Supplementary Material - An explicable machine learning approach for predicting 30-day septic mortality for ICU patients

Catalog

Supplement 1: The abbreviations of features.

abbreviation	specific meaning
_max	Maximum variable during ICU
_min	Minimum variable during ICU
_mean	Mean variable during ICU
Inr	The ratio of a patient's clotting time to a standardized clotting time
Bun	Blood Urea Nitrogen
Wbc	White Blood Cell
Spo2	Peripheral Oxygen Saturation
Sbp	Systolic Blood Pressure
Dbp	Diastolic Blood Pressure
Sus_anti_period	The delay in initiation of patient treatment relative to first observation of suspicion of infection
Cul_anti_period	The interval in days between antibiotic and culture time
vent_status	‘1’ means high flow oxygen therapy ‘2’ means invasive ventilation ‘3’ means tracheostomy ‘4’ means non-invasive ventilation ‘5’ means pure oxygen therapy

Supplement 2: Implementation details of model

Algorithm design

In this study, we applied a Keras neural network model with two hidden layers, including a dropout layer with a 0.2 deactivation probability to prevent overfitting. The sigmoid function was used in each layer for its smoothness, differentiability, and effectiveness in optimization algorithms during training.
The output function of each hidden layer can be expressed as:

$$a^i = \frac{e^{w^{[i]}x+b^{[i]}}}{e^{w^{[i]}x+b^{[i]}}+1} \quad (1)$$

a^{i} is the output of the hidden layer, $w^{[\mathrm{i}]}$ is the weight matrix of hidden layer i, x is the 25 feature vectors of the input, and $b^{[\mathrm{i}]}$ is the bias term of the hidden layer, the input data is weighted by a weight matrix $w^{[\mathrm{i}]}$, then sigmoid is applied and finally a bias term $b^{[\mathrm{i}]}$ is added, i can take three values, each representing the i-th layer of the neural network. In this way, the output of hidden layer a^{i} is nonlinearly transformed by the sigmoid function to produce a value between 0 and 1.
The neural network model employs a binary cross-entropy loss function to train and improve prediction accuracy:

$$loss(y_i, s_i) = -\frac{1}{N}\sum_{i=1}^{N}(y_i\, log(s_i) + (1-y_i)\, log(1-s_i)) \quad (2)$$

$loss(y_i, \mathrm{s}_i)$ is the loss function of the model, i denotes a certain sample, and y_i denotes the true values of the i-th sample, s_i represents the output probability of the model, usually the value of s_i processed by the sigmoid function, which represents the probability that the sample belongs to the positive category. N is the number of samples, in this study the value of N is 16902.

Based on Gradient Boosting Decision Trees (GBDT) principles, XGBoost is an advanced gradient-boosting algorithm introduced by Chen in 2016 [37]. XGBoost handles both classification and regression problems, enhancing flexibility and robustness. It tracks feature usage for splits and calculates feature gain, thus improving model interpretability.

The objective function of our model can be written as

$$\mathcal{L}(\emptyset) = -\left[\sum_{i=1}^{N}(y_i\, log(\mathrm{s}_i) + (1-y_i)log(1-\mathrm{s}_i))\right] + \gamma T + \frac{1}{2}\lambda\sum_{j=1}^{T} w_j^2 \quad (3)$$

This formula consists of a loss function and a regularization term, which are used to train the model and control the complexity of the model, respectively. The loss function used in this model is logistic regression, and the regularization terms are L1 and L2 regularization. i denotes a certain sample, and y_i , $\mathrm{s}_i$denotes the true and predicted values of the i-th sample, respectively, T represents the number of leaf

nodes, w represents the weight, and γ and λ indicate penalty terms for various complexity terms.

The second-order Taylor expansion of this formula is carried out. According to the forward distribution algorithm, for T trees, the structure of the first $(T-1)$ trees has been determined and can be regarded as constants, the following formula can be obtained by removing the constant terms in the formula and merging the similar terms:

$$\mathcal{L}(\emptyset) = \sum_{j=1}^{M}\left[(\frac{1-y_j}{1-p_j}-\frac{y_j}{p_j})w_j+\frac{1}{2}\left(\frac{y_j}{p_j^2}+\frac{1-y_j}{(1-p_j)^2}+\lambda\right)w_j^2\right]+\gamma T \tag{4}$$

In this formula, the training samples are grouped by leaf nodes, and all samples x_i belonging to the j-th leaf node are grouped into a leaf node sample set, and M represents the total number of leaf nodes.

This equation is the objective function of XGBoost, which for a specific j-th leaf node is:

$$f(w_j) = (\frac{1-y_j}{1-p_j}-\frac{y_j}{p_j})w_j+\frac{1}{2}\left(\frac{y_j}{p_j^2}+\frac{1-y_j}{(1-p_j)^2}+\lambda\right)w_j^2 \tag{5}$$

In such a one-dimensional quadratic objective function, the optimal value of the weight of each leaf node is:

$$w_j^* = -\frac{\left(\frac{y_j}{p_j^2}+\frac{1-y_j}{(1-p_j)^2}\right)}{(\frac{1-y_j}{1-p_j}-\frac{y_j}{p_j})+\lambda} \tag{6}$$

The optimal value of the objective function is:

$$\text{obj}^* = -\frac{1}{2}\sum_{j=1}^{T}\frac{\left(\frac{y_j}{p_j^2}+\frac{1-y_j}{(1-p_j)^2}\right)^2}{(\frac{1-y_j}{1-p_j}-\frac{y_j}{p_j})+\lambda}+\gamma T \tag{7}$$

By calculating this objective function, XGBoost minimizes total error, enhancing predictive performance on new dat.

MorSNX model uses bayesian optimization to select the optimal hyperparameter configuration to maximize the desired improvement in model performance before training on the data. Combining the characteristics of the base model, the Bayesian hyperparameter optimization process can be represented by the following equation. First the distribution of the objective function in the hyperparameter space is modeled by a Gaussian process, which can be expressed as:

$$loss(x) \sim \text{GP}(\mu(\text{x}), \text{K}(\text{x}, \text{x}')) \tag{8}$$

$loss(x)$ denotes the loss function of the base model, within MorSNX, the binary categorical logistic loss function is chosen for the base model loss function, x denotes a set of hyper-parameter configurations of the base model, $\mu(\text{x})$ is the mean function, which denotes the prediction of the mean value of $loss(x)$ under different hyper-

parameter configurations, and $\mathrm{K}(\mathrm{x},\mathrm{x}')$ is the covariance function, which denotes the correlation between the different hyper-parameter values x and x'.

$$x_i \leftarrow \mathrm{argmax}_{x\in X}[\Phi_{EI}(\mathrm{x})] \tag{9}$$

$$\Phi_{EI}(\mathrm{x}) = \int_{-\infty}^{loss^*(x)} \big(loss^*(x) - loss(x)\big)\mathrm{N}(loss(x);\mu(x),\mathrm{K}(x,x')d\,loss(x) \tag{10}$$

The above equation represents the expected improvement in hyperparameter optimization, $\Phi_{EI}(\mathrm{x})$ denotes the expected improvement under a given hyperparameter configuration, $loss^*(x)$ is the value of the optimal objective function to which the model is fitted, and N is a Gaussian distribution, which denotes the probability distribution under a given mean and covariance function.

The Bayesian optimization algorithm will follow the feedback from the objective function obtained from each computation and select new hyperparameter configurations for evaluating expected improvement, calculating the expected improvement under each possible hyperparameter configuration x. After calculating the expected improvement, the Bayesian optimization selects the hyperparameter configuration x with the maximum expected improvement as the next sampling point. This process continues for many iterations until the best hyperparameter configuration is found or a predetermined number of iterations is reached.

Criteria for model evaluation

In this study, we evaluated each model using AUROC, precision, recall, accuracy, and F1 scores to discriminate between septic patients' survival within 30 days in the ICU. The formula for each metric is as follows:

$$\text{Accuracy} = \frac{\text{True Positive}(TP) + \text{True negative}(TN)}{\text{All predictions outcomes}} \tag{11}$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{False Positive}(FP)} \tag{12}$$

$$\text{Recall} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}(FN)} \tag{13}$$

$$F1 - \text{Score} = \frac{2\times\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \tag{14}$$

Supplement 3: Detection of feature missing-rate of MIMIC-IV

Missing values were identified by calculating their proportion in the dataset, with a threshold set at 0.2. Any patient data or feature variables with missing rates exceeding this threshold were removed, resulting in a final dataset of 14,879 patient records and 43 features. For data with missing rates below 20%, we used imputation techniques: means for numerical data, modes for character data, and zeros for null entries.

Table 1 Missing rates for each feature in MIMIC-IV.

No.	Feature-name	Missing-rate	No.	Feature-name	Missing-rate
1	crp_max	0.769892	27	creatinine_min	0.001227
2	height_mean	0.359411	28	creatinine_max	0.001227
3	vent_status	0.08453	29	sbp_min	0.001067
4	inr_max	0.057634	30	sbp_mean	0.001067
5	temperature_max	0.05075	31	sbp_max	0.001067
6	urine_max	0.027109	32	dbp_min	0.001067
7	aniongap_min	0.003415	33	dbp_mean	0.001067
8	aniongap_max	0.003415	34	dbp_max	0.001067
9	hemoglobin_min	0.002028	35	heart_rate_max	0.000961
10	hemoglobin_max	0.002028	36	sus_anti_period	0
11	wbc_min	0.001921	37	stay_recorded	0
12	wbc_max	0.001921	38	specimen_count	0
13	hematocrit_min	0.001761	39	sofa_score	0
14	hematocrit_max	0.001761	40	sapsii_prob_max	0
15	sodium_min	0.001708	41	sapsii	0
16	sodium_max	0.001708	42	positive_culture	0
17	bicarbonate_min	0.001548	43	metastatic_solid_tumor_max	0
18	bicarbonate_max	0.001548	44	los_icu	0
19	chloride_min	0.001494	45	los_hospital	0
20	chloride_max	0.001494	46	gender	0
21	bun_min	0.001441	47	death_within_30_days	0
22	bun_max	0.001441	48	cul_anti_period	0
23	resp_rate_max	0.001387	49	charlson_score_max	0
24	spo2_min	0.001227	50	antibiotic_num	0
25	spo2_mean	0.001227	51	age_mean	0
26	spo2_max	0.001227			

Supplement 4: Feature outlier detection of MIMIC-IV

We applied a 3σ outlier detection method based on standard deviation to identify significant deviations from the dataset's average. The threshold was set at values higher or lesser than three times the standard deviation from the mean (μ±3σ), and abnormal values were assessed for each variable, considering clinical knowledge to understand their origins. If data anomalies were due to a patient's condition, no action was taken while errors due to data errors were removed. In cases with only a few abnormal values, we replaced them with the mean or mode depending on column characteristics.

Table 2 The results obtained by using the 3σ outlier detection from MIMIC-IV, the outlier ratio is the proportion of outliers for each feature.

No.	Features	Outlier Ratio	No.	Features	Outlier Ratio
1	metastatic_solid_tumor_max	8.48%	25	sbp_min	1.10%
2	bun_min	2.25%	26	chloride_max	1.08%
3	sofa_score	2.21%	27	dbp_min	1.08%
4	creatinine_min	2.21%	28	temperature_max	1.06%
5	bun_max	2.18%	29	sbp_max	1.03%
6	antibiotic_num	2.07%	30	aniongap_min	0.97%
7	creatinine_max	2.04%	31	wbc_min	0.97%
8	los_icu	1.98%	32	sapsii	0.89%
9	sus_anti_period	1.98%	33	spo2_mean	0.88%
10	spo2_min	1.96%	34	sbp_mean	0.85%
11	spo2_max	1.92%	35	dbp_mean	0.83%
12	inr_max	1.88%	36	wbc_max	0.83%
13	specimen_count	1.79%	37	heart_rate_max	0.65%
14	aniongap_max	1.73%	38	hematocrit_max	0.44%
15	los_hospital	1.70%	39	hematocrit_min	0.44%
16	sodium_min	1.55%	40	hemoglobin_max	0.37%
17	bicarbonate_max	1.51%	41	hemoglobin_min	0.31%
18	sodium_max	1.46%	42	charlson_score_max	0.20%
19	urine_max	1.36%	43	age_mean	0.20%
20	dbp_max	1.28%	44	sapsii_prob_max	0.00%
21	resp_rate_max	1.25%	45	vent_status	0.00%
22	bicarbonate_min	1.22%	46	positive_culture	0.00%
23	cul_anti_period	1.18%	47	death_within_30_days	0.00%
24	chloride_min	1.17%			

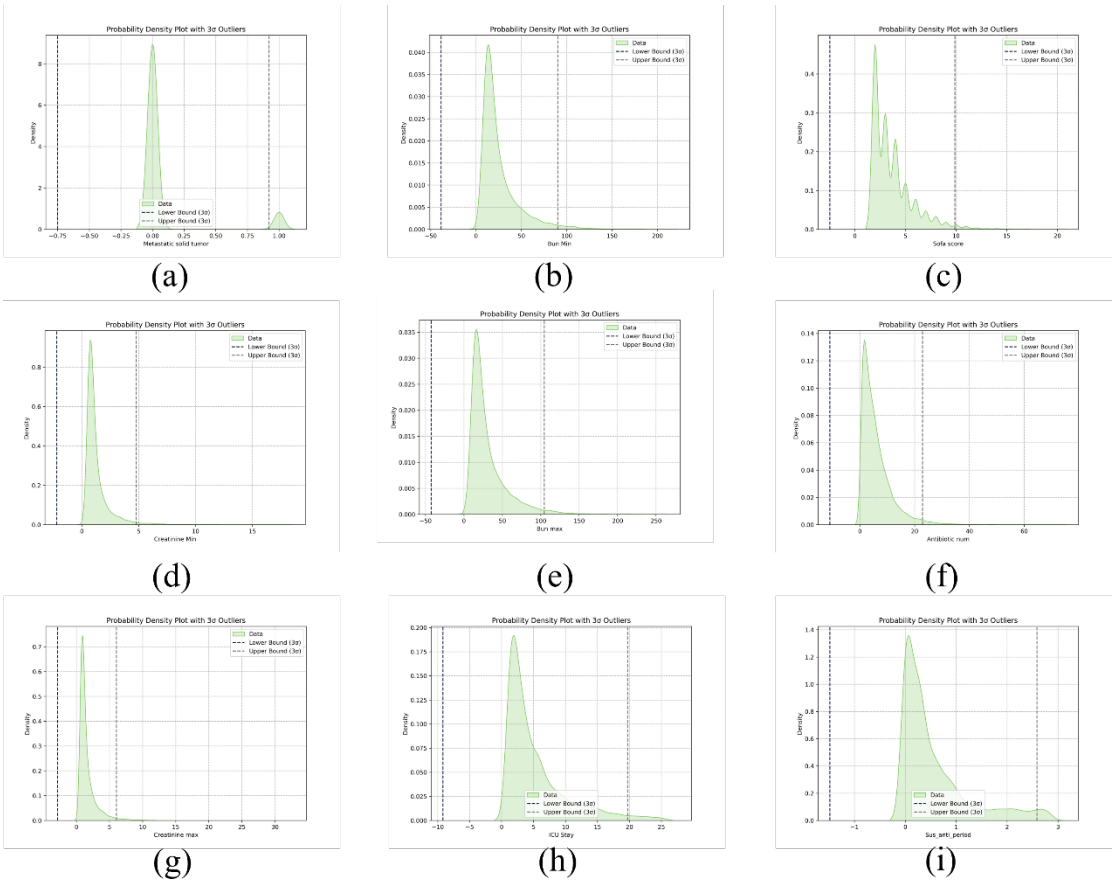

Figure 1 Probability density plot of 3σ outlier detection in MIMIC-IV. Each of the 9 plots represents a probability density plot of outliers for different features, which are the 9 features with a higher outlier ratio.
(metastatic_solid_tumor_max; bun_min; sofa_score; creatinine_min; bun_max; antibiotic_num; creatinine_max; los_icu; sus_anti_period).

Supplement 5: Different methods for feature selection

This study compares a recursive feature elimination (RFE) algorithm, which combines gradient boosting tree concepts to remove irrelevant features, with the mutual information and correlation coefficient methods. The goal is to select the most favorable subset of features for a learner based on its performance.

Table 3 Performance of different feature selection methods.

Methods	AUROC	Accuracy	Precision	Recall	F1 Score
Correlation coefficient	0.8343	0.8182	0.611	0.3889	0.4753
MIC	0.8812	0.8491	0.7819	0.3984	0.5279
RFE+GBT	0.9359	0.8599	0.8928	0.779	0.832

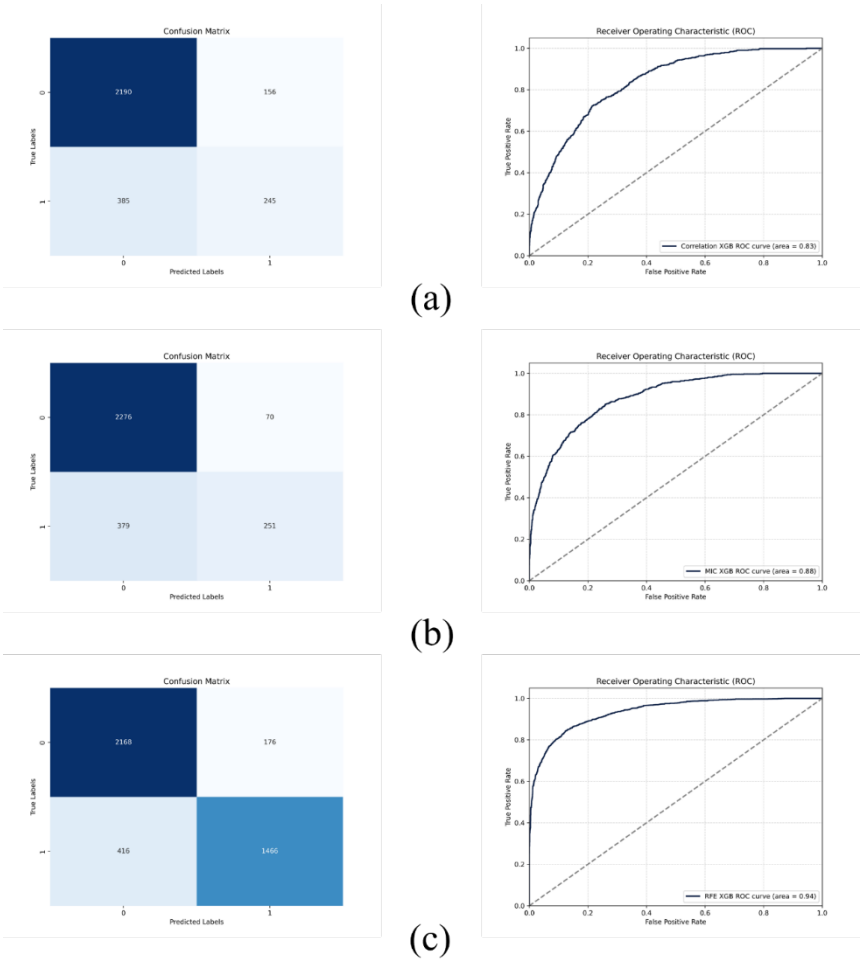

Figure 2 confusion matrix and ROC results obtained from different feature selection methods, by using XGBoost as test model, the ROC areas for correlation coefficient (a), mutual information (b), and RFE (c) were 0.8343, 0.8812, 0.9359. RFE+GBT we used is the optimal feature selection method.

Supplement 6: PDP and Calibration curves of MIMIC-IV

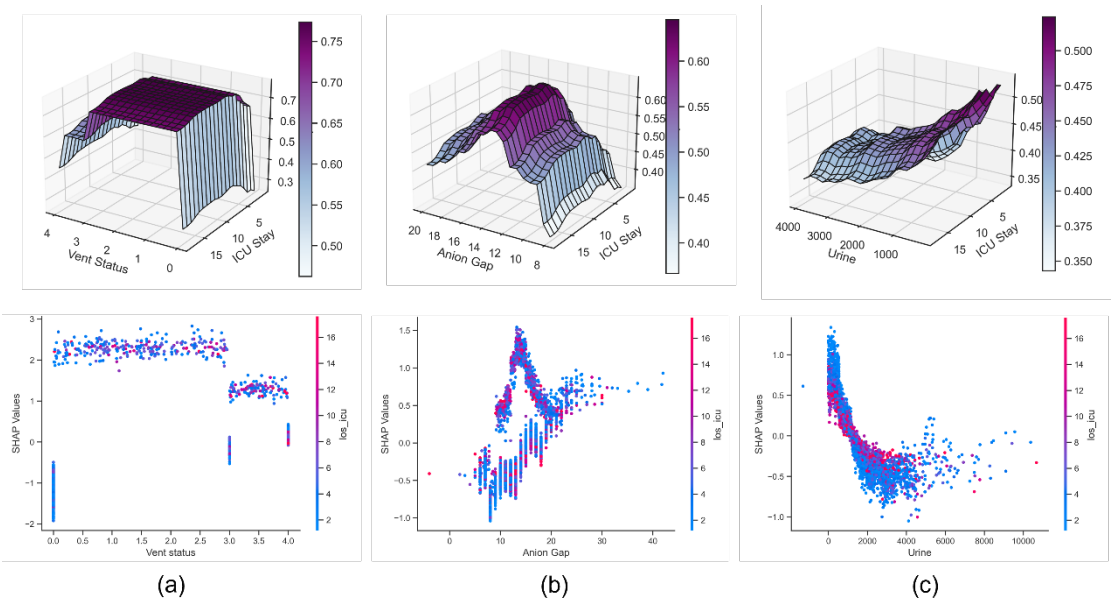

Figure 3 Using PDP (upper part) and SHAP scatter plots (lower part) to analyze the impact of the top three features on predicting the risk of sepsis death with the length of ICU stay. The x-axis of the PDP chart represents each characteristic value, the y-axis represents the number of days in ICU, and the z-axis represents the impact on the patient's mortality risk. The darker the color, the greater the impact. Fig (a) reflects that as the number of days of ICU stay increases, the risk of death is highest when the ventilation status values are 1, 2 and 3; Fig (b) reflects that as the number of days of ICU stay increases, the impact of the anion gap size on patient death initially increases and then decreases, reaching the peak when the value is 15; Fig (c) reflects the negative correlation between urine output and death risk as the number of days in ICU increases. The lower the urine output, the greater the risk of death, especially when the urine output is less than 1000ml.

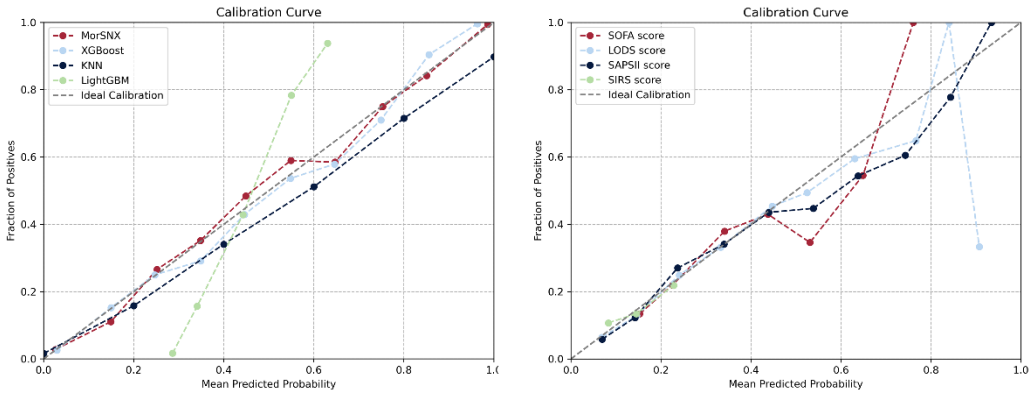

Figure 4 Calibration curves of MorSNX model and traditional clinical scoring systems in the independent test cohort. (a) compares MorSNX and other ML models. (b) shows clinical scoring systems' calibration curves. X-axis is the predicted mortality, while Y-axis is the actual mortality. Our MorSNX model predicts a mortality that is very close to the actual mortality.

Supplement 7: Basic information of the extracted variables in the eICU external validation cohort

To validate the generalization ability of our model, we extracted7,155 sepsis patients from the eICU dataset to form an external validation cohort based on the same cohort inclusion and exclusion criteria. The basic information of variables extracted from the eICU external validation queue is shown in sTable 4.

Table 4 Demographic and clinical characteristics for the ICU admissions included into eICU dataset.

Features	Survive	Death	P
Number	6405	750	
Baseline variables and in-hospital factors			
Age_mean	66.00(54.00, 76.00)	70.00(58.00, 78.00)	<0.001
Sex (%)			
Female	3467(54.1%)	417(55.6%)	0.444
Male	2938(45.9%)	333(44.4%)	
Vital signs			
los_hospital (Days)	7.61(4.75, 12.83)	5.36(3.06, 10.85)	<0.001
los_icu (Days)	8.18(5.13, 13.72)	5.85(2.84, 11.15)	<0.001
Hematocrit (%)	30.80(26.60, 35.40)	29.70(26.00, 34.90)	0.150
HeartRate_max (times/min)	123.00(108.00, 139.00)	140.00(125.00, 155.00)	<0.001
HeartRate_min (times/min)	66.00(55.00, 76.00)	103.00(87.00, 109.00)	<0.001
Resprate (times/min)	31.00(14.00, 38.00)	33.00(26.00, 39.00)	<0.001
Temperature (℃)	37.14(37.01, 38.12)	37.63(36.65, 38.98)	<0.001
Spo2_max (%)	99.00(97.00, 100.00)	100.00(96.00, 103.00)	0.440
Spo2_min (%)	82.00(73.00, 88.00)	65.00(48.00, 75.90)	<0.001
Spo2_mean (%)	95.00(95.00, 98.00)	96.88(95.08, 98.51)	<0.001
Urine (mL)	1318.46(678.97, 2288.22)	675.90(223.08, 1447.24)	<0.001
Laboratory parameters			
Aniongap_max (mEq/L)	12.00(11.00, 15.90)	14.15(11.00, 20.00)	<0.001
Aniongap_min (mEq/L)	6.00(5.00, 8.10)	6.00(5.00, 10.03)	<0.001
Bicarbonate_max (mmol/L)	28.00(26.00, 31.00)	27.00(23.00, 30.00)	<0.001
Bicarbonate_min (mmol/L)	20.00(17.00, 23.00)	17.00(13.00, 20.00)	<0.001
Inr_max	1.20(1.10, 1.50)	1.55(1.20, 2.71)	<0.001
Inr_min	1.10(1.10, 1.30)	1.20(1.10, 1.50)	<0.001
Sodium (mmol/L)	138.00(134.00, 141.00)	137.00(133.00, 141.00)	0.301
Chloride_max (mmol/L)	110.00(106.00, 114.00)	111.00(106.00, 116.00)	<0.001
Chloride_min (mmol/L)	99.00(95.00, 103.00)	99.00(94.00, 103.00)	<0.001
Bun (mmol/L)	25.00(15.00, 42.00)	35.00(23.00, 56.00)	<0.001
Wbc (10^9/L)	13.37(8.40, 19.10)	15.30(8.19, 23.4)	0.389
Creatinine (mg/dL)	1.20(0.73, 2.04)	1.83(1.03, 2.90)	<0.001
Chloride_max (mmol/L)	110.00(106.00, 114.00)	111.00(106.00, 116.00)	<0.001

Chloride_min (mmol/L)	99.00(95.00, 103.00)	99.00(94.00, 103.00)	0.816
Chloride_mean (mmol/L)	104.92(101.25, 108.27)	105.19(100.94, 109.53)	0.240
Vent_status (%)			
1	1665(26%)	278(37%)	<0.001
2	1409(22%)	233(31%)	
3	2498(39%)	143(19%)	
4	833(13%)	96(13%)	

Table 5 Demographic and clinical characteristics for the ICU admissions included into eICU dataset. Among these, feature 'Temperature' and feature 'Hemoglobin' are not considered in outlier detection because the missing rate exceeds the 0.2 threshold.

Features	Missing-rate	Outlier Ratio
Age_mean	0	0.01%
Gender	0	0.00%
Los_hospital (Days)	0	0.00%
Los_icu (Days)	0	0.60%
Hematocrit (%)	0.054237	0.00%
HeartRate_max (times/min)	0.008586	0.69%
HeartRate_min (times/min)	0.008586	0.05%
Resprate (times/min)	0.054237	0.00%
Temperature (℃)	0.861312	/
Spo2_max (%)	0.013559	0.49%
Spo2_min (%)	0.013559	2.58%
Spo2_mean (%)	0.013559	0.98%
Urine (mL)	0.054237	1.67%
Aniongap_max (mEq/L)	0.196444	1.83%
Aniongap_min (mEq/L)	0.196444	1.14%
Bicarbonate_max (mmol/L)	0.075772	1.24%
Bicarbonate_min (mmol/L)	0.075772	0.74%
Inr_max	0.179957	2.54%
Inr_min	0.179957	1.71%
Sodium (mmol/L)	0.054237	0.00%
Chloride_max (mmol/L)	0.012105	0.87%
Chloride_min (mmol/L)	0.012105	1.10%
Bun (mmol/L)	0.054237	1.57%
Wbc (10^9/L)	0.054237	1.11%
Creatinine (mg/dL)	0.054237	1.86%
Hemoglobin_max (mmol/L)	0.795721	/
Hemoglobin_min (mmol/L)	0.795721	/
Hemoglobin_mean (mmol/L)	0.795721	/
Vent_status	0.054237	0.00%

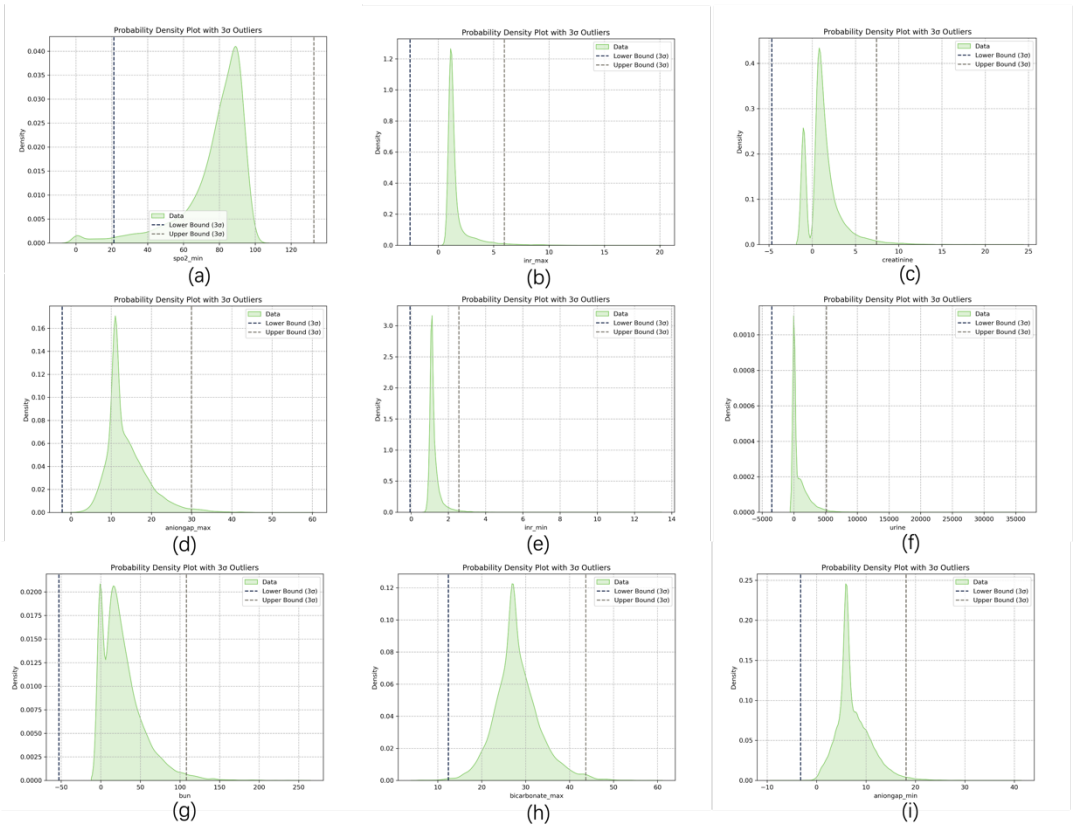

Figure 5 Probability density plot of 3σ outlier detection in eICU. Each of the 9 plots represents a probability density plot of outliers for different features, which are the 9 features with a higher outlier ratio. (‘spo2_min’, ‘inr_max’, ‘creatinine’, ‘aniongap_max’, ‘inr_min’, ‘urine’, ‘bun’, ‘bicarbonate_max’, ‘aniongap_min’).