Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Combined Serum NGAL and Fetuin-A to Predict 28-Day Mortality in Patients with Sepsis and Risk Prediction Model Construction

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ARTICLE INFO

Original paper

Article history:
Received: September 17, 2022
Accepted: November 13, 2022
Published: November 30, 2022

Keywords:

Sepsis, NGAL Fetuin-A , 28-day mortality

ABSTRACT

It was to investigate the predictive value of NGAL and Fetuin-A for 28-day mortality in patients with sepsis, and to construct a mortality risk prediction model. 120 patients admitted to The Affiliated Hospital of Xuzhou Medical University Hospital were grouped. Serum biochemical parameters were measured and scale scores were performed. The patient data were divided into a training set and test set in a ratio of 7:3, and the logistic regression model and random forest model were included to evaluate the 28-day mortality prediction efficacy of each index and model. The results showed that WBC, PLT, RBCV, and PLR decreased, SCr, Lac, PCT, D-dimer, NPR, NGAL, and Fetuin-A increased, APACHE II scale, SOFA scale, and OASIS scale scores increased in the death group ($P < 0.05$). SCr ≥ 408 μmol/L, Lac ≥ 2.3 mmol/L, PCT ≥ 30 ng/mL, D-dimer ≥ 2.33 mg/L, PLR ≥ 190, APACHE II ≥ 18 points, SOFA ≥ 2, OASIS ≥ 30, NGAL ≥ 352 mg/L, and Fetuin-A ≥ 0.32 g/L were found to be risk factors for 28-day death, while WBC ≥ 12×10^9/L, PLT ≥ 172×10^3/μL, and RBCV ≥ 30% were found to be protective factors for 28-day mortality. The predicted AUCs of APACHE II, SOFA, OASIS, NGAL, Fetuin-A, NGAL & Fetuin-A, logistic regression model, and random forest model were 0.80, 0.71, 0.77, 0.69, 0.86, 0.92, 0.83, and 0.81. NGAL combined with Fetuin-A has good prediction efficacy in 28-day mortality in septic patients.

Doi: http://dx.doi.org/10.14715/cmb/2022.68.11.9

Introduction

Sepsis refers to a type of organ dysfunction clinical syndrome that can endanger the life and health of patients caused by the body's imbalance of infection response, which has high morbidity and mortality (1). Sepsis development can trigger septic shock, multiple organ dysfunction syndrome, cardiac dysfunction, and other diseases, and sepsis are one of the main factors leading to death in critically ill patients in ICU, and ICU mortality and in-hospital mortality in such patients reach more than 25% and 35%, respectively (2,3). Mortality in sepsis is associated with disease severity, as well as with early diagnosis as prognostic evaluation (4). Therefore, it is very important to find the indicators for early diagnosis and evaluation of the prognosis of patients with sepsis in clinical practice to effectively control the process of sepsis and reduce the mortality of patients. At present, the evaluation systems used to diagnose sepsis or in-hospital death in clinical practice include systemic inflammatory response syndrome, sequential organ failure assessment (SOFA), quick SOFA (aSOFA), and so on (5). In addition, it also includes acute physiology and chronic health evaluation (APACHE), which is widely used in the ICU, but its calibration in the prediction of the risk of death in ICU patients is low (6).

Neutrophil gelatinase-associated lipocalin (NGAL) was first discovered in neutrophil peroxidase granules and belongs to the lipocalin superfamily, which can be used to predict the 28-day risk of death in septic patients (7). Fetuin-A is a calcification inhibitor that is able to induce an inflammatory response during metabolism in vivo (8). However, it has been confirmed that some non-specific inflammatory markers can be used in the prognostic evaluation of adult sepsis patients (9). NGAL has some predictive value for sepsis but has low predictive specificity for disease severity. Moreover, machine learning technology also plays a very important role in the clinical field of critical care medicine, which can assist physicians in the diagnosis of diseases, outcome prediction, and clinical decision-making (10). Machine learning has been used in the construction of clinical prediction models for sepsis, and has achieved good results (11).

In order to construct a reasonable and feasible sepsis mortality prediction model, the clinical data of sepsis patients were included to compare the differences in blood basic indicators and NGAL and Fetuin-A levels among 28-day survival and death patients, and a 28-day mortality risk prediction model was also constructed. The aim was to lay the foundation for improving the predictive efficacy of mortality risk in septic patients.

Materials and Methods

General information

According to the inclusion and exclusion criteria, 120 patients with sepsis who received treatment in The Affiliated Hospital of Xuzhou Medical University Hospital from May 2019 to March 2022 were selected as the study subjects, including 87 males and 33 females, with an average age of (57.31 ± 12.53) years. Inclusion criteria: (i) patients

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aged over 16 years old; (ii) patients meeting the diagnostic criteria of sepsis, and confirmed by imaging and laboratory tests; (iii) patients with complete clinical data; (iv) patients who have good treatment compliance. Exclusion criteria: (i) patients combined with malignant tumor; (ii) primary immunodeficiency; (iii) patients needing to receive emergency surgery at admission; (iv) death or discharge within 24 hours after admission; (v) pregnant or lactating women; (vi) clinical data missing, outcome measures are not clear. It obtained approval from the ethics committee of The Affiliated Hospital of Xuzhou Medical University Hospital (Approval No.: *), and the patients or their families were informed of the procedures and signed the informed consent form.

Collection of clinical data

Telephone, WeChat, or outpatient visits were used for a 28-day follow-up period, and the endpoint time was all-cause death. Patients were divided into a survival group (n = 80) and a death group (n = 40) according to their survival at 28 days.

(i) Basic data: The clinical data of all patients were collected, including age, gender, body mass index (BMI), and length of hospital stay.

(ii) Serological parameters: 5 mL of fasting venous blood was collected from the patients at admission, and serum was collected after anticoagulant treatment. The levels of white blood cell count (WBC), red blood cell volume (RBCV), platelet count (PLT), serum creatinine (SCr), and blood urea nitrogen (BUN) in the serum were measured using an automatic hematology analyzer. Serum levels of lactic acid (Lac) were measured by a blood gas analyzer. Serum C-reactive protein (CRP) and procalcitonin (PCT) levels were measured by microparticle enzyme immunoassay. D-dimer levels in serum were measured using immunoturbidimetry. Blood levels of NGAL and Fetuin-A were measured by enzyme-linked immunosorbent assay. Neutrophil to platelet ratio (NPR) and platelet to lymphocyte ratio (PLR) was calculated.

(iii) Scale score: APACHE II scale (12) was used to evaluate the acute physiology, age, and chronic health of patients. The total scores of each dimension were 20 points, 20 points, and 10 points, respectively. The total score on the APACHE II scale was 50 points. The higher the score, the more severe the patient's condition. Respiratory system function, PLT, bilirubin, circulatory system function, Glasgow coma scale (GCS), and renal function were evaluated by the SOFA scale (13). The total score on the SOFA scale was 24 points. The higher the score, the worse the prognosis of patients. The Oxford acute severity of illness score (OASIS) scale (14) was used to evaluate patient age, length of hospital stay before ICU, heart rate, mean arterial pressure, respiratory rate, body temperature, mechanical ventilation on the first day of ICU, emergency surgery before ICU, 24-hour urine volume on the first day of ICU, and GCS score, and the total score of the OASIS scale was 73 points, and the higher the score, the worse the prognosis of patients.

Statistical analysis

SPSS 19.0 software was used for the statistical analysis of data. Data with less than 5% missing outcome measures were supplemented completely by means. The clinical data were randomly divided into a training set and validation set according to the ratio of 7:3. Statistical analysis of outcome measures was performed using SPSS 19.0 software, enumeration data were expressed as frequency (%), and chi-square test was used for comparison between groups; measurement data were expressed as mean ± standard deviation $(\bar{x} \pm s)$, and an independent sample *t*-test was used for comparison between groups.

The training set data were selected to construct a 28-day mortality risk prediction model for sepsis patients, logistic regression models were constructed using the MASS package in R software, and variables included in the models were selected according to the previous univariate analysis results. Variance inflation factor (VIF) was used to determine the collinearity between variables. It was considered that VIF > 5.0 and $P < 0.05$ had significant collinearity between variables. After excluding such variables, other variables were included in the logistic regression model for analysis. Random forest models were constructed using the Random Forest package. A random forest model was needed to select the optimal parameters according to mean square error (MES). The receiver operating characteristic curve (ROC) and Youden index were drawn to select the optimal cutoff point, and the predictive sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (PLR'), negative likelihood ratio (NLR'), and area under the concentration-time curve (AUC) of the risk prediction model were calculated. The above indicators were used to evaluate the performance of the risk prediction model. Differences were considered statistically significant at $P < 0.05$.

Results

Analysis of general data of patients with sepsis

According to the 28-day survival, 120 patients with sepsis were divided into a survival group and a death group, including 80 patients and 40 patients, respectively. A comparative analysis of the basic data of patients in different groups showed that there was no significant difference in gender ratio, mean age, mean BMI, and mean body temperature between the survival group and the death group ($P > 0.05$). However, systolic blood pressure and diastolic blood pressure were higher and heart rate was lower in the survival group than in the death group, and the differences were statistically significant ($P < 0.05$). Results are shown in Table 1.

Comparison of serum parameters in sepsis patients with different survival periods

The serum levels of WBC, PLT, RBCV, SCr, Lac, CRP, BUN, PCT, D-dimer, NPR, and PLR were compared between the survival group and the death group. It was found that there was no significant difference in serum CRP and BUN levels between sepsis patients in the survival and death groups ($P > 0.05$). Compared with the survival group, the serum WBC, PLT, RBCV, and PLR levels in sepsis patients in the death group were significantly lower, and the differences were statistically significant ($P < 0.05$). Compared with the survival group, the serum levels of SCr, Lac, PCT, D-dimer, and NPR in patients with sepsis in the death group were significantly increased, and the differences were statistically significant ($P < 0.05$). The results are shown in Figure 1.

Table 1. Analysis of general data of sepsis patients with different survival conditions.

Information	Survival group (n=80)	Death group (n=40)	t/χ^2	*P*
Gender [n (%)]			0.291	0.653
Male	59 (73.8)	28 (70.0)		
Female	21 (26.3)	12 (30.0)		
Age (years)	58.94±9.82	59.42±7.39	0.785	0.479
BMI (kg/m^2)	23.51±2.74	24.03±3.21	0.650	0.311
Heart rate (beats/min)	86.30±10.53	90.22±17.63	6.792	<0.001
Systolic blood pressure (mmHg)	117.72±10.91	104.59±8.84	6.895	<0.001
Diastolic blood Pressure (mmHg)	61.37±5.27	57.46±6.60	7.114	<0.001
Body temperature (℃)	36.79±0.54	36.55±0.46	0.681	0.709

Comparison of scores of each scale in sepsis patients with different survival periods

The differences in the APACHE II scale, SOFA scale, and OASIS scale scores between sepsis patients in the survival and death groups were compared. The scores of the APACHE II scale, SOFA scale, and OASIS scale in sepsis patients in the survival group were (14.07 ± 2.81), (1.73 ± 0.28), and (23.61 ± 3.78), respectively; the scores of sepsis patients in death group were (22.65 ± 4.43), (2.32 ± 0.51), and (43.76 ± 4.41), respectively. It was found that the APACHE II scale, SOFA scale, and OASIS scale scores were significantly increased in the death group compared with the survival group ($P < 0.05$) (Figure 2).

Comparison of serum NGAL and Fetuin-A levels in sepsis patients with different survival periods

The serum levels of NGAL and Fetuin-A were compared between the survival group and the death group. The serum levels of NGAL and Fetuin-A in the survival group were (316.73 ± 35.61) mg/L and (0.21 ± 0.03) g/L, respectively; the serum levels of NGAL and Fetuin-A in the death group were (579.82 ± 59.95) mg/L and (0.60 ± 0.05) g/L, respectively. Compared with the survival group, the serum NGAL and Fetuin-A levels were significantly increased in the death group ($P < 0.05$). The results are shown in Figure 3.

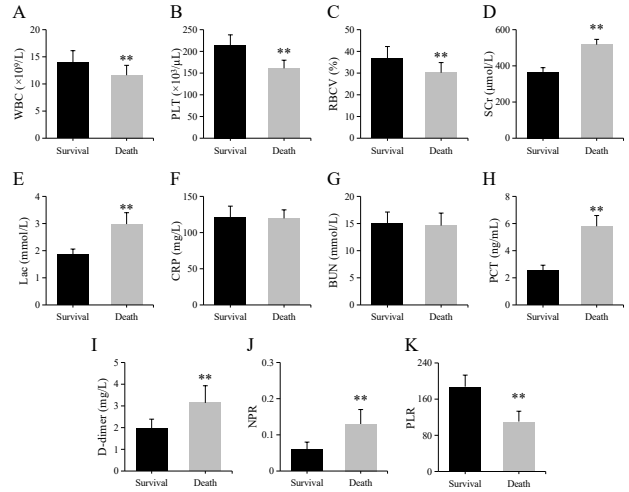

Figure 1. Comparison of blood routine parameters in sepsis patients with different survival conditions. (A) WBC level; (B) PLT level; (C) RBCV level; (D) SCr level; (E) Lac level; (F) CRP level; (G) BUN level; (H) PCT level; (I) D-dimer level; (J) NPR level; (K) PLR level; compared with the survival group, $^{**}P < 0.01$.

Analysis of 28-day mortality risk factors in patients with sepsis

The training set was used to construct the risk prediction model. The logistic regression model showed that the VIF value of each variable was less than 5%, so it indicated that there was no obvious collinear relationship between each variable and it could be directly included in the model for analysis. According to the multivariate logistic regression model, 12 independent factors were identified, including PLT, RBCV, SCr, Lac, PCT, D-dimer, NLR, APACHE II, SOFA, OASIS, NGAL, and Fetuin-A. Among them, PLT and RBCV were independent protective factors for 28-day death in septic patients, while SCr, Lac, PCT, D-dimer, NLR, APACHE II, SOFA, OASIS, NGAL, and Fetuin-A were independent risk factors (Table 2).

A random forest model for mortality risk prediction was constructed, and the number of independent trees in the random forest model should be 251 according to the MSE minimum, and the forest node purity improvement value was performed and plotted. Age ≥ 70 years (OR =

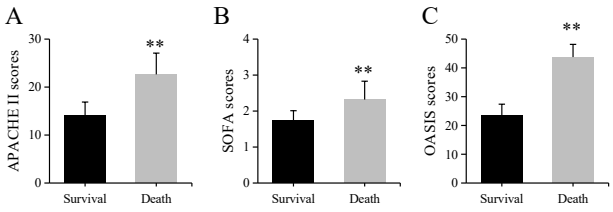

Figure 2. Comparison of scores of each scale in sepsis patients with different survival conditions. (A) APACHE II scale score; (B) SOFA scale score; (C) OASIS scale score; compared with the survival group, $^{**}P < 0.01$.

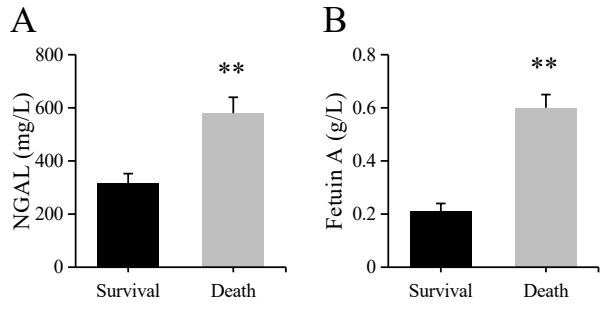

Figure 3. Comparison of serum NGAL and Fetuin-A levels in septic patients with different survival conditions. (A) NGAL level; (B) Fetuin-A level; (C) OASIS scale score; compared with the survival group, $^{**}P < 0.01$.

Table 2. Multivariate logistic regression analysis of 28-day death in patients with sepsis.

Variables	β	S.E.	Wald	P	OR	95% CI	
						Lower limit	Upper limit
PLT	-0.341	0.051	4.781	0.038	0.894	0.398	1.341
RBCV	-0.408	0.180	5.553	0.029	0.912	0.590	1.362
SCr	0.431	0.062	23.692	<0.001	1.126	0.781	1.719
Lac	0.553	0.041	25.118	<0.001	1.475	1.122	1.805
PCT	0.398	0.083	26.703	<0.001	1.892	1.307	2.216
D-dimer	0.509	0.060	24.164	<0.001	1.654	1.288	2.052
NLR	0.671	0.108	25.092	<0.001	1.341	1.031	1.708
APACHE II	0.440	0.095	22.267	<0.001	1.790	1.145	2.239
SOFA	0.569	0.057	23.141	<0.001	2.117	1.434	2.890
OASIS	0.247	0.069	24.558	<0.001	1.875	1.352	2.344
NGAL	0.533	0.074	27.890	<0.001	1.609	1.176	2.151
Fetuin-A	0.451	0.120	25.617	<0.001	2.141	1.403	2.892

1.228; 95% CI = 0.931 ~ 1.672), heart rate ≥ 92 beats/min (OR = 0.630; 95% CI = 0.226 ~ 1.028), SCr ≥ 408 μmol/L (OR = 1.291; 95% CI = 1.019 ~ 1.683), Lac ≥ 2.3 mmol/L (OR = 1.504; 95% CI = 1.182 ~ 1.895), PCT ≥ 30 ng/mL (OR = 2.151; 95% CI = 1.344 ~ 3.569), D-dimer ≥ 2.33 mg/L (OR = 1.518; 95% CI = 1.252 ~ 2.196), PLR ≥ 190 (OR = 0.906; 95% CI = 0.412 ~ 1.167), APACHE II ≥ 18 (OR = 1.747; 95% CI = 1.240 ~ 2.891), SOFA ≥ 2 (OR = 2.016; 95% CI = 1.448 ~ 3.093), OASIS ≥ 30 points (OR = 1.895; 95% CI = 1.451 ~ 2.337), NGAL ≥ 352 mg/L (OR = 1.760; 95% CI = 1.326 ~ 1.995), and Fetuin-A ≥ 0.32 g/L (OR = 2.179; 95% CI = 1.659 ~ 3.240) were risk factors for 28-day death in septic patients; WBC ≥ 12 × 10^9/L (OR = 0.489; 95% CI = 0.116 ~ 0.894), PLT ≥ 172 × 10^3/μL (OR = 0.671; 95% CI = 0.301 ~ 0.968), and RBCV ≥ 30% (OR = 0.652; 95% CI = 0.245 ~ 0.978) were protective factors for 28-day death in septic patients (Figure 4).

Efficacy evaluation of 28-day mortality risk prediction model in septic patients

ROCs were drawn to compare the efficacy of clinical indicators APACHE II, SOFA, OASIS, NGAL, Fetuin-A and risk prediction model logistic regression model, random forest model for 28-day death prediction in patients with sepsis, and the sensitivity, specificity, PPV, NPV, PLR' NLR', and AUC of the assessment indicators were calculated. Predicted AUCs for APACHE II, SOFA, OASIS, NGAL, Fetuin-A, NGAL & Fetuin-A, logistic regression model, and random forest model was found to be 0.80, 0.71, 0.77, 0.69, 0.86, 0.92, 0.83, and 0.81, respectively (Figure 5 and Figure 6).

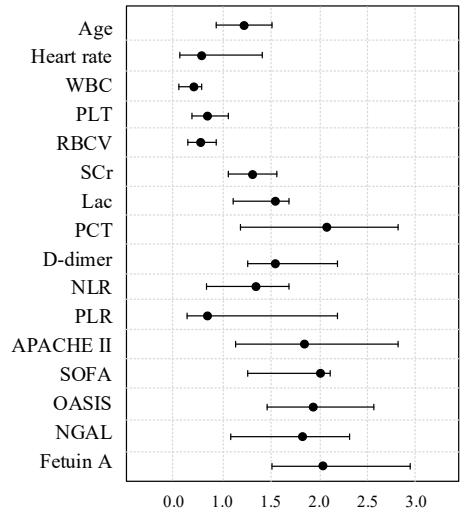

Figure 4. Random forest model analysis of risk factors of 28-day mortality in patients with sepsis.

Discussion

Sepsis is a disease caused by inflammatory dysregulation caused by infection, which can cause organ failure and has a high mortality rate in clinical practice, and is also the main cause of death in critically ill patients in the

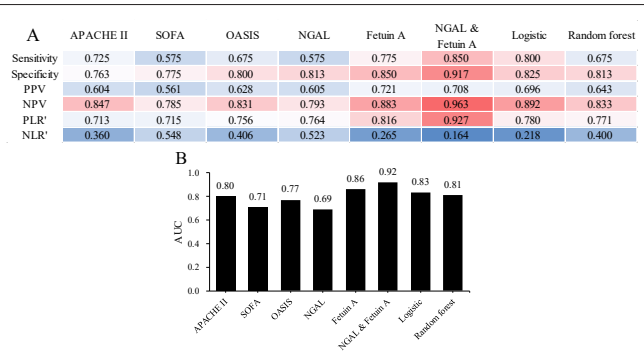

Figure 5. Predictive efficacy analysis of each index and model for 28-day death in patients with sepsis.

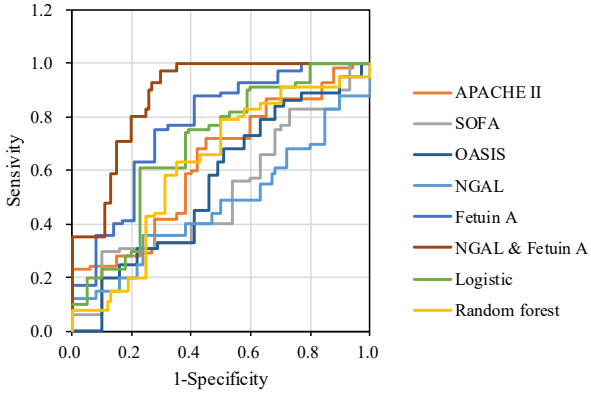

Figure 6. ROCs of each index and model for predicting 28-day death in patients with sepsis.

ICU (15). At present, the main clinical methods used for the treatment of sepsis are fluid resuscitation, antibacterial drugs, and respiratory support therapy (16). Studies have confirmed that PCT, CRP, SOFA score, and SIRS score are all prognostic factors in patients with sepsis (17). Disease severity score OASIS is a commonly used severe score system for ICU patients, which can be used for prognosis prediction of sepsis patients and evaluation system of disease severity (18). However, the pathogenesis of sepsis is very complex, and the efficacy of a single index for predicting the prognosis of sepsis patients is limited. Therefore, it is very important to find prognostic predictors with strong sensitivity, high specificity, and high accuracy for the clinical treatment of patients.

According to the 28-day survival of patients with sepsis, they were divided into a survival group and a death group, and the differences in the clinical data between the two groups were compared. The results showed that serum WBC, PLT, RBCV, and PLR levels were significantly decreased, while SCr, Lac, PCT, D-dimer, and NPR levels were significantly increased in patients with sepsis in the death group. Studies have confirmed that factors such as prolonged malnutrition and viral infection can lead to a decrease in WBC levels in the peripheral blood of patients (19). Decreased PLT increases the risk of bleeding in patients, and in severe cases, it can cause visceral bleeding or cerebral hemorrhage in patients, and even affect the patient's life (20). RBCV is the ratio of red blood cell volume to whole blood volume in peripheral blood, and anemia triggers a decrease in RBCV (21). SCr is an important indicator for assessing renal function in patients, and normal SCr levels in adults are within 30 to 106 μmol/L, and exceeding normal values can be regarded as renal insufficiency (22). Increased levels of Lac may be due to impaired clearance mechanisms leading to the retention of acidic metabolites in the body, indicating infectious disease or acidosis (23). PCT is an indicator used to assess the degree of systemic inflammatory response. Patients with elevated PCT expression have a significant infection, which has been widely used in the evaluation of sepsis and multiple organ failure (24). D-dimer is a product generated after fibrinolysis in the body, and elevated D-dimer indicates thrombosis and lysis in the patient' body, while sepsis can affect the coagulation system to some extent, which in turn leads to systemic disseminated intravascular coagulation (25). PLT, RBCV, SCr, Lac, PCT, D-dimer, NLR, APACHE II, SOFA, and OASIS were independent risk factors or protective factors affecting 28-day mortality in septic patients.

NGAL is a multifunctional protein, which is mainly secreted by activated neutrophils and released into the blood due to a patient body infection, so it can be used as an indicator for the assessment of acute infection (26). Under normal physiological conditions, NGAL showed a tendency for low expression in neutrophils and organ epithelial cells (27). It has been confirmed that NGAL is involved in cell differentiation and apoptosis, inflammatory response, immune response, and lipid metabolism (28). Chang et al. (2018) (29) evaluated the efficacy of serum NGAL in predicting 28-day mortality in patients with severe sepsis and found that serum NGAL levels were increased in patients with sepsis who died, and its AUC for 28-day mortality prediction in patients with sepsis was 0.752, which was superior to creatinine levels. This is consistent with the finding that serum NGAL levels were higher in septic patients who died than in surviving patients. Fetuin-A is a liver-synthesized glycoprotein that inhibits calcium and phosphorus deposition in the body (30). Karampela and Dalamaga (2021) (31) confirmed that septic liver dysfunction was associated with a decrease in Fetuin-A levels, and the serum bilirubin/Fetuin-A ratio was increased in patients who died of sepsis, which can be used to predict the prognosis of septic patients. This is similar to the finding that serum levels of Fetuin-A were higher in patients who died of sepsis than in surviving patients. In addition, NGAL and Fetuin-A were shown to be risk factors for 28-day mortality in patients with sepsis, and the predictive efficacy of NGAL combined with Fetuin-A was better than that of NGAL alone and Fetuin-A alone, indicating that NGAL and Fetuin-A can be used as biological markers for predicting the prognosis of sepsis.

Logistic regression and random forest prediction models for 28-day mortality risk in sepsis patients were constructed, and it was found that the prediction accuracy and stability of the logistic regression model and random forest model were similar. The multivariate logistic regression model was used to predict PLT and RBCV as independent protective factors for 28-day death in patients with sepsis, while SCr, Lac, PCT, D-dimer, NLR, APACHE II, SOFA, OASIS, NGAL, and Fetuin-A were independent risk factors. Random forest prediction showed that age ≥ 70 years, heart rate ≥ 92 beats/min, SCr ≥ 408 μmol/L, Lac ≥ 2.3 mmol/L, PCT ≥ 30 ng/mL, D-dimer ≥ 2.33 mg/L, PLR ≥ 190, APACHE II ≥ 18 points, SOFA ≥ 2 points, OASIS ≥ 30 points, NGAL ≥ 352 mg/L, and Fetuin-A ≥ 0.32 g/L were risk factors for 28-day death in septic patients, while WBC ≥ 12 × 10^9/L, PLT ≥ 172 × 10^3/μL, and RBCV ≥ 30% were protective factors for 28-day death in septic patients. Random forest prediction model analysis obtained more indicators than the logistic regression model because the random forest model has the ability of high-dimensional data processing, which can apply various predictor variables to improve the accuracy (32).

Conclusion

The efficacy of the 28-day mortality risk prediction model in sepsis patients was evaluated, and it was found that serum NGAL and Fetuin-A could be used as 28-day mortality predictors in sepsis patients, and NGAL combined with Fetuin-A had better predictive efficacy. However, only the clinical data of 120 patients with sepsis were included to construct a 28-day mortality risk prediction model. Because the included sample size is limited, the sensitivity and specificity of constructing a prediction model need to be improved. In conclusion, the results can lay a foundation for improving the prognostic predictive efficacy of sepsis patients.

References

1. Purcarea A, Sovaila S. Sepsis, a 2020 review for the internist. Rom J Intern Med 2020; 58 (3):129-137.
2. Ni J, He J, Kang L, Zhong Z, Wang L, Yin S. Effects of dexmedetomidine pretreatment on rats with sepsis-induced acute kidney injury and miR-146a expression. Cell Mol Biol (Noisy-le-grand) 2020; 66 (2):93-98.
3. Hecker A, Reichert M, Reuß CJ, Schmoch T, Riedel JG, Schneck E, Padberg W, Weigand MA, Hecker M. Intra-abdominal sepsis:

new definitions and current clinical standards. Langenbecks Arch Surg 2019; 404 (3): 257-271.
4. Hilarius KWE, Skippen PW, Kissoon N. Early Recognition and Emergency Treatment of Sepsis and Septic Shock in Children. Pediatr Emerg Care 2020; 36 (2): 101-106.
5. Matics TJ, Sanchez-Pinto LN. Adaptation and Validation of a Pediatric Sequential Organ Failure Assessment Score and Evaluation of the Sepsis-3 Definitions in Critically Ill Children. JAMA Pediatr 2017; 171 (10): e172352.
6. Asai N, Ohashi W, Sakanashi D, Suematsu H, Kato H, Hagihara M, Watanabe H, Shiota A, Koizumi Y, Yamagishi Y, Mikamo H. Combination of Sequential Organ Failure Assessment (SOFA) score and Charlson Comorbidity Index (CCI) could predict the severity and prognosis of candidemia more accurately than the Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) score. BMC Infect Dis 2021; 21 (1): 77.
7. Albert C, Zapf A, Haase M, Röver C, Pickering JW, Albert A, Bellomo R, Breidthardt T, Camou F, Chen Z, Chocron S, Cruz D, de Geus HRH, Devarajan P, Di Somma S, Doi K, Endre ZH, Garcia-Alvarez M, Hjortrup PB, Hur M, Karaolanis G, Kavalci C, Kim H, Lentini P, Liebetrau C, Lipcsey M, Mårtensson J, Müller C, Nanas S, Nickolas TL, Pipili C, Ronco C, Rosa-Diez GJ, Ralib A, Soto K, Braun-Dullaeus RC, Heinz J, Haase-Fielitz A. Neutrophil Gelatinase-Associated Lipocalin Measured on Clinical Laboratory Platforms for the Prediction of Acute Kidney Injury and the Associated Need for Dialysis Therapy: A Systematic Review and Meta-analysis. Am J Kidney Dis 2020; 76 (6): 826-841.e1.
8. Al-Ayadhi LY, Alghamdi FA, Altamimi LA, Alsughayer LY, Alhowikan AM, Halepoto DM. The possible link between Fetuin-A Protein and Neuro-inflammation in Children with Autism Spectrum Disorder. Pak J Med Sci 2021; 37 (4): 1166-1171.
9. Hwang JS, Kim KH, Park J, Kim SM, Cho H, Lee Y, Han IO. Glucosamine improves survival in a mouse model of sepsis and attenuates sepsis-induced lung injury and inflammation. J Biol Chem 2019; 294 (2): 608-622.
10. Zhou X, Li Y, Liang W. CNN-RNN Based Intelligent Recommendation for Online Medical Pre-Diagnosis Support. IEEE/ACM Trans Comput Biol Bioinform 2021; 18 (3): 912-921.
11. Fleuren LM, Klausch TLT, Zwager CL, Schoonmade LJ, Guo T, Roggeveen LF, Swart EL, Girbes ARJ, Thoral P, Ercole A, Hoogendoorn M, Elbers PWG. Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy. Intensive Care Med 2020; 46 (3): 383-400.
12. Bahtouee M, Eghbali SS, Maleki N, Rastgou V, Motamed N. Acute Physiology and Chronic Health Evaluation II score for the assessment of mortality prediction in the intensive care unit: a single-centre study from Iran. Nurs Crit Care 2019; 24 (6): 375-380.
13. Fernando SM, Tran A, Taljaard M, Cheng W, Rochwerg B, Seely AJE, Perry JJ. Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection: A Systematic Review and Meta-analysis. Ann Intern Med 2018; 168 (4): 266-275.
14. Chen Q, Zhang L, Ge S, He W, Zeng M. Prognosis predictive value of the Oxford Acute Severity of Illness Score for sepsis: a retrospective cohort study. PeerJ 2019; 7: e7083.
15. Mei B, Li J, Zuo Z. Dexmedetomidine attenuates sepsis-associated inflammation and encephalopathy via central α2A adrenoceptor. Brain Behav Immun 2021; 91: 296-314.
16. Haak BW, Prescott HC, Wiersinga WJ. Therapeutic Potential of the Gut Microbiota in the Prevention and Treatment of Sepsis. Front Immunol 2018; 9: 2042.
17. Qu Z, Zhu Y, Wang M, Li W, Zhu B, Jiang L, Xi X. Prognosis and Risk Factors of Sepsis Patients in Chinese ICUs: A Retrospective Analysis of a Cohort Database. Shock 2021; 56 (6): 921-926.
18. Bowles KH, Murtaugh CM, Jordan L, Barrón Y, Mikkelsen ME, Whitehouse CR, Chase JD, Ryvicker M, Feldman PH. Sepsis Survivors Transitioned to Home Health Care: Characteristics and Early Readmission Risk Factors. J Am Med Dir Assoc 2020; 21 (1): 84-90.e2.
19. Crouser ED, Parrillo JE, Seymour C, Angus DC, Bicking K, Tejidor L, Magari R, Careaga D, Williams J, Closser DR, Samoszuk M, Herren L, Robart E, Chaves F. Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker. Chest 2017; 152 (3): 518-526.
20. Li X, Li T, Wang J, Feng Y, Ren C, Xu Z, Yang J, Zhang Q, An C. Clinical Value of C-Reactive Protein/Platelet Ratio in Neonatal Sepsis: A Cross-Sectional Study. J Inflamm Res 2021; 14: 5123-5129.
21. Wang Z, Zhang L, Li S, Xu F, Han D, Wang H, Huang T, Yin H, Lyu J. The relationship between hematocrit and serum albumin levels difference and mortality in elderly sepsis patients in intensive care units-a retrospective study based on two large database. BMC Infect Dis 2022; 22 (1): 629.
22. Wang Y, Zhang H, Tang X, Li X. A retrospective study on risk factors for prognosis of children with sepsis. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2020; 32 (6): 707-710.
23. Ma H, Liu H, Wu C, Huang L. Diagnostic Value of Serum Heparin Binding Protein, Blood Lactic Acid Combined with hs-CRP in Sepsis and Its Relationship with Prognosis. Evid Based Complement Alternat Med 2021; 2021: 5023733.
24. Kyriazopoulou E, Liaskou-Antoniou L, Adamis G, Panagaki A, Melachroinopoulos N, Drakou E, Marousis K, Chrysos G, Spyrou A, Alexiou N, Symbardi S, Alexiou Z, Lagou S, Kolonia V, Gkavogianni T, Kyprianou M, Anagnostopoulos I, Poulakou G, Lada M, Makina A, Roulia E, Koupetori M, Apostolopoulos V, Petrou D, Nitsotolis T, Antoniadou A, Giamarellos-Bourboulis EJ. Procalcitonin to Reduce Long-Term Infection-associated Adverse Events in Sepsis. A Randomized Trial. Am J Respir Crit Care Med 2021; 203 (2): 202-210.
25. Lorusso F, Inchingolo F, Scarano A. The Impact of Covid-19 on the Scientific Production Spread: A Five-Month Biblio-Metric Report of the Worldwide Research Community. Acta Medica Mediterranea 2020; 3357-3360.
26. Crescenzi E, Leonardi A, Pacifico F. NGAL as a Potential Target in Tumor Microenvironment. Int J Mol Sci 2021; 22 (22): 12333.
27. Latoch E, Konończuk K, Taranta-Janusz K, Muszyńska-Rosłan K, Szymczak E, Wasilewska A, Krawczuk-Rybak M. Urine NGAL and KIM-1: tubular injury markers in acute lymphoblastic leukemia survivors. Cancer Chemother Pharmacol 2020; 86 (6): 741-749.
28. Lee SA, Noel S, Kurzhagen JT, Sadasivam M, Pierorazio PM, Arend LJ, Hamad AR, Rabb H. $CD4^+$ T Cell-Derived NGAL Modifies the Outcome of Ischemic Acute Kidney Injury. J Immunol 2020; 204 (3): 586-595.
29. Chang W, Zhu S, Pan C, Xie JF, Liu SQ, Qiu HB, Yang Y. Predictive utilities of neutrophil gelatinase-associated lipocalin (NGAL) in severe sepsis. Clin Chim Acta 2018; 481: 200-206.
30. Fajol A. Fetuin-A, fibroblast growth factor 23 and inflammation in critically ill patients with sepsis. Metabol Open 2021; 12:100129.
31. Karampela I, Dalamaga M. Serum bilirubin to fetuin-A ratio as a prognostic biomarker in critically ill patients with sepsis. Metabol Open 2021; 10:100094.
32. Wan Z, Dong Y, Yu Z, Lv H, Lv Z. Semi-Supervised Support Vector Machine for Digital Twins Based Brain Image Fusion. Front Neurosci 2021; 15: 705323.