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RESEARCH ARTICLE

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Potential of circulating lncRNA CASC2 as a biomarker in reflecting the inflammatory cytokines, multi-organ dysfunction, disease severity, and mortality in sepsis patients

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Abstract

Background: Long noncoding RNA (lncRNA) cancer susceptibility candidate gene 2 (CASC2) inhibits inflammation and multi-organ dysfunction in various ways. The present study was intended to explore the potency of blood lncRNA CASC2 as a biomarker for sepsis management.

Methods: Totally, 184 sepsis patients and 30 healthy controls were enrolled. The reverse transcription-quantitative polymerase chain reaction was used to detect lncRNA CASC2 expression in peripheral blood mononuclear cell samples from the subjects. Mortality during 28 days was recorded in sepsis patients.

Results: LncRNA CASC2 was decreased in sepsis patients [median (interquartile range [IQR]): 0.473 (0.241–0.773)] by comparison to healthy controls [median (IQR): 1.019 (0.676–1.685)] ($p < 0.001$). In sepsis patients, lncRNA CASC2 was negatively correlated with Acute Physiology and Chronic Health Evaluation II (APACHE II) ($p = 0.001$), Sequential Organ Failure Assessment (SOFA) ($p < 0.001$), SOFA-respiratory system ($p = 0.010$), SOFA-coagulation ($p = 0.020$), SOFA-liver ($p = 0.019$), and SOFA-renal ($p = 0.010$) scores, but was not related to SOFA-nervous ($p = 0.466$) and SOFA-cardio vascular system ($p = 0.059$) scores. Additionally, lncRNA CASC2 was negatively related to tumor necrosis factor-α ($p = 0.024$), interleukin (IL)-1β ($p = 0.013$), and IL-17A ($p = 0.002$), but was not linked to IL-6 ($p = 0.112$) or IL-10 ($p = 0.074$). Furthermore, lncRNA CASC2 was lower in sepsis deaths [median (IQR): 0.286 (0.166–0.475)] than in survivors [median (IQR): 0.534 (0.296–0.811)] ($p < 0.001$). Simultaneously, Kaplan–Meier (KM) curve analysis also observed that lncRNA CASC2 was inversely related to accumulating mortality in sepsis patients ($p = 0.003$). While lncRNA CASC2 could independently predict lower mortality risk.

Conclusion: Circulating lncRNA CASC2 inadequacy indicates the release of inflammatory cytokines, severe multi-organ injuries, and increased mortality in sepsis patients.

KEYWORDS
inflammation, lncRNA CASC2, mortality, organ injury, sepsis

1 | INTRODUCTION

Sepsis is symbolized by the systemic inflammatory response and multi-organ failure; globally, there are about 49 million sepsis patients each year, of which 11 million patients die from sepsis [1–3]. In China, sepsis is also a prevalent infectious disease; it has been reported that among every 100 patients in the intensive care unit, there are 21 sepsis cases, whose mortality rate within 90 days has reached nearly 36% [4,5]. Apart from these, complications contributed by sepsis, including acute kidney injury (AKI), acute lung injury (ALI), disseminated intravascular coagulation, etc., are crucial causes of poor prognosis in sepsis patients [6–9]. In order to improve this situation, biomarkers need to be found to ameliorate the management of sepsis.

Long noncoding RNA (lncRNA) cancer susceptibility candidate gene 2 (CASC2), located on chromosome 10 of the human genome, hinders inflammation, and sepsis-induced multi-organ injuries through various signaling pathways according to previous studies [10–14]. For instance, lncRNA CASC2 suppresses the inflammation through microRNA (miR)-27b/TGF-β activated kinase 1 and MAP3K7-binding protein 2 (TAB2) axis in lipopolysaccharide (LPS)-induced ALI. [11] Regarding the regulation of lncRNA CASC2 in multi-organ injury, lncRNA CASC2 reduces sepsis-induced AKI by inversely mediating the miR-155/nuclear factor (NF)-κB axis. [10] Furthermore, lncRNA CASC2 ameliorates sepsis-induced ALI by reversely regulating the miR-152-3p/pyruvate dehydrogenase kinase 4 (PDK4) axis. [12] Taking into account the aforementioned evidence, it was hypothesized that lncRNA CASC2 might have the potential as a biomarker for sepsis management. However, limited studies report that.

Thus, this study aimed to investigate the linkage of circulating lncRNA CASC2 level with inflammatory cytokines, multi-organ injury, disease severity, and mortality in sepsis patients.

2 | METHODS

2.1 | Subjects

This study successively recruited 184 sepsis patients treated between February 2018 and June 2021. The recruitment criteria were: (i) diagnosed as sepsis per sepsis-3 criteria published in 2016 [3]; (ii) aged over 18 years; (iii) treated for sepsis within 24 h of symptom onset; (iv) patients or their guardians volunteered to cooperate with the collection of peripheral blood (PB) samples. Patients who were complicated with a solid tumor or hematological malignancy were excluded. Besides, patients during pregnancy or lactating were ineligible for inclusion as well. In addition, from February 2018 to June 2021, this study also enrolled 30 healthy subjects as healthy controls. The enrollment criteria for healthy controls were set as: (i) had no history of sepsis or severe infection; (ii) had no abnormities in medical examinations; (iii) willing to provide PB samples. The study was permitted by Ethics Committee. All participants or their guardians signed the informed consent.

2.2 | Collection of clinical data and PB samples

Clinical characteristics of sepsis patients were obtained after recruitment. Besides, the sepsis patients were closely followed up for 28 days, and mortality during follow-up was recorded. PB samples were obtained from sepsis patients within 1 day after the diagnosis of sepsis, as well as from healthy controls within 1 day after enrollment.

2.3 | Detection of lncRNA CASC2 expression

Peripheral blood mononuclear cell (PBMC) samples were isolated from collected PB samples of sepsis patients and healthy controls to detect lncRNA CASC2 expression by reverse transcription-quantitative polymerase chain reaction (RT-qPCR). Briefly, RNA was extracted by PureZOL RNA isolation reagent (Bio-Rad), which was subsequently submitted to perform reverse transcription using PrimeScript™ RT reagent Kit (Takara). Thereafter, qPCR was carried out with SYBR® Green Realtime PCR Master Mix (Toyobo). The thermocycling condition was 1 cycle of 95°C for 60 s, 40 cycles of 95°C for 15 s and 60°C for 60 s. The lncRNA CASC2 expression was calculated by the $2^{-\Delta\Delta Ct}$ method, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as an internal reference. The primers were drafted in accordance with a previous study [15]. For analysis, lncRNA CASC2 expression was classified per median and quartile values in sepsis patients (1/4 quartile, 0.241; median, 0.473; 3/4 quartile, 0.773).

2.4 | Detection of inflammatory cytokine level

Serum samples were separated from collected PB samples of sepsis patients to examine the levels of inflammatory cytokines (including tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-10, and IL-17A) by enzyme-linked immunosorbent assay (ELISA) using commercial Human ELISA Kits. The kits used in the study included Human TNF-α ELISA Kit (Cat. ab285312), Human IL-1β ELISA Kit (Cat. ab214025), Human IL-6 ELISA Kit (Cat. ab178013), Human IL-10 ELISA Kit (Cat. ab185986), and Human IL-17A ELISA Kit (Cat. ab216167). All kits were purchased from Abcam System, China, and the procedures of ELISA were performed in strict accordance with the instructions from the manufacturers.

2.5 | Statistics

Graphics were constructed using GraphPad Prism 7.02 (GraphPad Software Inc.,), and statistical analyses were carried out using SPSS 24.0 (IBM,). Comparison analysis was carried out using Wilcoxon rank-sum test or Kruskal-Wallis H rank-sum test. Correlation analysis was performed using Spearman's rank correlation test. The ability of lncRNA CASC2 expression in distinguishing subjects was assessed using receiver operating characteristic (ROC) curves. Accumulating mortality rate was presented using Kaplan–Meier curves and

evaluated by a log-rank test. Factors related to accumulating mortality were evaluated using forward-stepwise multivariate Cox's proportional hazards regression analysis. Factors related to mortality risk were evaluated using forward-stepwise multivariate logistic regression analysis. p value <0.05 was considered significant.

3 | RESULTS

3.1 | Clinical characteristics of sepsis patients

184 sepsis patients were enrolled in this study with a mean age of 59.6±12.0 years; besides, there were 60 (32.6%) females and 124 (67.4%) males. In terms of primary infection sites, there were 68 (37.0%) patients with abdominal infection, 54 (29.3%) patients with a respiratory infection, 37 (20.1%) patients with skin and soft tissue infection, and 25 (13.6%) patients with other infections. Regarding primary organisms, there were 102 (55.4%), 52 (28.3%), 18 (9.8%), and 32 (17.4%) patients infected with G- bacteria, G+ bacteria, fungus, and other organisms, correspondingly. Meanwhile, the median (interquartile range (IQR)) value of C-reactive protein (CRP) was 63.0 (43.0–91.8) mg/L; the mean value of the Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 11.3±5.2. Concerning Sequential Organ Failure Assessment (SOFA) score, the mean value was 4.8±2.1; specifically, the mean values of the SOFA-respiratory, SOFA-coagulation, SOFA-nervous, SOFA-liver, SOFA-renal, and SOFA-cardio vascular system scores were 1.1±0.7, 0.9±0.8, 0.8±0.7, 0.7±0.7, 0.7±0.7, and 0.6±0.6, respectively (Table 1).

TABLE 1 Clinical characteristics of sepsis patients

Items	Sepsis patients (N = 184)
Age (years), mean±SD	59.6±12.0
Gender, No. (%)	
Female	60 (32.6)
Male	124 (67.4)
BMI (kg/m^2), mean±SD	23.5±3.6
Smoke status, No. (%)	
Never	123 (66.8)
Former	31 (16.8)
Current	30 (16.3)
History of drink, No. (%)	64 (34.8)
History of hypertension, No. (%)	74 (40.2)
History of hyperlipidemia, No. (%)	29 (15.8)
History of diabetes, No. (%)	23 (12.5)
History of CKD, No. (%)	16 (8.7)
History of CCVD, No. (%)	38 (20.7)
Primary infection site, No. (%)	
Abdominal infection	68 (37.0)
Respiratory infection	54 (29.3)
Skin and soft tissue infection	37 (20.1)
Other infections	25 (13.6)
Primary organism, No. (%)	
G- bacteria	102 (55.4)
G+ bacteria	52 (28.3)
Fungus	18 (9.8)
Others	32 (17.4)
Culture-negative	25 (13.6)
CRP (mg/L), median (IQR)	63.0 (43.0–91.8)
APACHE II score, mean±SD	11.3±5.2
SOFA score, mean±SD	4.8±2.1
SOFA-respiratory system score	1.1±0.7
SOFA-coagulation score	0.9±0.8
SOFA-nervous system score	0.8±0.7
SOFA-liver score	0.7±0.7
SOFA-renal system score	0.7±0.7
SOFA-cardio vascular system score	0.6±0.6

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BMI, body mass index; CCVD, cerebrovascular and cardiovascular diseases; CKD, chronic kidney disease; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

3.2 | LncRNA CASC2 in sepsis patients and healthy controls

LncRNA CASC2 was reduced in sepsis patients (median (IQR): 0.473 (0.241–0.773)) compared with healthy controls (median (IQR): 1.019 (0.676–1.685)) (p <0.001) (Figure 1A). Further ROC curve revealed that lncRNA CASC2 had a decent capacity in differentiating sepsis patients from healthy controls (area under curve (AUC): 0.815, 95% confidence interval (CI): 0.730–0.900) (Figure 1B). Particularly, the sensitivity and specificity were 1.000 and 0.250 using 1/4 quartile of lncRNA CASC2 (0.241) as the cut-off value; the sensitivity and specificity were 0.867 and 0.500 using the median of lncRNA CASC2 (0.473) as the cut-off value; the sensitivity and specificity were 0.700 and 0.750 using 3/4 quartile of lncRNA CASC2 (0.773) as the cut-off value (Figure 1C).

3.3 | Association of lncRNA CASC2 with primary infection site and primary organism

LncRNA CASC2 was differentially expressed in sepsis patients with varied primary infection sites (p = 0.018), particularly, lncRNA CASC2 was highest in patients with abdominal infection (median (IQR): 0.602 (0.361–0.844)), followed by skin and soft tissues infection (median (IQR): 0.442 (0.302–0.712)), other infections (median (IQR): 0.433 (0.180–0.965)), while the lowest in respiratory infection (median (IQR): 0.353 (0.231–0.661)) (Table 2). Regarding primary organisms, no differences in lncRNA CASC2 were found between patients with or without G- bacteria, G+ bacteria, fungus, other organisms, or culture-negative (all p >0.05).

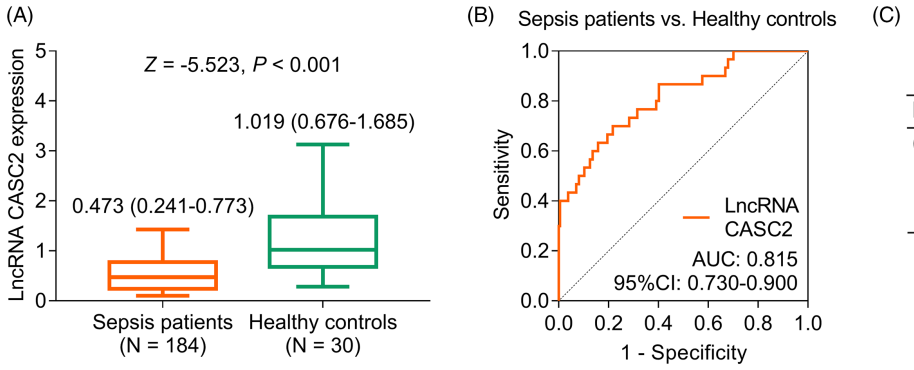

FIGURE 1 LncRNA CASC2 was reduced in sepsis patients compared with healthy controls. LncRNA CASC2 in sepsis patients and healthy controls (A). ROC curve of lncRNA CASC2 in distinguishing sepsis patients from healthy controls (B), different sensitivity and specificity when lncRNA CASC2 at 1/4 quartile, median, and 3/4 quartile in sepsis patients was set as the cut-off value (C)

TABLE 2 Correlation of lncRNA CASC2 expression with primary infection site and primary organism

Items	LncRNA CASC2 expression Median (IQR)	X^2/Z value	*p* value
Primary infection site		10.047	0.018
Abdominal infection	0.602 (0.361–0.844)		
Respiratory infection	0.353 (0.231–0.661)		
Skin and soft tissue infection	0.442 (0.302–0.712)		
Other infections	0.433 (0.180–0.965)		
Primary organism			
G- bacteria		−1.341	0.180
No	0.431 (0.200–0.771)		
Yes	0.522 (0.270–0.775)		
G+ bacteria		−0.706	0.480
No	0.468 (0.239–0.741)		
Yes	0.515 (0.265–0.832)		
Fungus		−1.142	0.254
No	0.484 (0.260–0.775)		
Yes	0.314 (0.186–0.757)		
Others		−0.173	0.862
No	0.473 (0.230–0.782)		
Yes	0.461 (0.301–0.724)		
Culture-negative		−1.289	0.198
No	0.508 (0.244–0.776)		
Yes	0.367 (0.214–0.630)		

Abbreviations: lncRNA CASC2, long noncoding RNA cancer susceptibility candidate 2; IQR, interquartile range.

3.4 | Linkage of lncRNA CASC2 with disease severity and multiple organ injury

The correlation analysis illustrated that lncRNA CASC2 was negatively related to APACHE II ($p = 0.001$) (Figure 2A), SOFA ($p < 0.001$) (Figure 2B), SOFA-respiratory ($p = 0.010$) (Figure 2C), SOFA-coagulation ($p = 0.020$) (Figure 2D), SOFA-liver ($p = 0.019$) (Figure 2F), and SOFA-renal system scores ($p = 0.010$) (Figure 2G) in sepsis patients, while no correlation was found in lncRNA CASC2 with SOFA-nervous ($p = 0.466$) (Figure 2E) or SOFA-cardio vascular system scores ($p = 0.059$) (Figure 2H).

3.5 | Correlation between lncRNA CASC2 expression and inflammatory cytokines

Subsequently, it was observed that lncRNA CASC2 was negatively correlated with TNF-α ($p = 0.024$) (Figure 3A), IL-1β ($p = 0.013$) (Figure 3B), and IL-17A ($p = 0.002$) (Figure 3E) in sepsis patients;

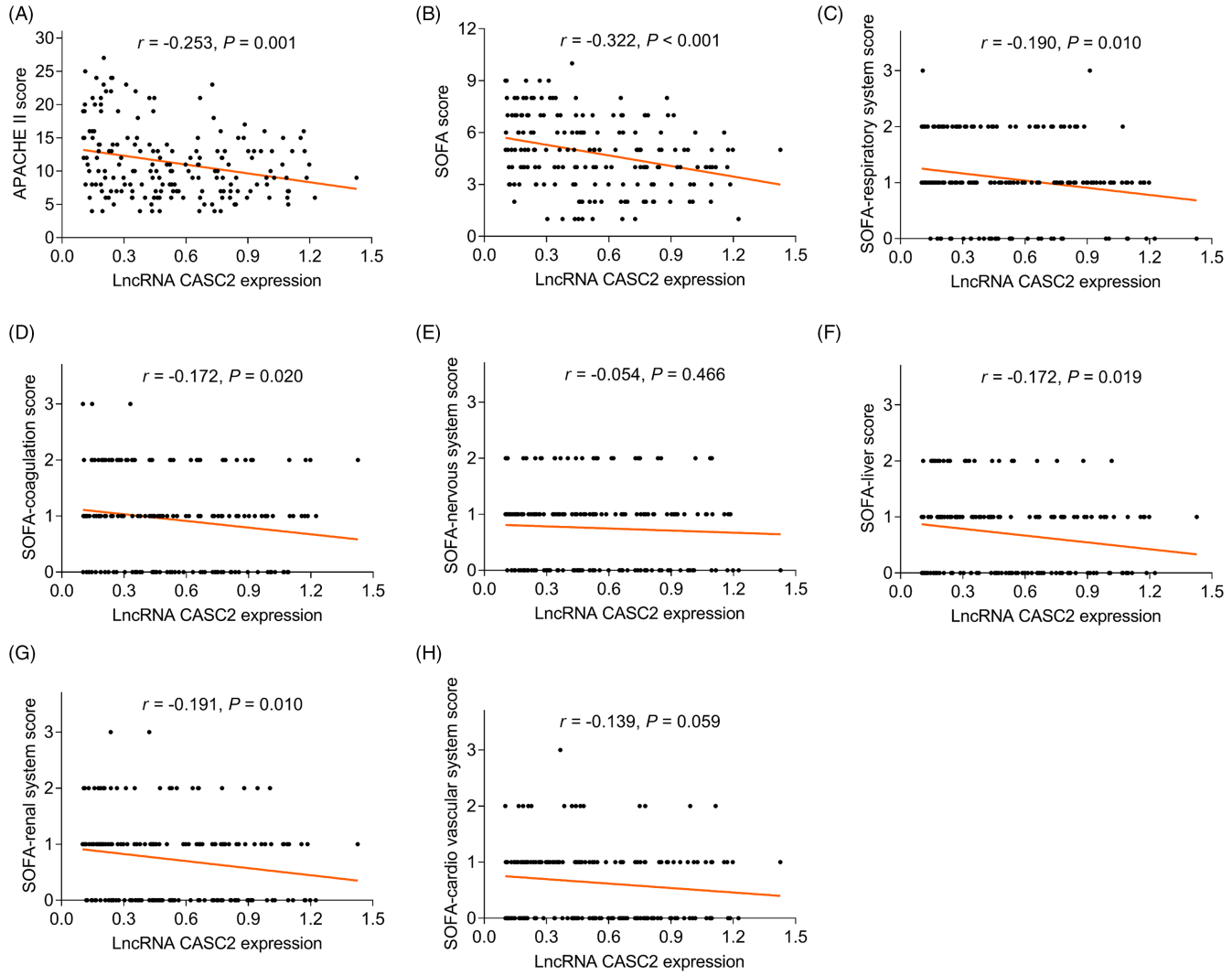

FIGURE 2 LncRNA CASC2 was negatively correlated with APACHE II and SOFA scores. Correlation of lncRNA CASC2 with APACHE II (A), SOFA (B), SOFA-respiratory (C), SOFA-coagulation (D), SOFA-nervous (E), SOFA-liver (F), SOFA-renal (G), and SOFA-cardio vascular system (H) scores in sepsis patients

whereas no correlation was observed in lncRNA CASC2 with IL-6 ($p = 0.112$) (Figure 3C) or IL-10 ($p = 0.074$) (Figure 3D).

3.6 | Correlation between lncRNA CASC2 expression and mortality

LncRNA CASC2 was decreased in sepsis deaths (median (IQR): 0.286 (0.166–0.475)) compared with survivors (median (IQR): 0.534 (0.296–0.811)) ($p < 0.001$) (Figure 4A). Meanwhile, the ROC curve exhibited that lncRNA CASC2 had an acceptable capacity in distinguishing sepsis deaths from survivors (AUC: 0.722, 95% CI: 0.635–0.810) (Figure 4B). Moreover, lncRNA CASC2 was cut off by 1/4 quartile (0.241), median (0.473), and 3/4 quartile (0.773) in sepsis patients; then the Kaplan– Meier (KM) curve was applied to further explore the relation between lncRNA CASC2 and accumulating mortality. It was found that the accumulating mortality was enhanced in patients with lncRNA CASC2 ≤ 0.473 compared those with lncRNA CASC2 > 0.473 ($p = 0.001$) (Figure 4C), while the accumulating mortality was highest in patients with lncRNA CASC2 ≤ 0.241, followed by patients with lncRNA CASC2 of 0.241–0.473, patients with lncRNA CASC2 of 0.473–0.773, and lowest in patients with lncRNA CASC2 > 0.773 ($p = 0.003$) (Figure 4D).

3.7 | Multivariate Cox's proportional hazards regression analysis for accumulating mortality

History of drink (yes vs. no) (hazard ratio [HR] = 2.631, $p = 0.008$), primary organism-fungus (yes vs. no) (HR = 4.230, $p = 0.002$), primary organism-culture-negative (yes vs. no) (HR = 5.786, $p < 0.001$), and higher SOFA score (HR = 1.498, $p < 0.001$) were all independently linked to higher accumulating mortality in sepsis patients (Table 3).

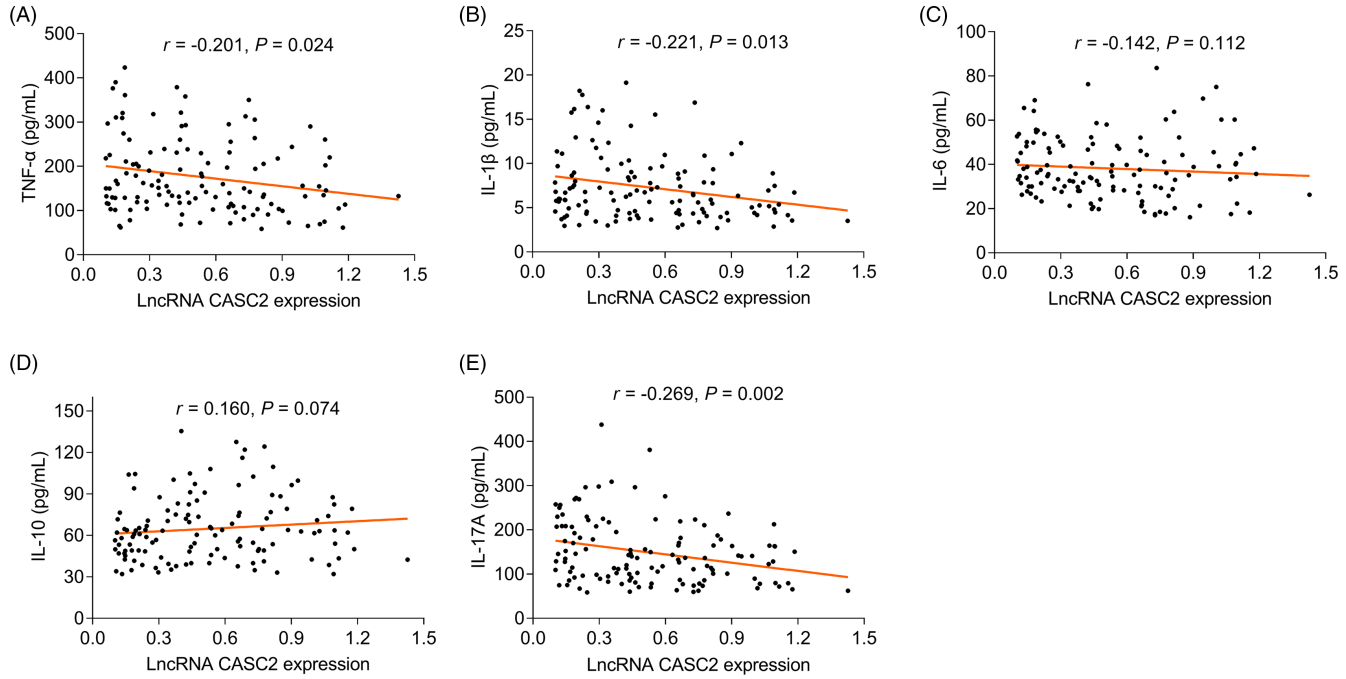

FIGURE 3 LncRNA CASC2 was reversely related to TNF-α, IL-1β, and IL-17A. Association of lncRNA CASC2 with TNF-α (A), IL-1β (B), IL-6 (C), IL-10 (D), and IL-17A (E) in sepsis patients

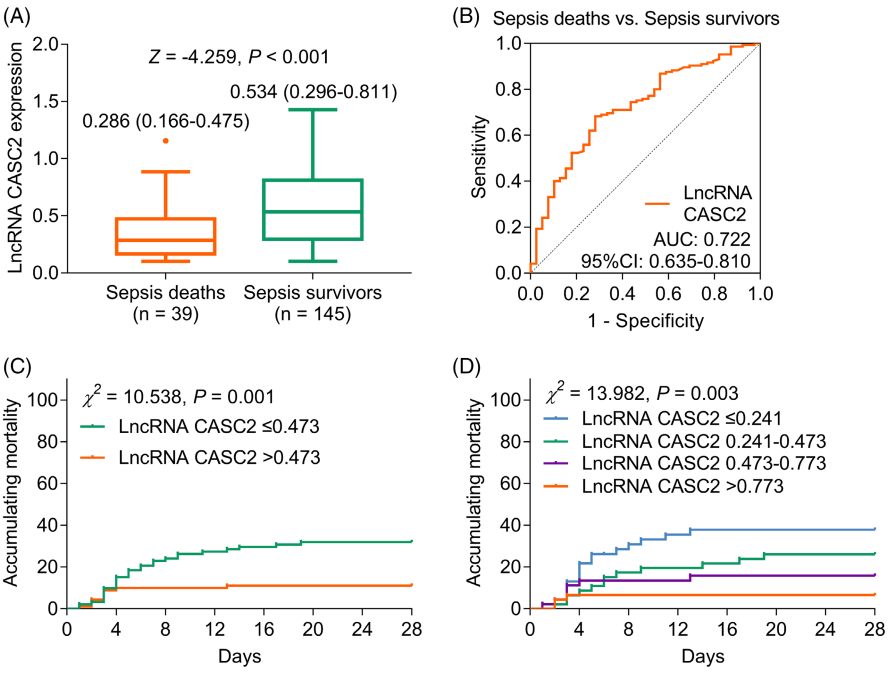

FIGURE 4 LncRNA CASC2 was reduced in sepsis deaths and negatively correlated with accumulating mortality. LncRNA CASC2 in sepsis deaths and survivors (A). ROC curve of lncRNA CASC2 in separating sepsis deaths from survivors (B), accumulating mortality in patients with lncRNA CASC2 ≤ 0.473 and lncRNA>0.473, respectively (C), accumulating mortality in patients with lncRNA CASC2 ≤ 0.241, lncRNA CASC2 within 0.241–0.473, lncRNA CASC2 within 0.473–0.773, and lncRNA CASC2 > 0.773, respectively (D)

3.8 | Multivariate logistic regression analysis for mortality risk

LncRNA CASC2 (high vs. low) (odds ratio [OR] = 0.414, $p = 0.046$), primary organism-G- bacteria (yes vs. no) (OR = 0.335, $p = 0.008$), and primary organism-others (yes vs. no) (OR = 0.210, $p = 0.049$) were all independently linked with lower mortality risk in sepsis patients, whereas, higher APACHE II score (OR = 1.118, $p = 0.004$) was independently correlated with higher mortality risk in sepsis patients (Table 4).

4 | DISCUSSION

The primary findings of this study were as follows: (1) Comparing sepsis patients to healthy controls, the lncRNA CASC2 was

inadequately expressed; (2) lncRNA CASC2 was reversely linked with disease severity and multi-organ injuries; (3) lncRNA CASC2 was negatively associated with inflammation; (4) lncRNA CASC2 could predict high mortality in sepsis patients.

LncRNA CASC2 is found to be dysregulated in several diseases characterized by inflammation and organ injury. [10,16–18] For instance, lncRNA CASC2 is upregulated in the pancreatic tissues of acute pancreatitis patients.[18] Meanwhile, lncRNA CASC2 is insufficiently expressed in the serum of rheumatoid arthritis patients.[16] At the same time, lncRNA CASC2 is diminished in the serum of septic AKI patients. [10] Moreover, a study reveals that lncRNA CASC2 is deficiently expressed in septic ALI mice. [17] Similarly, this research found that lncRNA CASC2 was decreased in sepsis patients by comparison with healthy controls. The explanation would be that lncRNA CASC2 was able to inhibit inflammation and multi-organ injuries by acting as a competing endogenous RNA (ceRNA) of miR-155, miR-27b, and miR-144-3p, which directly promote the release of NF-κB, TAB2, and aquaporin-1 (AQP1), [10,11,17] therefore reducing the incidence of sepsis. Consequently, lncRNA CASC2 was downregulated in sepsis patients. Moreover, it was also observed that when lncRNA CASC2 expression at 3/4 quartile (0.773) in sepsis patients was served as the cut-off point, the overall prominent sensitivity and specificity were achieved to discriminate sepsis patients from healthy controls. This information indicated that lncRNA CASC2 measurement might assist in sepsis diagnosis.

LncRNA CASC2 suppresses the miR-27b/TAB2 axis to reduce LPS-induced ALI. [11] Meanwhile, lncRNA CASC2 reversely modulates the miR-152-3p/PDK4 axis, therefore ameliorating sepsis-induced ALI. [12] Moreover, lncRNA CASC2 represses the miR-155/NF-κB axis, hence improving the sepsis-induced AKI. [10] The above evidence reveals that lncRNA CASC2 hinders organ injuries through various pathways. [10–12,17,19] Thus, this study further assessed the relationship between lncRNA CASC2 and multi-organ injuries in sepsis patients. It was clear that lncRNA CASC2 was inversely linked with multiple organ injuries (reflected by total SOFA score), as well as respiratory, coagulation, liver, and renal injury (reflected by SOFA sub-scales) in sepsis patients. A potential explanation could be that lncRNA CASC2 inhibited sepsis-induced injury in multiple organs, including respiratory, coagulation, liver, and renal injuries through various signaling pathways, such as the miR-545-3p/miR-545-3p/peroxisome proliferator-activated receptor-α (PPARA) axis, the miR-155/NF-κB axis, miR-144-3p/AQP1 axis, and the miR-152-3p/PDK4 axis. [10,12,17,20]

Consequently, it was linked to multiple organ injuries negatively. Subsequently, it was also found that lncRNA CASC2 reversely corresponded to disease severity (reflected by SOFA and APACHE II scores). The possible reason might be that lncRNA CASC2 could induce organ injuries by different signaling pathways as mentioned above. Besides, it was negatively correlated with inflammation in sepsis patients, thereby reflecting the septic severity.

It has been reported that lncRNA CASC2 could regulate inflammation. [10,11,21] For example, lncRNA CASC2 inhibits proinflammatory cytokines release (TNF-α, IL-6, and IL-1β) in diabetic nephropathy. [21] In addition, lncRNA CASC2 suppresses the release of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in LPS-induced ALI. [11] Then it was also observed in this study that lncRNA CASC2 was reversely linked to TNF-α, IL-1β, and IL-17A in sepsis patients. The possible explanation might be that lncRNA CASC2 could inversely modulate inflammation by various signaling pathways, including miR-155/NF-κB, miR-27b/TAB2, and miR-144/suppressor of cytokine signaling 2 (SOCS2) axes. [10,11,21]

In order to investigate the function of lncRNA CASC2 in the prognosis of sepsis patients, lncRNA CASC2 in sepsis survivors and deaths was further compared. It was found that lncRNA CASC2 was decreased in sepsis deaths compared with survivors, and it could identify sepsis deaths from survivors. Meanwhile, lncRNA CASC2 was inversely associated with accumulating mortality. Moreover, lncRNA CASC2 could independently predict lower mortality risk in sepsis patients. The potential reason could be that as mentioned above, lncRNA CASC2 was negatively linked with disease severity, inflammation, and multi-organ injuries, [10–12] therefore reflecting the mortality in sepsis patients. Thus, lncRNA CASC2 was negatively associated with sepsis mortality.

There were several limitations that existed in this study: (1) this was a single-center study, which would lead to a selection bias, (2) this study only discussed the feasibility of lncRNA CASC2 as a biomarker in sepsis patients, and further confirmation is needed to determine whether lncRNA CASC2 is applicable as a biomarker to other infectious diseases, (3) the mechanism by which lncRNA CASC2 participated in pathogenesis and progression of sepsis requires a more comprehensive understanding, which might facilitate the future development of therapeutics based on this lncRNA,

TABLE 3 Multivariate Cox's proportional hazards regression analysis for accumulating mortality

Items	*p* value	HR	95% CI	
			Lower	Upper
History of drink (yes vs. no)	0.008	2.631	1.290	5.366
Primary organism-fungus (yes vs. no)	0.002	4.230	1.721	10.396
Primary organism-culture-negative (yes vs. no)	<0.001	5.786	2.662	12.574
Higher SOFA score	<0.001	1.498	1.260	1.781

Abbreviations: CI, confidence interval; HR, hazard ratio; SOFA, Sequential Organ Failure Assessment.

TABLE 4 Multivariate logistic regression analysis for mortality risk

Items	*p* value	OR	95% CI	
			Lower	Upper
LncRNA CASC2 (high vs. low)	0.046	0.414	0.174	0.984
Primary organism-G- bacteria (yes vs. no)	0.008	0.335	0.149	0.751
Primary organism-others (yes vs. no)	0.049	0.210	0.044	0.996
Higher APACHE II score	0.004	1.118	1.037	1.205

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; lncRNA CASC2, long noncoding RNA cancer susceptibility candidate 2; OR, odds ratio.

(4) the clinical role of lncRNA CASC2 for infantile sepsis patients needed to further explore.

In conclusion, lncRNA CASC2 insufficiency reflects the release of inflammatory cytokines, serious multi-organ injuries, and higher mortality in sepsis patients. Clinically, lncRNA CASC2 could serve as a biomarker for monitoring the disease severity and predicting the prognosis, which might realize the stratified management of sepsis patients.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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