Long non-coding RNA MALAT1 serves as an independent predictive biomarker for the diagnosis, severity and prognosis of patients with sepsis

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Abstract. The present prospective study was conducted to investigate the independent risk and predictive value of plasma long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) as a biomarker for the diagnosis, severity and prognosis of sepsis. A total of 120 patients with sepsis and 60 healthy controls (HCs) were recruited. The expression levels of plasma MALAT1 were detected by quantitative PCR. The results demonstrated that the plasma levels of MALAT1 were significantly increased in patients with sepsis compared with HCs (P<0.001), in patients with septic shock compared with in patients without septic shock (P<0.001), and in non-survivors compared with in survivors (P<0.001). MALAT1 plasma levels exhibited weak positive correlation with serum procalcitonin levels (r=0.253; P=0.005), arterial lactate levels (r=0.488; P<0.001), sepsis-related organ failure assessment scores (r=0.566; P<0.001), and acute physiology and chronic health evaluation II scores (r=0.517; P<0.001) in patients with sepsis. Multivariate logistic regression analysis revealed that high MALAT1 expression was an independent risk factor for sepsis (P<0.001), septic shock (P=0.030) and poor prognosis (P=0.015). In addition, the receiver operating characteristic curve exhibited a significant predictive value for MALAT1 in distinguishing patients with sepsis from HCs with an area under the curve (AUC) of 0.910, patients with septic shock from patients without shock with an AUC of 0.836, and non-survivors from survivors with an AUC of 0.886. In conclusion, plasma MALAT1 may serve as a biomarker for the diagnosis, severity and prognosis of sepsis.

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Introduction

Sepsis is defined as life-threatening organ dysfunction caused by an abnormal host response to infection, and septic shock is a subset of sepsis (1). Clinically, organ dysfunction can be represented by an increase in the sepsis-related organ failure assessment (SOFA) score of 2 points or more; septic shock can be identified by a vasopressor requirement to maintain mean arterial pressure ≥65 mmHg and a serum lactate level >2 mmol/l in the absence of hypovolemia (2). Sepsis has a high mortality rate and is one of the main causes of death in intensive care units (ICUs) worldwide (3). Despite recent progress in the development of anti-infective drugs and life support treatments, the mortality associated with sepsis, particularly septic shock, is still high (4). The pathogenesis of sepsis is complicated and has not yet been fully elucidated (5). The major pathophysiological mechanisms underlying sepsis include systemic inflammation, immune imbalance, multiple organ dysfunction and gene polymorphism (6). Early diagnosis and intervention are the most effective methods to reduce the mortality rates of patients with sepsis (7). The severity and prognosis of sepsis are determined by procalcitonin (PCT) and lactate (Lac) levels, SOFA (2), and acute physiology and chronic health evaluation II (APACHE II) (8). However, there is still a lack of precise biomarkers and intervention targets for sepsis.

Advances in human genome-wide analysis have revealed that ~2% of the genome is composed of protein-coding genes, whereas the remaining 98% of genome transcripts serve no protein-coding functions (9). Long non-coding RNAs (lncRNAs) are a class of non-protein-coding RNAs with a length of >200 nucleotides that are widely involved in cell proliferation, differentiation and apoptosis through regulating target gene expression (10). The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) was first identified in non-small cell lung cancer (11) and is among the most studied lncRNAs (12). MALAT1 is involved in a variety of physiological and pathological processes,

including neurodevelopment (13), skeletal myogenesis (14), angiogenesis (15), cancer (16), and cardiovascular (17) and neurological (18) diseases. Recent studies have reported that MALAT1 is also associated with infection and immune-mediated inflammatory diseases, such as sepsis (19), systemic lupus erythematosus (20), multiple sclerosis (21) and rheumatoid arthritis (22), by regulating the inflammatory response through multiple target genes and signaling pathways. However, the clinical value of MALAT1 in the diagnosis, severity and prognosis of sepsis has not been reported. Therefore, the aim of the present study was to determine the expression levels of plasma MALAT1 in patients with sepsis and to evaluate whether MALAT1 may serve as an independent predictive biomarker for patients with sepsis.

Materials and methods

Participants. A total of 120 patients with sepsis were admitted to the ICU of The First People's Hospital of Yancheng between June 2016 and June 2018, and were consecutively recruited for this prospective cohort study. The management of sepsis and septic shock was performed in accordance with the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (1). The inclusion criteria for the present study were as follows: i) Patients who met the aforementioned diagnostic criteria for sepsis and/or septic shock; ii) patients aged between 18 and 80 years; and iii) the primary causes of sepsis and septic shock were pulmonary infection, abdominal infection, urinary tract infection and/or bacteremia. Patients <18 or >80 years, pregnant and/or lactating patients, those with tumors, blood disease, organ dysfunction and immune-mediated inflammatory disease were excluded. During the same period, 60 healthy volunteers with matching age and sex were recruited as healthy controls (HCs). The inclusion criteria were as follows: i) Subjects aged between 18 and 80 years; and ii) subjects with good physical and mental health. HCs with a history of immune-mediated inflammatory disease, severe infection, organ dysfunction, cancer, or immunosuppressive therapy were excluded. HCs who were pregnant and/or lactating at the time of recruitment were also excluded.

This study was approved by the Ethics Committee of The First People's Hospital of Yancheng and complied with the ethics standards of the Declaration of Helsinki. All participants or their statutory guardians provided written informed consent.

Study design. Firstly, the expression levels of MALAT1 in plasma samples from HCs and patients with sepsis were analyzed and compared between patients with sepsis and HCs, patients with and without septic shock, as well as survivors and non-survivors. Subsequently, the correlation between MALAT1 expression levels and conventional evaluation indicators of sepsis, including PCT and Lac levels, as well as SOFA and APACHE II scores, was evaluated. Multivariate logistic regression was used to analyze whether MALAT1 may serve as an independent risk factor for the diagnosis, severity and prognosis of sepsis. Finally, the predictive values of MALAT1 in distinguishing patients with sepsis from HCs, patients with septic shock from those without septic shock, and non-survivors from survivors were evaluated.

Blood sample preparation. The blood samples of all subjects were collected within 24 h of admission. Elbow venous blood (10 ml/subject) was divided into two parts: One (5 ml) was collected into a vacutainer tube containing EDTA (Becton, Dickinson and Company) for plasma separation; the other part (5 ml) was collected into a vacutainer tube containing clot activator and polymer gel (Becton, Dickinson and Company) for serum separation. To obtain plasma/serum, the whole blood was centrifuged at 2,500 x g for 15 min at 4˚C. All samples were stored at -80˚C until further processing.

Data collection. The clinical data of patients with sepsis were collected within 24 h following admission, and included age, sex, serum PCT levels, arterial Lac levels, SOFA and APACHE II scores. Patients were assessed by a senior physician for sepsis severity (septic shock or no shock). The prognosis of patients with sepsis for 28 days following admission (survival or non-survival) was also recorded. Age, sex and PCT levels were recorded in HCs. The serum PCT levels were detected by chemiluminescent immunoassay (Wuhan EasyDiagnosis Biomedicine Co., Ltd.; cat. no. ED75440-Hu) according to the manufacturer's protocol. Lac levels were detected by arterial blood gas analysis.

Reverse transcription-quantitative PCR (RT-qPCR). Total RNA was extracted from isolated plasma using TRIzol® reagent (Invitrogen; Thermo Fisher Scientific, Inc.) and was reverse transcribed into cDNA using the PrimeScript™ RT reagent kit (Takara Bio, Inc.), according to the manufacturer's protocol. Subsequently, the expression levels of MALAT1 were determined using SYBR Premix Ex Taq™ II (Takara Bio, Inc.) on the ABI Prism 7300 RT-qPCR system (Applied Biosystems; Thermo Fisher Scientific, Inc.). PCR was performed under the following conditions: Denaturation at 50˚C for 2 min, followed by 40 cycles of 95˚C for 15 sec and 60˚C for 1 min. The relative expression levels of MALAT1 were calculated using the $2^{-\Delta\Delta Cq}$ method (23) and GAPDH was used as internal reference. The primer sequences used were as follows: MALAT1, forward 5'-GTGATGCGAGTTGTTCTCCG-3' reverse 5'-CTGGCT GCCTCAATGCCTAC-3'; and GAPDH, forward 5'-GAGTCA ACGGATTTGGTCGT-3' and reverse 5'-TTGATTTTGGAG GGATCTCG-3'.

Statistical analysis. Data are expressed as the mean ± standard deviation, median and interquartile range or count. PASW Statistics 18.0 (SPSS Inc.) and GraphPad Prism 8.0 (GraphPad Software, Inc.) were used for statistical analysis. The comparisons between two groups were performed using unpaired Student's t-test, Mann-Whitney test or χ^2 test as appropriate. Spearman's correlation was used to analyze the correlation between plasma MALAT1 and PCT, Lac, SOFA and APACHE II scores. Multivariate logistic regression and receiver operating characteristic (ROC) curve analyses were performed to determine the predictive value of independent risk factors for the diagnosis, severity and prognosis of sepsis. Risk factors with $P<0.15$ from the univariate analyses (Student's t-test, Mann-Whitney test and χ^2 test) were included in the multivariate logistic regression analysis. $P<0.05$ was considered to indicate a statistically significant difference.

Table I. Univariate analysis of clinicopathological characteristics between HCs and patients with sepsis.

Factor	HCs (n=60)	Sepsis (n=120)	P-value
Age, years	47.68±10.25	50.35±8.47	0.085[a]
Sex, n			0.082[b]
Male	36	54	
Female	24	66	
PCT, ng/ml	0.30 (0.14-0.40)	5.65 (0.68-12.28)	<0.001[c]
Lac, mmol/l	-	3.39 (2.22-5.83)	-
SOFA score	-	7.38±3.89	-
APACHE II score	-	15.21±4.69	-

[a]Student's t-test; [b]χ^2 test; [c]Mann-Whitney test. Data are presented as the mean ± standard deviation, median and interquartile range or count. APACHE II, acute physiology and chronic health evaluation II; HCs, healthy controls; Lac, lactate; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

Results

MALAT1 as an independent risk factor for sepsis. Univariate analysis revealed that age (P=0.085) and sex (P=0.082) were not significantly different between patients with sepsis and HCs (Table I). However, PCT (P<0.001) and MALAT1 (P<0.001) levels were significantly higher in patients with sepsis compared with those in HCs (Fig. 1A). In addition, multivariate logistic regression analysis revealed that high MALAT1 expression (P<0.001) and PCT (P=0.007) levels were independent predictive factors for sepsis risk, whereas, age (P=0.161) and sex (P=0.084) exhibited no association with sepsis risk (Table II).

Table II. Multivariate logistic regression of risk factors for sepsis.

Factor	P-value	OR	95% CI
Age	0.161	1.050	0.981-1.123
Sex (male vs. female)	0.084	3.009	0.861-10.514
MALAT1	<0.001	7.446	3.259-17.012
PCT	0.007	12.233	1.960-76.353

CI, confidence interval; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; OR, odds ratio; PCT, procalcitonin.

Diagnostic value of MALAT1 for sepsis. ROC curve analysis revealed that MALAT1 had significant diagnostic value for sepsis with an area under curve (AUC) of 0.910 (Fig. 1B); however, the diagnostic value of MALAT1 was lower compared with that of PCT (AUC=0.928; Fig. 1C). The optimal cut-off point for the level of MALAT1 that distinguished patients with sepsis from HCs was >1.895, and the specificity and sensitivity were 85 and 83.33%, respectively. In addition, the optimal cut-off point for PCT level that distinguished patients with sepsis from HCs was <0.5, and the specificity and sensitivity were 93.33 and 81.67%, respectively.

Correlation between plasma MALAT1 levels and conventional evaluation indicators of sepsis. Spearman's correlation analysis revealed that MALAT1 plasma levels exhibited weak positive correlations with PCT levels (r=0.253; P=0.005), Lac levels (r=0.488; P<0.001), SOFA scores (r=0.566; P<0.001) and APACHE II scores (r=0.517; P<0.001) in patients with sepsis (Fig. 2).

MALAT1 is an independent risk factor for septic shock. As presented in Table III, univariate analysis revealed that age (P=0.124), sex (P=0.912) and PCT level (P=0.257) were not significantly associated with the occurrence of septic shock. However, Lac levels (P<0.001), SOFA scores (P<0.001), APACHE II scores (P<0.001) and MALAT1 levels (P<0.001; Fig. 3A) were significantly higher in patients with septic shock compared with in those without septic shock. In addition, multivariate logistic regression analysis demonstrated that high MALAT1 (P=0.030) or Lac (P=0.027) levels, and SOFA (P=0.001) and APACHE II (P=0.011) scores were independent risk factors for septic shock, whereas age (P=0.368) exhibited no association with the severity of sepsis (Table IV).

Diagnostic value of MALAT1 level for septic shock. ROC curve analysis exhibited significant predictive value for MALAT1 (AUC=0.836) in distinguishing patients with septic shock from those without septic shock (Fig. 3B). This value was higher compared with that for Lac (AUC=0.830; Fig. 3C), but lower compared with those for SOFA (AUC=0.908; Fig. 3D) and APACHE II (AUC=0.856; Fig. 3E) scores. At the optimal cut-off point of >3.665 for MALAT1 levels, the specificity and sensitivity were 92.42 and 70.37%, respectively. At the optimal cut-off point of >3.215 for Lac levels, the specificity and sensitivity were 74.24 and 81.48%, respectively. At the optimal cut-off point of >6 for SOFA scores, the specificity and sensitivity were 83.33 and 87.04%, respectively. At the optimal cut-off point of >13 for APACHE II scores, the specificity and sensitivity were 71.21 and 87.04%, respectively.

MALAT1 is an independent risk factor for poor prognosis of sepsis. As presented in Table V, univariate analysis revealed that age (P=0.496) and sex (P=0.939) were not significantly different between survivors and non-survivors. However, septic

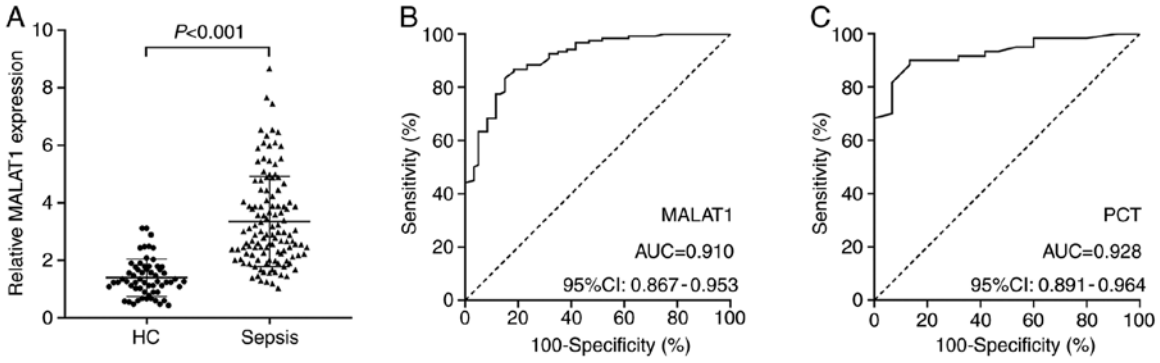

Figure 1. Relative expression and predictive value of MALAT1 plasma levels in distinguishing patients with sepsis from HCs. (A) Plasma MALAT1 expression was significantly increased in patients with sepsis compared with HCs. (B and C) Receiver operating characteristic curves for (B) MALAT1 and (C) PCT levels. CI, confidence interval; HC, healthy control; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PCT, procalcitonin.

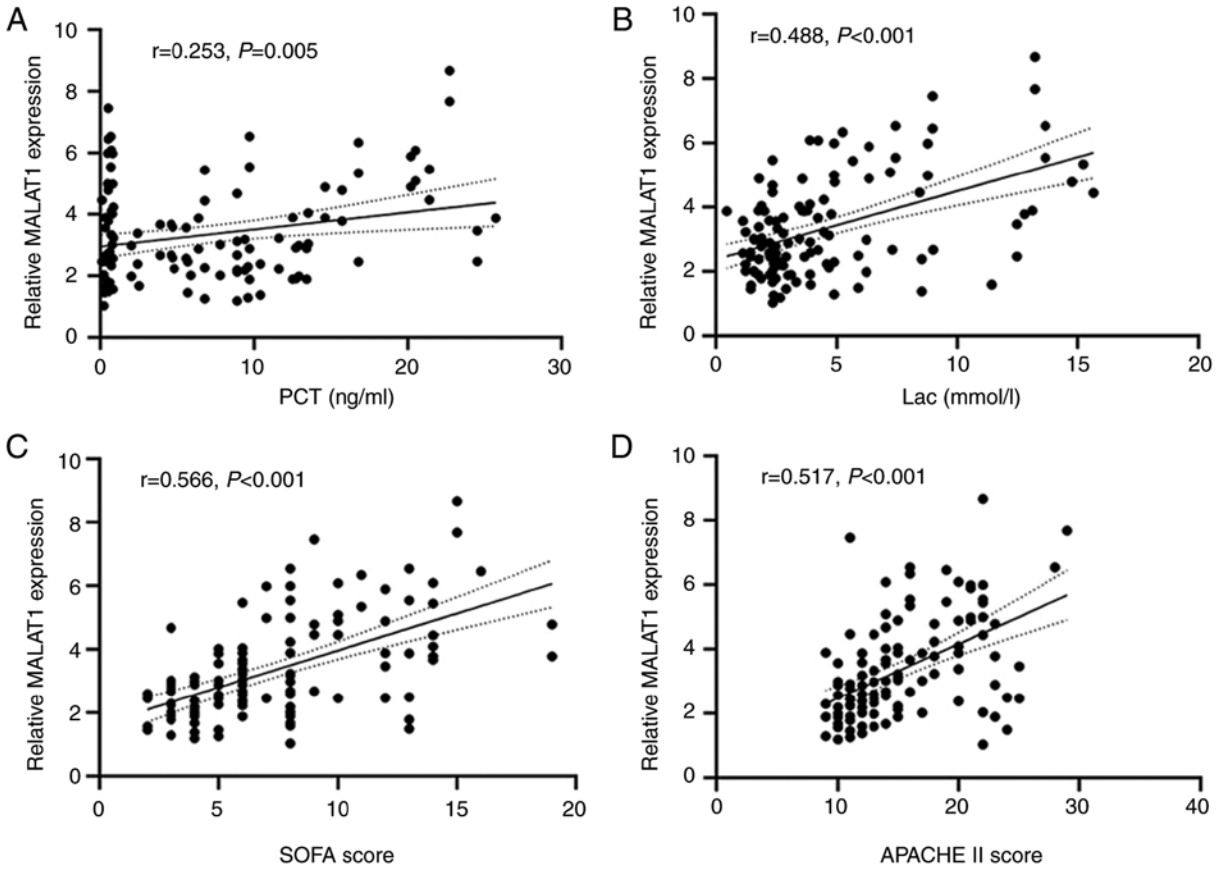

Figure 2. Correlation between MALAT1 plasma levels and conventional evaluation indicators of sepsis. (A-D) MALAT1 plasma levels exhibited weak positive correlations with (A) PCT and (B) Lac levels, as well as (C) SOFA and (D) APACHE II scores in patients with sepsis. APACHE II, acute physiology and chronic health evaluation II; Lac, lactate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

shock (P<0.001), PCT levels (P=0.038), Lac levels (P<0.001), and SOFA (P<0.001) and APACHE II (P<0.001) scores, as well as MALAT1 plasma levels (Fig. 4A; P<0.001) were significantly increased in non-survivors compared with survivors. Further multivariate logistic regression analysis demonstrated that high MALAT1 (P=0.015) and Lac (P=0.023) levels, SOFA (P=0.011) and APACHE II (P=0.028) scores, and septic shock (P=0.043) were all independent predictive factors for poor prognosis of sepsis, whereas PCT levels (P=0.156) were not associated with prognosis in patients with sepsis (Table VI).

Prognostic value of MALAT1 level for sepsis. ROC curve analysis exhibited significant predictive value for MALAT1 levels (AUC=0.886) at distinguishing non-survivors from survivors (Fig. 4B), which was higher compared with Lac levels (AUC=0.868; Fig. 4C) and APACHE II scores (AUC=0.868; Fig. 4E), but lower compared with SOFA scores (AUC=0.943; Fig. 4D). At the optimal cut-off point of >3.62 for MALAT1 levels, the specificity and sensitivity were 89.47 and 81.82%, respectively. At the optimal cut-off point of >3.51 for Lac levels, the specificity and sensitivity were 75 and

Table III. Univariate analysis of clinicopathological characteristics between patients with and without septic shock.

Factor	No septic shock (n=66)	Septic shock (n=54)	P-value
Age, years	49.27±8.90	51.67±7.80	0.124[a]
Sex, n			0.912[b]
Male	30	24	
Female	36	30	
PCT, ng/ml	5.90 (2.00-10.40)	5.50 (0.50-14.88)	0.257[c]
Lac, mmol/l	2.34 (1.72-3.72)	5.07 (3.54-8.98)	<0.001[c]
SOFA score	4.97±2.13	10.31±3.51	<0.001[c]
APACHE II score	12.70±3.13	18.28±4.57	<0.001[c]

[a]Student's t-test; [b]χ^2 test; [c]Mann-Whitney test. Data are presented as the mean ± standard deviation, median and interquartile range or count. APACHE II, acute physiology and chronic health evaluation II; HCs, healthy controls; Lac, lactate; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

Table IV. Multivariate logistic regression of risk factors for septic shock.

Factor	P-value	OR	95% CI
Age, years	0.368	1.036	0.959-1.119
MALAT1	0.030	2.030	1.070-3.851
Lac	0.027	1.405	1.039-1.901
SOFA	0.001	1.580	1.196-2.086
APACHE II	0.011	1.268	1.057-1.522

APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; Lac, lactate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; OR, odds ratio; SOFA, sepsis-related organ failure assessment.

88.64%, respectively. At the optimal cut-off point of >6 for SOFA scores, the specificity and sensitivity were 77.63 and 93.18%, respectively. At the optimal cut-off point of >15 for APACHE II scores, the specificity and sensitivity were 86.84 and 77.27%, respectively.

Discussion

MALAT1 is ubiquitously expressed in the majority of human tissues and body fluids, which suggests that MALAT1 may be a potential biomarker for disease diagnosis, prognosis and treatment (24). A large proportion of current studies focus on the underlying molecular mechanisms of MALAT1 function in the regulation of various pathophysiological processes (12,25,26); however, few studies have been conducted to investigate the clinical application of MALAT1 as a biomarker (21,27). To the best of our knowledge, the present study is the first to evaluate the independent risk and predictive value of MALAT1 as a biomarker for the diagnosis, severity and prognosis of sepsis.

MALAT1 is located on human chromosome 11q13 (28), and serves pivotal roles in the inflammatory regulation of sepsis and septic organ dysfunction; for instance, the downregulation of MALAT1 attenuated cardiac inflammation and microvascular endothelial cell injury in rats with sepsis by inhibiting the inflammatory response and apoptosis (29,30). The knockdown of MALAT1 suppressed lipopolysaccharide (LPS)-induced acute kidney and lung injury by alleviating the inflammatory response through the microRNA-146a/NF-κB pathway (31,32). In addition, MALAT1 has been demonstrated to be upregulated in LPS-induced macrophages and chondrocytes, whereas the knockdown of MALAT1 enhanced LPS-induced inflammatory injury by increasing the expression levels of the tumor necrosis factor (TNF)-α and interleukin (IL)-6 through negative regulation of the NF-κB pathway (33-35). These results indicated that MALAT1 may be a pro- or anti-inflammatory regulator in different tissues and cells induced by LPS, which may be associated with the imbalance in the immune system during septic injury. Similarly, the results of the present study demonstrated that MALAT1 plasma levels were significantly increased in patients with sepsis. Higher expression levels of MALAT1 were also observed in patients with septic shock and those who succumbed to sepsis compared with the respective control groups.

To determine whether MALAT1 was associated with the diagnosis, severity and prognosis of sepsis, the correlation between MALAT1 levels and conventional indicators of sepsis, including PCT and Lac levels, as well as SOFA and APACHE II scores, was further evaluated. PCT is ubiquitously expressed in parathyroid glands during bacterial infection and is likely to be induced by TNF-α and IL-6 (36). PCT has been used in the diagnosis of sepsis for decades; in the present study, PCT levels were identified as an independent risk and diagnostic factor for sepsis, and MALAT1 levels exhibited a weak positive correlation with PCT levels. Dahaba and Metzler (37) reported that PCT levels were closely correlated with the severity of sepsis and exhibited a significant predictive value for the prognosis of sepsis on day 6 following admission. However, PCT levels had no independent predictive value for the severity and prognosis of sepsis in the present study, which may be due to the smaller sample size and earlier time of PCT level analysis (within 24 h of admission). Arterial Lac levels, SOFA and APACHE II scores are commonly used to assess the severity and prognosis of sepsis (2,8). In accordance with previous studies, the results of the present study demonstrated that high Lac levels, SOFA

Table V. Univariate analysis of clinicopathological characteristics between survivors and non-survivors.

Factor	Survivors (n=76)	Non-survivors (n=44)	P-value
Age, years	49.95±7.97	51.05±9.33	0.496[a]
Sex, n			0.939[b]
Male	34	20	
Female	42	24	
Septic shock, n			<0.001[b]
No	59	7	
Yes	17	37	
PCT, ng/ml	5.20 (0.70-9.40)	8.25 (0.67-20.20)	0.038[c]
Lac, mmol/l	2.37 (1.77-3.70)	6.11 (3.97-11.60)	<0.001[c]
SOFA score	5.18±2.15	11.16±3.25	<0.001[c]
APACHE II score	13.03±3.31	18.98±4.33	<0.001[c]

[a]Student's t-test; [b]χ^2 test; [c]Mann-Whitney test. Data are presented as the mean ± standard deviation, median and interquartile range or count. APACHE II, acute physiology and chronic health evaluation II; HCs, healthy controls; Lac, lactate; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

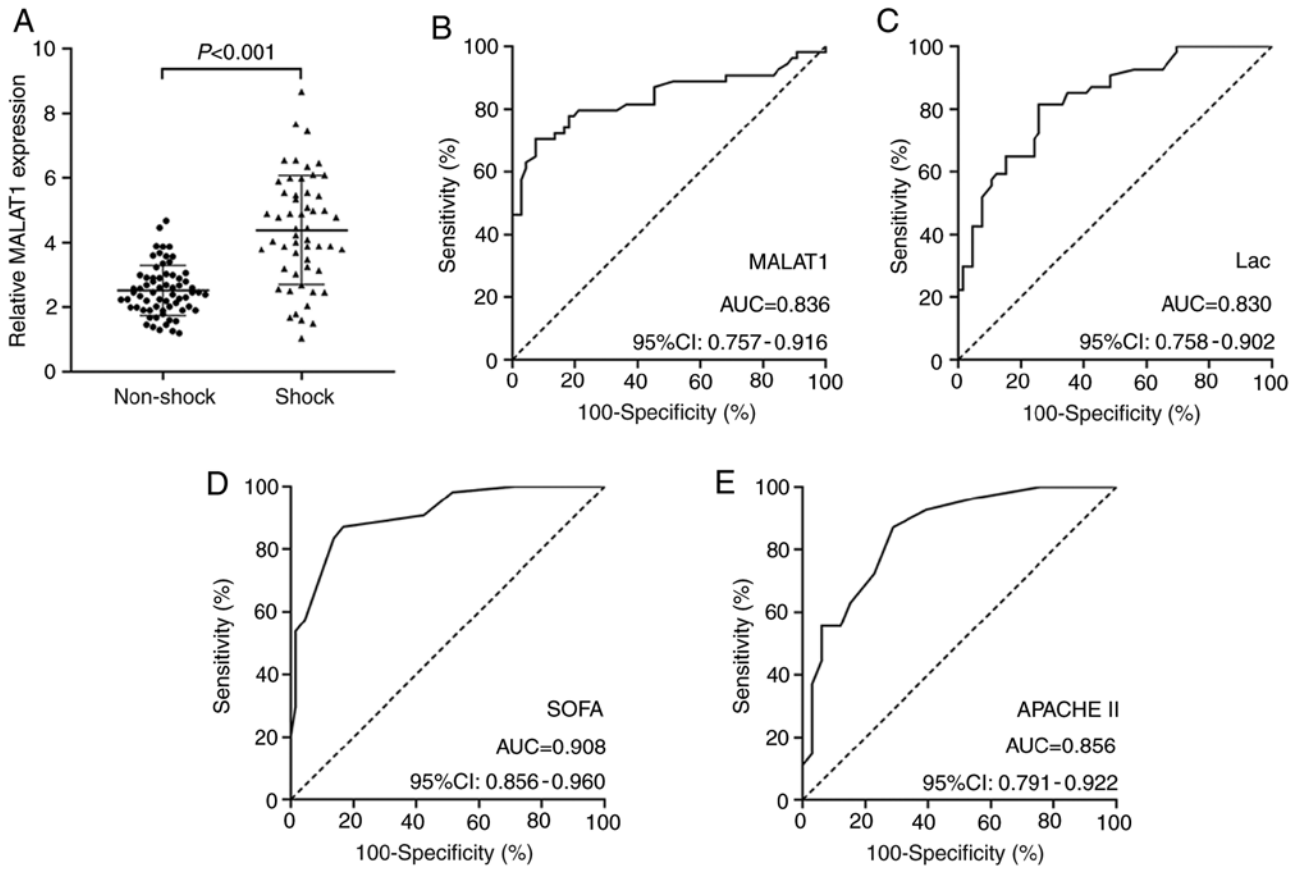

Figure 3. Relative expression and predictive value of MALAT1 plasma levels in distinguishing patients with septic shock from those without septic shock. (A) MALAT1 expression was significantly increased in patients with septic shock compared with those without septic shock. (B-E) Receiver operating characteristic curves for (B) MALAT1 and (C) Lac levels, (D) SOFA and (E) APACHE II scores. APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; Lac, lactate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; Non-shock, patients with sepsis without septic shock; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

and APACHE II scores were independent predictive factors for the severity and mortality of sepsis. In addition, MALAT1 levels exhibited a weak positive correlation with Lac levels, SOFA and APACHE II scores. These results suggested that plasma MALAT1 expression may be associated with the diagnosis, severity and prognosis of sepsis.

Table VI. Multivariate logistic regression of mortality risk factors for sepsis.

Factor	P-value	OR	95% CI
Septic shock (yes vs. no)	0.043	50.144	1.133-2,219.541
MALAT1	0.015	3.819	1.303-11.189
PCT	0.156	1.133	0.954-1.345
Lac	0.023	1.933	1.096-3.410
SOFA	0.011	4.054	1.379-11.917
APACHE II	0.028	1.719	1.062-2.782

APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; Lac, lactate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; OR, odds ratio; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

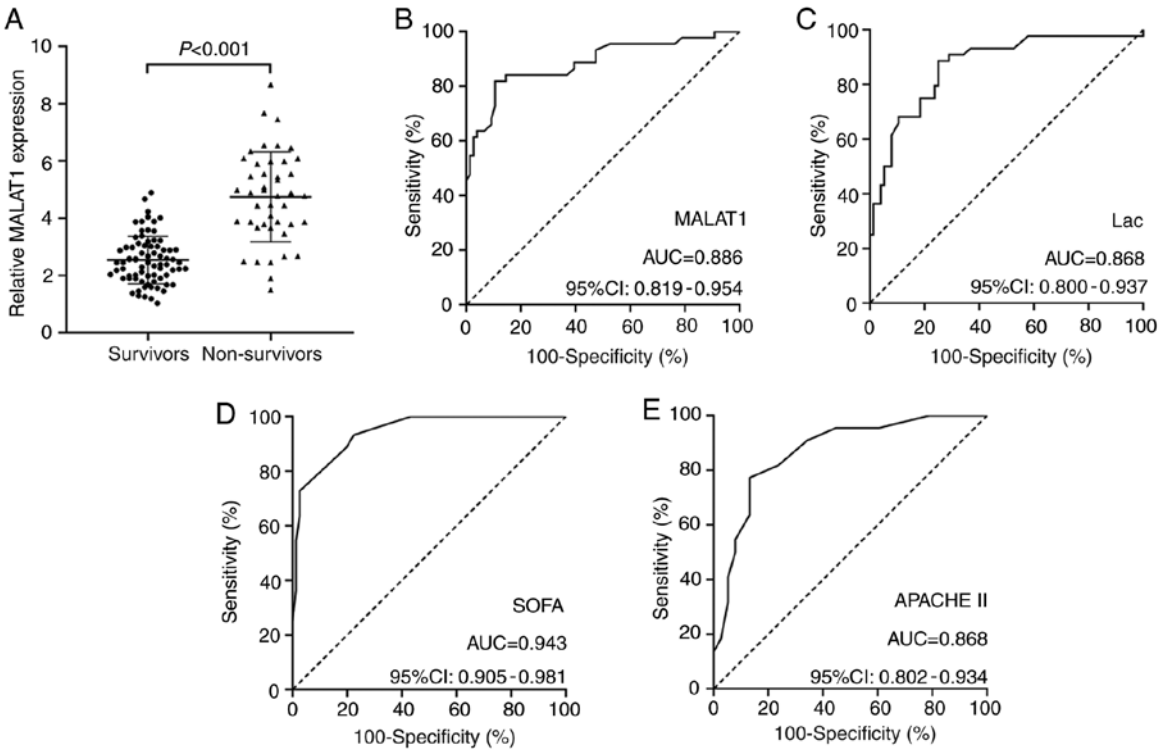

Figure 4. Relative expression and predictive value of MALAT1 plasma levels in distinguishing non-survivors from survivors. (A) MALAT1 expression was significantly increased in non-survivors compared with survivors. (B-E) Receiver operating characteristic curves for (B) MALAT1 and (C) Lac levels, (D) SOFA and (E) APACHE II scores. APACHE II, acute physiology and chronic health evaluation II; CI, confidence interval; Lac, lactate; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PCT, procalcitonin; SOFA, sepsis-related organ failure assessment.

The diagnostic and prognostic value of MALAT1 has been investigated in various types of cancer and diabetic retinopathy (27,38). Recently, two studies reported the predictive values of the plasma lncRNAs nuclear enriched abundant transcript 1 and intersectin 1-2 for the diagnosis and prognosis of sepsis (39,40). In the present study, multivariate logistic regression analysis revealed that MALAT1 was an independent risk biomarker for the diagnosis, severity and poor prognosis of sepsis. The results of the ROC curve analysis revealed significant predictive value for MALAT1 in differentiating patients with sepsis from HCs, patients with septic shock from those without septic shock, and non-survivors from survivors. These results indicated that MALAT1 might serve as a biomarker for the diagnosis, severity and prognosis of sepsis. It could be speculated that MALAT1 may regulate the inflammatory response to infection by targeting various genes and signaling pathways, inducing the development and progression of sepsis and increasing the risk of mortality.

There were certain limitations in this study. Firstly, this study was performed in a single center and the sample size was relatively small. Secondly, as a diagnostic biomarker, only the predictive value of MALAT1 in the diagnosis of sepsis was evaluated, whereas detailed mechanistic studies were not performed. The role and mechanism of MALAT1 in the pathogenesis of sepsis require further investigation. Thirdly, the 28-day follow-up period was relatively short, and MALAT1 expression was measured only once for each

participant. A longer follow-up period, in addition to the continuous measurements of MALAT1, may yield more persuasive results regarding MALAT1 and sepsis-associated mortality. Finally, a systemic inflammatory response syndrome (SIRS) category was not set in this study. Sepsis was initially defined as an infection with at least two of the four SIRS criteria (41); since SIRS criteria do not reflect poor prognosis, sepsis is currently defined as a dysregulated host response to infection with a SOFA score ≥2 points (2). The emphasis of this new definition is placed on mortality prediction rather than early diagnosis. Thus, the distinction between sepsis and SIRS still presents difficulty in early diagnosis of sepsis. Further mechanistic studies are necessary to determine whether MALAT1 may be a useful biomarker in distinguishing sepsis from SIRS.

In conclusion, the results of the present study demonstrated that plasma MALAT1 was upregulated in patients with sepsis, and may serve as a potential biomarker for the diagnosis, severity and prognosis of sepsis. Further investigations with larger sample sizes from multiple centers and detailed mechanistic studies are required to evaluate the clinical application of MALAT1 as a biomarker and therapeutic target for sepsis.

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Availability of data and materials

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

Authors' contributions

LS and JC designed and coordinated the study. JC, YH and YD collected the samples and data. LS, LZ and YD performed the statistical analyses and produced graphs. YH and LZ drafted the manuscript. LS and YD revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the First People's Hospital of Yancheng and complied with the ethics standards of the Declaration of Helsinki. All participants or their statutory guardians provided written informed consent. All identifying information of each participant was removed from this study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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