Prediction of prognosis in sepsis patients by the SOFA score combined with miR-150

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Abstract

Background. The sequential organ failure assessment (SOFA) score, designed to evaluate sepsis-associated organ dysfunction in intensive care unit (ICU) patients, is associated with the prognosis of sepsis patients. MicroRNA-150 (miR-150) is one of the first miRs to be detected in patients with sepsis and other critical illnesses, and to have an association with the prognosis of critical illness and sepsis.

Objectives. To assess the predictive value of the combination of the SOFA score and miR-150 levels for the prognosis of sepsis patients.

Materials and methods. We retrospectively included 437 adult patients with sepsis who were divided into a death group (n = 138, 31.6%) and a survival group (n = 299, 68.4%), according to their survival status at the 28-day follow-up. Binary logistic regression was performed to identify independent associations. Receiver operator characteristic (ROC) curve was employed to assess the predictive values. The Z-test was used to compare the area under curve (AUC).

Results. Multivariate analysis demonstrated that miR-150 (odds ratio (OR): 0.549, 95% confidence interval (95% CI) [0.372, 0.826], $p < 0.001$), the SOFA score (OR: 1.216, 95% CI [1.039, 1.807], $p = 0.008$), age, procalcitonin (PCT), and septic shock were independently associated with 28-day mortality of sepsis patients following the adjustment for chronic renal failure, hypertension, diabetes mellitus, activated partial thromboplastin time (APTT), serum creatinine (SCr), blood urea nitrogen (BUN), and total bilirubin (TBil). The AUC of miR-150, the SOFA score and their combination in predicting the 28-day mortality of sepsis patients was 0.762 (standard error (SE): 0.023, 95% CI [0.717, 0.808]), 0.735 (SE: 0.025, 95% CI [0.687, 0.784]) and 0.886 (SE: 0.015, 95% CI [0.857, 0.916]), respectively. The AUC of their combined prediction was significantly greater than the independent prediction (0.886 compared to 0.762, $Z = 4.516$, $p < 0.001$; 0.886 compared to 0.735, $Z = 5.179$, $p < 0.001$). The sensitivity and specificity of combination prediction were 86.2% and 80.6%, respectively.

Conclusions. The combination of the SOFA score and miR-150 could improve the prediction of prognosis in sepsis patients.

Key words: prognosis, sepsis, prediction, sequential organ failure assessment score, miR-150

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Background

Sepsis, defined as a life-threatening organ dysfunction, is induced by an altered systemic host response to infection.[1] It is the major cause of intensive care unit (ICU) admission and is correlated with concurrent multiple organ dysfunction syndrome.[2,3] Sepsis and subsequent multiple organ failure account for a large portion of morbidity and mortality in ICU patients.[4,5] In spite of advances in sepsis awareness and management, it still has a high mortality rate.[6,7] Thus, it is critical to precisely evaluate the prognosis of patients with sepsis.

The pathogenesis of sepsis is complex, and a variety of different factors may affect its prognosis. The sequential organ failure assessment (SOFA) score, designed to evaluate sepsis-associated organ dysfunction in ICU patients,[8] is associated with the prognosis of sepsis patients.[9] However, this scoring system does not include any factors associated with pathophysiology of sepsis itself, and only assesses relevant clinical parameters. Established biomarkers for sepsis patients mainly included procalcitonin (PCT), C-reactive protein (CRP) and interleukin-6 (IL-6), but they are nonspecific and have a limited diagnostic value. Considerable efforts have been made to identify new biomarkers in the context of sepsis. Recently, microRNAs (miRs) have received extensive attention in sepsis research. The miRs play a crucial role in both, innate and adaptive immunity in pathological disorders, such as bacterial infection, atherosclerosis, diabetes, and rheumatoid arthritis.[10] Many miRs regulate proinflammatory processes in sepsis through the direct targeting of the tumor necrosis factor (TNF) signaling pathway. In addition, miRs can modulate the expressions of sepsis-related genes, such as TNF and IL-6, 2 genes which can themselves regulate the expression of certain miRs, demonstrating their deep involvement in the pathogenesis of sepsis. The miR-150 is one of the first to be detected in patients with sepsis and critical illness. It has previously been confirmed that miR-150 is associated with the prognosis of critical illness and sepsis.[11]

Objectives

Herein, we investigated whether a combination of the SOFA score and miR-150 could predict the prognosis of sepsis patients.

Materials and methods

Patients

A total of 487 adult patients with sepsis who were admitted to the Department of Critical Care Medicine of Central Hospital of Jiangjin District (Chongqing, China) according to the Sepsis-3 classification criteria,[1] were retrospectively recruited between January 2018 and June 2020. All medical and nursing data were reviewed by the consulting physician, the components of the SOFA score for each system were collected and the SOFA score on day 1 following admission was computed. The patients were divided into the "death group" and "survival group", according to their survival status at the 28-day follow-up. This study conformed to the Declaration of Helsinki and was approved by the Ethical Committee of Central Hospital of Jiangjin District, Chongqing (approval No. JJ2018017036). Written informed consent was obtained from either patients or their legal guardians.

Inclusion and exclusion criteria

Study inclusion criteria consisted of: 1) meeting the Sepsis-3 classification criteria; 2) age ≥18 years and <90 years; and 3) completed medical and nursing data. Exclusion criteria included: 1) pulmonary embolism, acute myocardial infarction, cancer, trauma, and human immunodeficiency virus (HIV) infection; 2) breastfeeding or pregnancy; 3) recent major surgeries; and 4) patients lost to follow-up.

Detection of miR-150 expression levels using quantitative real-time polymerase chain reaction

Peripheral blood samples were collected prior to therapeutic interventions, centrifuged at 2000 g for 10 min and then stored at –70°C until the detection of miR-150. Total RNA was extracted with TRIzol (Invitrogen, Waltham, USA). The 1st strand of miR-150 was synthesized using 2 µg total RNA through the miRNA First Strand cDNA Synthesis Tailing Reaction Kit (Sangon Biotech, Shanghai, China). Quantitative real-time polymerase chain reaction (qRT-PCR) was conducted with a 7500 Real-Time PCR System (Applied Biosystems, Waltham, USA), using iQ SYBR® Green Supermix (Bio-Rad, Hercules, USA). The *U6* was used as a reference gene. The miR-150 expression levels were evaluated using the $2^{-\Delta\Delta Ct}$ method. The primers were synthesized by Sangon Biotech as follows: 5′-TCTCCCAACCCTTGTACCAGTG-3′ for miR-150 forward, 5′-GCAAATTCGTGAAGCGTTCCATA-3′ for *U6* forward and 5′-AACGAGACGACGACAGAC-3′ for the universal miR primer.

Statistical analyses

The normality of continuous variables was tested with the Kolmogorov–Smirnov test. Among them, the normally distributed variables were described using the mean ± standard deviation (SD) and compared for intergroup differences with Student's t test. Non-normally distributed variables were described using the median (M) and interquartile range (IQR), and they were compared for intergroup differences using a Mann–Whitney U test.

Categorical variables were described with number and percentage (%) and compared for intergroup differences with a χ^2 test. Then, binary logistic regression analysis was performed for two-sided variables, and $p < 0.10$ was used in univariate analysis to identify independent associations. Receiver operator characteristic (ROC) curve was employed to assess the values of the SOFA score, miR-150 and their combination in predicting 28-day mortality. The ROC curve of the combination of SOFA score and miR-150 was drawn using the probability derived from binary logistic regression analysis. The Z-test was used to compare the area under curve (AUC). The Youden index was computed to determine the optimal cutoff, providing the best sensitivity and specificity. Sensitivity, specificity, accuracy, false positive rate (FPR), false negative rate (FNR), positive predictive value (PPV), and negative predictive value (NPV) were also computed. Statistical analysis was performed with SPSS v. 17.0 (SPSS Inc., Chicago, USA), and statistical significance was set at $p < 0.05$ for two-sided variables.

Results

Univariate analysis

Among the 487 sepsis patients, 29 (5.9%) were excluded due to incomplete medical and nursing data, 16 (3.2%) were excluded due to other serious disease or recent major surgeries, and 5 (1%) were excluded due to being lost to follow-up. Therefore, 437 patients were included and divided into the death group (n = 138, 31.6%) and survival group (n = 299, 68.4%).

Univariate analysis (Table 1) demonstrated that the differences in age, chronic renal failure, hypertension, serum creatinine (SCr), activated partial thromboplastin time (APTT), PCT, septic shock, miR-150, and the SOFA score were statistically significant between the death group and the survival group ($p < 0.05$), and the differences in the remaining variables were not statistically significant. However, diabetes mellitus, blood urea nitrogen (BUN) and total bilirubin (TBil) had p-values of <0.10.

Multivariate analysis

Multivariate analysis was performed for the following variables: age, chronic renal failure, hypertension, SCr, APTT, PCT, septic shock, miR-150, the SOFA score, diabetes mellitus, BUN, and TBil (Table 2). These results demonstrated that miR-150 (odds ratio (OR) = 0.549, 95% confidence interval (95% CI) [0.372, 0.826], $p < 0.001$), the SOFA score (OR = 1.216, 95% CI [1.039, 1.807], $p = 0.008$), age, PCT, and septic shock were independently associated with the 28-day mortality of sepsis patients when the analysis is adjusted for chronic renal failure, hypertension, diabetes mellitus, APTT, SCr, BUN, and TBil.

Predictive value

The AUC of miR-150 (Fig. 1), the SOFA score and their combination (Fig. 2) in predicting 28-day mortality of sepsis patients was 0.762 (standard error (SE) = 0.023, 95% CI [0.717, 0.808]), 0.735 (SE = 0.025, 95% CI [0.687, 0.784]) and 0.886 (SE = 0.015, 95% CI [0.857, 0.916]), respectively. The AUC of miR-150 (Fig. 1) was consistent with that of 1/miR-150 (Fig. 2). The predictive power of the AUC together with the SOFA score was significantly greater than independent predictions (0.886 compared to 0.762, $Z = 4.516$, $p < 0.001$; 0.886 compared to 0.735, $Z = 5.179$, $p < 0.001$). Clinical utility indexes of miR-150, the SOFA score and their combination in predicting 28-day mortality of sepsis patients are demonstrated in Table 3. The AUC for combination prediction of the quick SOFA score plus miR-150 was 0.806 (SE = 0.022, 95% CI [0.763, 0.848]) (Fig. 3).

Discussion

The SOFA score, ranging from 0 to 24, is a well-known tool for evaluating patients with sepsis and septic shock. It collates the amount and severity of organ failures in 6 organs, including coagulative function, respiratory, cardiovascular, kidney, liver, and neurology systems. Higher scores are associated with higher probability of mortality. Vafaei et al. investigated the predictive values of the SOFA, Mortality in Emergency Department Sepsis (MEDS) and Predisposition, Infection, Response and Organ Dysfunction (PIRO) scores for 30-day mortality in sepsis patients.[12] Their results showed that the AUCs of the SOFA, MEDS and PIRO scores were 0.87, 0.94 and 0.83, respectively, and the MEDS score had the optimal performance in the prediction of 30-day mortality. Raith et al. found that an increase of 2 or more in the SOFA score had a higher prognostic accuracy for in-hospital mortality than the qSOFA score or the systemic inflammatory response syndrome (SIRS) criteria.[13] Liu et al. assessed the prognostic accuracy of the SOFA score, qSOFA score and lactate level on the mortality of sepsis patients through the public Medical Information Mart for Intensive Care III database (MIMIC III).[14] Their results showed that the AUCs of the SOFA score, qSOFA score and lactate level were 0.686, 0.664 and 0.547, respectively. Karakike et al. evaluated the performance of the early change of SOFA score in predicting 28-day mortality of sepsis patients.[9] Their results demonstrated that an early change of SOFA score was a more scalar, direct measurement tool for treatment effect of sepsis compared with traditional mortality endpoints. Iba et al. also demonstrated that the change of SOFA score was strongly associated with the 28-day sepsis mortality disseminated intravascular coagulation patients.[15] In our study, the AUC of the SOFA score for predicting 28-day mortality of sepsis patients was 0.735.

Table 1. Results of univariate analysis between death group and survival group

Variables	All patients (n = 437)	Death group (n = 138)	Survival group (n = 299)	χ^2/Z/t	p-value
Male, n (%)	273 (62.5%)	91 (65.9%)	182 (60.9%)	1.036	0.309
Age [years], mean ±SD	68.40 ±7.82	72.54 ±7.53	66.49 ±7.96	9.714	<0.001
Smoking, n (%)	191 (43.7%)	57 (41.3%)	134 (44.8%)	0.473	0.491
Drinking, n (%)	84 (19.2%)	23 (16.7%)	61 (20.4%)	0.848	0.357
BMI [kg/m^2], mean ±SD	23.82 ±5.64	23.52 ±5.75	23.96 ±5.59	–1.279	0.201
Comorbidities, n (%)					
Diabetes mellitus	121 (27.7%)	46 (33.3%)	75 (25.1%)	3.210	0.073
Chronic renal failure	100 (22.9%)	43 (31.2%)	57 (19.1%)	7.828	0.005
Hypertension	187 (42.8%)	69 (50.0%)	118 (39.5%)	4.281	0.038
COPD	45 (10.3%)	16 (11.6%)	29 (9.7%)	0.367	0.545
Chronic liver disease	29 (6.6%)	11 (8.0%)	18 (6.0%)	0.580	0.446
Chronic coronary disease	92 (21.1%)	31 (22.5%)	61 (20.4%)	0.242	0.623
Laboratory examinations					
WBC [×10^9/L], M (IQR)	11.53 (7.75)	10.74 (7.52)	11.82 (7.83)	–0.291	0.769
ALB [g/L], mean ±SD	29.70 ±5.08	29.52 ±4.03	29.78 ±5.56	–1.176	0.249
PLT [×10^9/L], M (IQR)	154.65 (116.72)	148.96 (104.87)	157.79 (122.35)	–0.174	0.875
LYM [×10^9/L], M (IQR)	1.08 (7.98)	1.02 (5.86)	1.11 (8.97)	–0.647	0.526
NEU [×10^9/L], M (IQR)	11.95 (11.26)	13.58 (11.47)	11.06 (11.15)	1.613	0.112
BUN [mmol/L], M (IQR)	9.02 (9.37)	11.17 (11.28)	7.98 (8.36)	1.814	0.069
TBil [µmol/L], M (IQR)	13.21 (9.98)	15.48 (10.77)	12.03 (9.62)	1.887	0.058
SCr [µmol/L], M (IQR)	86.91 (89.27)	108.81 (169.59)	75.89 (54.36)	2.485	0.019
APTT [s], M (IQR)	41.02 (11.87)	42.57 (17.96)	40.25 (8.78)	2.013	0.038
PT [s], M (IQR)	15.37 (2.79)	15.66 (2.52)	15.21 (2.93)	1.587	0.124
INR	1.23 (0.33)	1.28 (0.35)	1.21 (0.32)	1.136	0.143
PCT [µg/L], M (IQR)	1.21 (5.92)	3.08 (11.27)	0.32 (3.29)	3.479	<0.001
Site of infection, n (%)					
Abdominal/pelvic	103 (23.6%)	27 (19.6%)	76 (25.4%)	1.795	0.180
Respiratory	138 (31.6%)	46 (33.3%)	92 (30.8%)	0.287	0.592
Blood	49 (11.2%)	19 (13.8%)	30 (10.0%)	1.323	0.250
Urinary	69 (15.8%)	18 (13.0%)	51 (17.1%)	1.144	0.285
Skin and soft tissue	41 (9.4%)	15 (10.9%)	26 (8.7%)	0.525	0.469
Others	37 (8.5%)	13 (9.4%)	24 (8.0%)	0.237	0.627
Septic shock	219 (50.1%)	86 (62.3%)	133 (44.5%)	12.017	0.001
miR-150 (mean ±SD)	1.91 ±1.11	1.56 ±0.82	2.07 ±1.25	–22.573	<0.001
SOFA score (mean ±SD)	7.91 ±4.09	9.94 ±4.86	6.97 ±3.74	13.628	<0.001

SD – standard deviation; BMI – body mass index; COPD – chronic obstructive pulmonary disease; WBC – white blood cell; M – median; IQR – interquartile range; ALB – albumin; PLT – platelet count; LYM – lymphocyte count; NEU – neutrophils count; BUN – blood urea nitrogen; TBil – total bilirubin; SCr – serum creatinine; APTT – activated partial thromboplastin time; PT – prothrombin time; INR – international normalized ratio; PCT – procalcitonin; SOFA – sequential organ failure assessment; M – median; IQR – interquartile range.

Recent studies have shown that the combination of multiple biomarkers had a higher predictive value for 30-day mortality of sepsis patients compared to the SOFA score.[16,17] Moreover, when there is an additional set of biomarkers that can be added to the SOFA score, there were significant improvements in the prognostic accuracy for mortality of sepsis patients.[18] The miRs represent a new group of endogenous, small (from 19 to 23 nucleotides) RNA molecules that do not encode proteins, but regulate gene expression based on sequence complementarity principles.[19,20] Studies indicate that miRs occupy only about 1% of the human genome, but modulate up to 60% of all protein-coding genes.[21,22] Thus, miRs are considered a part of complicated regulatory networks in the gene expression of both, pathophysiological and physiological processes.

Table 2. Results of multivariate analysis between the death group and the survival group

Variables	β	SE	Wald χ^2	OR	95% CI	p-value
miR-150	–0.227	0.081	8.763	0.549	[0.372, 0.826]	<0.001
SOFA score	0.183	0.075	6.604	1.216	[1.039, 1.807]	0.008
Septic shock	0.312	0.119	5.718	2.153	[1.142, 4.219]	0.019
Age	0.135	0.068	4.237	1.194	[1.031, 1.463]	0.041
PCT	0.089	0.017	5.096	1.158	[1.022, 1.596]	0.032
Chronic renal failure	0.094	0.023	1.568	1.127	[0.904, 1.348]	0.208
Hypertension	–0.075	0.012	0.204	0.913	[0.857, 1.165]	0.645
Diabetes mellitus	0.101	0.020	2.538	1.148	[0.911, 1.438]	0.107
APTT	0.090	0.010	2.314	1.096	[0.897, 1.265]	0.132
SCr	0.116	0.021	3.409	1.152	[0.917, 1.494]	0.073
BUN	0.068	0.006	1.382	1.087	[0.826, 1.197]	0.254
TBil	0.073	0.009	1.494	1.089	[0.841, 1.206]	0.220

SE – standard error; OR – odds ratio; 95% CI – 95% confidence interval; SOFA – sequential organ failure assessment; PCT – procalcitonin; APTT – activated partial thromboplastin time; SCr – serum creatinine; BUN – blood urea nitrogen; TBil – total bilirubin.

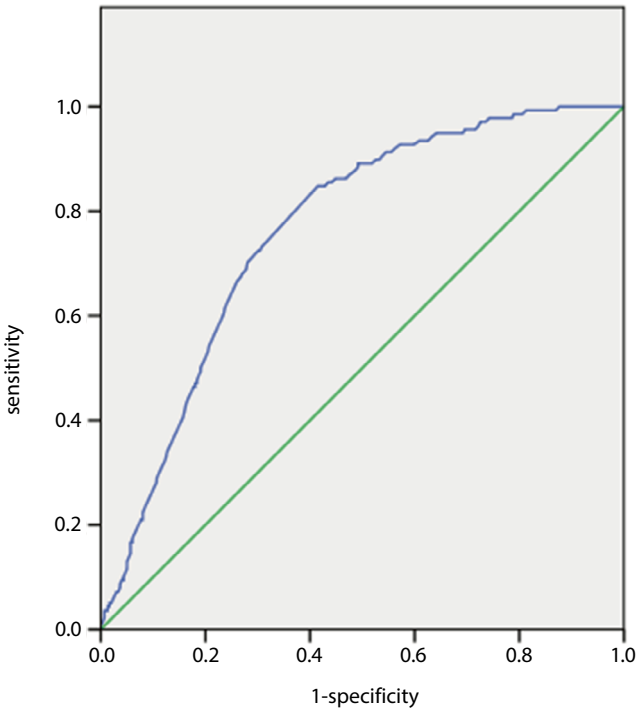

Fig. 1. Receiver operator characteristic (ROC) curve of miR-150 when predicting the 28-day mortality of sepsis patients

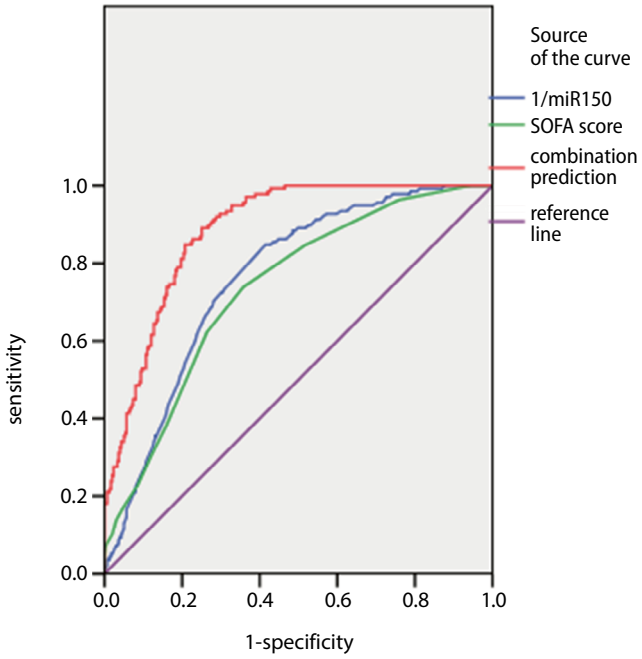

Fig. 2. Receiver operator characteristic (ROC) curves of 1/miR-150, sequential organ failure assessment (SOFA) score and combination of miR-150 and SOFA score in predicting the 28-day mortality of sepsis patients

Abnormal expression of miRs has been reported not only in highly modulated mechanisms such as cell death, aging and development,[23] but also in the initiation of complicated diseases such as sepsis, inflammation and infection,[24–27] partly because miRs can be detected in the blood and serve as biomarkers.[28–30] Circulating miRs are especially stable in the conditions that would generally degrade most of RNAs. Additionally, miRs are relatively small, generally possess a less complicated chemical structure and do not undergo post-processing modifications. Therefore, circulating miRs may be superior to other types of serum-based biomarkers.[31] The miR-150 belongs to part of a group of miRs including miR-155, miR-223, miR-181, and the miR-17-92 cluster.[32] The upregulation of miR-150 expression in B-cells can lead to decreased c-Myb levels and prevent the transition from pro-B to pre-B cells. At a functional level, the downregulation of miR-150 expression is detected in cell lines, as well as in primary leukocytes derived from human volunteers upon the lipopolysaccharides administration.[33] Accordingly, mice with miR-150 knockout showed significant changes in their responses to different inflammatory stimuli,[34] implying a deep involvement of miR-150 in the activation process of immune cells during sepsis and inflammation. Several reports have identified miR-150 as a constituent of miRs panels,

Table 3. Clinical utility indices of miR-150, the SOFA score and their combination in predicting 28-day mortality of sepsis patients

Predictors	AUC	SE	p-value	95% CI		Best cut-off	Sensitivity	Specificity	Accuracy	FPR	FNR	PPV	NPV	Youden index
				lower bound	upper bound									
miR-150	0.762	0.023	<0.001	0.717	0.808	1.78	76.8%	62.2%	66.8%	51.6%	14.7%	48.4%	85.3%	0.39
SOFA score	0.735	0.025	<0.001	0.687	0.784	8.85	75.4%	60.5%	65.2%	53.2%	15.8%	46.8%	84.2%	0.36
Combination of miR-150 and SOFA score	0.886	0.015	<0.001	0.857	0.916	N/A	86.2%	80.6%	82.4%	32.8%	7.3%	67.2%	92.7%	0.67

SOFA – sequential organ failure assessment; AUC – area under curve; SE – standard error; 95% CI – 95% confidence interval; FPR – false positive rate; FNR – false negative rate; PPV – positive predictive value; NPV – negative predictive value; N/A – not applicable.

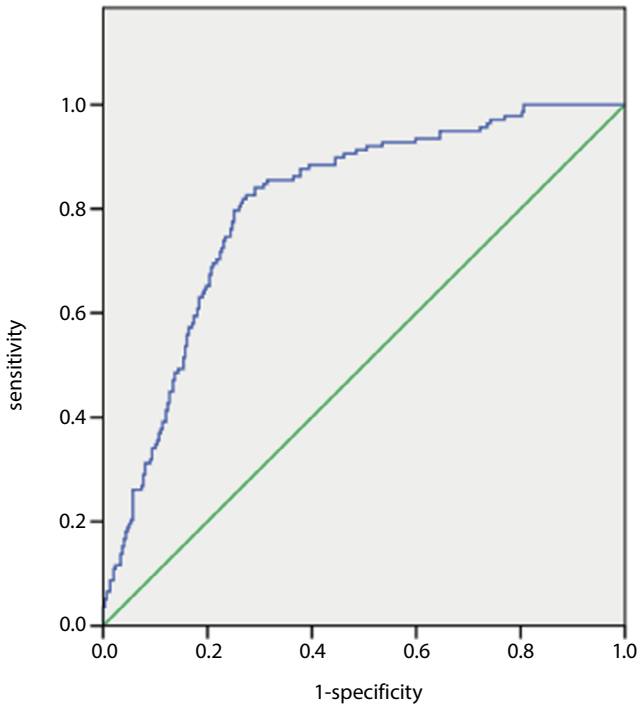

Fig. 3. Receiver operator characteristic (ROC) curve of the quick sequential organ failure assessment (SOFA) score plus miR-150 in predicting the 28-day mortality of sepsis patients

which are deregulated in peripheral blood mononuclear cells/leukocytes of sepsis patients compared with healthy controls through microarray-based gene expression analysis.[35–37] Vasilescu et al. demonstrated that miR-150 expression was significantly reduced in both plasma and leukocytes of patients with sepsis, which was associated with an elevated SOFA score, sepsis severity and elevated levels of proinflammatory cytokines.[35] Ma et al. found that miR-150 levels were lower in 2 independent cohorts of sepsis patients than in healthy controls or patients with noninfectious systemic inflammatory response syndrome (SIRS).[38] Roderburg et al. detected the levels of circulating miR-150 in healthy controls and a cohort of critically ill patients.[11] Their results demonstrated that miR-150 levels were decreased in patients with septic disease, but the difference was not statistically significant, suggesting that the potential of miR-150 levels was rather limited in differentiating between septic and non-septic disease. Nevertheless, they found a significant association between decreased miR-150 levels and impaired prognosis of patients with critical illness, implying that miR-150 was more suitable to be a prognostic indicator than a diagnostic indicator. In addition, Huang et al. demonstrated that miR-150 might be correlated with the pathogenesis of neonatal sepsis through targeting BCL-11B, based on the analysis of the expression profile data of E-MTAB-4785.[39]

In our study, miR-150 expression levels were lower in non-survivors than in survivors, and the AUC of miR-150 expression levels applied in predicting mortality was 0.762. The combination of the SOFA score and miR-150 expression levels had a higher predictive value than the SOFA score or miR-150 expression levels. The AUC was up to 0.886 with a sensitivity of 86.2% and specificity of 80.6%. In addition, we evaluated the predictive value of the quick SOFA score plus miR-150 for the 28-day mortality of sepsis patients, and the AUC was 0.806. The data lend themselves to be utilized as a possible predictive bedside test for sepsis patients in emergency departments.

Limitations

The limitations of this study mainly included a small sample size and a short follow-up time. Our next focus will be to evaluate the predictive value of the SOFA score combined with miR-150 for prognosis in sepsis patients on the basis of a large sample and a long follow-up time.

Conclusions

The combination of the SOFA score and miR-150 could improve the prediction of prognosis in sepsis patients.

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