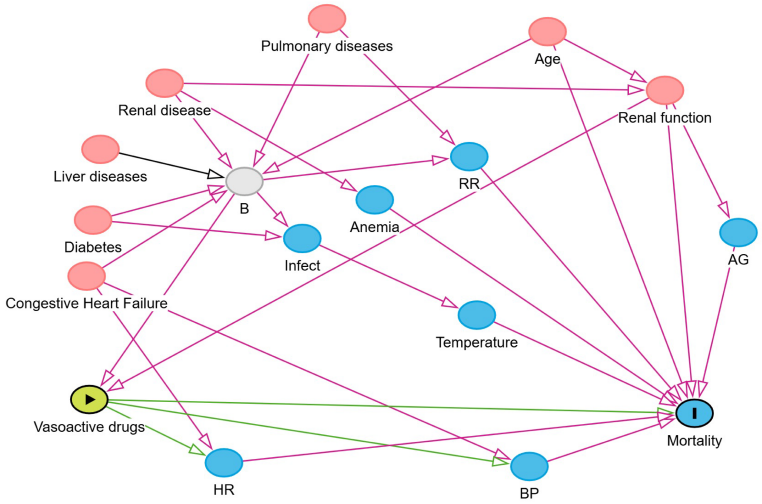


Supplementary Figure 6 Clinical features screening. The x-axis is the number of features incorporated into the model and the y-axis is the area under the ROC curve AUC comparing four machine learning models. In balancing the model complexity and the efficacy of the model, 11 features and BPNN were finally chosen to be incorporated as clinical features screening.

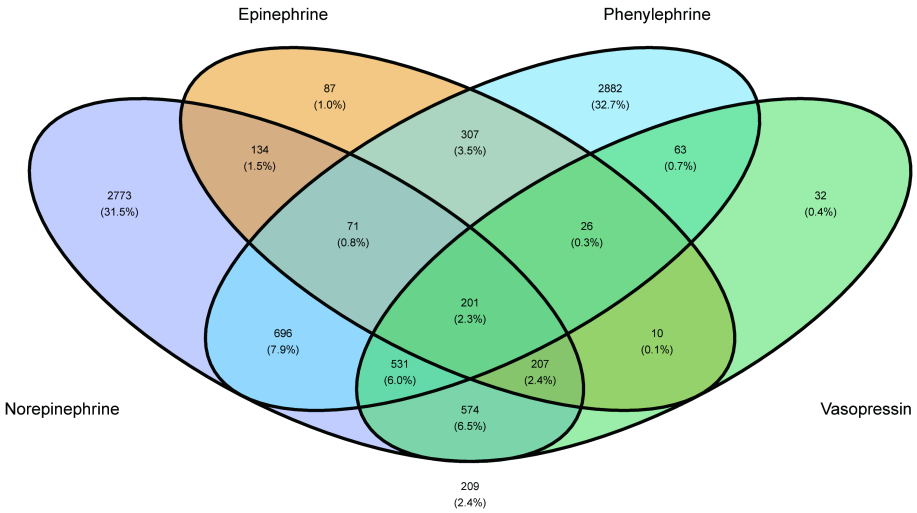


Supplementary Figure 7 SHAP plot for the importance of clinical features. In the upper panel, each sample represents a point, red represents a high level of feature importance, blue represents a low level of feature importance, if most of the red samples are to the left of 0 it means that the variable is negatively correlated with the model, and vice versa it is positively correlated; the lower panel averages the SHAP values, which allows us to determine the importance of the variable to the model as a whole, and since

we have repeated sampling of SHAP, thus estimating confidence intervals for the importance of each variable to the model.



Supplementary Figure 8 Confounding factors by DAG. Based on the medical background, we described in detail the relationships between various covariates, exposure factors (vasoactive drugs), and mortality outcomes using a DAG. The yellow circle represents the exposure factor (vasoactive drugs), and the dark blue circle represents the outcome variable (mortality). Light blue circles denote ancestors of the outcome, while pink circles indicate ancestors of both the exposure and the outcome. Gray circles represent unobserved (latent) variables, such as B, which stands for the patient's unpredictable physical fitness, nutritional level, immunity, vasoactive drug responsiveness, etc. Green lines depict causal paths, whereas pink lines represent biasing paths. In this study, there is one direct causal path: Vasoactive drugs → Mortality. Additionally, there are two indirect causal paths: Vasoactive drugs → BP → Mortality and Vasoactive drugs → HR → Mortality. It is essential to ensure that these three causal paths are open and all the backdoor paths are closed.



Supplementary Figure 9 The use of vasoactive drugs. This Venn diagram shows the use of four vasoactive drugs (how they are used in combination). The reasons for not showing dopamine and dobutamine are the small number of cases in which they are used.

Supplementary Table 1 Compare different clustering methods.

Clustering	Silhouette Score	Calinski-Harabasz Index	Davies-Bouldin Index	Dunn Index
K-means (Euclidean)	0.038	1397.062	3.547	0.129
Birch	0.007	752.225	5.102	0.149
OPTICS	-0.148	3.455	1.726	0.130
Agglomerative	0.007	752.225	5.102	0.149
GMM	0.023	271.554	9.729	0.104
SOM	0.028	926.525	4.361	0.103
K-means (Mahalanobis)	0.013	374.177	6.427	0.064

*K-means (Euclidean): K-means Clustering - Partitions data into K spherical clusters using Euclidean distance, optimal for uniformly distributed data. OPTICS: Ordering Points To Identify the Clustering Structure - Density-based method detecting clusters of varying density and handling noise. BIRCH: Balanced Iterative Reducing and Clustering using Hierarchies - Memory-efficient hierarchical pre-clustering for large datasets. Agglomerative: Agglomerative Hierarchical Clustering - Builds a hierarchical tree structure by iteratively merging nearest clusters. GMM: Gaussian Mixture Model - Probabilistic model assuming data from multiple Gaussian distributions, suitable for complex cluster shapes. K-means (Mahalanobis): Mahalanobis Distance-adjusted K-means Clustering.

Supplementary Table 2 Criteria for defining the sepsis phenotype.

Characteristic	Mean	Standard Deviation	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Mean HR	86.3585	14.5676	0.2306	-0.4159	0.0840	0.3484
Minimum HR	68.0465	14.5653	0.1851	-0.2828	0.0923	0.1974
Maximum HR	110.9762	21.6338	0.2211	-0.4113	0.0801	0.3570
Mean SBP	116.7963	15.1073	1.0063	-0.2595	-0.1102	-0.5745
Minimum SBP	85.2321	16.0531	0.7455	-0.0722	-0.1150	-0.5918
Maximum SBP	153.6318	24.1044	0.7428	-0.2985	-0.0240	-0.3102
Mean DBP	61.8251	9.7836	0.9600	-0.3661	-0.0572	-0.3898
Minimum DBP	42.1262	10.6090	0.7617	-0.1324	-0.1565	-0.5052
Maximum DBP	94.7281	21.7726	0.6270	-0.4108	0.1363	-0.1090
Mean MAP	76.9610	9.7297	1.1324	-0.3515	-0.1552	-0.5297

Characteristic	Mean	Standard Deviation	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Minimum MAP	53.5080	13.3522	0.7114	-0.0683	-0.1285	-0.5621
Maximum MAP	113.7263	31.2548	0.4714	-0.2937	0.0022	-0.0412
Mean RR	19.6996	3.8602	0.1313	-0.4057	0.1979	0.3703
Minimum RR	11.3574	3.6643	0.1518	-0.2185	0.1289	0.0940
Maximum RR	30.6070	7.2072	0.1434	-0.3664	0.2201	0.2857
Mean Temperature	36.8894	0.5210	0.3501	-0.1189	0.0296	-0.2286
Minimum Temperature	36.1455	0.7776	0.2619	-0.0859	0.1540	-0.2677
Maximum Temperature	37.6552	0.8166	0.2814	-0.1459	-0.0300	-0.0571
Mean PO2	128.8344	75.6872	-0.1656	0.5418	-0.5150	-0.3633
Minimum PO2	76.1075	49.0658	-0.0194	0.3614	-0.3568	-0.3353
Mean PCO2	41.9304	9.2415	-0.2203	-0.1450	1.3123	-0.3826
Minimum PCO2	36.1494	8.7771	-0.1338	-0.1296	1.2339	-0.4394
Maximum PCO2	49.1698	14.2728	-0.2238	-0.1004	0.9326	-0.1981
Mean FiO2	56.1790	15.5711	-0.1290	0.1013	-0.0794	0.0398
Minimum FiO2	45.8020	13.9099	-0.0636	0.0180	0.0120	0.0447
Maximum FiO2	73.0950	24.9468	-0.2003	0.2029	-0.2011	0.0472
Mean Base Excess	-0.8779	4.4376	0.0537	0.0848	0.9273	-0.7792
Minimum Base Excess	-3.3620	5.6936	0.1054	0.0915	0.8153	-0.7782
Maximum Base Excess	1.3431	4.5282	-0.0378	0.0663	0.8589	-0.6137
Mean RBC	3.4459	0.6453	0.3286	0.0142	0.1080	-0.4315
Maximum Hemoglobin	11.2648	2.0251	0.3086	0.1564	-0.3425	-0.3524
Mean RDW	15.5043	2.3956	-0.2357	-0.3242	0.3846	0.5245
Mean MCH	30.0277	2.7288	0.0183	0.1718	-0.6402	0.1054
Mean MCV	91.4900	7.2658	-0.0739	-0.0389	-0.2039	0.2505
Mean MCHC	32.8447	1.6254	0.1557	0.3845	-0.8743	-0.2022
Mean Platelet	193.6190	105.8644	0.0465	-0.1313	0.4805	-0.1487
Mean WBC	11.8236	8.7337	-0.0336	-0.1389	-0.0488	0.2927

Characteristic	Mean	Standard Deviation	Phenotype A	Phenotype B	Phenotype C	Phenotype D
Mean Basophils	0.2643	0.3032	0.0197	0.1019	0.0514	-0.2052
Minimum Basophils	0.1780	0.2490	0.0249	0.0936	0.0694	-0.2258
Maximum Basophils	0.3634	0.4711	0.0314	0.0665	0.0216	-0.1358
Mean Eosinophils	1.0083	1.6238	-0.0633	0.0925	0.0988	-0.1454
Minimum Eosinophils	0.7096	1.3880	-0.0509	0.0819	0.0768	-0.1383
Mean Lymphocytes	12.1832	9.0343	0.0055	0.1843	-0.1208	-0.2088
Mean Monocytes	5.7017	3.5089	0.0732	-0.0822	0.1175	-0.0212
Maximum Monocytes	6.7543	4.5685	0.0590	-0.0723	0.0952	-0.0005
Minimum Neutrophils	77.6435	12.5625	0.0019	-0.0901	0.0895	0.0765
Mean Albumin	3.1421	0.6032	0.1336	0.2416	-0.0483	-0.4898
Minimum Albumin	3.0049	0.6471	0.1391	0.2199	-0.0212	-0.4814
Maximum Albumin	3.2819	0.6263	0.1431	0.2206	-0.0447	-0.4612
Mean AG	14.3454	3.6386	0.0014	-0.4176	-0.2094	0.7903
Mean BUN	28.6166	21.5807	-0.2209	-0.3621	0.0817	0.7587
Mean Calcium	8.3296	0.6880	0.1249	0.0250	0.3053	-0.3751
Mean Chloride	103.7880	5.9954	0.1444	0.1876	-0.5876	-0.0682
Mean Sodium	138.4804	4.6458	0.2175	-0.0011	0.0755	-0.2577
Mean Potassium	4.1512	0.5006	-0.2370	-0.0976	0.1083	0.3267
Mean Glucose	137.3811	47.7132	0.0958	-0.2045	0.0204	0.2129
Minimum Glucose	103.5529	33.7666	0.1319	-0.0619	0.0161	-0.0382
Mean Creatinine	1.5748	1.5620	-0.1181	-0.3015	-0.0621	0.6398
Mean INR	1.5183	0.7437	-0.2215	-0.2294	0.0513	0.5671
Mean PTT	38.1791	16.2879	-0.2274	-0.1670	-0.0170	0.4971
Minimum PTT	31.0052	9.0783	-0.2391	-0.1732	-0.0054	0.5033

*HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RR: respiratory rate; PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide; FiO2: Fraction of inspired oxygen; RBC: red blood cell count; RDW: red distribution width; MCH: mean corpuscular

hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; Platelet: platelet count; WBC: White blood cell count; Basophils: percentage of basophils; Eosinophils: percentage of eosinophils; Lymphocytes: percentage of lymphocytes; Monocytes: percentage of monocytes; Neutrophils: percentage of neutrophils; AG: anion gap; BUN: blood urea nitrogen; Glucose: blood glucose; INR: international normalized ratio; PTT: partial thromboplastin time.
* Phenotypes A, B, C, and D represent specific parameters of the clusters. The data can be standardized to determine the phenotype to which each sepsis patient belongs based on euclidean distance.

Supplementary Table 3 Baseline sepsis characteristics from the MIMIC cohort.

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
N	33177	8158	12240	5005	7774		
Type							
Surgical vs. non-surgical						795.312	<0.001
Non-surgical sepsis	23626 (71.21%)	4822 (59.11%)	9058 (74.00%)	3881 (77.54%)	5865 (75.44%)		
Surgical sepsis	9551 (28.79%)	3336 (40.89%)	3182 (26.00%)	1124 (22.46%)	1909 (24.56%)		
community-acquired vs. hospital-acquired sepsis						203.634	<0.001
community-acquired sepsis	30042 (90.55%)	7221 (88.51%)	10951 (89.47%)	4518 (90.27%)	7352 (94.57%)		
hospital-acquired sepsis	3135 (9.45%)	937 (11.49%)	1289 (10.53%)	487 (9.73%)	422 (5.43%)		
Clinical features							
Mean HR (median [IQR])	85.17 (76.08-95.70)	89.24 (79.95-99.16)	79.90 (72.20-87.80)	86.79 (77.20-97.32)	90.63 (80.41-101.97)	3557.675	<0.001
Minimum HR (median [IQR])	67.00 (59.00-77.00)	70.00 (61.00-80.00)	63.00 (56.00-71.00)	69.00 (60.00-78.00)	70.00 (60.00-81.00)	1743.594	<0.001
Maximum HR (median [IQR])	109.00 (95.00-124.00)	114.00 (101.25-128.00)	100.00 (89.00-112.00)	112.00 (98.00-126.00)	117.00 (102.00-133.00)	3707.595	<0.001
Mean SBP (median [IQR])	114.62 (106.31-125.56)	131.08 (121.67-140.90)	112.09 (105.67-119.39)	113.58 (106.11-122.72)	107.41 (100.74-114.76)	10899.221	<0.001
Minimum SBP (median [IQR])	85.00 (76.00-94.00)	96.00 (87.00-106.00)	85.00 (77.00-91.00)	84.00 (76.00-91.00)	77.00 (68.00-85.00)	7348.069	<0.001
Maximum SBP (median [IQR])	151.00 (137.00-168.00)	169.00 (156.00-184.88)	145.00 (133.00-158.00)	151.00 (138.00-166.00)	144.00 (131.00-158.00)	6368.193	<0.001
Mean DBP (median [IQR])	61.04 (55.24-67.46)	70.58 (64.86-76.78)	58.28 (53.55-62.79)	61.12 (55.84-66.53)	57.90 (52.63-63.21)	9795.743	<0.001
Minimum DBP (median [IQR])	42.00 (36.00-48.00)	50.00 (44.00-56.00)	41.00 (36.00-46.00)	41.00 (35.00-47.00)	38.00 (31.00-44.00)	6913.302	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Maximum DBP (median [IQR])	92.00 (80.00-106.00)	104.00 (93.00-119.00)	84.00 (74.00-95.00)	95.00 (83.00-109.00)	90.00 (78.00-103.00)	6014.603	<0.001
Mean MAP (median [IQR])	75.83 (70.43-82.38)	86.85 (82.00-92.64)	73.61 (69.53-77.63)	75.08 (70.47-80.18)	71.79 (67.11-76.47)	13569.508	<0.001
Minimum MAP (median [IQR])	55.00 (48.00-61.00)	63.00 (57.00-69.00)	54.00 (48.00-59.00)	53.00 (47.00-59.00)	49.00 (40.00-55.00)	7902.734	<0.001
Maximum MAP (median [IQR])	107.00 (96.00-122.00)	121.00 (110.00-136.00)	100.00 (92.00-111.00)	109.00 (97.00-123.00)	104.00 (93.00-119.00)	5536.802	<0.001
Mean RR (median [IQR])	19.19 (16.93-21.93)	19.79 (17.46-22.48)	17.79 (16.08-19.88)	20.15 (17.81-22.75)	20.70 (18.02-23.79)	3451.354	<0.001
Minimum RR (median [IQR])	11.00 (9.00-14.00)	12.00 (10.00-14.00)	11.00 (8.50-13.00)	12.00 (9.50-14.00)	12.00 (9.00-14.00)	954.916	<0.001
Maximum RR (median [IQR])	29.50 (26.00-34.00)	31.00 (26.50-36.00)	27.00 (24.00-31.00)	31.00 (27.00-36.00)	32.00 (28.00-36.00)	3000.922	<0.001
Mean Temperature (median [IQR])	36.87 (36.63-37.17)	37.02 (36.77-37.36)	36.82 (36.59-37.08)	36.87 (36.66-37.15)	36.78 (36.52-37.09)	1645.985	<0.001
Minimum Temperature (median [IQR])	36.33 (35.89-36.56)	36.44 (36.17-36.67)	36.33 (35.72-36.56)	36.39 (36.11-36.56)	36.28 (35.61-36.50)	1463.728	<0.001
Maximum Temperature (median [IQR])	37.50 (37.11-38.11)	37.72 (37.22-38.44)	37.39 (37.06-37.90)	37.44 (37.11-38.06)	37.44 (37.06-38.11)	856.098	<0.001
Mean PO2 (median [IQR])	108.81 (72.00-170.00)	104.00 (71.00-148.69)	160.85 (99.00-232.03)	79.62 (56.64-109.50)	93.81 (63.00-127.89)	5587.933	<0.001
Minimum PO2 (median [IQR])	65.00 (42.00-93.00)	66.00 (44.00-92.00)	81.00 (56.00-115.00)	50.00 (37.00-70.00)	50.00 (37.00-73.00)	3842.676	<0.001
Mean PCO2 (median [IQR])	40.61 (36.50-45.55)	39.60 (35.67-44.00)	40.33 (37.00-43.67)	51.33 (45.50-59.87)	38.00 (33.80-42.50)	7679.046	<0.001
Minimum PCO2 (median [IQR])	35.00 (31.00-40.00)	35.00 (31.00-39.00)	35.00 (31.00-39.00)	45.00 (39.00-52.00)	32.00 (28.00-37.00)	7356.609	<0.001
Maximum PCO2 (median [IQR])	47.00 (41.00-54.00)	44.00 (39.00-51.00)	46.00 (41.00-52.00)	57.00 (49.00-72.00)	45.00 (38.00-52.00)	3970.853	<0.001
Mean FiO2 (median [IQR])	51.67 (45.00-65.00)	50.00 (43.33-61.31)	55.00 (46.67-66.67)	50.00 (43.33-63.33)	52.22 (45.00-66.00)	455.676	<0.001
Minimum FiO2 (median [IQR])	40.00 (40.00-50.00)	40.00 (40.00-50.00)	40.00 (40.00-50.00)	40.00 (40.00-50.00)	40.00 (40.00-50.00)	78.314	<0.001
Maximum FiO2 (median [IQR])	70.00 (50.00-100.00)	60.00 (50.00-100.00)	100.00 (50.00-100.00)	60.00 (50.00-100.00)	70.00 (50.00-100.00)	1039.657	<0.001
Mean Base Excess (median [IQR])	-0.50 (-3.00-1.14)	-0.33 (-2.50-1.00)	-0.33 (-2.00-1.00)	2.19 (0.00-5.67)	-3.87 (-7.00--1.00)	8135.756	<0.001
Minimum Base Excess (median [IQR])	-2.00 (-6.00-0.00)	-2.00 (-5.00-0.00)	-2.00 (-5.00-0.00)	0.00 (-1.00-4.00)	-7.00 (-11.00--3.00)	7421.067	<0.001
Maximum Base Excess (median [IQR])	1.00 (-1.00-4.00)	1.00 (0.00-3.00)	1.00 (0.00-3.00)	4.00 (1.00-8.00)	-1.00 (-4.00-1.00)	5954.13	<0.001
Mean RBC (median [IQR])	3.38 (2.99-3.85)	3.63 (3.17-4.11)	3.41 (3.06-3.81)	3.44 (3.00-3.94)	3.10 (2.73-3.50)	2534.72	<0.001
Maximum Hemoglobin (median [IQR])	11.10 (9.80-12.60)	11.80 (10.40-13.30)	11.50 (10.30-12.80)	10.30 (9.10-11.70)	10.30 (9.10-11.70)	2944.942	<0.001
Mean RDW (median [IQR])	14.93 (13.79-16.66)	14.45 (13.52-15.80)	14.32 (13.40-15.57)	16.02 (14.60-17.73)	16.23 (14.82-18.10)	5042.882	<0.001
Mean MCH (median [IQR])	30.18 (28.63-31.60)	30.20 (28.75-31.62)	30.54 (29.26-31.80)	28.67 (26.54-30.37)	30.30 (28.70-31.95)	2069.471	<0.001
Mean MCV (median [IQR])	91.20 (87.25-95.60)	90.78 (87.00-95.00)	90.88 (87.33-94.75)	90.43 (85.00-95.33)	92.75 (88.45-98.00)	606.18	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Mean MCHC (median [IQR])	32.92 (31.82-33.93)	33.12 (32.17-34.07)	33.48 (32.57-34.37)	31.50 (30.45-32.48)	32.55 (31.50-33.53)	5701.846	<0.001
Mean Platelet (median [IQR])	176.00 (123.67-240.50)	184.94 (132.75-245.75)	164.40 (123.25-219.00)	220.33 (159.33-301.29)	158.00 (98.25-232.70)	1563.879	<0.001
Mean WBC (median [IQR])	10.52 (7.70-14.08)	10.46 (7.83-13.75)	10.10 (7.53-13.04)	10.13 (7.50-13.77)	11.95 (8.10-17.13)	661.22	<0.001
Mean Basophils (median [IQR])	0.20 (0.10-0.37)	0.20 (0.10-0.40)	0.20 (0.10-0.40)	0.20 (0.10-0.40)	0.10 (0.00-0.30)	832.589	<0.001
Minimum Basophils (median [IQR])	0.10 (0.00-0.30)	0.10 (0.00-0.30)	0.10 (0.00-0.30)	0.10 (0.00-0.30)	0.00 (0.00-0.20)	936.338	<0.001
Maximum Basophils (median [IQR])	0.20 (0.10-0.50)	0.30 (0.10-0.50)	0.30 (0.10-0.50)	0.30 (0.10-0.50)	0.20 (0.00-0.40)	568.62	<0.001
Mean Eosinophils (median [IQR])	0.50 (0.10-1.20)	0.40 (0.10-1.10)	0.65 (0.20-1.50)	0.55 (0.15-1.40)	0.30 (0.02-1.00)	919.972	<0.001
Minimum Eosinophils (median [IQR])	0.20 (0.00-0.90)	0.20 (0.00-0.80)	0.30 (0.00-1.00)	0.20 (0.00-1.00)	0.10 (0.00-0.50)	859.702	<0.001
Mean Lymphocytes (median [IQR])	10.00 (6.74-15.20)	10.20 (7.00-15.10)	11.60 (8.00-17.30)	9.53 (6.40-14.40)	8.60 (5.00-12.90)	1394.973	<0.001
Mean Monocytes (median [IQR])	5.05 (3.65-7.10)	5.25 (3.95-7.35)	5.00 (3.50-6.75)	5.35 (4.00-7.55)	5.00 (3.20-7.03)	234.542	<0.001
Maximum Monocytes (median [IQR])	5.60 (4.00-8.40)	6.00 (4.30-8.80)	5.40 (4.00-8.00)	6.00 (4.40-9.10)	5.60 (4.00-8.20)	207.62	<0.001
Minimum Neutrophils (median [IQR])	80.60 (72.25-85.60)	80.54 (72.16-85.50)	79.40 (70.97-84.50)	81.10 (73.10-86.30)	81.95 (74.00-87.00)	362.192	<0.001
Mean Albumin (median [IQR])	3.15 (2.70-3.55)	3.20 (2.85-3.60)	3.30 (2.90-3.70)	3.12 (2.72-3.50)	2.80 (2.40-3.29)	2492.639	<0.001
Minimum Albumin (median [IQR])	3.00 (2.50-3.40)	3.10 (2.70-3.50)	3.10 (2.70-3.60)	3.00 (2.60-3.40)	2.70 (2.20-3.10)	2371.938	<0.001
Maximum Albumin (median [IQR])	3.30 (2.90-3.80)	3.40 (3.00-3.80)	3.40 (3.00-3.90)	3.30 (2.80-3.70)	3.00 (2.50-3.40)	2189.92	<0.001
Mean AG (median [IQR])	13.75 (12.00-16.00)	14.00 (12.50-15.83)	12.67 (11.25-14.25)	13.33 (11.60-15.33)	16.43 (14.00-19.57)	6379.268	<0.001
Mean BUN (median [IQR])	21.67 (14.50-35.80)	18.60 (12.75-29.00)	17.80 (13.00-25.20)	24.50 (16.17-38.75)	38.33 (24.15-58.20)	5881.237	<0.001
Mean Calcium (median [IQR])	8.30 (7.90-8.72)	8.40 (8.00-8.80)	8.30 (7.96-8.70)	8.50 (8.10-8.90)	8.03 (7.60-8.50)	1792.002	<0.001
Mean Chloride (median [IQR])	104.00 (100.33-107.33)	104.50 (101.25-108.00)	105.00 (102.33-107.50)	100.40 (96.75-104.00)	103.60 (98.61-108.00)	2423.897	<0.001
Mean Sodium (median [IQR])	138.50 (136.00-141.00)	139.33 (136.83-142.00)	138.50 (136.50-140.50)	138.86 (136.00-141.67)	137.29 (134.12-140.33)	960.409	<0.001
Mean Potassium (median [IQR])	4.10 (3.81-4.41)	3.97 (3.73-4.28)	4.09 (3.83-4.34)	4.13 (3.85-4.50)	4.24 (3.87-4.67)	1107.689	<0.001
Mean Glucose (median [IQR])	125.40 (107.50-153.43)	129.00 (110.00-158.79)	120.50 (105.75-140.00)	126.22 (106.43-157.00)	132.00 (108.21-169.79)	649.787	<0.001
Minimum Glucose (median [IQR])	98.00 (84.00-116.00)	101.00 (88.00-121.00)	98.00 (86.00-112.00)	98.00 (83.00-117.00)	94.00 (78.00-117.00)	345.122	<0.001
Mean Creatinine (median [IQR])	1.05 (0.76-1.68)	0.95 (0.72-1.38)	0.92 (0.72-1.20)	1.05 (0.72-1.63)	1.91 (1.17-3.27)	5250.717	<0.001
Mean INR (median [IQR])	1.30 (1.15-1.55)	1.21 (1.10-1.40)	1.25 (1.13-1.40)	1.30 (1.15-1.60)	1.53 (1.28-2.16)	3799.82	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Mean PTT (median [IQR])	32.27 (28.23-41.35)	30.19 (27.00-35.73)	31.50 (28.07-37.53)	32.10 (28.20-40.80)	39.17 (31.48-54.77)	2902.143	<0.001
Minimum PTT (median [IQR])	29.00 (26.10-33.20)	27.70 (25.20-31.00)	28.30 (25.80-31.70)	29.30 (26.30-33.40)	32.30 (27.90-39.10)	2588.071	<0.001
Demographics features							
Age (median [IQR])	68.01 (56.90-78.82)	63.85 (52.34-76.21)	68.70 (58.37-78.78)	70.31 (59.54-80.45)	69.23 (58.19-80.16)	568.809	<0.001
Sex (%)						29.787	<0.001
F	14011 (42.23%)	3316 (40.65%)	4860 (39.71%)	2429 (48.53%)	3406 (43.81%)		
M	19166 (57.77%)	4842 (59.35%)	7380 (60.29%)	2576 (51.47%)	4368 (56.19%)		
Scale features							
SOFA (median [IQR])	6.00 (4.00-9.00)	5.00 (3.00-7.00)	5.00 (4.00-8.00)	6.00 (4.00-8.00)	9.00 (6.00-13.00)	4711.526	<0.001
APSIII (median [IQR])	51.00 (38.00-70.00)	47.00 (35.00-62.00)	42.00 (32.00-57.00)	54.00 (43.00-70.00)	70.00 (55.00-92.00)	6620.764	<0.001
OASIS (median [IQR])	34.00 (28.00-41.00)	33.00 (28.00-39.00)	32.00 (26.00-38.00)	35.00 (29.00-41.00)	39.00 (32.00-46.00)	2461.618	<0.001
GCS (median [IQR])	14.00 (10.00-15.00)	13.00 (9.00-14.00)	14.00 (11.00-15.00)	13.00 (10.00-14.00)	13.00 (9.00-15.00)	560.046	<0.001
Comorbidities features							
Myocardial Infarct (%)						251.242	<0.001
No	27262 (82.17%)	7059 (86.53%)	10118 (82.66%)	4101 (81.94%)	5984 (76.97%)		
Yes	5915 (17.83%)	1099 (13.47%)	2122 (17.34%)	904 (18.06%)	1790 (23.03%)		
Congestive Heart Failure (%)						1627.316	<0.001
No	22212 (66.95%)	6203 (76.04%)	9079 (74.17%)	2455 (49.05%)	4475 (57.56%)		
Yes	10965 (33.05%)	1955 (23.96%)	3161 (25.83%)	2550 (50.95%)	3299 (42.44%)		
Chronic Pulmonary Disease (%)						1414.119	<0.001
No	23827 (71.82%)	6288 (77.08%)	9382 (76.65%)	2511 (50.17%)	5646 (72.63%)		
Yes	9350 (28.18%)	1870 (22.92%)	2858 (23.35%)	2494 (49.83%)	2128 (27.37%)		
Liver Disease (%)						1027.709	<0.001
No	27662 (83.38%)	6882 (84.36%)	10740 (87.75%)	4452 (88.95%)	5588 (71.88%)		
Yes	5515 (16.62%)	1276 (15.64%)	1500 (12.25%)	553 (11.05%)	2186 (28.12%)		
Renal Disease (%)						1546.193	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
No	24561 (74.03%)	6404 (78.50%)	10118 (82.66%)	3459 (69.11%)	4580 (58.91%)		
Yes	8616 (25.97%)	1754 (21.50%)	2122 (17.34%)	1546 (30.89%)	3194 (41.09%)		
Diabetes (%)						383.815	<0.001
No	22365 (67.41%)	5643 (69.17%)	8883 (72.57%)	2990 (59.74%)	4849 (62.37%)		
Yes	10812 (32.59%)	2515 (30.83%)	3357 (27.43%)	2015 (40.26%)	2925 (37.63%)		
Nervous System Disease (%)						583.066	<0.001
No	27362 (82.47%)	6010 (73.67%)	10398 (84.95%)	4274 (85.39%)	6680 (85.93%)		
Yes	5815 (17.53%)	2148 (26.33%)	1842 (15.05%)	731 (14.61%)	1094 (14.07%)		
Malignant Tumor (%)						77.276	<0.001
No	27865 (83.99%)	6948 (85.17%)	10463 (85.48%)	4131 (82.54%)	6323 (81.34%)		
Yes	5312 (16.01%)	1210 (14.83%)	1777 (14.52%)	874 (17.46%)	1451 (18.66%)		
Treatment							
Transplantation						138.077	<0.001
No	32481 (97.90%)	7977 (97.78%)	12095 (98.82%)	4915 (98.20%)	7494 (96.40%)		
Yes	696 (2.10%)	181 (2.22%)	145 (1.18%)	90 (1.80%)	280 (3.60%)		
Immunosuppressive therapy						750.676	<0.001
No	24226 (73.02%)	5846 (71.66%)	9920 (81.05%)	3156 (63.06%)	5304 (68.23%)		
Yes	8951 (26.98%)	2312 (28.34%)	2320 (18.95%)	1849 (36.94%)	2470 (31.77%)		
Surgical conditions							
surgery						1684.577	<0.001
No	18271 (55.07%)	4533 (55.57%)	5117 (41.81%)	3500 (69.93%)	5121 (65.87%)		
Yes	14906 (44.93%)	3625 (44.43%)	7123 (58.19%)	1505 (30.07%)	2653 (34.13%)		
Cardiovascular surgery						4208.526	<0.001
No	28519 (85.96%)	7736 (94.83%)	8542 (69.79%)	4816 (96.22%)	7425 (95.51%)		
Yes	4658 (14.04%)	422 (5.17%)	3698 (30.21%)	189 (3.78%)	349 (4.49%)		
Lung surgery						68.877	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
No	28823 (86.88%)	7058 (86.52%)	10825 (88.44%)	4194 (83.80%)	6746 (86.78%)		
Yes	4354 (13.12%)	1100 (13.48%)	1415 (11.56%)	811 (16.20%)	1028 (13.22%)		
Kidney surgery						51.807	<0.001
No	32850 (99.01%)	8087 (99.13%)	12143 (99.21%)	4976 (99.42%)	7644 (98.33%)		
Yes	327 (0.99%)	71 (0.87%)	97 (0.79%)	29 (0.58%)	130 (1.67%)		
Liver surgery						98.054	<0.001
No	31391 (94.62%)	7673 (94.05%)	11592 (94.71%)	4868 (97.26%)	7258 (93.36%)		
Yes	1786 (5.38%)	485 (5.95%)	648 (5.29%)	137 (2.74%)	516 (6.64%)		
Abdomen surgery						194.011	<0.001
No	29926 (90.20%)	7410 (90.83%)	11162 (91.19%)	4648 (92.87%)	6706 (86.26%)		
Yes	3251 (9.80%)	748 (9.17%)	1078 (8.81%)	357 (7.13%)	1068 (13.74%)		
Nerves surgery						1188.843	<0.001
No	29820 (89.88%)	6617 (81.11%)	10959 (89.53%)	4768 (95.26%)	7476 (96.17%)		
Yes	3357 (10.12%)	1541 (18.89%)	1281 (10.47%)	237 (4.74%)	298 (3.83%)		
Outcomes							
Hospital Mortality (%)						2647.422	<0.001
No	27699 (83.49%)	7207 (88.34%)	11286 (92.21%)	4115 (82.22%)	5091 (65.49%)		
Yes	5478 (16.51%)	951 (11.66%)	954 (7.79%)	890 (17.78%)	2683 (34.51%)		
Hospital length of stay, days (median [IQR])	8.87 (5.21-16.36)	9.59 (5.72-16.82)	7.39 (4.92-13.18)	9.97 (5.87-17.19)	10.53 (5.52-19.87)	517.885	<0.001
ICU length of stay, days (median [IQR])	2.91 (1.54-6.03)	3.08 (1.69-6.51)	2.21 (1.28-4.36)	3.39 (1.85-6.76)	3.66 (1.92-7.56)	1065.985	<0.001

* HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RR: respiratory rate; PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide; FiO2: Fraction of inspired oxygen; RBC: red blood cell count; RDW: red distribution width; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; Platelet: platelet count; WBC: White blood cell count; Basophils: percentage of basophils; Eosinophils: percentage of eosinophils; Lymphocytes: percentage of lymphocytes; Monocytes: percentage of monocytes; Neutrophils: percentage of neutrophils; AG: anion gap; BUN: blood urea nitrogen; Glucose: blood glucose; INR: international normalized ratio; PTT: partial thromboplastin time.

* Immunosuppressive therapy includes methylprednisolone, hydrocortisone, prednisone, dexamethasone, cyclophosphamide, methotrexate, cyclosporine, azathioprine, hydroxychloroquine, azacitidine, rituximab, infliximab, and etanercept.

Supplementary Table 4 Baseline sepsis characteristics from the eICU cohort.

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
N	21496	5675	7481	3119	5221		
Type							
Surgical vs. non-surgical						2.067	0.559
Non-surgical sepsis	20304 (94.45%)	5363 (94.50%)	7048 (94.21%)	2960 (94.90%)	4933 (94.48%)		
Surgical sepsis	1192 (5.55%)	312 (5.50%)	433 (5.79%)	159 (5.10%)	288 (5.52%)		
community-acquired vs. hospital-acquired sepsis						31.014	<0.001
community-acquired sepsis	19714 (91.71%)	5158 (90.89%)	6802 (90.92%)	2881 (92.37%)	4873 (93.33%)		
hospital-acquired sepsis	1782 (8.29%)	517 (9.11%)	679 (9.08%)	238 (7.63%)	348 (6.67%)		
Clinical features							
Mean HR (median [IQR])	91.04 (80.18-102.09)	94.64 (84.78-104.64)	84.42 (74.91-94.62)	91.42 (81.14-101.86)	96.70 (85.71-108.30)	2134.136	<0.001
Minimum HR (median [IQR])	71.00 (61.00-82.00)	75.00 (64.00-86.00)	67.00 (59.00-78.00)	71.00 (61.00-82.00)	74.00 (63.00-86.00)	804.404	<0.001
Maximum HR (median [IQR])	116.00 (100.00-132.00)	119.00 (105.00-135.00)	106.00 (93.00-122.00)	117.00 (103.00-133.00)	125.00 (109.00-141.00)	1976.108	<0.001
Mean SBP (median [IQR])	112.11 (103.63-123.36)	127.94 (118.09-138.67)	108.76 (102.07-116.44)	112.15 (104.80-121.33)	105.20 (98.36-112.54)	6945.271	<0.001
Minimum SBP (median [IQR])	81.00 (70.00-93.00)	95.00 (83.00-109.00)	80.00 (71.00-90.00)	80.00 (70.00-90.00)	71.00 (61.00-81.00)	5141.4	<0.001
Maximum SBP (median [IQR])	150.00 (133.00-168.00)	167.00 (152.00-185.00)	141.00 (127.00-155.00)	152.00 (136.00-168.00)	144.00 (129.00-161.00)	3670.644	<0.001
Mean DBP (median [IQR])	61.11 (55.30-67.66)	70.65 (65.87-76.59)	58.39 (53.81-63.10)	60.56 (55.73-65.77)	57.01 (51.95-62.00)	7839.547	<0.001
Minimum DBP (median [IQR])	41.00 (34.00-50.00)	51.00 (43.00-58.00)	41.00 (34.00-47.00)	40.00 (33.00-47.00)	35.00 (27.00-42.00)	4947.937	<0.001
Maximum DBP (median [IQR])	91.00 (78.00-104.00)	100.00 (89.00-116.00)	84.00 (73.00-95.00)	92.00 (80.00-104.00)	89.00 (77.00-103.00)	2525.251	<0.001
Mean MAP (median [IQR])	75.64 (69.41-83.20)	88.23 (82.09-95.01)	72.67 (67.87-77.39)	75.54 (70.30-81.13)	70.73 (65.88-75.83)	9163.886	<0.001
Minimum MAP (median [IQR])	54.00 (46.00-63.00)	66.00 (58.00-76.00)	53.00 (47.00-60.00)	53.00 (46.00-60.00)	47.00 (38.00-54.00)	5817.756	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Maximum MAP (median [IQR])	105.00 (93.00-120.00)	118.00 (107.00-133.00)	97.00 (87.00-108.00)	106.00 (95.00-120.00)	102.00 (90.00-116.00)	3762.857	<0.001
Mean RR (median [IQR])	20.67 (18.07-23.80)	21.50 (18.76-24.75)	19.46 (17.24-22.00)	20.64 (18.19-23.64)	21.91 (18.92-25.31)	1237.415	<0.001
Minimum RR (median [IQR])	13.00 (10.00-16.00)	14.00 (11.00-17.00)	13.00 (10.00-16.00)	13.00 (10.00-16.00)	13.00 (9.00-16.00)	318.473	<0.001
Maximum RR (median [IQR])	31.00 (26.00-37.00)	32.00 (26.00-39.00)	28.00 (24.00-34.00)	32.00 (27.00-38.00)	33.00 (28.00-40.00)	1268.423	<0.001
Mean Temperature (median [IQR])	36.88 (36.61-37.21)	36.98 (36.72-37.36)	36.85 (36.60-37.15)	36.88 (36.63-37.20)	36.78 (36.49-37.14)	583.673	<0.001
Minimum Temperature (median [IQR])	36.30 (35.90-36.50)	36.39 (36.10-36.60)	36.30 (35.90-36.60)	36.30 (35.90-36.50)	36.10 (35.60-36.40)	771.546	<0.001
Maximum Temperature (median [IQR])	37.60 (37.10-38.50)	37.80 (37.20-38.70)	37.50 (37.10-38.30)	37.70 (37.20-38.40)	37.60 (37.10-38.40)	272.036	<0.001
Mean PO2 (median [IQR])	92.33 (74.50-123.43)	89.63 (73.00-117.27)	99.75 (78.00-137.83)	85.60 (71.00-107.00)	91.60 (74.00-121.20)	489.025	<0.001
Minimum PO2 (median [IQR])	71.00 (56.00-96.50)	69.80 (56.00-92.95)	78.00 (59.00-115.00)	66.20 (54.00-82.00)	69.00 (54.00-90.00)	520.52	<0.001
Mean PCO2 (median [IQR])	37.00 (32.50-44.00)	36.14 (32.10-42.00)	36.30 (32.60-41.76)	50.95 (43.00-60.07)	34.65 (29.60-40.00)	4332.318	<0.001
Minimum PCO2 (median [IQR])	33.30 (28.20-39.00)	33.00 (28.70-38.00)	33.00 (28.70-38.00)	42.30 (36.00-50.05)	30.30 (25.40-35.00)	3401.174	<0.001
Maximum PCO2 (median [IQR])	41.00 (34.60-51.00)	39.70 (34.00-47.80)	40.00 (34.10-48.00)	58.00 (47.00-76.30)	38.00 (32.60-47.00)	3421.651	<0.001
Mean FiO2 (median [IQR])	0.47 (0.32-0.67)	0.45 (0.31-0.63)	0.47 (0.31-0.66)	0.49 (0.35-0.67)	0.50 (0.33-0.70)	132.462	<0.001
Minimum FiO2 (median [IQR])	0.35 (0.28-0.50)	0.35 (0.28-0.44)	0.35 (0.28-0.45)	0.40 (0.30-0.50)	0.36 (0.28-0.50)	106.151	<0.001
Maximum FiO2 (median [IQR])	0.55 (0.33-1.00)	0.50 (0.32-1.00)	0.60 (0.32-1.00)	0.52 (0.36-1.00)	0.60 (0.35-1.00)	91.911	<0.001
Mean Base Excess (median [IQR])	-1.60 (-5.50-0.93)	-1.35 (-4.72-0.90)	-1.43 (-4.70-0.65)	1.83 (-0.73-5.00)	-5.33 (-9.25--1.50)	3950.311	<0.001
Minimum Base Excess (median [IQR])	-3.40 (-9.00-0.20)	-2.90 (-7.80-0.20)	-3.00 (-8.00-0.00)	0.60 (-2.30-3.60)	-8.80 (-13.30--3.10)	3769.792	<0.001
Maximum Base Excess (median [IQR])	0.20 (-2.70-3.00)	0.20 (-2.50-2.80)	0.20 (-2.10-2.80)	3.20 (0.40-7.00)	-1.20 (-6.00-1.50)	2263.798	<0.001
Mean RBC (median [IQR])	3.56 (3.11-4.02)	3.80 (3.34-4.24)	3.56 (3.13-3.97)	3.60 (3.17-4.08)	3.28 (2.88-3.75)	1364.582	<0.001
Maximum Hemoglobin (median [IQR])	11.70 (10.10-13.30)	12.40 (10.80-14.10)	11.90 (10.40-13.40)	11.10 (9.70-12.70)	10.80 (9.50-12.40)	1267.529	<0.001
Mean RDW (median [IQR])	15.45 (14.26-17.16)	14.90 (13.88-16.30)	15.03 (14.00-16.50)	16.35 (14.95-18.35)	16.30 (14.95-18.25)	1890.34	<0.001
Mean MCH (median [IQR])	29.80 (28.07-31.33)	29.87 (28.27-31.23)	30.20 (28.68-31.68)	28.50 (26.50-30.10)	29.82 (28.05-31.52)	1049.808	<0.001
Mean MCV (median [IQR])	90.80 (86.28-95.33)	90.25 (86.00-94.42)	91.30 (87.12-95.62)	89.75 (84.21-94.75)	91.25 (86.42-96.33)	202.163	<0.001
Mean MCHC (median [IQR])	32.75 (31.88-33.60)	32.95 (32.17-33.70)	33.00 (32.27-33.77)	31.67 (30.74-32.55)	32.65 (31.77-33.60)	2335.607	<0.001
Mean Platelet (median [IQR])	183.67 (125.00-253.00)	194.00 (140.58-259.67)	173.25 (119.67-235.25)	217.80 (160.17-296.50)	165.00 (100.33-241.45)	747.288	<0.001
Mean WBC (median [IQR])	12.47 (8.80-17.15)	12.43 (9.07-16.53)	11.35 (7.95-15.47)	12.60 (9.18-17.00)	14.50 (9.70-20.60)	607.257	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Mean Basophils (median [IQR])	0.03 (0.00-0.33)	0.00 (0.00-0.32)	0.10 (0.00-0.35)	0.05 (0.00-0.33)	0.00 (0.00-0.25)	167.657	<0.001
Minimum Basophils (median [IQR])	0.00 (0.00-0.10)	0.00 (0.00-0.10)	0.00 (0.00-0.10)	0.00 (0.00-0.10)	0.00 (0.00-0.10)	103.309	<0.001
Maximum Basophils (median [IQR])	0.10 (0.00-0.60)	0.00 (0.00-0.60)	0.10 (0.00-0.70)	0.10 (0.00-0.60)	0.00 (0.00-0.40)	145.438	<0.001
Mean Eosinophils (median [IQR])	0.50 (0.00-1.32)	0.40 (0.00-1.16)	0.63 (0.00-1.57)	0.50 (0.00-1.33)	0.33 (0.00-1.00)	285.502	<0.001
Minimum Eosinophils (median [IQR])	0.00 (0.00-0.50)	0.00 (0.00-0.30)	0.00 (0.00-1.00)	0.00 (0.00-0.60)	0.00 (0.00-0.20)	199.643	<0.001
Mean Lymphocytes (median [IQR])	8.30 (5.05-13.00)	8.50 (5.50-13.25)	9.33 (6.00-14.75)	8.00 (5.00-12.25)	7.00 (4.30-10.80)	589.904	<0.001
Mean Monocytes (median [IQR])	6.00 (4.20-8.00)	6.00 (4.33-8.04)	6.08 (4.38-8.25)	6.17 (4.50-8.27)	5.45 (3.67-7.50)	220.225	<0.001
Maximum Monocytes (median [IQR])	7.90 (5.50-10.00)	8.00 (6.00-10.00)	8.00 (6.00-10.10)	8.00 (6.00-10.30)	7.00 (5.00-10.00)	170.247	<0.001
Minimum Neutrophils (median [IQR])	80.78 (72.67-86.25)	81.00 (73.35-86.25)	79.40 (70.80-85.00)	81.75 (74.00-87.00)	82.00 (73.60-87.10)	222.492	<0.001
Mean Albumin (median [IQR])	2.70 (2.25-3.13)	2.90 (2.45-3.30)	2.80 (2.40-3.20)	2.70 (2.27-3.10)	2.30 (1.90-2.70)	2427.813	<0.001
Minimum Albumin (median [IQR])	2.40 (2.00-2.90)	2.60 (2.20-3.10)	2.50 (2.20-3.00)	2.50 (2.10-2.90)	2.10 (1.70-2.50)	2388.686	<0.001
Maximum Albumin (median [IQR])	3.00 (2.40-3.50)	3.20 (2.70-3.60)	3.10 (2.60-3.60)	2.90 (2.40-3.40)	2.60 (2.10-3.00)	1955.702	<0.001
Mean AG (median [IQR])	11.33 (8.80-14.38)	11.50 (9.00-14.20)	10.33 (8.00-13.00)	10.33 (7.75-13.00)	13.83 (10.97-17.22)	2296.372	<0.001
Mean BUN (median [IQR])	26.75 (17.00-42.25)	23.00 (15.00-34.71)	22.67 (15.00-34.20)	26.75 (17.25-41.40)	42.00 (27.75-61.50)	2872.829	<0.001
Mean Calcium (median [IQR])	8.18 (7.72-8.63)	8.33 (7.92-8.78)	8.18 (7.78-8.60)	8.35 (7.95-8.80)	7.83 (7.32-8.32)	1682.595	<0.001
Mean Chloride (median [IQR])	104.50 (100.50-108.50)	104.50 (101.00-108.00)	105.50 (101.75-109.00)	102.00 (98.20-106.00)	104.40 (99.50-109.00)	645.73	<0.001
Mean Sodium (median [IQR])	138.00 (135.25-141.00)	138.33 (135.75-141.00)	138.30 (135.60-141.00)	138.25 (135.50-141.14)	137.43 (134.00-141.00)	128.938	<0.001
Mean Potassium (median [IQR])	3.98 (3.67-4.37)	3.90 (3.63-4.22)	3.92 (3.65-4.23)	4.08 (3.73-4.47)	4.16 (3.75-4.67)	744.812	<0.001
Mean Glucose (median [IQR])	129.40 (108.29-161.94)	134.40 (112.00-171.99)	122.50 (104.94-148.44)	133.02 (110.43-164.64)	133.00 (109.00-168.79)	408.198	<0.001
Minimum Glucose (median [IQR])	92.00 (76.00-111.00)	97.00 (82.00-117.00)	91.00 (77.00-107.00)	94.00 (78.00-114.00)	88.00 (68.00-110.00)	395.518	<0.001
Mean Creatinine (median [IQR])	1.30 (0.88-2.15)	1.14 (0.82-1.71)	1.14 (0.82-1.67)	1.16 (0.78-1.93)	2.18 (1.36-3.47)	2729.832	<0.001
Mean INR (median [IQR])	1.30 (1.16-1.70)	1.25 (1.10-1.55)	1.30 (1.15-1.60)	1.30 (1.15-1.70)	1.50 (1.25-2.20)	1153.814	<0.001
Mean PTT (median [IQR])	33.50 (29.10-41.00)	32.70 (28.60-38.00)	33.00 (29.00-39.02)	33.20 (29.00-39.90)	36.90 (31.45-47.50)	835.678	<0.001
Minimum PTT (median [IQR])	31.00 (27.50-36.00)	30.00 (27.00-34.00)	30.50 (27.00-34.70)	31.00 (27.30-35.00)	33.50 (29.00-40.60)	808.46	<0.001
Demographics features							

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
Age (median [IQR])	68.00 (57.00-79.00)	65.00 (54.00-77.00)	69.00 (57.00-80.00)	68.00 (58.00-77.00)	69.00 (58.00-79.00)	122.576	<0.001
Sex (%)						43.978	<0.001
F	10482 (48.76%)	2597 (45.76%)	3617 (48.35%)	1638 (52.52%)	2630 (50.37%)		
M	11014 (51.24%)	3078 (54.24%)	3864 (51.65%)	1481 (47.48%)	2591 (49.63%)		
Scale features							
SOFA (median [IQR])	6.00 (4.00-9.00)	5.00 (4.00-8.00)	6.00 (4.00-8.00)	6.00 (4.00-8.00)	8.00 (6.00-11.00)	1910.812	<0.001
APSIII (median [IQR])	52.00 (38.00-69.00)	46.00 (34.00-61.00)	47.00 (36.00-61.00)	51.00 (38.00-67.00)	67.00 (52.00-87.00)	2281.894	<0.001
OASIS (median [IQR])	28.00 (22.00-36.00)	27.00 (21.00-33.00)	26.00 (21.00-33.00)	29.00 (23.00-36.00)	33.00 (25.00-41.00)	1124.908	<0.001
GCS (median [IQR])	13.00 (8.00-15.00)	13.00 (8.00-15.00)	14.00 (9.00-15.00)	12.00 (7.00-14.00)	10.00 (6.00-14.00)	701.527	<0.001
Comorbidities features							
Myocardial Infarct (%)						6.213	0.102
No	20879 (97.13%)	5535 (97.53%)	7262 (97.07%)	3031 (97.18%)	5051 (96.74%)		
Yes	617 (2.87%)	140 (2.47%)	219 (2.93%)	88 (2.82%)	170 (3.26%)		
Congestive Heart Failure (%)						95.934	<0.001
No	19632 (91.33%)	5237 (92.28%)	6897 (92.19%)	2707 (86.79%)	4791 (91.76%)		
Yes	1864 (8.67%)	438 (7.72%)	584 (7.81%)	412 (13.21%)	430 (8.24%)		
Chronic Pulmonary Disease (%)						422.042	<0.001
No	19558 (90.98%)	5131 (90.41%)	6945 (92.84%)	2554 (81.89%)	4928 (94.39%)		
Yes	1938 (9.02%)	544 (9.59%)	536 (7.16%)	565 (18.11%)	293 (5.61%)		
Liver Disease (%)						229.927	<0.001
No	20468 (95.22%)	5476 (96.49%)	7171 (95.86%)	3046 (97.66%)	4775 (91.46%)		
Yes	1028 (4.78%)	199 (3.51%)	310 (4.14%)	73 (2.34%)	446 (8.54%)		
Renal Disease (%)						156.686	<0.001
No	18917 (88.00%)	5134 (90.47%)	6717 (89.79%)	2701 (86.60%)	4365 (83.60%)		
Yes	2579 (12.00%)	541 (9.53%)	764 (10.21%)	418 (13.40%)	856 (16.40%)		
Diabetes (%)						44.965	<0.001

Characteristic	Overall	Phenotype A	Phenotype B	Phenotype C	Phenotype D	statistical value	p value
No	18846 (87.67%)	4965 (87.49%)	6679 (89.28%)	2640 (84.64%)	4562 (87.38%)		
Yes	2650 (12.33%)	710 (12.51%)	802 (10.72%)	479 (15.36%)	659 (12.62%)		
Nervous System Disease (%)						18.804	<0.001
No	20589 (95.78%)	5387 (94.93%)	7173 (95.88%)	3019 (96.79%)	5010 (95.96%)		
Yes	907 (4.22%)	288 (5.07%)	308 (4.12%)	100 (3.21%)	211 (4.04%)		
Malignant Tumor (%)						29.491	<0.001
No	20256 (94.23%)	5423 (95.56%)	7024 (93.89%)	2941 (94.29%)	4868 (93.24%)		
Yes	1240 (5.77%)	252 (4.44%)	457 (6.11%)	178 (5.71%)	353 (6.76%)		
Treatment							
Transplantation						13.93	0.003
No	21374 (99.43%)	5635 (99.30%)	7452 (99.61%)	3108 (99.65%)	5179 (99.20%)		
Yes	122 (0.57%)	40 (0.70%)	29 (0.39%)	11 (0.35%)	42 (0.80%)		
Immunosuppressive therapy						157.648	<0.001
No	17775 (82.69%)	4640 (81.76%)	6423 (85.86%)	2367 (75.89%)	4345 (83.22%)		
Yes	3721 (17.31%)	1035 (18.24%)	1058 (14.14%)	752 (24.11%)	876 (16.78%)		
Outcomes							
Hospital Mortality (%)						1676.412	<0.001
No	17727 (82.47%)	5135 (90.48%)	6665 (89.09%)	2572 (82.46%)	3355 (64.26%)		
Yes	3769 (17.53%)	540 (9.52%)	816 (10.91%)	547 (17.54%)	1866 (35.74%)		
Hospital length of stay, days (median [IQR])	7.09 (4.12-12.36)	7.04 (4.38-12.00)	6.83 (4.14-11.89)	7.84 (4.81-12.94)	7.20 (3.14-13.34)	54.749	<0.001
ICU length of stay, days (median [IQR])	2.00 (1.00-4.00)	2.00 (1.00-3.00)	1.00 (1.00-3.00)	2.00 (1.00-5.00)	2.00 (1.00-5.00)	310.343	<0.001

* HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; RR: respiratory rate; PO2: partial pressure of oxygen; PCO2: partial pressure of carbon dioxide; FiO2: Fraction of inspired oxygen; RBC: red blood cell count; RDW: red distribution width; MCH: mean corpuscular hemoglobin; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; Platelet: platelet count; WBC: White blood cell count; Basophils: percentage of basophils; Eosinophils: percentage of eosinophils; Lymphocytes: percentage of lymphocytes; Monocytes: percentage of monocytes; Neutrophils: percentage of neutrophils; AG: anion

gap; BUN: blood urea nitrogen; Glucose: blood glucose; INR: international normalized ratio; PTT: partial thromboplastin time.

* Immunosuppressive therapy includes methylprednisolone, hydrocortisone, prednisone, dexamethasone, cyclophosphamide, methotrexate, cyclosporine, azathioprine, hydroxychloroquine, azacitidine, rituximab, infliximab, and etanercept.

Supplementary Table 5 Sensitivity analysis of Restricted Cubic Spline (RCS) nodes selection.

	Nodes 3	Nodes 4	Nodes 5	Nodes 6
AIC	487481.33	486545.43	486296.13	486198.98
BIC	487777.04	486898.00	486705.57	486665.29
logLik	-243714.67	-243241.71	-243112.06	-243058.49
AUROC	0.815(0.814,0.816)	0.815(0.814,0.816)	0.816(0.814,0.817)	0.816(0.814,0.817)

Supplementary Table 6 Differences in Norepinephrine Equivalence (NEE) dosages and abnormal conditions in different sepsis phenotypes.

Characteristic	A				B				C				D			
	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage
N	1089	494	505	90	3862	2480	1247	135	1199	477	609	113	2653	493	1437	723
Hypotension																
No	954 (87.60%)	430 (87.04%)	449 (88.91%)	75 (83.33%)	1379 (35.71%)	871 (35.12%)	458 (36.73%)	50 (37.04%)	629 (52.46%)	270 (56.60%)	301 (49.43%)	58 (51.33%)	999 (37.66%)	217 (44.02%)	543 (37.79%)	239 (33.06%)
Yes	135 (12.40%)	64 (12.96%)	56 (11.09%)	15 (16.67%)	2483 (64.29%)	1609 (64.88%)	789 (63.27%)	85 (62.96%)	570 (47.54%)	207 (43.40%)	308 (50.57%)	55 (48.67%)	1654 (62.34%)	276 (55.98%)	894 (62.21%)	484 (66.94%)
Hypoxemia																
No	589 (54.09%)	292 (59.11%)	259 (51.29%)	38 (42.22%)	2928 (75.82%)	2025 (81.65%)	815 (65.36%)	88 (65.19%)	430 (35.86%)	177 (37.11%)	216 (35.47%)	37 (32.74%)	1032 (38.90%)	201 (40.77%)	582 (40.50%)	249 (34.44%)

Characteristic	A				B				C				D			
	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage	Overall	Low Dosage	Medium Dosage	High Dosage
Yes	500 (45.91%)	202 (40.89%)	246 (48.71%)	52 (57.78%)	934 (24.18%)	455 (18.35%)	432 (34.64%)	47 (34.81%)	769 (64.14%)	300 (62.89%)	393 (64.53%)	76 (67.26%)	1621 (61.10%)	292 (59.23%)	855 (59.50%)	474 (65.56%)
Hypercapnia																
No	1030 (94.58%)	461 (93.32%)	481 (95.25%)	88 (97.78%)	3727 (96.50%)	2406 (97.02%)	1190 (95.43%)	131 (97.04%)	519 (43.29%)	214 (44.86%)	263 (43.19%)	42 (37.17%)	2474 (93.25%)	467 (94.73%)	1363 (94.85%)	644 (89.07%)
Yes	59 (5.42%)	33 (6.68%)	24 (4.75%)	2 (2.22%)	135 (3.50%)	74 (2.98%)	57 (4.57%)	4 (2.96%)	680 (56.71%)	263 (55.14%)	346 (56.81%)	71 (62.83%)	179 (6.75%)	26 (5.27%)	74 (5.15%)	79 (10.93%)
Metabolic acidosis																
No	791 (72.64%)	381 (77.13%)	347 (68.71%)	63 (70.00%)	3306 (85.60%)	2234 (90.08%)	976 (78.27%)	96 (71.11%)	1123 (93.66%)	450 (94.34%)	577 (94.75%)	96 (84.96%)	939 (35.39%)	247 (50.10%)	568 (39.53%)	124 (17.15%)
Yes	298 (27.36%)	113 (22.87%)	158 (31.29%)	27 (30.00%)	556 (14.40%)	246 (9.92%)	271 (21.73%)	39 (28.89%)	76 (6.34%)	27 (5.66%)	32 (5.25%)	17 (15.04%)	1714 (64.61%)	246 (49.90%)	869 (60.47%)	599 (82.85%)
High inflammatory																
No	448 (41.14%)	231 (46.76%)	181 (35.84%)	36 (40.00%)	1520 (39.36%)	928 (37.42%)	527 (42.26%)	65 (48.15%)	528 (44.04%)	219 (45.91%)	261 (42.86%)	48 (42.48%)	885 (33.36%)	197 (39.96%)	475 (33.05%)	213 (29.46%)
Yes	641 (58.86%)	263 (53.24%)	324 (64.16%)	54 (60.00%)	2342 (60.64%)	1552 (62.58%)	720 (57.74%)	70 (51.85%)	671 (55.96%)	258 (54.09%)	348 (57.14%)	65 (57.52%)	1768 (66.64%)	296 (60.04%)	962 (66.95%)	510 (70.54%)
Renal insufficiency																
No	695 (63.82%)	351 (71.05%)	298 (59.01%)	46 (51.11%)	2841 (73.56%)	1916 (77.26%)	842 (67.52%)	83 (61.48%)	652 (54.38%)	274 (57.44%)	332 (54.52%)	46 (40.71%)	591 (22.28%)	121 (24.54%)	343 (23.87%)	127 (17.57%)
Yes	394 (36.18%)	143 (28.95%)	207 (40.99%)	44 (48.89%)	1021 (26.44%)	564 (22.74%)	405 (32.48%)	52 (38.52%)	547 (45.62%)	203 (42.56%)	277 (45.48%)	67 (59.29%)	2062 (77.72%)	372 (75.46%)	1094 (76.13%)	596 (82.43%)

* Low Dosage: ≤ 0.1 ug/kg/min; Medium Dosage: 0.1-0.5 ug/kg/min; High Dosage: ≥ 0.5 ug/kg/min; Hypotension: SBP ≤ 90 mmHg or DBP ≤ 60 mmHg; Hypoxemia: PaO2 ≤ 60 mmHg; Hypercapnia: PaCO2 ≥ 50 mmHg; Metabolic acidosis: Base Excess ≤ -3 mmol/L; High inflammatory: WBC ≥ 10×10^9/L; Renal insufficiency: Male: creatinine ≥ 1.2 mg/dL, Female: creatinine ≥ 1.1 mg/dL.