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The associations of long non-coding RNA taurine upregulated gene 1 and microRNA-223 with general disease severity and mortality risk in sepsis patients

Ning Li, MM, Sisi Wu, MM, Li Yu, MM*

Abstract

This study aimed to investigate the correlation of long non-coding RNA taurine upregulated gene 1 (lncRNA TUG1) with microRNA-223 (miR-223) as well as their associations with risk, severity, and mortality of sepsis.

Totally122 sepsis patients and 122 healthy controls were enrolled. Plasma lncRNA TUG1 and miR-223 levels were detected by reverse transcription quantitative polymerase chain reaction. General severity of sepsis was assessed within 24 hours after admission using acute pathologic and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score. Patients were intensively followed up until death or 28 days after enrollment to assess mortality.

LncRNA TUG1 expression was decreased ($P < .001$) but miR-223 expression ($P < .001$) was elevated in sepsis patients. Additionally, a negative correlation of lncRNA TUG1 expression with miR-223 expression was observed in sepsis patients ($P < .001$). Moreover, in sepsis patients, lncRNA TUG1 expression was negatively correlated with respiratory infection, serum creatinine (Scr), white blood cell (WBC), C-reactive protein (CRP), APACHE II score, and SOFA score but positively correlated with albumin (all $P < .05$); miR-223 expression was negatively correlated with skin and soft tissue infection and albumin but positively correlated with Scr, WBC, CRP, APACHE II score, and SOFA score (all $P < 0.05$). As to mortality, lncRNA TUG1 expression was decreased ($P = .001$) but miR-223 was elevated ($P < .001$) in 28-day sepsis deaths compared with 28-day sepsis survivors.

Our findings offer the potential of lncRNA TUG1 and miR-223 as biomarkers for progression and prognosis of sepsis.

Abbreviations: AKI = acute kidney injury, APACHE = acute pathologic and chronic health evaluation, AUC = area under the curve, CI = confidence interval, GAPDH = Glyceraldehyde-3-phos5phate dehydrogenase, HIV = human immunodeficiency virus, K-M = Kaplan-Meier, lncRNAs = Long non-coding RNAs, miR-223 = miRNA-223, PB = peripheral blood, PMVECs = primary murine pulmonary microvascular endothelial cells, ROC = Receiver operating characteristic, RT-qPCR = reverse transcription quantitative polymerase chain reaction, SOFA = sequential organ failure assessment, TUG1 = taurine upregulated gene 1.

Keywords: disease severity, long non-coding RNA taurine upregulated gene 1, microRNA-223, mortality, sepsis

1. Introduction

Sepsis is characterized by dysregulated inflammatory response to infectious pathogens, and leads to life-threatening organ dysfunctions.[1,2] According to a Chinese statistical report, the occurrence of sepsis is estimated to be 461 cases per 100,000 populations per year.[3] Despite the understanding of the pathophysiology and the improved protocolized care, the in-hospital deaths related to sepsis is continually increased, moreover, the survivors of sepsis may suffer impaired physical functions, cognitive defects, and even high readmission rates or long-term mortality.[4–6] Thus, exploration of sensitive biomarkers for early diagnosis and sepsis progression is needed, which may help improve the outcomes of sepsis patients.

Long non-coding RNAs (lncRNAs) play crucial regulatory roles in gene transcription and chromatin modification, and the dysregulation of lncRNAs have been revealed to be tightly related to human diseases.[7] LncRNA taurine upregulated gene 1 (TUG1) is a lncRNA which associates with pathology of various cancers.[8,9] Recently, some experiments have uncovered that lncRNA TUG1 overexpression suppresses cell apoptosis and alleviates inflammation in lipopolysaccharide (LPS)-treated primary murine pulmonary microvascular endothelial cells (PMVECs), while its knockout promotes sepsis-associated acute

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NL and SW contributed equally to this work.

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kidney injury (AKI) by the regulation of NF-κB signaling pathway, suggesting the role of lncRNA TUG1 in sepsis pathology.[10,11] Moreover, an interesting study discloses that lncRNA TUG1 protects HK-2 cells against LPS-induced inflammatory injury by regulating miRNA-223 (miR-223), more importantly, miR-233 has been widely identified as a biomarker for increased sepsis risk and poor prognosis.[7,12,13]

Given that lncRNA TUG1 is implicated in the protection against inflammation and organ injury of sepsis, and it has a negative regulation on miR-223 who promotes inflammation and predicts poor prognosis in sepsis, we speculated that lncRNA TUG1 might play a role in sepsis occurrence and progression by the interaction with miR-223, whereas the related evidence was limited. Hence, this present study aimed to investigate the association of lncRNA TUG1 expression with sepsis risk, and explore its correlation with disease severity, mortality and miR-223 expression in sepsis patients.

2. Methods

2.1. Participants

A total of 122 sepsis patients who admitted in The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology were consecutively enrolled in this study during August 2017 and September 2019. The inclusion criteria were:

1. diagnosed as sepsis according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[14];
2. aged above 18 years old.

The exclusion criteria were:

1. complicated with other fatal diseases (e.g., hematologic malignancies and solid tumors);
2. infected with human immunodeficiency virus (HIV);
3. transferred from other hospitals;
4. received immunosuppressive therapy within 3 months before enrollment;
5. pregnant or lactating women.

In addition, 122 healthy subjects who underwent health examination in The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology between October 2019 and December 2019 were recruited as healthy controls. The screening criteria of healthy controls were:

1. age- and gender-matched with sepsis patients;
2. without hematological malignancies or solid tumors;
3. no history of sepsis or other severe infections;
4. no obvious abnormalities in biochemical indexes;
5. not pregnant or lactating women.

2.2. Ethics

This study was approved by the Institutional Review Board of The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology. All procedures were performed according to the Declaration of Helsinki. The number of Ethics approvement was whzxh-2016–10. All participants or their family members provided the written informed consent before enrollment.

2.3. Data and sample collection

The clinical characteristics of sepsis patients were recorded after admission including demographics, complications, primary infection site, primary organism, and major biochemical indexes. The peripheral blood (PB) samples of sepsis patients were collected after admission, and the PB samples of healthy controls were collected at enrollment. After collection, the PB samples were centrifuged at 3000 g for 15 minutes under 4°C to separate plasma, and the plasma samples were then stored at −80°C until further detection.

2.4. Disease severity assessment

The severity of sepsis was assessed within 24 hours after admission using the acute pathologic and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score. The APACHE II system was composed of 2 parts: a physiology score and a heath score. The total APACHE II score ranged from 0 to 71, and a higher score reflected a more severe sepsis.[15] In SOFA system, a total of 6 organs (respiration, cardiovascular, coagulation, central nervous system, liver, and renal) were assessed. The total SOFA score ranged from 0 to 24, and a higher score represented a more severe organ dysfunction.[16]

2.5. LncRNA TUG1 and miR-223 detection

The expressions of lncRNA TUG1 and miR-223 in plasma samples were detected by reverse transcription quantitative polymerase chain reaction (RT-qPCR). In brief, total RNA was extracted using QIAamp RNA Blood Mini Kit (Qiagen, Duesseldorf, Nordrhein-Westfalen, German), and the reverse transcription to cDNA was performed using PrimeScript RT reagent Kit (Takara, Dalian, Liaoning, China). Then, the qPCR process was performed using SYBR Premix DimerEraser (Takara, Dalian, Liaoning, China). The lncRNA TUG1 and miR-223 relative expressions were calculated by the $2^{-\Delta\Delta CT}$ method. Glyceraldehyde-3-phos5phate dehydrogenase (GAPDH) was used as the internal reference for lncRNA TUG1, and U6 was used as the internal reference for miR-223. The information of primer sequences was as follows: lncRNA TUG1 forward primer: 5' AGGTAGAACCTCTATGCATTTTGTG 3', reverse primer: 5' ACTCTTGCTTCACTACTTCATCCAG 3'; miR-223 forward primer: 5' ACACTCCAGCTGGGTGTCAGTTTGTCAAAT 3', reverse primer: 5' TGTCGTGGAGTCGGCAATTC 3'; GAPDH, forward primer: 5' TGACCACAGTCCATGCCATCAC 3', reverse primer: 5' GCCTGCTTCACCACCTTCTTGA 3'; U6 forward primer: 5' CTCGCTTCGGCAGCACATATACTA 3'; reverse primer: 5' ACGAATTTGCGTGTCATCCTTGC 3'.

2.6. Follow-up

Intensive follow-ups were performed for the patients until death or 28 days after enrollment. During follow-up, the survival status of patients was documented, and all patients were grouped as survivors or deaths based on the 28-day survival status. Accumulating mortality was calculated from the date of admission to the date of death or completion of the 28-day follow-up.

2.7. Statistical analysis

SPSS 24.0 (IBM, Chicago, IL, USA) was used for statistical analyses and GraphPad Prism 7.01 (GraphPad Software, San

Table 1

Clinical characteristics of sepsis patients.

Items	Sepsis patients (N = 122)
Age (years), mean±SD	53.8 ± 11.1
Gender, No. (%)	
Female	52 (42.6)
Male	70 (57.4)
BMI, (kg/m^2), mean±SD	22.6 ± 3.6
Smoke, No. (%)	44 (36.1)
COPD, No. (%)	21 (17.2)
Cardiomyopathy, No. (%)	52 (42.6)
Chronic kidney failure, No. (%)	20 (16.4)
Cirrhosis, No. (%)	26 (21.3)
Primary infection site, No. (%)	
Abdominal infection	44 (36.1)
Respiratory infection	25 (20.4)
Skin and soft tissue infection	23 (18.8)
Blood stream infection	14 (11.5)
CNS infection	8 (6.6)
Other infections	8 (6.6)
Primary organism, No. (%)	
Gram-negative bacteria	68 (55.7)
Gram-positive bacteria	25 (20.5)
Anaerobes	13 (10.7)
Fungus	7 (5.7)
Mycoplasmas	4 (3.3)
Total culture negative	25 (20.5)
Scr (mg/dL), mean±SD	2.2 ± 1.4
Albumin (g/L), mean±SD	29.5 ± 10.6
WBC (10^9/L), mean±SD	19.3 ± 10.5
CRP (mg/L), mean±SD	103.1 ± 77.9
APACHE II score, mean±SD	13.6 ± 6.3
SOFA score, mean±SD	6.1 ± 2.7

APACHE II = acute physiology and chronic health evaluation II, BMI = body mass index, CNS = central nervous system, COPD = chronic obstructive pulmonary disease, CRP = C-reactive protein, Scr = serum creatinine, SD = standard deviation, SOFA = sequential organ failure assessment, WBC = white blood cell.

Diego, California, USA) was used to plot the figures. Student *t* test was used to compare the difference between 2 groups. Spearmans rank correlation test was used for correlation analysis between 2 variables. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) with 95% confidence interval (CI) were used to assess the performance of variables in predicting sepsis susceptibility and 28-day mortality risk. Kaplan–Meier (K-M) curve was plotted to illuminate the accumulating mortality, and log-rank test was used to compare the difference of accumulating mortality between 2 groups. P value $<.05$ was considered statistically significant.

3. Results

3.1. Characteristics of sepsis patients

Totally 122 sepsis patients including 52 (42.6%) females and 70 (57.4%) males were enrolled in this study (Table 1). Regarding the primary infection sites, 44 (36.1%), 25 (20.4%), 23 (18.8%), 14 (11.5%), 8 (6.6%), and 8 (6.6%) patients had abdominal infection, respiratory infection, skin and soft tissue infection, blood stream infection, CNS infection, and other infections, respectively. With regard to the major biochemical indexes, the median values of Scr, albumin, WBC and CRP were 2.2 ± 1.4 mg/dl, 29.5 ± 10.6 g/L, 19.3 ± 10.5 ×10^9/L, and 103.1 ± 77.9 mg/L, respectively. As to general disease severity, the mean APACHE II score was 13.6 ± 6.3 and the mean value of SOFA score was 6.1 ± 2.7. The additionally and detailed information of baseline characteristics was displayed in Table 1.

3.2. LncRNA TUG1 and miR-223 expressions in sepsis patients and healthy controls

LncRNA TUG1 expression was decreased in sepsis patients compared to healthy controls ($P < .001$) (Fig. 1A), while miR-223 expression was elevated in sepsis patients compared to healthy controls ($P < .001$) (Fig. 1B). Besides, ROC curves showed that both lncRNA TUG1 expression (AUC: 0.846, 95%CI: 0.797–0.894) and miR-223 expression (AUC: 0.924, 95%CI: 0.892–0.956) had excellent abilities to distinguish sepsis patients from healthy controls (Fig. 1C).

3.3. Correlation of lncRNA TUG1 and miR-223 in sepsis patients

According to the Spearman rank correlation test analysis, lncRNA TUG1 expression was negatively correlated with miR-223 expression in sepsis patients ($P < .001$, $r = -0.450$) (Fig. 2).

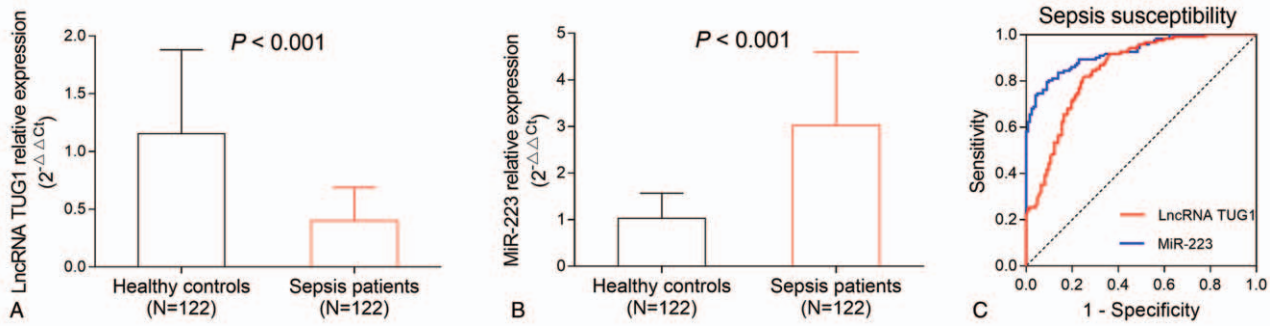

Figure 1. Comparison of lncRNA TUG1 and miR-223 expressions between sepsis patients and healthy controls. Comparison of lncRNA TUG1 expression (A) and miR-223 expression (B) between sepsis and healthy controls. The abilities of lncRNA TUG1 and miR-223 for distinguishing sepsis from healthy controls assessed by ROC curves (C). AUC of lncRNA TUG1 expression was 0.846 (95%CI: 0.797–0.894); AUC of miR-223 expression was 0.924 (95%CI: 0.892–0.956). LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223, ROC = receiver operating characteristic, AUC = area under the curve.

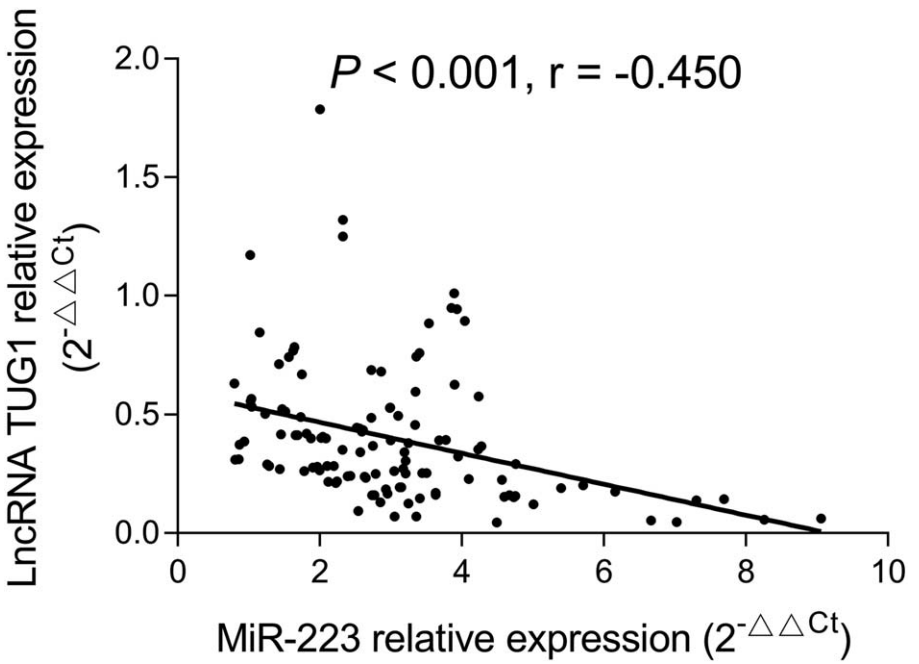

Figure 2. Association of lncRNA TUG1 expression and miR-223 expression in sepsis patients. LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223.

3.4. Correlations of lncRNA TUG1 and miR-223 expressions with primary infection sites, primary organisms, and major biochemical indexes in sepsis patients

LncRNA TUG1 low expression was associated with respiratory infection ($P=.030$) and other infections ($P=.021$), but no association of lncRNA TUG1 expression with abdominal infection ($P=.207$), skin and soft tissue infection ($P=.791$), blood stream infection ($P=.678$), or CNS infection ($P=.267$) was observed in sepsis patients (Fig. 3A). Moreover, miR-223 low expression was associated with skin and soft tissue infection ($P=.041$), while no correlation of miR-223 expression with abdominal infection ($P=.924$), respiratory infection ($P=.212$), blood stream infection ($P=.960$), CNS infection ($P=.052$), or other infections ($P=.378$) was found in sepsis patients (Fig. 3B). As to primary organisms, no correlation of lncRNA TUG1 expression with gram-negative bacteria, gram-positive bacteria, anaerobes, fungus, mycoplasmas, or total culture was observed in sepsis patients (all $P>.05$) (Fig. 3C). Meanwhile, no correlation of miR-223 expression with these primary organisms was found (all $P>.05$) (Fig. 3D) in sepsis patients.

Furthermore, regarding the major biochemical indexes, lncRNA TUG1 expression was negatively correlated with Scr ($P=.010$, $r=-0.233$), WBC ($P=.011$, $r=-0.229$) and CRP ($P<.001$, $r=-0.548$) levels but positively correlated with albumin level ($P=.036$, $r=0.190$); miR-223 expression was positively correlated with Scr ($P=.010$, $r=0.232$), WBC ($P=.033$, $r=0.193$) and CRP ($P<.001$, $r=0.359$) levels but negatively correlated with albumin level ($P<.001$, $r=-0.427$) in sepsis patients (Table 2).

3.5. Correlations of lncRNA TUG1 and miR-223 expressions with general disease severity in sepsis patients

LncRNA TUG1 expression was negatively correlated with APACHE II score ($P<.001$, $r=-0.354$) (Fig. 4A) and SOFA score ($P<.001$, $r=-0.385$) (Fig. 4C) in sepsis patients. MiR-223 expression was positively correlated with APACHE II score ($P<.001$, $r=0.526$) (Fig. 4B), and SOFA score ($P<.001$, $r=0.390$) (Fig. 4D) in sepsis patients.

3.6. Correlations of lncRNA TUG1 and miR-223 expressions with mortality in sepsis patients

There were 32 patients who died and 90 patients who survived during the 28-day follow-up. LncRNA TUG1 expression was decreased in 28-day deaths than that in 28-day survivors ($P=.001$) (Fig. 5A). Moreover, miR-223 expression was increased in 28-day deaths than that in 28-day survivors ($P<.001$) (Fig. 5B).

3.7. Predictive values of lncRNA TUG1 expression and miR-223 expression for 28-day mortality risk in sepsis patients

ROC curves displayed that both lncRNA TUG1 low expression (AUC: 0.705, 95%CI: 0.598–0.811) and miR-223 high expression (AUC: 0.711, 95%CI: 0.619–0.803) could predict increased 28-day mortality risk in sepsis patients (Fig. 6A). Moreover, APACHE II score (AUC: 0.798, 95%CI: 0.713–0.884) and SOFA score (AUC: 0.789, 95%CI: 0.698–0.880) also predicted raised 28-day mortality risk, and they had better predictive values for 28-day mortality risk in sepsis patients than that of lncRNA TUG1. Besides, the major biochemical index Scr predicted increased 28-day mortality risk in sepsis patients with a higher predictive value (AUC: 0.758, 95%CI: 0.665–0.851) than lncRNA TUG1 did. Meanwhile, other major biochemical indexes including albumin (AUC: 0.626, 95%CI: 0.503–0.749), WBC (AUC: 0.618, 95%CI: 0.515–0.721), and CRP (AUC: 0.706, 95%CI: 0.596–0.815) were also able to predict elevated 28-day mortality risk in sepsis patients with non-inferior predictive

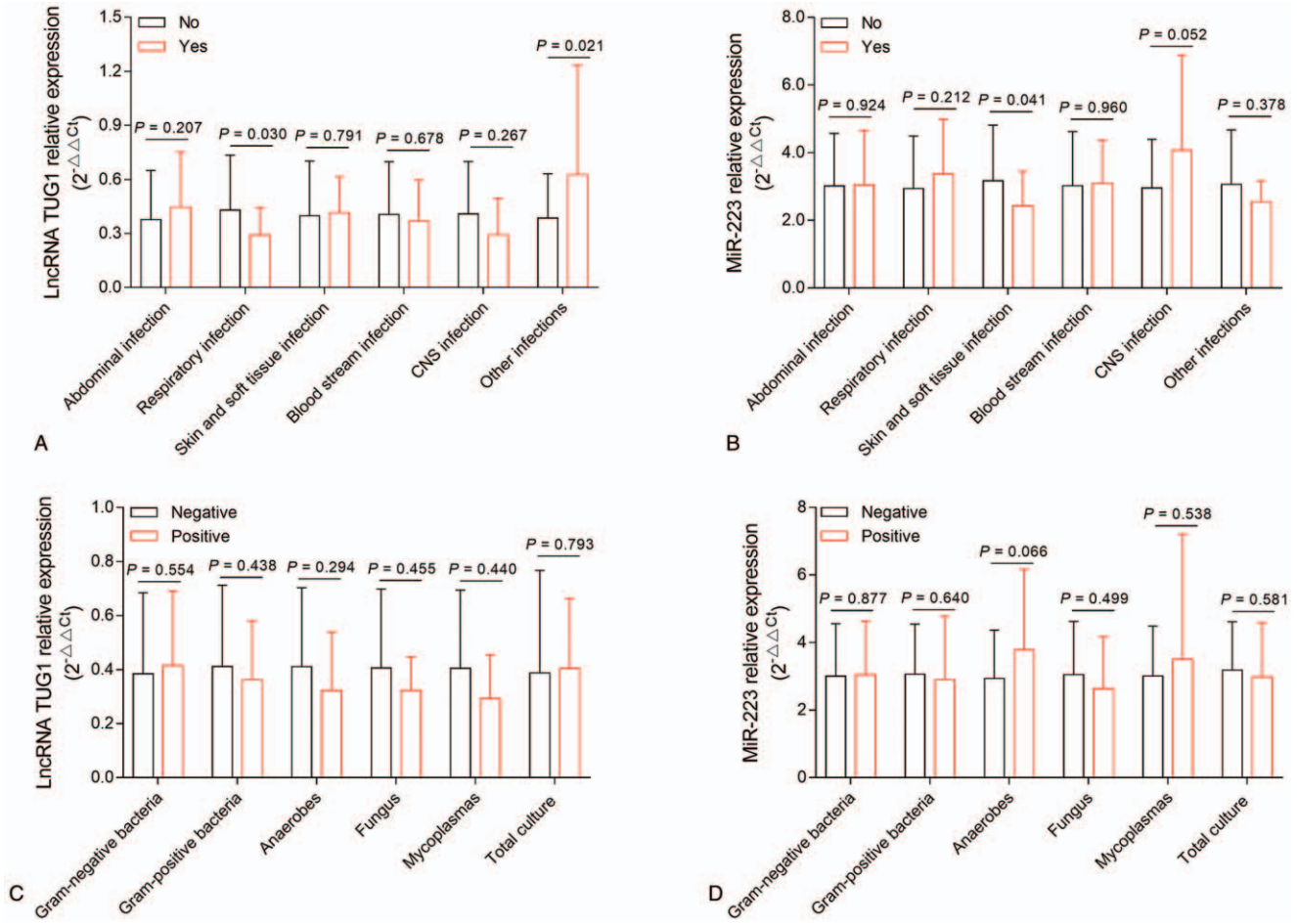

Figure 3. Associations of lncRNA TUG1 and miR-223 expressions with primary infection sites and primary organisms in sepsis patients. Association of lncRNA TUG1 expression (A) and miR-223 expression (B) with primary infection sites. Association of lncRNA TUG1 expression (C) and miR-223 expression (D) with primary organisms. LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223, CNS = central nervous system.

values than lncRNA TUG1 (Fig. 6B). In addition, the combination of lncRNA TUG1 and miR-223 also had a good predictive value for raised 28-day mortality risk with AUC of 0.751 (95% CI: 0.662–0.841) (Fig. 6C).

3.8. Correlations of lncRNA TUG1 and miR-223 expressions with accumulating mortality

K-M curves disclosed that lncRNA TUG1 expression was negatively correlated with accumulating mortality (P=.009) (Fig. 7A), while miR-223 expression was positively correlated with accumulating mortality (P=.002) (Fig. 7B) in sepsis patients.

Table 2

Correlation of lncRNA TUG1 and miR-223 with major biochemical indexes.

	LncRNA TUG1		MiR-223	
Items	***P* value**	***r***	***P* value**	***r***
Scr	.010	−0.233	.010	0.232
Albumin	.036	0.190	<.001	−0.427
WBC	.011	−0.229	.033	0.193
CRP	<.001	−0.548	<.001	0.359

Correlation was determined by Spearman rank correlation test. CRP = C-reactive protein, lncRNA TUG1 = long noncoding RNA taurine-upregulated gene1, miR-223 = microRNA-223, Scr = serum creatinine, WBC = white blood cell.

4. Discussion

Most investigations focus on the role of lncRNA TUG1 expression in disease diagnose and progression in different types of cancer.[17–19] As to its role in inflammatory diseases, one study shows that lncRNA TUG1 expression is decreased in colonic mucosa tissue of ulcerative colitis patients compared to healthy controls.[20] Besides, another study displays that lncRNA TUG1 is downregulated in the serum of sepsis-associated AKI patients compared to healthy controls.[11] Combining the previous indications that lncRNA TUG1 participates in the suppression of cell apoptosis and alleviation of inflammation responses in sepsis, we hypothesized that lncRNA TUG1 might have impact on sepsis occurrence and progression. However, direct evidence is limited. The present study enrolled 122 sepsis patients and 122 healthy subjects to explore the correlation of lncRNA TUG1 expression with risk and disease severity of sepsis. We observed that lncRNA TUG1 level was reduced in sepsis patients compared to healthy controls, and its low expression could distinguish sepsis patients from healthy controls. Moreover, its expression

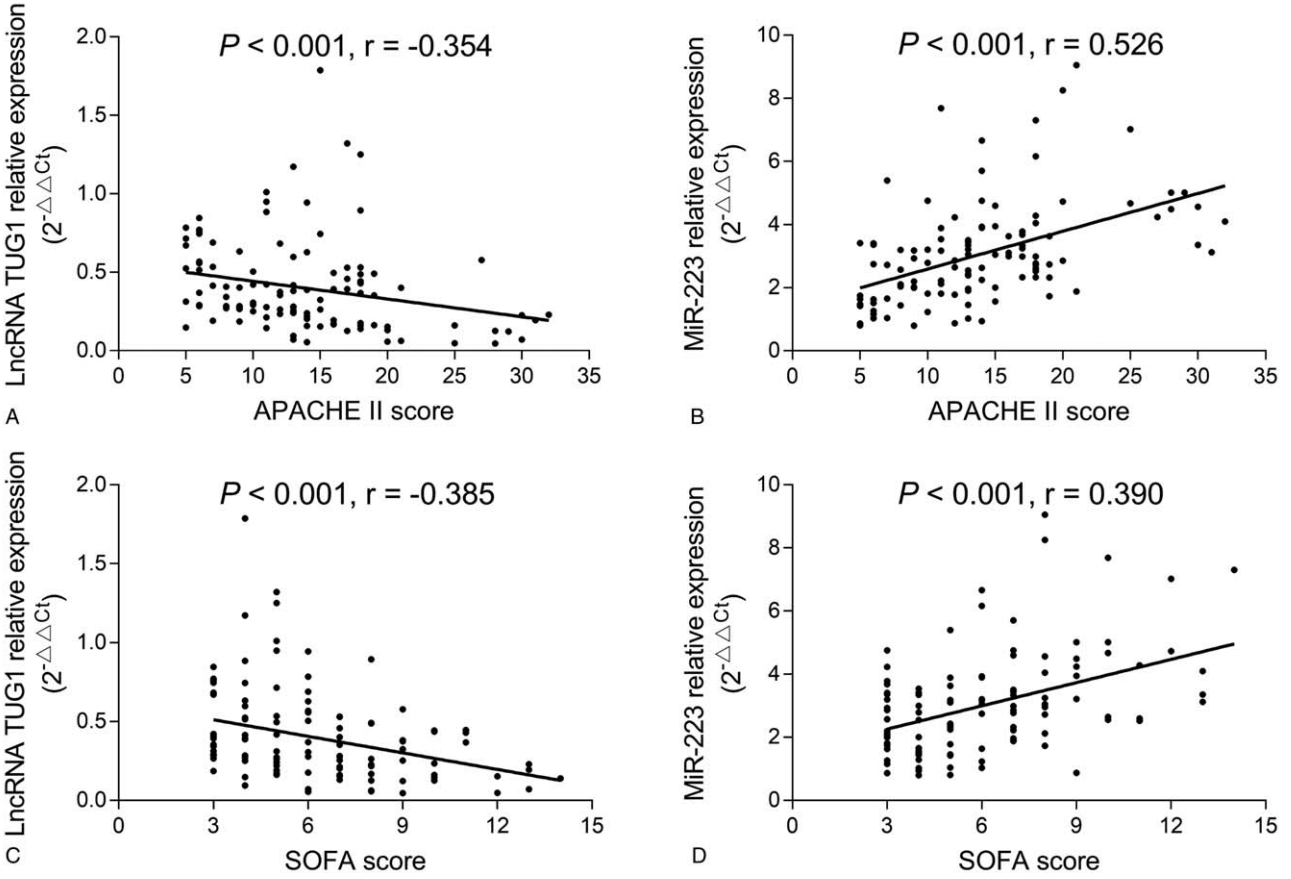

Figure 4. Associations of lncRNA TUG1 and miR-223 expressions with disease severity scores in sepsis patients. Correlations of lncRNA TUG1 expression (A) and miR-223 expression (B) with APACHE II score in sepsis patients. Correlations of lncRNA TUG1 expression (C) and miR-223 expression (D) with SOFA score in sepsis patients. LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223, APACHE II = acute pathologic and chronic health evaluation II, SOFA = sequential organ failure assessment.

was negatively correlated with APACHE II score, SOFA score, Scr level, WBC level, CRP level but positively correlated to albumin level in sepsis patients. There are a few possible reasons: firstly, lncRNA TUG1 may regulate its target miRNAs and further regulate the inflammation-related pathways (such as NF-κB and JAK/STAT signaling pathways) to inhibit the release of excess inflammatory factors, thereby relieving the systematic inflammatory reactions and preventing multiple organ or tissue damages, thus lncRNA TUG1 low expression predicts raised sepsis risk.[21,22] Secondly, lncRNA TUG1 decreases the

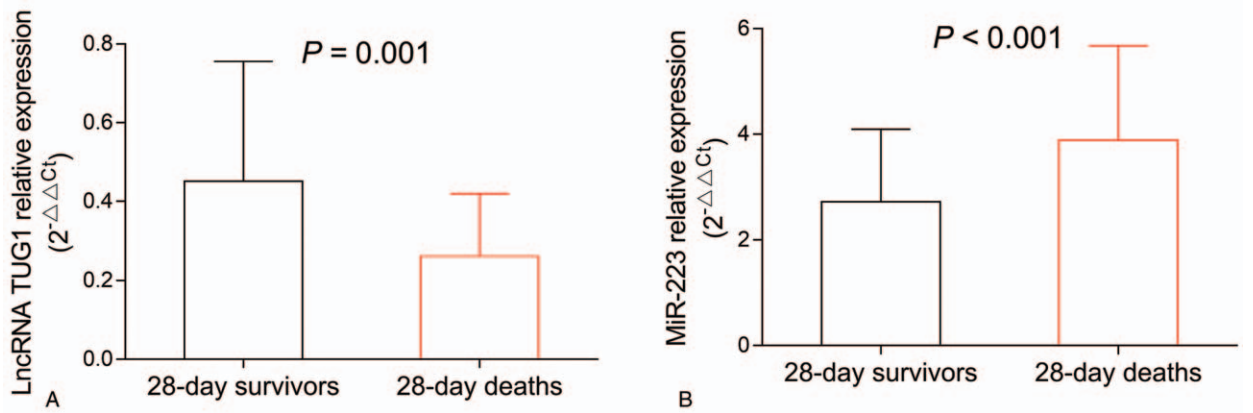

Figure 5. Comparisons of lncRNA TUG1 and miR-223 expressions between 28-day deaths and 28-day survivors. Comparison of lncRNA TUG1 expression between 28-day deaths and 28-day survivors (A). Comparison of miR-223 expression between 28-day deaths and 28-day survivors (B). LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223.

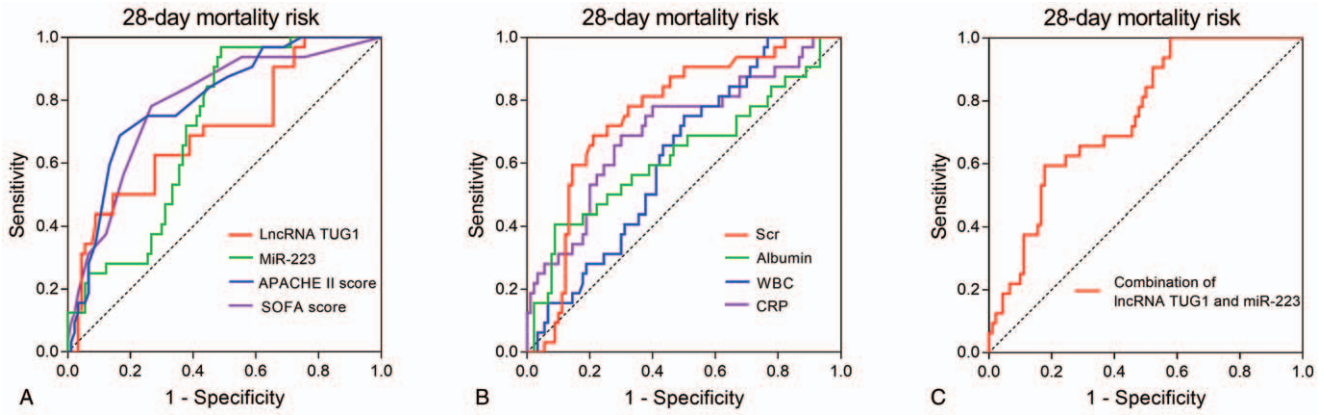

Figure 6. Predictive values of lncRNA TUG1 and miR-223 expressions for 28-day mortality risk in sepsis patients. Predictive values of lncRNA TUG1 expression, miR-223 expression, APACHE II score and SOFA score for 28-day mortality risk (A). Predictive values of Scr, albumin, WBC, and CRP levels for 28-day mortality risk (B). Predictive values of the combination of lncRNA TUG1 and miR-223 for 28-day mortality risk (C). AUC of lncRNA TUG1 low expression was 0.705 (95%CI: 0.598–0.811); AUC of miR-223 high expression was 0.711 (95%CI: 0.619–0.803); AUC of APACHE II score was 0.798 (95%CI: 0.713–0.884); AUC of SOFA score was 0.789 (95%CI: 0.698–0.880); AUC of Scr was 0.758 (95%CI: 0.665–0.851); AUC of albumin was 0.626 (95%CI: 0.503–0.749); AUC of WBC was 0.618, 95% CI: 0.515–0.721); AUC of CRP was 0.706, (95%CI: 0.596–0.815); AUC of the combination of lncRNA TUG1 and miR-223 was 0.751 (95%CI: 0.662–0.841). APACHE II = acute pathologic and chronic health evaluation, AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223, Scr = serum creatinine, SOFA = sequential organ failure assessment, WBC = white blood cell.

inflammatory cytokine productions and reduces cell apoptosis, thereby attenuating inflammation level and organ dysfunctions, thus, lncRNA TUG1 expression is negatively correlated with general disease severity and related to major biochemical index levels that indicate milder inflammation in sepsis patients.[23] Moreover, our present study found that lncRNA TUG1 expression was negatively correlated with the accumulating mortality, and its low expression predicted increased 28-mortality risk in sepsis patients, which might be due to the impaction of lncRNA TUG1 on decreasing inflammation and alleviating disease progression. Therefore, patients with lncRNA TUG1 high expression may have better treatment outcomes leading to prolonged survival, while low lncRNA TUG1 expression predicts increased 28-day mortality.

MiR-223 is highly expressed in patients with type 2 diabetes mellitus, rheumatoid arthritis, and human immunodeficiency virus-1 infection.[24–26] In sepsis, miR-223 has been identified as a biomarker for disease progression or poor prognosis, for instance, it is able to distinguish patients with severe sepsis and septic shock from mild sepsis, and it is increased in non-survivor group compared to survivor group.[27,28] Interestingly, miR-233 is found to be regulated by lncRNA TUG1 via activation of PI3K/AKT and inactivation of NF-κB pathways, thereby protecting HK-2 cells from LPS-induced inflammatory injury.[13] Based on the previous evidences that lncRNA TUG1 contributed to attenuating the initiation and progression of sepsis, meanwhile, miR-223 might promote inflammation and was regulated by lncRNA TUG1 in sepsis, we inferred that lncRNA TUG1 might decrease the sepsis occurrence and alleviate progression by regulating miR-223 in sepsis patients. However, this is rarely reported in clinical practices. Our present study assessed the association of lncRNA TUG1 expression with miR-223 expression, and investigated the correlation of miR-223 expression with risk, severity, major inflammation indexes and

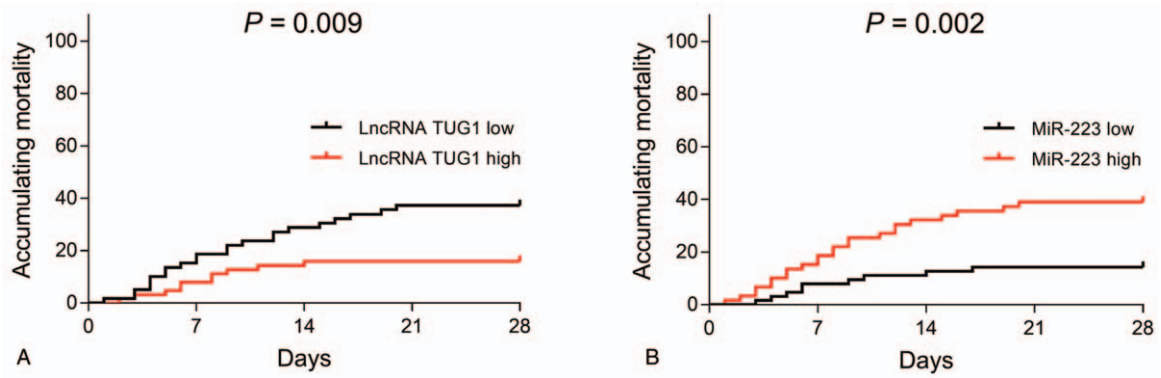

Figure 7. Associations of lncRNA TUG1 and miR-223 expressions with accumulating mortality in sepsis patients. Accumulating mortality in lncRNA TUG1 high expression patients and lncRNA TUG1 low expression patients (A). Accumulating mortality in miR-223 high expression patients and miR-223 low expression patients (D). LncRNA TUG1 = long non-coding RNA taurine upregulated gene 1, miR-223 = microRNA-223.

mortality of sepsis. We found that lncRNA TUG1 expression was negatively associated with miR-223 expression, and miR-223 expression was increased in sepsis patients compared to healthy controls. Meanwhile, miR-223 high expression correlated with aggravated disease severity, major biochemical indexes indicating increased inflammation, and elevated mortality in sepsis patients. Our results suggested that lncRNA TUG1 might help decrease the occurrence and severity of sepsis and facilitate prolonging the survival of sepsis patients via its interaction with miR-223.

There were some limitations in this present study:

1. The sample size of 122 patients was relatively small, which might result in a low statistical efficacy.
2. Only lncRNA TUG1 expression and miR-223 expression after admission were detected, while their expressions from treatment initiation to the 28-day or the date of death were not detected in this present study, which needed to be further investigated.

To conclude, lncRNA TUG1 has a negative interaction with miR-223 and they both correlate with risk, severity and mortality of sepsis, offering the potential of lncRNA TUG1 and miR-223 as biomarkers for progression and prognosis of sepsis.

Author contributions

Conceptualization: Li Yu.
Data curation: Ning Li, Sisi Wu.
Formal analysis: Ning Li, Sisi Wu.
Investigation: Ning Li, Sisi Wu.
Methodology: Ning Li, Sisi Wu.
Resources: Li Yu.
Supervision: Li Yu.
Validation: Li Yu.
Writing – original draft: Ning Li, Sisi Wu.
Writing – review & editing: Li Yu.

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