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Constructing an early warning model for elderly sepsis patients based on machine learning

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Sepsis is a serious threat to human life. Early prediction of high-risk populations for sepsis is necessary especially in elderly patients. Artificial intelligence shows benefits in early warning. The aim of the study was to construct an early machine warning model for elderly sepsis patients and evaluate its performance. We collected elderly patients from General Hospital of Ningxia Medical University emergency department and intensive care unit from 01 January 2021 to 01 August 2023. The clinical data was divided into a training set and a test set. A total of 2976 patients and 12 features were screened. We used 8 machine learning models to build the warning model. In conclusion, we developed a model based on XGBoost with an AUROC of 0.971, AUPRC of 0.862, accuracy of 0.95, specificity of 0.964 and F1 score of 0.776. Of all the features, baseline APTT played the most important role, followed by baseline lymphocyte count. Higher level of baseline APTT and lower level of baseline lymphocyte count may indicate higher risk of sepsis occurrence. We developed a high-performance early warning model for sepsis in old age based on machine learning in order to facilitate early treatment but also need further external validation.

Keywords Sepsis, Early warning model, Machine learning (ML), XGBoost

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection[1]. As a serious risk to human health, sepsis has received wide attention because of the high morbidity and mortality rate[2,3]. According to statistics, there were 48.9 million sepsis patients in the world with 11 million deaths[4]. A cross-sectional survey from China showed there were one in five patients affected by sepsis in ICU and the mortality rate as high as 35.5%[5]. Age as an independent risk factor for mortality in sepsis[6,7], it is found that sepsis imposes a serious healthcare burden especially in the elderly[8]. In a study with a median age of 75 showed that both hospital and ICU mortality rates exceeded 30%[9]. This is attributed to a variety of reasons, for example, the old have more underlying diseases before onset[10], decreased immune function[11,12] and higher rate of resistant pathogens infection such as methicillin-resistant S. aureus (MRSA)[13,14]. As a result, geriatric patients have higher sepsis incidence, more serious disease manifestations and more difficulties in diagnosis and treatment[15–17]. In addition, elderly sepsis patients have a high risk of complications such as kidney injury[18], which will bring serious medical burden.

Early diagnosis constitutes a decisive factor for improvements in prognosis and outcomes of sepsis[19,20]. So, it is necessary that not only pay attention to the means of treatment, but also focus on its diagnosis and early prediction[21]. However, diagnosis and early prediction of sepsis is complex and requires a comprehensive assessment. Meanwhile, sepsis has a fraction of missed diagnosis[22] and exists subjectivity, that is why we need to find new diagnostic tools.

With the advancement of technology, AI receives increasing attention and play an important role in the area of healthcare[23,24]. Nowadays, studies show that machine learning as a new tool in health care plays a significant role in sepsis diagnosis[25–28]. It shown that, compared with traditional scoring systems like SOFA, MEWS, machine learning demonstrates better diagnostic capability and sensitivity in sepsis prediction[29].

This study we focus on elderly patients with sepsis. By collecting a number of clinical indicators, using 8 machine learning model methods to construct the warning model and comparing the results, the best performing model was chosen to construct an early warning model of sepsis to find high-risk patients. At the same time, the characteristic variables in the data were further analyzed to find diagnostic and predictive indicators and the association between different clinical characteristics and the disease. This model is expected to show the

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potential of machine learning in clinical disease prediction by providing earlier and more accurate identification during clinical work which may increase patient survival period.

Materials and methods

Research objects

This study collected elderly patients from General Hospital of Ningxia Medical University emergency department and intensive care unit from 01 January 2021 to 01 August 2023. This study was approved by the Ethics Committee of General Hospital of Ningxia Medical University (KYLL-2022-0543), and we committed that the entire process was conducted in accordance with the principles expressed in the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion criteria: First, this study set the patients (number of visits) who had the discharge diagnosis of sepsis to positive cohort. Also, it set the patients (number of visits) who used antibiotics or had the diagnosis includes infection but not sepsis to negative cohort. Then we further set the inclusion criteria as: (1) Age ≥ 60 years old. (2) Negative number of visits who had length of hospitalization more than 24 h. (3) Positive number of visits had been diagnosed with sepsis more than 24 h who didn't have definitive diagnosis of sepsis upon admission to the hospital.

Exclusion criteria: Patients already had diagnosis related to sepsis on admission.

Outcome

The primary outcome of this study was to predict whether the patient would occur sepsis 24 h after admission to the hospital.

Data pre-processing

Using the median to fill in missing values. Using min–max to standardize data. During feature selection, using least absolute shrinkage and selection operator (LASSO) regression for initial feature screening, followed by the random forest approach to further simplify the features. LASSO regression was performed using the coordinate descent method. During the regularization parameter selection process, 200 parameters were selected in the 10^{-5} to 10^{2}, and Lasso regression combined with five-fold cross validation was used to traverse all parameters to select the optimal parameter. And random forest used bootstrap sampling and default parameter values.

Statistical analysis

The clinical machine learning model was built on windows 11 using python 3.8.3. There were 8 machine learning models used in this research. Model performance was evaluated using area under the receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity, precision, F1 score, area under precision recall curve (AUPRC), and Kappa coefficient. Choosing the best model by comparison and using SHAP for interpretability analysis of the model.

Results

Patient characteristics

According to information gathered in accordance with the electronic health record (EHR) of General Hospital of Ningxia Medical University emergency departments and intensive care units, after initial screening for inclusion and exclusion criteria, this study initially included a total of 15,690 patients including 1656 positive and 14,034 negative. By further setting more concrete inclusion and exclusion criteria, a total of 4304 patients including 425 positive and 3879 negative were retained in the second segment. After data cleaning to remove visits with too many missing values, a total of 2976 patients were ultimately collected in this study including 313 positive and 2663 negative (see Fig. 1). According to the final inclusion of the patients, there were 1674 males and 1302 females. Among them, the oldest was 97 years old, the youngest was 60 years old, and the median age was 72 years old.

Feature screening

This study initially incorporated 429 features. The number of remaining features after removing the features with the same value and those that were completely missing is 273. Afterwards, more than 80% of the missing features were removed after data cleaning, and a total of 211 usable features were included. In the process of model building feature selection, the initial feature screening was performed on the basis of LASSO regression, and a total of 35 features had been screened (see Figs. 2 and 3). Afterwards, the random forest approach was used to find the further simplification of the features and finally obtained 13 features. Excluding the feature 'sex', the remaining 12 features were used to build models (see Fig. 4).

Data set splitting method

Randomization of the data into training set and test set at a ratio of 7:3. The training set contained sample of 2083 which the number of positive samples was 219 and the number of negative samples was 1864. The number of test set was 893 including 94 positive samples and 799 negative samples. SMOTE oversampling of training set was performed in order to sample the number of minority class samples to the same as the number of majority class samples, which could equalize the number of positives and negatives. In the process, the number of nearest neighbors was 5. After that, this study used 8 machine learning models to build a sepsis prediction model.

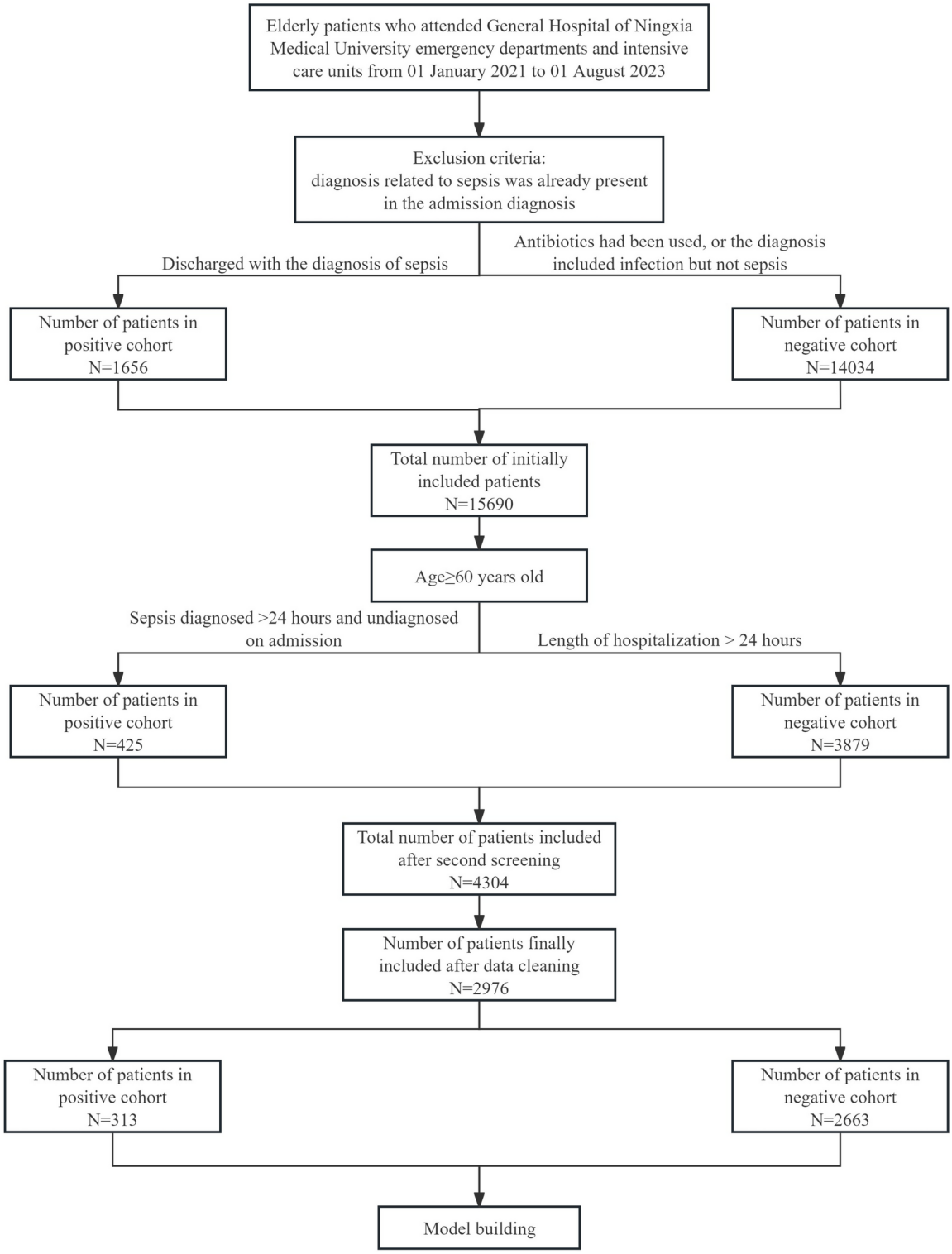

Fig. 1. Data incorporation flowchart. Patient inclusion and exclusion criteria, and flowchart for modeling data screening.

Modeling result

Using 8 machine learning models including support vector machine (SVM), naive bayes (NB), K nearest neighbor (KNN), logistic regression (LR), decision tree (DT), AdaBoost, extreme gradient boosting (XGBoost) and random forest (RF) to build the sepsis warning model.

Comparing evaluation metrics across all models, XGBoost demonstrated the best predictive performance which had the highest AUROC (0.971), the highest AUPRC (0.862), the highest accuracy (0.95), the highest F1

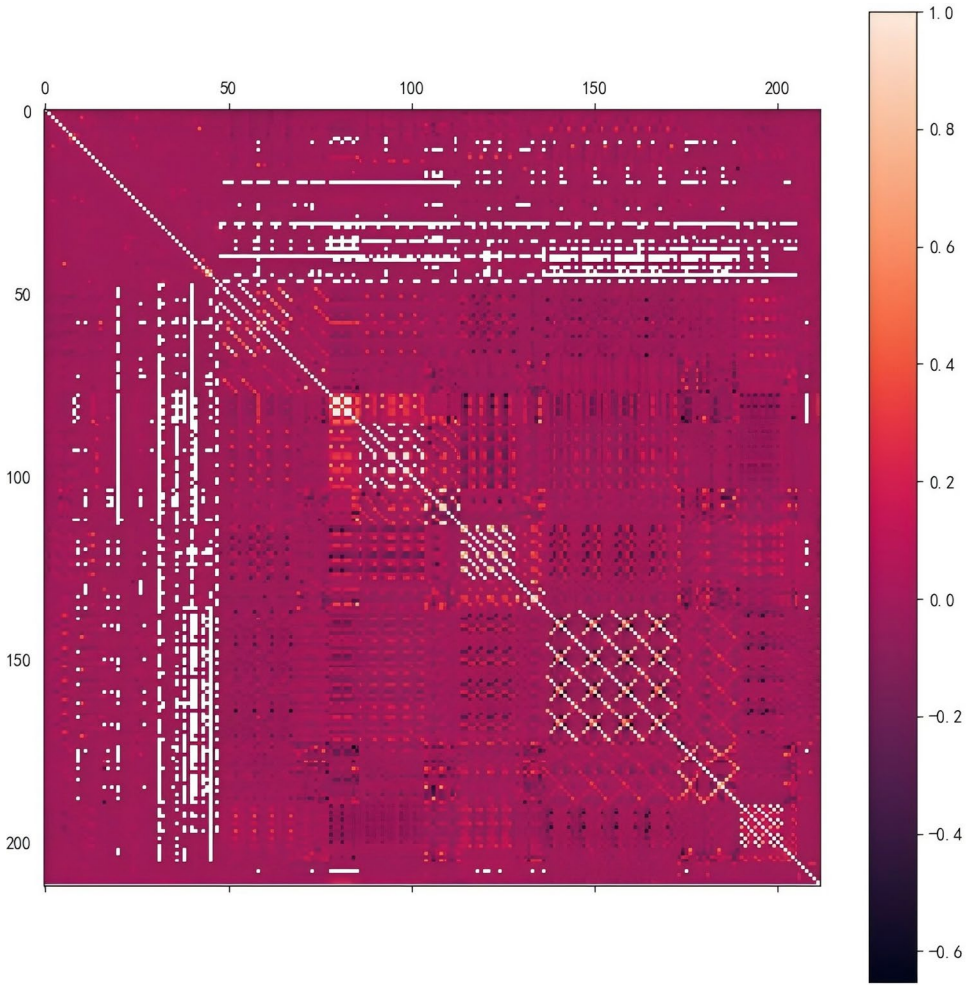

Fig. 2. Pearson correlation map of all features. Characterization of the 2976 patients ultimately included in the constructed model yielded full feature pearson correlograms.

score (0.776) and the highest Kappa coefficient (0.748). The brier score of XGBoost was 0.04 (see Table 1; Figs. 5 and 6). The probability calibration curve indicated that XGBoost machine learning model exhibited preferable predictive performance between true probability and predicted probability (see Fig. 7).

Model interpretability (SHAP)

We found that XGBoost worked best in predicting patients who would occur sepsis 24 h after admission to the hospital. Then interpreting predictive models with SHAP to observe the effect of each feature on the predicted outcome of the model, we made importance plot of model features in order to know what were the important features in sepsis early warning model. The plot showed that baseline APTT (activated partial thromboplastin time) had the greatest impact on sepsis prediction. Baseline lymphocyte count and latest bicarbonate level also played important roles at the same time (see Fig. 8). Focusing on the impact of features positively or negatively on the output of the model result, higher baseline APTT may lead to higher risk of probability of sepsis. Meanwhile, the decrease in baseline lymphocyte count was expected to have a positive effect on the prediction of sepsis which meant lower baseline lymphocyte count indicating higher risk of sepsis occurrence (see Fig. 9). In addition, we further drew the SHAP partial dependence plot in Supplementary Fig. 1, hoping to show the influence of specific features on the model prediction results more intuitively. However, the influence of each feature on the model prediction is not completely consistent with the SHAP plot.

Localizing the interpretation of predictions in the model for specific populations of positive and negative patients (see Figs. 10 and 11). Figure 10 shows that the features baseline APTT, baseline lymphocyte count, baseline platelet count, sodium maximum, rate of first change of albumin, potassium minimum, latest bicarbonate, baseline monocyte count and creatinine minimum will push the results to the side of the positive patient.

Discussion

With the development of the society, the concern of population ageing is becoming increasingly prominent. As the result of China's seventh national population census showed that the percentage of elderly population was

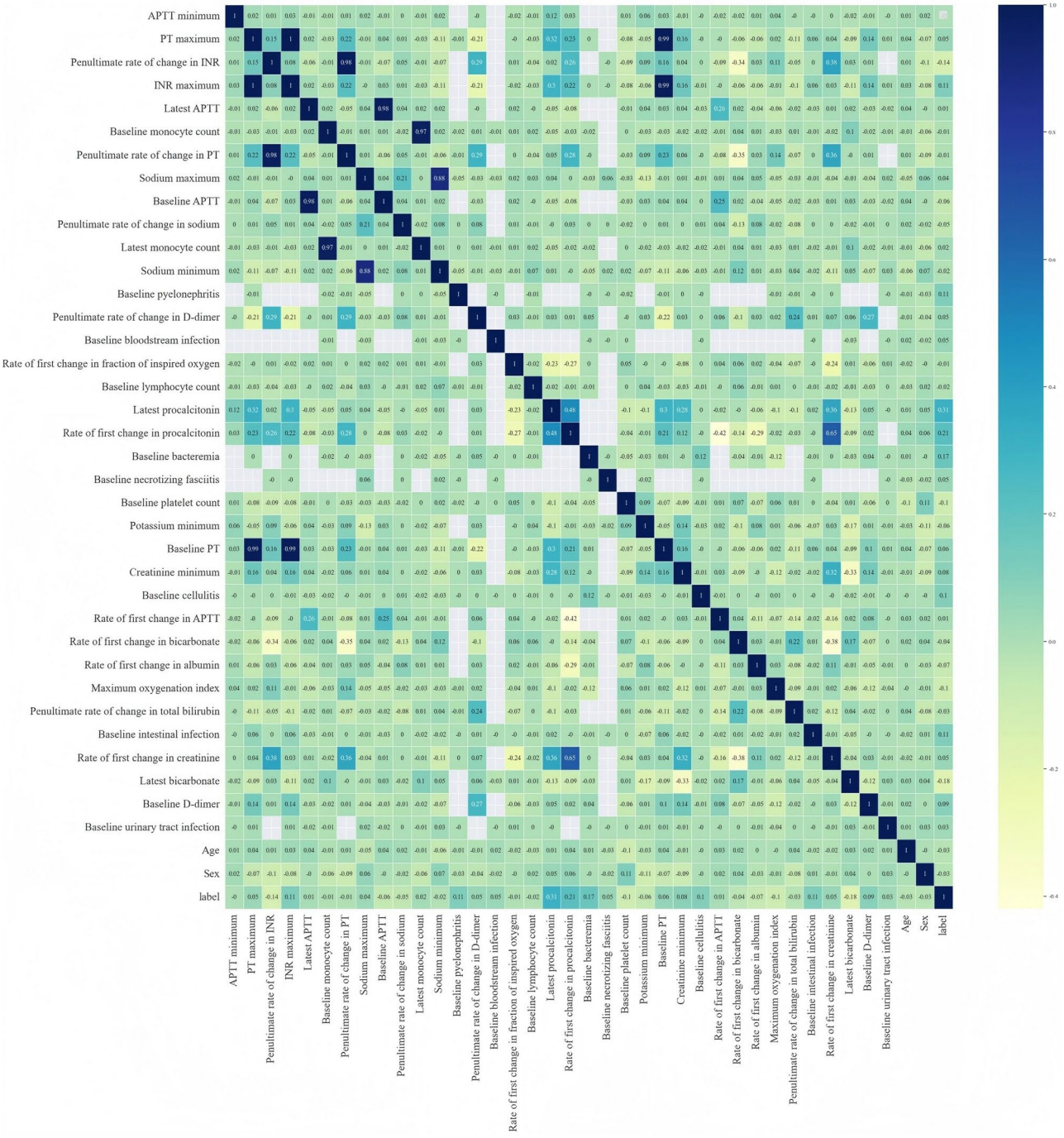

Fig. 3. Pearson correlation plot of 35 features. Pearson correlation plot of 35 features obtained from the preliminary screening of LASSO regression.

increasing compared to 2010[30]. Up to 2020, population over 60 years old reached 18.7% and in Ningxia Hui autonomous region the percentage of this population reached 13.52%[30]. Growing number of elderly people brings more troublesome health issues such as sepsis. According to the studies, the reason why old people have higher risk of sepsis occurrence[31,32] may attributable to immunosenescence which means decreased immunity and enhanced susceptibility to inflammation with age[33,34]. However, the diagnosis of sepsis is pretty difficult in the old people[35]. It will be helpful if there is a reliable tool to help the doctors to recognize this disease.

AI is gradually becoming a power tool for decision-making and treatment in the medical field. Now, machine learning can integrate both statistical data analysis and computer technique to gain useful information from the huge amount of data[36]. As an emerging and prospective mean of artificial intelligence, machine learning shows great potential in medical field for the past few years[37–39]. Machine learning can save health care costs, increase diagnostic power, and be more scalable[40,41]. With the purpose of constructing a reliable clinical tool,

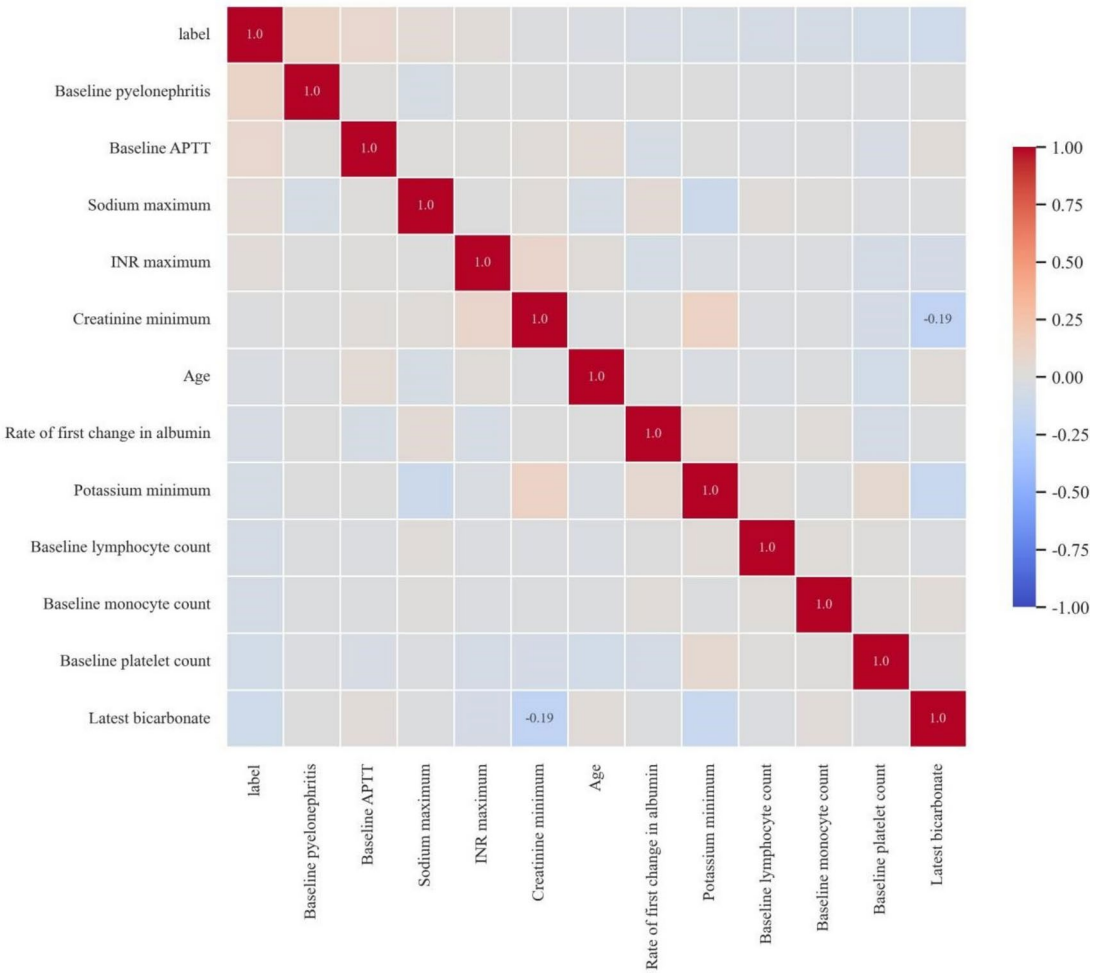

Fig. 4. Modeling feature correlation heat map. Pearson correlation heatmap of 12 features ultimately used to construct the machine learning model.

Model	Accuracy	Sensitivity	Specificity	Precision	F1 score	AUROC	AUPRC	Kappa coefficient
NB	0.534 (0.499, 0.567)	0.872 (0.800, 0.935)	0.494 (0.459, 0.532)	0.169 (0.135, 0.204)	0.283 (0.233, 0.332)	0.785 (0.729, 0.842)	0.368 (0.265, 0.474)	0.129 (0.091, 0.164)
KNN	0.729 (0.700, 0.757)	0.713 (0.611, 0.804)	0.731 (0.699, 0.763)	0.238 (0.187, 0.287)	0.356 (0.291, 0.414)	0.779 (0.723, 0.836)	0.42 (0.336, 0.491)	0.236 (0.173, 0.294)
SVM	0.681 (0.652, 0.710)	0.851 (0.773, 0.920)	0.661 (0.628, 0.691)	0.228 (0.186, 0.273)	0.36 (0.302, 0.417)	0.801 (0.746, 0.856)	0.356 (0.269, 0.45)	0.232 (0.182, 0.284)
LR	0.595 (0.562, 0.627)	0.766 (0.678, 0.848)	0.574 (0.54, 0.609)	0.175 (0.138, 0.212)	0.285 (0.234, 0.335)	0.706 (0.644, 0.767)	0.192 (0.138, 0.267)	0.137 (0.092, 0.179)
DT	0.898 (0.879, 0.918)	0.702 (0.607, 0.798)	0.921 (0.902, 0.938)	0.512 (0.424, 0.596)	0.592 (0.513, 0.67)	0.812 (0.758, 0.866)	0.623 (0.55, 0.697)	0.535 (0.447, 0.624)
AdaBoost	0.869 (0.845, 0.890)	0.819 (0.732, 0.892)	0.875 (0.851, 0.899)	0.435 (0.361, 0.508)	0.568 (0.495, 0.635)	0.923 (0.886, 0.961)	0.673 (0.57, 0.764)	0.499 (0.423, 0.572)
XGBoost	0.95 (0.935, 0.964)	0.83 (0.756, 0.900)	0.964 (0.951, 0.977)	0.729 (0.648, 0.818)	0.776 (0.712, 0.84)	0.971 (0.947, 0.995)	0.862 (0.801, 0.917)	0.748 (0.678, 0.818)
RF	0.94 (0.925, 0.954)	0.766 (0.676, 0.850)	0.96 (0.946, 0.972)	0.692 (0.598, 0.779)	0.727 (0.652, 0.794)	0.963 (0.937, 0.990)	0.748 (0.644, 0.841)	0.693 (0.611, 0.768)

Table 1. Summary of evaluation indicators for eight models.

this study used 8 machine learning models to build an early warning model predicting sepsis in elderly patients. Among them, XGBoost, RF and AdaBoost theses three models showed better model performance. In the model performance comparison table, XGBoost and RF had a smaller gap. By comparison, XGBoost belongs to the Boosting algorithm and trains the tree iteratively[42]. XGBoost has high prediction accuracy, specializes in

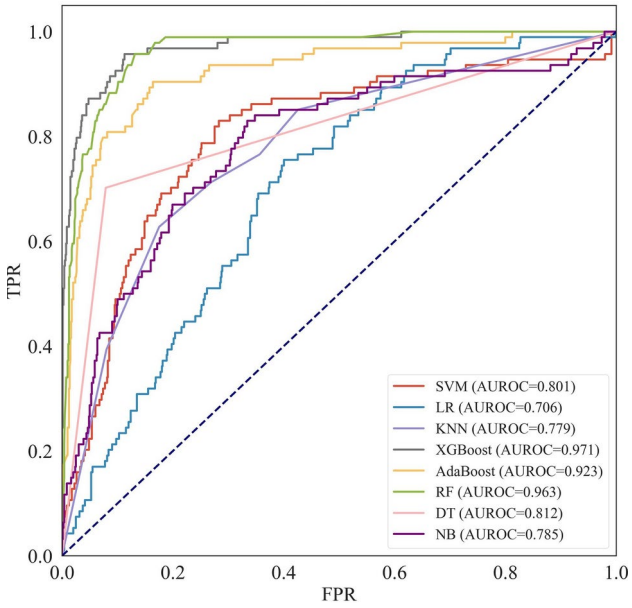

Fig. 5. ROC curves of eight machine learning models. This figure shows the ROC curves for eight models with false positive rate (FPR) as the horizontal coordinate and true positive rate (TPR) as the vertical coordinate in order to evaluate the predictive capacity of individual models which the AUROC has been calculated. In this figure, the grey curve represents XGBoost which has the highest AUROC of 0.971. RF which is the green curve has the second highest AUROC of 0.963. AdaBoost is represented by the yellow curve in the third position. The AUROC of LR is the lowest among all models represented by the blue curve.

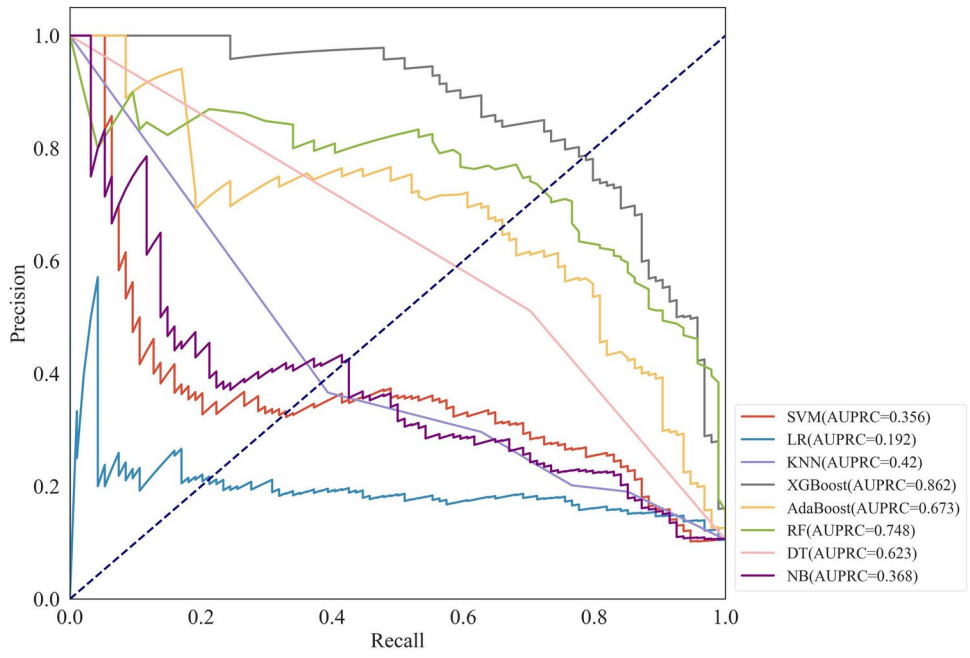

Fig. 6. Precision recall (PR) curves of eight machine learning models. PR curve plot containing eight machine learning models is constructed with recall as the horizontal coordinate and precision as the vertical coordinate so that model performance can be evaluated and compared. In a similar manner, the AUPRC is calculated separately for each model in it. It shows that, the AUPRC of XGBoost (grey curve), RF (green curve) and AdaBoost (yellow curve) are in the top three of all the models with values of 0.862, 0.748, 0.673 respectively. Similar to the ROC curve, LR (blue curve) exhibits the lowest level of AUPRC which is 0.192, followed by SVM (red curve) and NB (purple curve) which the levels of AUPRC are 0.356 and 0.368.

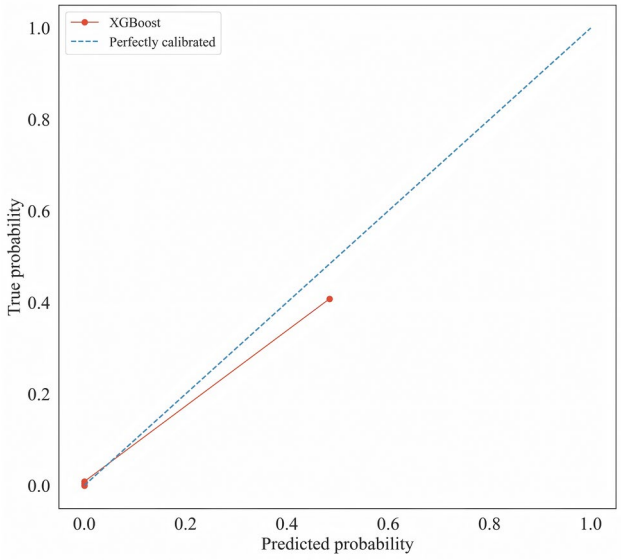

Fig. 7. Probability calibration curve of XGBoost.

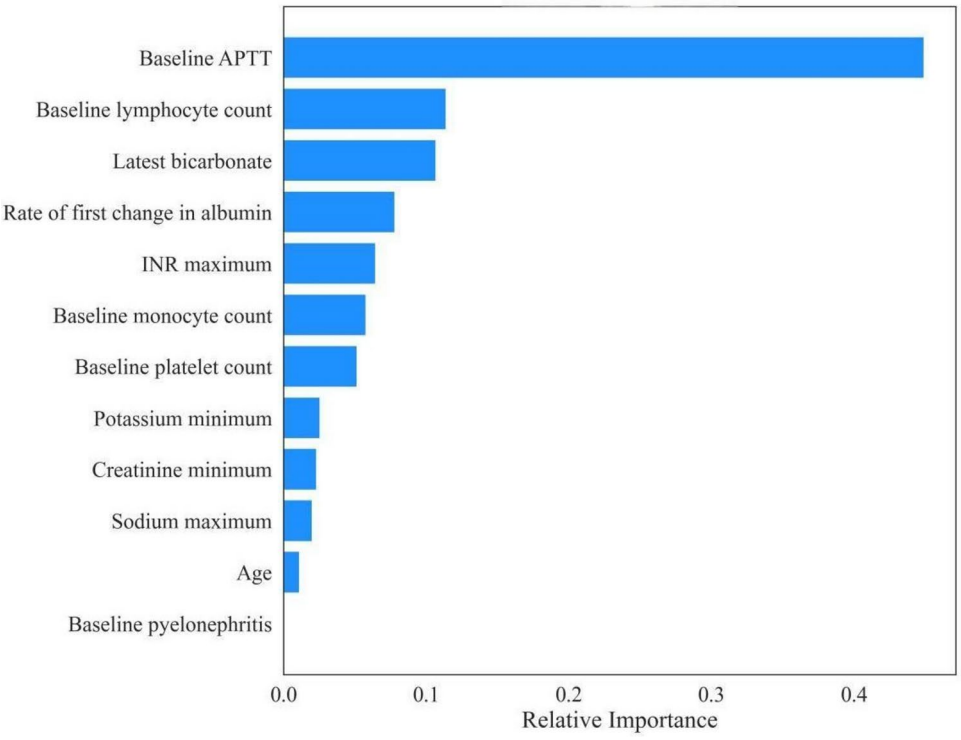

Fig. 8. Importance of features predicting sepsis in XGBoost model. Ignore the positive and negative effects of features on model prediction and take the mean absolute value of SHAP to rank the importance of features, we find that baseline APTT plays the most important role in the warning model followed closely by baseline lymphocyte count and latest bicarbonate. Admission baseline features presence of pyelonephritis (baseline pyelonephritis) appears to be less important in the forecasting process in the chart.

complex and nonlinear relationships, and can be used for flexible data processing, but needs to be interpreted with the help of SHAP. RF belongs to the Bagging algorithm, which has the advantages of strong anti-overfitting ability and high robustness[43]. However, RF has shortcomings such as slow prediction speed, processes data with a bias toward high-frequency categories and has large memory consumption[44,45]. More studies showed that XGBoost had higher prediction accuracy and model generalization ability[44,46]. In our study, XGBoost also

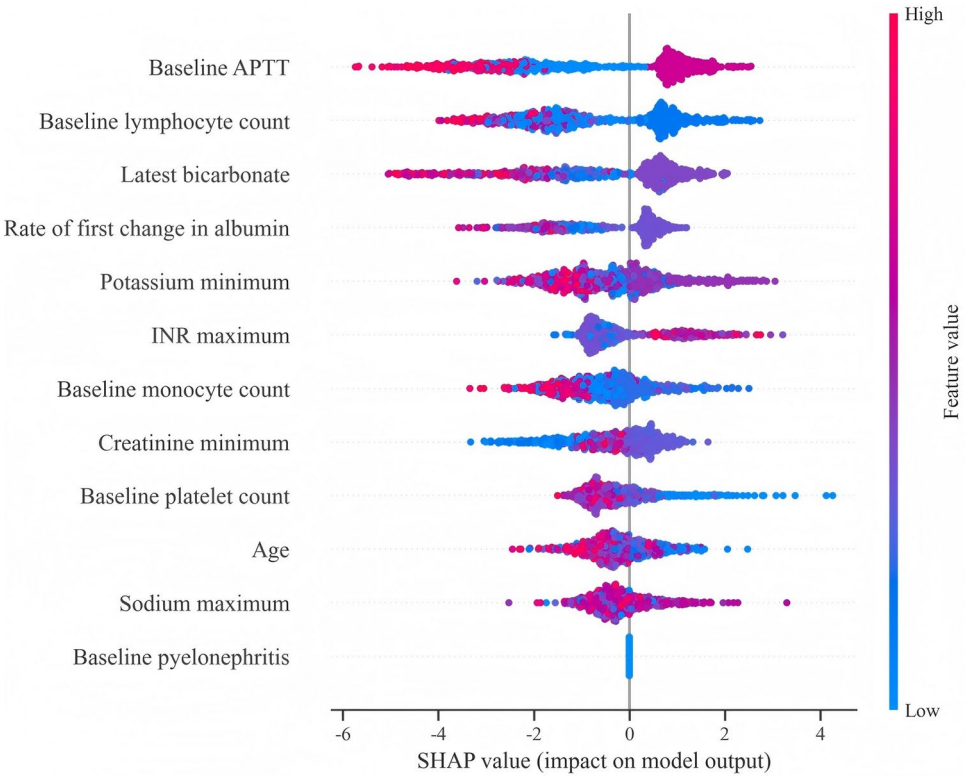

Fig. 9. The SHAP value figure reflects the impact of each important feature on the model output. In this chart, the y-axis is determined by the feature value and the x-axis is determined by the SHAP value, in which the color represents the level of the feature value (red is high and blue is low).

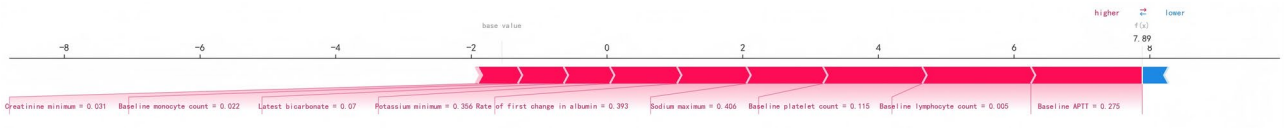

Fig. 10. XGBoost model positive patients predicted SHAP force figure. This chart provides interpretability of single model prediction. The longer length of the arrows on the X-axis represents the greater influence of the feature. Features that have a positive impact on the predicted outcome are shown in red, while conversely, features that have a negative impact are shown in blue. Base value is − 1.549.

Fig. 11. XGBoost model negative patients predicted SHAP force figure. Base value is − 1.549.

showed this advantage. There was an another research showed that compared with SOFA score, XGBoost had higher performance with advantages of timeliness and flexibility in sepsis diagnosis[47].

Not only the machine model can provide early warning of the disease, but also it can find the significant features to predict the disease. During the study, we chose LASSO regression and random forest to screen clinical features for model construction improving the efficiency of feature selection[48]. LASSO regression has high computational efficiency, can improve the problem of overfitting caused by complex features and high-dimensional data[49–52], improve the recognition accuracy by screening key features[53], and improve the generalization ability of the model[54]. Its advantages have been demonstrated in many studies such as fracture identification and tumor identification[53,55]. Random forests have similar advantages.

In this study, conducting interpretable analysis of the sepsis machine warning model through SHAP revealed that baseline APTT was the most important model predictive feature in the model based on XGBoost. As we all

know that, there is an interaction between inflammation and coagulation[56,57]. When sepsis occurs, it activates coagulation system. Meanwhile, coagulation can also promote inflammation[58]. Abnormal coagulation system promotes organ dysfunction through endothelial cell injury and microthrombosis, which is one of the core characteristics of sepsis[59]. APTT as the common monitor of endogenous coagulation[60,61] closely related to sepsis, sepsis related organ damage and prognosis[61–64]. Currently there was a study showed that APTT had a positive correlation with levels of inflammatory markers blood neutrophil counts and CRP in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD)[57]. Moreover, more studies have found that APTT prolongation is correlated with mortality rate of sepsis patients in ICU[62,63]. When sepsis occurs, elevated inflammatory factors activate the coagulation system, deplete coagulation factors, and prolong APTT[65]. Prolonged baseline APTT is not only a marker of abnormal coagulation function, but also indicates elevated inflammation level and poor prognosis. However, there are few studies on the correlation between APTT changes and the pathological changes of sepsis, which still need to be further explored.

In the study also showed that baseline lymphocyte count played an important role. Elderly patients experience a progressive decline in immunity, which means immunosenescence, leading to increased pathogen susceptibility and higher risk of infection[12]. Lymphocyte count can reflect immune response to the infection of the organism[66]. The researchers found that, decreased lymphocyte count will lead to increased risk of infection[67,68]. When sepsis occurs, apoptosis of cells leading to a decrease in the number of lymphocyte which promotes immune suppression ultimately causing unsatisfactory endings[69–71]. As a result, it is probably necessary for doctors to alert the patients with high level of APTT and low level of lymphocyte count at the time of admission may indicate that the patient has coagulopathy and immune dysfunction, probably means high possibility of sepsis occurrence.

However, we can see that the SHAP partial dependence plot does not give exactly the same results as the SHAP value figure. This may due to the fact that the interaction effect between different features is ignored in SHAP partial dependence plot, just showing the marginal effect of a single feature, and possibly extrapolating the data distribution dependence to the data sparse region. While the SHAP value figure shows the global importance of features for the model output, and shows positive and negative correlation. The differences between the two exhibited in this study may reflect the complex interaction between model complexity and clinical characteristics. In the follow-up study, we will further increase the sample size to improve the stability and reliability of SHAP results. At the same time, we will further explore the possible interaction between the modeling features.

This research has its strengths and limitations. In this research we developed a new clinical tool using machine learning approach through a relatively large population which has great performance with higher degree of accuracy and good model fit providing more objective early warning and early diagnosis of sepsis. Through the sepsis warning model, it can provide individualized early warning of sepsis occurrence based on the corresponding clinical characteristics data of the patient by reporting the probability of sepsis risk and setting up risk alerts, which can provide a basis for early intervention, and help doctors to make early corresponding treatment plans, with a view to improving the prognosis of elderly sepsis patients through early detection, early diagnosis and early treatment.

We tried to maximize the sample size as much as possible and pre-processed the collected data to control the data bias as much as possible and to improve the quality of the data[72,73]. However, there are some limitations in this study. As this study is a single-center research which only collected patients from 2 sections of same hospital may have data bias and confounding variables. In the following study, we will further conduct external validation to expand the sample size and the collection of variables, and increase the data diversity to improve the generalization ability of the model. We plan to first collect data from different periods in our hospital from the same department, as well as data from different department sources. In the future, we will try to further expand our cooperation with other hospitals. With the increasing volume of data, we will actively apply efficient algorithms and data processing techniques to improve efficiency and ensure data scalability and computing resource requirements. Furthermore, in the subsequent application of the model, we will compare the results to scores like qSOFA, continually evaluate and test the performance of the model and improve it to ensure the accuracy and reliability of the model in order to increase the effectiveness of the model's application.

Conclusion

We developed an early warning model with better performance based on XGBoost model in order to predict whether the old patients will occur sepsis 24 h after admission to hospital which may improve clinical decision-making capacity and improve prognosis, although still need further external validation.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

XWM and XJM designed the work and contributed to data collection, and analysis. XJM, YQM and YM wrote this paper. XWM provided financial support and revised the manuscript.

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Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of General Hospital of Ningxia Medical University (KYLL-2022-0543), and we committed that the entire process was conducted in accordance with the principles expressed in the Declaration of Helsinki. All patients signed informed consent to participate in the study. Because the study was a retrospective study with no more than minimal risk to patients, the need for informed consent was waived. We were committed to making every effort to protect patient privacy and anonymity.

Consent for publication

Informed consent was obtained from all participants for publication.

Additional information

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