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An interpretable machine learning model for real-time sepsis prediction based on basic physiological indicators

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Abstract. – OBJECTIVE: In view of the important role of risk prediction models in the clinical diagnosis and treatment of sepsis, and the limitations of existing models in terms of timeliness and interpretability, we intend to develop a real-time prediction model of sepsis with high timeliness and clinical interpretability.

PATIENTS AND METHODS: We used eight real-time basic physiological monitoring indicators of patients, including heart rate, respiratory rate, oxygen saturation, mean arterial pressure, systolic blood pressure, diastolic blood pressure, temperature and blood glucose, extracted three-hour dynamic feature sequences, and calculated 3 linear parameters (mean, standard deviation, and endpoint value), a 24-dimensional feature vector was constructed, and finally a real-time sepsis prediction model was constructed based on the Local Interpretable Model-Agnostic Explanation (LIME) interpretability method.

RESULTS: The area under the receiver operating characteristic curve (AUROC), Accuracy and F1 scores of Extremely Randomized Trees we built were higher than those of other models, with AUROC above 0.76, showing the best performance. The Imbalance XGBoost has a high specificity (0.86) in predicting sepsis. The LIME local interpretable model we built can display a large amount of valid model prediction details for clinical workers' reference, including the prediction probability and the influence of each feature on the prediction result, thus effectively assisting the work of clinical workers and improving diagnostic efficiency.

CONCLUSIONS: This model can provide a real-time dynamic early warning of sepsis for critically ill patients under supervision and provide reference for clinical decision support. At the same time, interpretive analysis of sepsis prediction models can improve the credibility of the models.

Key Words:
Sepsis, Prediction, Machine learning, Linear parameter, Interpretable artificial intelligence.

Introduction

Sepsis is a clinical syndrome of life-threatening organ dysfunction caused by the body's disordered response to infection. It has a high morbidity and mortality rate and is a serious threat to the life and health of all mankind in the world. The prospective study, which examined data from 730 medical centers in 84 countries, showed that 29.5% of intensive care unit (ICU) patients worldwide developed sepsis, with a mortality rate of 25.8% in the ICU and 35.3% in the hospital, respectively. These data are significantly higher than the general population (ICU mean mortality 16.2%, hospital mean mortality 22.4%). In China, there are 20 cases of sepsis in every 100 ICU patients, and the proportion of septic shock is as high as 53.3%. In addition, sepsis accounted for 29.6% of total mortality and 32.1% of in-hospital mortality in ICU patients. Early identification of sepsis patients and the initiation of rapid and standardized cluster therapy (Bundle) have always been the core of the implementation of sepsis diagnosis and treatment guidelines. Patients with sepsis who completed the Bundle early after admission had a lower in-hospital mortality rate (22.6% *vs.* 23.6%), and a 1.04-fold increase in mortality for each hour of delay. Recently, it has been proposed that the 1-hour Bundle therapy strategy should replace the previous 3-hour and 6-hour bundles and become the basic strategy for initial management of septic shock.

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The pathogenesis of sepsis is complex, and the disease is difficult to control once it occurs, and the microbial diagnosis requires bacterial culture, which takes a long time. Therefore, it is of great significance to establish an intelligent system for real-time diagnosis of sepsis and early warning of the occurrence of sepsis for greatly reducing the clinical mortality of patients.

Currently, a variety of scoring systems have been created to evaluate the condition and prognosis of critical diseases, including non-specific scoring systems, such as Acute Physiological and Chronic Health Score (APACHE II score) and modified Early Warning score (MEWS score), as well as sepsis specific scoring system such as emergency sepsis mortality Score (MEDS score) and sepsis related Sequential Organ Failure score (SOFA score). The MEDS score was designed to rapidly assess the prognosis of patients with suspected infection, but studies have shown that it may underestimate mortality in patients with severe sepsis. SOFA scores are based on relevant laboratory parameters to objectively and dynamically assess the development and progression of organ dysfunction; however, each laboratory parameter is based on the patient's worst-case scenario for the day, which can affect timely diagnosis. The MEWS score requires only six physiological parameters and can be scored quickly, but it is not sensitive enough to assess the severity of sepsis. The APACHE II score is considered the gold standard for evaluating criticality and prognosis, with the disadvantage that it requires 12 clinical parameters and 7 laboratory parameters, and laboratory test parameters are not available in real time, making it a complex and time-consuming tool with limited application in emergency medicine. Therefore, a simple, real-time and accurate scoring system based on patients' basic physiological parameters is urgently needed to evaluate the condition and prognosis of patients with sepsis.

Machine learning technology is playing an increasingly important role in medical research, especially in the field of critical care medicine. The application of machine learning technology can well help intensive care physicians diagnose specific diseases, predict the outcome of diseases, and make clinical decisions[1-3]. In recent years, researchers[1,2,4,5] have proposed many machine learning methods for sepsis prediction. Compared with traditional methods, machine learning methods can effectively improve the accuracy of sepsis prediction. However, machine learning model is equivalent to a black box in the process of prediction. It feeds back a decision result through input. Although it improves the accuracy of prediction, it lacks interpretation. In the medical field, the risk of misjudgment is too great. It is not enough to only know the prediction accuracy of the model. Practitioners also need to know the judgment basis of each prediction, so as to analyze whether the prediction results are reliable. The interpretation model can make users trust the model and its prediction results, which is helpful for the popularization of the model. Local Interpretable Model-Agnostic Explanation (LIME) is a model-independent, locally interpretable explanation. The machine learning model is explained by the relationship between the individual features and the predicted results.

Therefore, in view of the important auxiliary role of risk prediction model in the clinical diagnosis and treatment of sepsis, as well as the limitations of existing models in terms of timeliness and explanatory ability, this study built a fast and clinically explanatory intelligent early warning method of sepsis based on the interpretable machine learning model and the use of patients' basic physiological monitoring indicators.

Patients and Methods

Data Sources

Data for this study were obtained from the medical information mark for intensive care IV (MIMIC-IV). Developed by MIT's Computational Physiology Laboratory, it contains data on patients admitted to the ICU or Emergency Department at Beth Israel Deaconess Medical Center between 2008 and 2019. There are mainly two kinds of basic data. One is clinical data, including demographic characteristics of patients, diagnostic information, laboratory testing information, microbial culture, medical imaging information, vital signs, etc. The other type of data is waveform data from bedside monitoring devices, which are vital sign parameters and event records (medical measures, medications). The database has been stripped of patient privacy information[6], these parameters were used to determine the survival state of patients.

Study Cohort and Variable Selection

This study was conducted according to the Chinese Guidelines for Emergency Treatment of Sepsis/Septic Shock (2018) to screen patients with

sepsis. Patients with positive results of body fluid culture and antibiotics are considered infected. Infected patients with SOFA score ≥2 was considered as sepsis patients. ICU patients without sepsis were selected as control cohort. A total of 1,118 patients were screened, including 550 patients with sepsis and 568 patients without sepsis. Based on the published methods, this study improved and used easy-to-collect real-time physiological indicators. There were 8 indicators included in the model: heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, temperature, oxygen saturation and blood glucose. In order to reduce the dependence of sepsis prediction on long-term feature sequence, the length of the feature sequence dependent on prediction was set as 3 hours. This means that after the patient completes three hours of basic physiological indicators monitoring, the model can start real-time prediction of sepsis. The extraction rules of dynamic features were as follows: for patients with sepsis, the occurrence time of septic shock was taken as 0 time, and the dynamic feature data was extracted 3 hours before 0 time. For the control cohort: the end point of recording dynamic feature data was taken as time 0, and the dynamic feature data was extracted three hours before time 0.

Data Preprocessing

In the data queue, if the dynamic feature data is missing, the linear interpolation method is used to fill the missing value. Three linear parameters (mean, standard deviation and end point) were calculated from the extracted three-hour dynamic characteristic sequence to form a 24-dimensional feature vector, which was used as an indicator to determine whether patients developed sepsis. Then, by stratified sampling, all samples are pressed by 8:2 and divided into the training set and the test set. For the imbalance of positive and negative samples in the training set and the test set, we did not adopt the over-sampling method to make the model better, because we believe that maintaining the imbalance of positive and negative samples is more applicable to the actual clinical situation, which is conducive to better judging the effect of the model in the actual clinical application.

Model Training

We compared five machine learning algorithms, including Random Forest (RF), XGBoost, Extremely Randomized Trees (ET), Support Vector Machine (SVM), and imbalance-XGBoost. XGBoost adds a regularization term to the cost function to control the complexity of the model. The regularization term contains the number of leaf nodes in the tree and the sum of squares of the L2 modulus of the score output at each leaf node. From the perspective of Bias-variance tradeoff, the regularization term reduces the variance of the model, making the learned model simpler and preventing overfitting, which is also a feature of XGBoost that is superior to the traditional GBDT. Meanwhile, XGBoost supports parallelism. The imbalance-XGBoost we used has the function of weighted and focal losses on the basis of XGBoost, which can tackle binary label-imbalanced classification tasks. AUROC, Accuracy, Sensitivity, Specificity and F1 score were used to evaluate and compare the performance of the model. Finally, the feature importance ranking is calculated according to the optimal model.

Statistical Analysis

In this study, independent sample *t*-test was used to determine if there was a statistical difference in physiological indicators between the two groups. In addition, the DeLong test method was used to calculate whether the area under the receiver operating characteristic curve (AUROC) difference of each model was statistically significant, so as to compare the predictive performance of each model. All tests were single tailed with an alpha level of 0.05 and were performed using the MATLAB software (V.R2016a) developed by MathWorks (Natick, MA, USA).

Results

Basic Physiological Indicators of Patients

A total of 1,118 patients with sepsis who met the criteria of sepsis were included in the study. Patients were randomly divided into the training group (894 cases) and the test group (224 cases) by a ratio of 8:2. *t*-test analysis was performed on physiological indicators between the two groups, and the results showed that there was no statistical difference in physiological indicators between the two groups, as shown in Table I.

Feature Importance Ranking

Based on the data after linear interpolation, three linear parameters (mean, standard deviation and endpoint value) were calculated for the

Table I. Comparison of basic physiological indicators between the training group and the test group.

	Training group (n = 894)	Test group (n = 224)	*p*-value
Heart rate (times/min)	86.1 (30.5-157.0)	86.5 (43.0-137.5)	0.814
Systolic blood pressure (mm/Hg)	119.6 (48.0-191.0)	115.5 (36.8-187.0)	0.075
Diastolic blood pressure (mm/Hg)	61.5 (10.0-116.0)	61.9 (19.0-121.0)	0.674
Mean arterial pressure (mm/Hg)	77.8 (24.3-149.0)	75.7 (8.0-127.0)	0.081
Respiratory rate (times/min)	19.8 (5.0-44.0)	19.6 (6.0-52.0)	0.594
Temperature (°C)	36.8 (31.7-40.4)	36.8 (33.1-39.9)	0.738
Blood oxygen (%)	96.0 (28.4-100.0)	95.6 (23.0-100.0)	0.418
Blood glucose (mg/dL)	140.6 (42-309.0)	139.3 (63.0-326.0)	0.754

$p < 0.05$, the difference between groups was statistically significant.

3-hour characteristic sequence of 8 indicators, finally 24 features were obtained. Then the Extremely Randomized Trees is used to analyze the feature importance, and the average Gini index of each feature in each decision tree is calculated to rank the feature importance. As can be seen from Figure 1, in the three-hour dynamic feature sequence, the mean heart rate, standard deviation of arterial pressure, standard deviation of final heart rate, standard deviation of diastolic blood pressure, average respiratory rate, mean arterial pressure, final arterial pressure, and standard deviation of body temperature rank at the top, and are far higher than other characteristic variables. This indicates that these eight features are the most important for the prediction of sepsis.

Model Performance

In this study, the Accuracy, Sensitivity, Specificity, F1 scores and AUROC of the sepsis prediction model built based on five machine learning algorithms are shown in Table II and Figure 2. The AUROC, Accuracy and F1 scores of Extremely Randomized Trees were all higher than those of other models, with AUROC above 0.76, showing the best performance. Among them, the AUROC of Random Forest (0.74) was slightly lower than Extremely Randomized Trees (0.76), the Accuracy of random forest (0.70) was lower than Extremely Randomized Trees (0.71). Because the data samples are not completely balanced, the imbalance-XGBoost has a high specificity (0.86) in predicting sepsis, which means that when imbalance-XGBoost predicts a patient's sepsis. The probability of the patient being diagnosed with sepsis is high, but its AUROC (0.72) is not outstanding. The Extremely Randomized Trees model maintained the best AUROC and was significantly better than XGBoost model (p=0.038, DeLong test), SVM model (p=0.004, DeLong

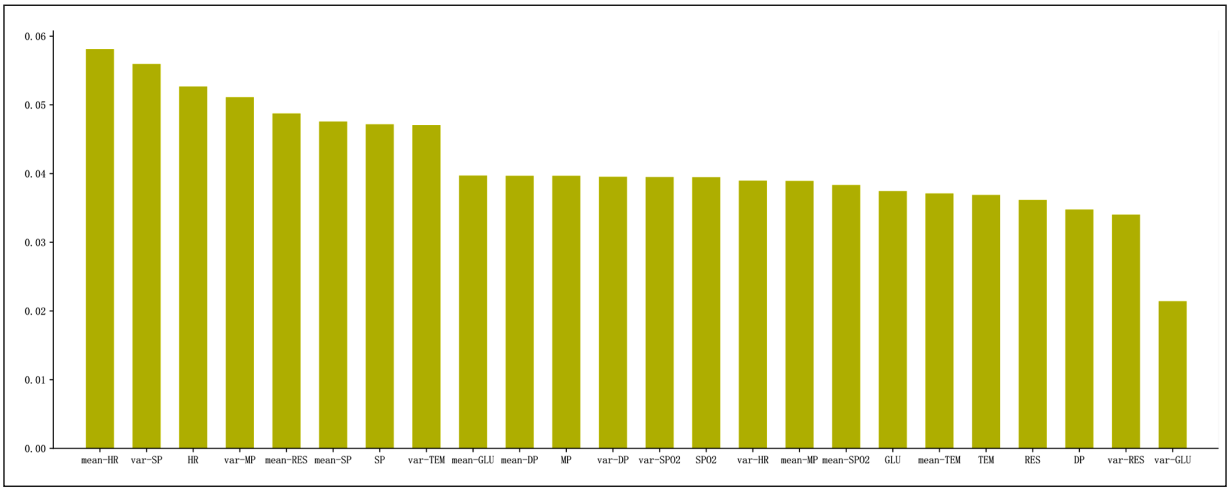

Figure 1. Feature importance ranking.

Table II. Comparison of results of different models.

Models	Accuracy	Specificity	Sensitivity	F1 scores	AUROC
ET	0.71 (0.69-0.73)	0.68 (0.67-0.69)	0.71 (0.70-0.73)	0.69 (0.68-0.71)	0.76 (0.75-0.77)
XGBOOST	0.65 (0.62-0.67)	0.70 (0.70-0.71)	0.63 (0.62-0.65)	0.66 (0.65-0.68)	0.73 (0.71-0.75)*
SVM	0.60 (0.60-0.61)	0.46 (0.45-0.47)	0.62 (0.61-0.63)	0.53 (0.51-0.54)	0.65 (0.63-0.67)*
RF	0.70 (0.69-0.71)	0.71 (0.70-0.72)	0.68 (0.68-0.69)	0.70 (0.69-0.71)	0.74 (0.71-0.76)*
Imb-XGBoost	0.63 (0.62-0.64)	0.86 (0.84-0.88)	0.59 (0.58-0.60)	0.70 (0.69-0.72)	0.72 (0.70-0.74)*

*Using random forest model as reference, the difference of AUROC was statistically significant ($p < 0.05$).

test), Random Forest model (p=0.025, DeLong test) and imbalance-XGBoost model (p=0.016, DeLong test).

We believe that only knowing the machine learning model to predict various performance indicators is not enough. In order to reduce the

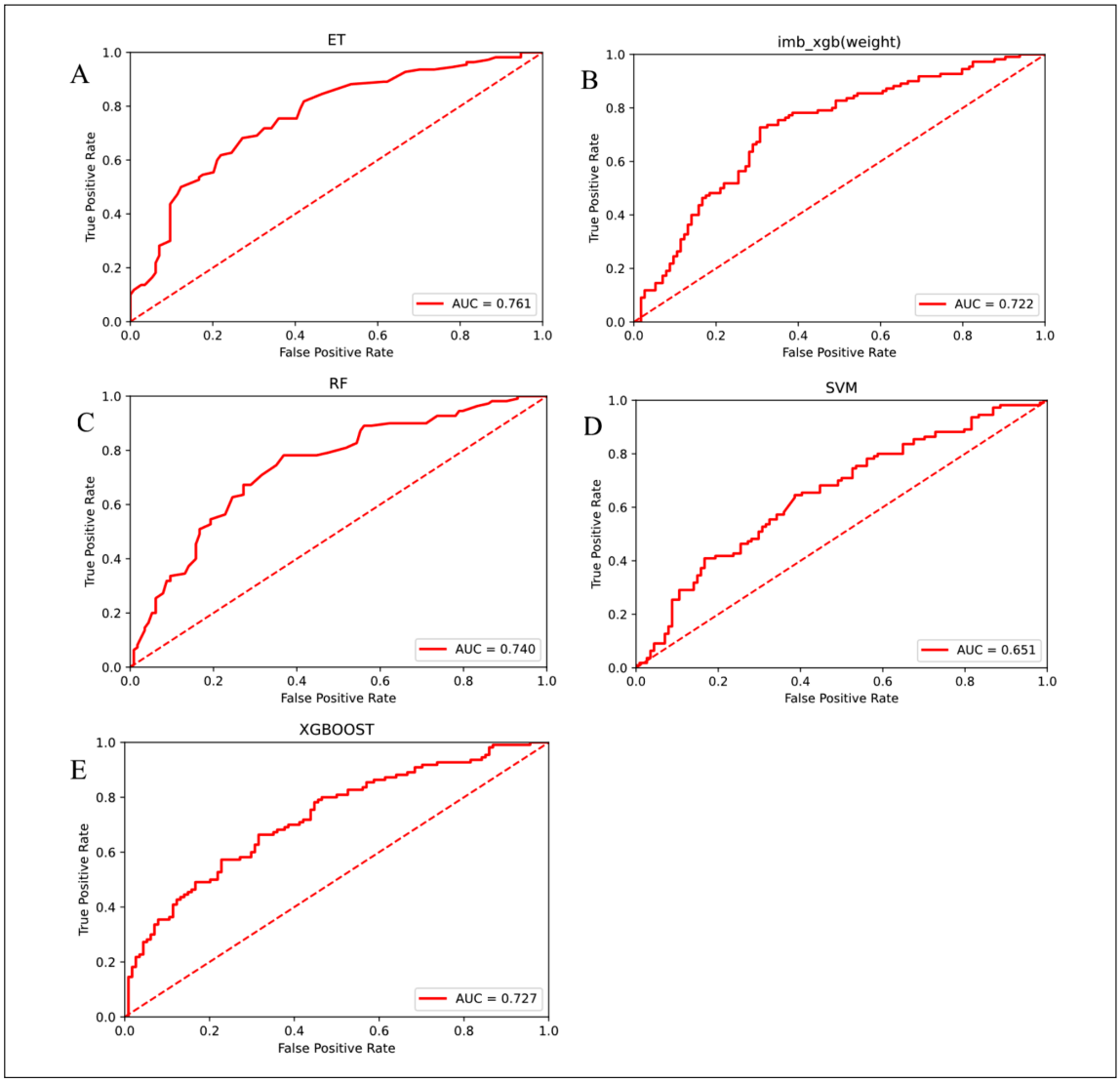

Figure 2. ROC curves of different models. **A**, Extremely Randomized Trees (AUC=0.761), **B**, Imbalance-XGBoost (AUC=0.722), **C**, Random Forest (AUC=0.740), **D**, SVM (AUC=0.651), **E**, XGBoost (AUC=0.727).

risk of using this model in clinical practice, it is also necessary to know the judgment basis of each prediction and the probability value of the predicted results. Therefore, we built the LIME local interpretable model to make clinical users trust the predicted results of this model.

The LIME local interpretable model works as follows: taking the 32nd ICU patient in the test set as an example, as shown in the prediction probabilities on the left side of Figure 3, the model predicts that this patient has a 77% probability of developing sepsis, and a 23% probability of not developing sepsis. This indicates that this patient has a high probability of developing sepsis, which can indicate that clinical workers should pay special attention to this patient. The basis for this prediction is shown in Figure 3, which shows the level of influence of each physiological indicator on whether the patient has sepsis from top to bottom. The yellow bar represents the positive influence of the patient on sepsis, the blue bar represents the negative influence of the patient on sepsis, and the length of the bar represents the degree of influence. Therefore, it can be seen from the figure that the standard deviation of 3-hour body temperature greater than 0.14 is the most important reason for the patient to suffer from sepsis. Other important reasons include that the standard deviation of the patient's 3-hour systolic blood pressure is greater than 8.99 and the endpoint value of the patient's systolic blood pressure is lower than 105, which can prompt clinical workers to pay attention to the large fluctuation of the patient's body temperature and systolic blood pressure, as well as the low systolic blood pressure. The features on the right of Figure 3 include mean-HR (mean of 3-hour heart rate), mean-SP (mean of 3-hour systolic blood pressure), var-HR (standard deviation of 3-hour heart rate), var-SP (standard deviation of 3-hour systolic blood pressure), etc. Taking the prediction probabilities of the 56th ICU patient in the test set as an example, as shown in the left part of Figure 4, the model predicts that this patient has a 26% probability of developing sepsis and a 74% probability of not developing sepsis, indicating that this patient has a high probability of not developing sepsis. Therefore, prompt clinical staff may slightly reduce their attention to the patient. The basis for this prediction is shown in Figure 4. It can be seen from the figure that the standard deviation of 3-hour body temperature being almost zero is the most important reason why this patient will not develop sepsis. Other important reasons include that the 3-hour mean systolic blood pressure of this patient is greater than 131.7 and the endpoint value of systolic blood pressure is greater than 132. Therefore, LIME local interpretable model can display a large amount of valid model prediction details for clinical workers' reference, thus effectively assisting clinical workers' work and improving diagnostic efficiency.

Discussion

As a clinical syndrome caused by infection, sepsis has high morbidity and mortality. The high mortality caused by septic shock can be better reduced only by effective early warning and timely and effective treatment of patients with sepsis. At present, although SOFA can predict sepsis development and mortality to a certain extent, the clinical application of real-time monitoring and early warning is limited because the laboratory parameters used in SOFA are based on the worst situa-

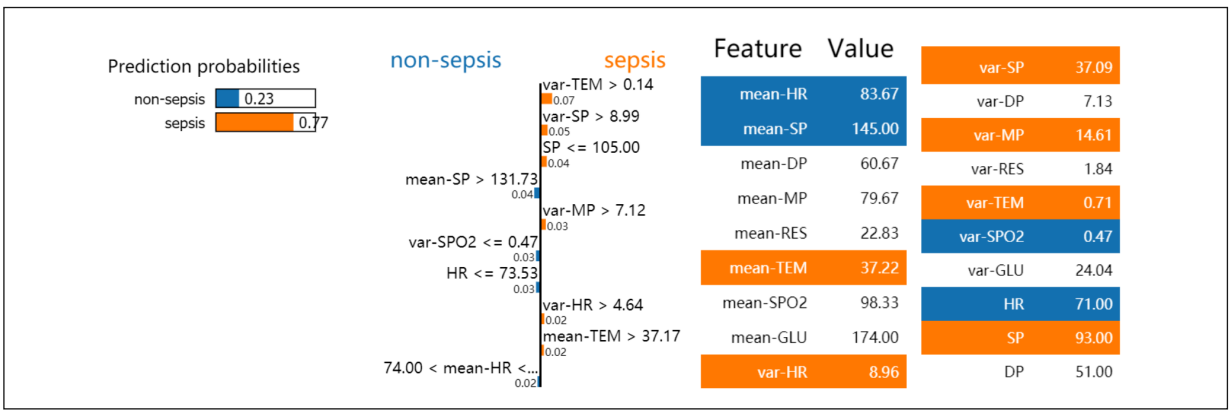

Figure 3. Interpretable sepsis prediction model (Take the 32nd ICU patient in the test set as an example).

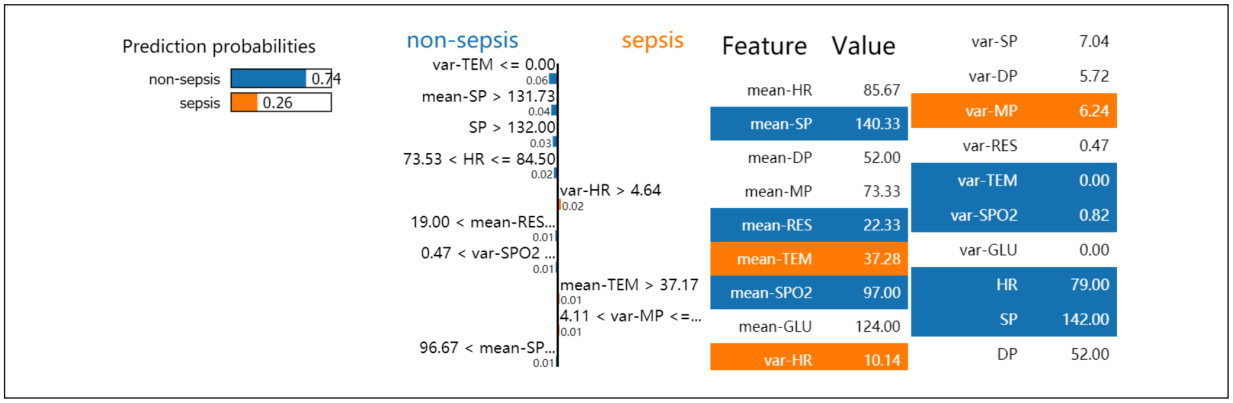

Figure 4. Interpretable sepsis prediction model (Take the 56th ICU patient in the test set as an example).

tion of the patient on the day. SOFA score can be used for rapid assessment of patients with sepsis, but it is not sensitive enough to assess the severity of sepsis. At present, researchers use the method of artificial intelligence machine learning to build a logistic regression warning model of sepsis based on the dynamic data of patients' basic vital signs and laboratory results. The above methods still have room for improvement in terms of improving the real-time and interpretability of the sepsis prediction model. In this study, an interpretable artificial intelligence model of real-time sepsis prediction was built by extracting 3-hour dynamic time series data of 8 non-invasive physiological indicators of patients, including heart rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, respiratory rate, body temperature, oxygen saturation and blood glucose. Three linear parameters, mean, standard deviation and end point value, were calculated. In this study, we compared the predictions of five machine learning models: Random Forest, XGBoost, Extremely Randomized Trees, Support Vector Machine and imbalance-XGBoost. The accuracy rate of Extremely Randomized Trees (0.71), sensitivity (0.71) and AUROC (0.76) are the highest. Imbalance-XGBoost has a high specificity in predicting sepsis (0.86). Therefore, a combination of Extremely Randomized Trees and Imbalance-XGBoost can be used to predict sepsis.

Limitations

Although this model achieves the expected effect, our study still has some limitations: 1. Some data in the cohort of patients with septic shock are missing, and the data finally applied to model training is linear interpolation, so it is not possible to evaluate the large fluctuations of indicators that may occur in the stage of data missing. If the model can be trained and verified with the same amount of data without missing, the accuracy of the results will be better. 2. Due to the small sample size, the relationship between each characteristic variable and sepsis cannot be fully explained. As the abundance and order of magnitude of subsequent data increase, it can be combined with deep learning models, such as long-term memory (LSTM) and convolutional neural network (CNN). In the future studies, more real-time parameters will be extracted from the sepsis database to further construct more effective features, so as to better explain the internal meaning of the dynamic changes of indicators and study the internal relationship between various physiological indicators and their impact on sepsis, so as to further improve the prediction accuracy and predict the occurrence of sepsis earlier.

Conclusions

In conclusion, compared with previous models, the explainable model of real-time sepsis prediction proposed in this study has higher accuracy and earlier prediction time. In addition, only eight of the most common non-invasive monitoring data were used in this study, which were obtained in real-time at the bedside and would not cause twice harm to patients. Meanwhile, LIME was used to interpret the model, which showed important features affecting each prediction in real time and improved the reliability of the model

prediction. This model can be used for equipment in hospital emergency and intensive care units. In future work, further improving the predictive ability of the model and interpreting the predictive model from different directions can be important research directions for the management of sepsis.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Ethics Approval
The data was from public dataset; therefore, the ethics approval was not applicable.

Informed Consent
The data was from public dataset; therefore, the informed consent of patients was not applicable.

Authors' Contribution
M.-W. Zhang conceptualized the idea. T.-Y. Zhang, M Zhong and Y.-Z. Cheng contributed to the manuscript preparation. All the authors reviewed and approved the final manuscript.

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Authors' Contribution
The Authors declare that they have no conflict of interests.

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