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RESEARCH ARTICLE

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Long non-coding RNA CRNDE and toll-like receptor 3 correlate with disease severity, inflammation, and mortality in sepsis

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Abstract

Objective: This study aimed to assess the interaction between long non-coding RNA colorectal neoplasia differentially expressed (lncRNA CRNDE) and toll-like receptor 3 (TLR3), and assess their correlations with disease severity, inflammation, and 28-days mortality in sepsis patients.

Methods: We consecutively enrolled 146 sepsis patients and 146 healthy controls (HCs), and collected their peripheral blood mononuclear cells to detect lncRNA CRNDE and TLR3 expressions using reverse transcription quantitative polymerase chain reaction. LncRNA CRNDE and TLR3 in sepsis patients were classified into four clusters according to quantile expressions (Quantile 1 (0%-24%), Quantile 2 (25%-50%), Quantile 3 (50%-74%), and Quantile 4 (75%-100%)) for correlation analysis.

Results: LncRNA CRNDE was upregulated in sepsis patients compared with HCs, and it showed good value in differentiating sepsis patients form HCs by receiver operating characteristic curve analysis. In sepsis patients, lncRNA CRNDE positively correlated with acute pathologic and chronic health evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) score, as well as serum creatinine (Scr). As for inflammation, lncRNA CRNDE positively correlated with C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin (IL)-1β, IL-6, and IL-8. Regarding mortality, lncRNA CRNDE positively correlated with 28-days mortality. Furthermore, lncRNA CRNDE positively correlated with TLR3, and TLR3 positively associated with APACHE II score, SOFA score, Scr, albumin, CRP, TNF-α, IL-1β, IL-6, IL-8, and 28-days mortality in sepsis patients.

Conclusion: LncRNA CRNDE interacts with TLR3, both of which correlate with advanced disease severity, inflammation, and higher 28-days mortality in sepsis patients.

KEYWORDS

inflammation, LncRNA CRNDE, mortality, sepsis, TLR3

Junhui Yang and Wei Liu contributed equally to this work.

1 | INTRODUCTION

Sepsis is a life-threatening organ dysfunction caused by dysregulated host response to infection, which affects over 30 million people annually with mortality up to 30%.[1,2] It is characterized by excessive inflammatory response, which is triggered by hyperactive innate immune system and causes significant elevation of inflammatory mediators in the peripheral blood, then eventually brings damage to the host or even death.[3] The management of sepsis relies on timely recognition, adequate administration of antibiotics, hemodynamic support, and identifying the source of infection.[4] Although efforts in therapeutic intervention as well as life support have been taken, the clinical outcomes are still unsatisfactory with significantly high hospitalization rate and mortality.[1] Despite of that, along with the increasing exposure to risk factors such as systemic inflammatory diseases, the incidence of sepsis is expanding globally.[5-7] These emphasize the importance of investigating the mechanism of sepsis pathogenesis and exploring novel biomarkers to forecast sepsis clinical outcomes.

Long non-coding RNA (lncRNA) colorectal neoplasia differentially expressed (CRNDE) is known as a critical gene that participates in inflammation development and progression of sepsis.[8,9] For instance, lncRNA CRNDE triggers inflammation through the toll-like receptor 3-nuclear factor-kappa B (TLR3-NF-κB)-cytokine signaling pathway and the downstream release of inflammatory cytokines.[10] In addition, knockdown of lncRNA CRNDE alleviates sepsis-related kidney injury via inactivating the TLR3/NF-κB pathway, which has been illustrated to induce inflammation and organ damage in sepsis.[11-14] Notably, TLR3 is closely related to innate immune and inflammatory responses, and it is previously shown to induce tissue necrosis and cause organ damage such as cardiac dysfunction during sepsis.[15,16] Based on this evidence, we hypothesized that lncRNA CRNDE might be implicated in disease progression and prognosis in sepsis patients through regulating TLR3. Thus, this study assessed the interaction of lncRNA CRNDE with TLR3 as well as their correlations with disease severity, inflammation, and 28-days mortality in sepsis patients.

2 | MATERIALS AND METHODS

2.1 | Subjects

Between January 2017 and October 2019, 146 sepsis patients treated in our hospital were continuously enrolled in this study. The inclusion criteria were as follows: (a) diagnosed as sepsis in accordance with the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[1]; (b) aged 18-80 years old; (c) no history of hematological malignancies or solid tumors; and (d) no history of human immunodeficiency virus (HIV) infection. The exclusion criteria were as follows: (a) received treatment in other hospital before admission to our hospital; (b) treated by immunosuppressive therapy within one month before enrollment; and (c) pregnant or breastfeeding women. Besides, during the same period, a total of 146 healthy subjects without inflammatory disorder were screened as healthy controls (HCs). And all HCs had no history of sepsis or malignancies and no obvious abnormity in biochemical indexes. The present study was approved by the Institutional Review Board of our hospital, and the written informed consents were collected from each participant or corresponding guardian (family member).

2.2 | Sample and data collection

Collection of peripheral blood samples for sepsis patients was performed within 24 hours after admission, which was also carried out for HCs after they signed the informed consents. All samples were treated by density gradient centrifugation post collection, and the peripheral blood mononuclear cells (PBMCs) as well as serum samples were separated then stored at −80°C for following detection. In addition, the demographics and chronic complications of sepsis patients were documented after enrollment. And the biochemical indexes and organ dysfunction severity of sepsis patients were assessed within 24 hours; meanwhile, the acute pathologic and chronic health evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) score were evaluated and recorded. Furthermore, all patients were treated as clinical practice of our hospital, and close supervision was performed until patients died in hospital or 28 days after enrollment. And the 28-days mortality was calculated for study analysis.

2.3 | LncRNA CRNDE and TLR3 detection in all subjects

The relative expressions of lncRNA CRNDE and TLR3 in PBMCs of all subjects were determined by reverse transcription quantitative polymerase chain reaction (RT-qPCR). The RNeasy Protect Mini Kit (Qiagen, Dusseldorf, Nordrhein-Westfalen, German) was used for total RNA extraction, and PrimeScript RT reagent Kit (Perfect Real Time) (Takara, Kusatsu, Shiga, Japan) was used for reverse transcription. PCR was performed using SYBR Premix DimerEraser (Takara, Kusatsu, Shiga, Japan) with GAPDH as internal reference, and the relative expressions of lncRNA CRNDE and TLR3 were calculated by $2^{-\Delta\Delta Ct}$ ($\Delta\Delta Ct = \Delta Ct$ sample$-\Delta Ct$ calibrator in which ΔCt sample $= Ct$ avg. lncRNA CRNDE or TLR3-Ct avg. GAPDH) method. The primers were as follows: LncRNA CRNDE, forward: TGGCGCTAACGGTCGGTAA, reverse: GCATCACACTTAACACCTCTCCT; TLR3, forward: GGCACTTCTCCACTCCAATGT, reverse: TGAAGACCACACGATGACTGAAT; and GAPDH, forward: GAGTCCACTGGCGTCTTCAC, reverse: ATCTTGAGGCTGTTGTCATACTTCT.

2.4 | Inflammatory cytokines detection in sepsis patients

Commercial enzyme-linked immunosorbent assay kits (Invitrogen, Waltham, Massachusetts, USA) were applied to determine the inflammatory cytokines including tumor necrosis factor-α (TNF-α),

interleukin-1β (IL-1β), IL-6, and IL-8 in serum of sepsis patients, since they were commonly investigated inflammatory cytokines in sepsis. The detection process was performed in strict accordance with the manufacturer's manual.

2.5 | Statistical analysis

Data were displayed as mean ± standard deviation (SD), median and interquartile range (IQR), or count and percentage. The comparison of the lncRNA CRNDE relative expression between sepsis patients and HCs was determined by the Wilcoxon rank-sum test. Receiver operating characteristic (ROC) curve and the area under the curve (AUC) with 95% confidence interval (CI) were used to assess the performance of lncRNA CRNDE expression in differentiating sepsis patients from HCs. For sepsis patients, according to the percentile of lncRNA CRNDE expression and TLR3 expression in all sepsis patients, they were classified into four clusters: Quantile 1 (0%-24%), Quantile 2 (25%-50%), Quantile 3 (50%-74%), and Quantile 4 (75%-100%). Correlation analysis between variables was determined by Spearman's rank correlation test. Comparison of 28-days mortality was determined by the chi-square test. P value < .05 was considered statistically significant. Statistical analysis was performed using SPSS version 24.0 (IBM, USA), and a figure was plotted using GraphPad Prism version 7.01 (GraphPad Software, USA).

3 | RESULTS

3.1 | Patients' characteristics

The sepsis patients were aged 57.1 ± 10.9 years in average, and there were 99/47 males/females (Table 1). There were 23 (15.8%), 51 (34.9%), 14 (9.6%), and 24 (16.4%) patients chronically complicated with chronic obstructive pulmonary disease, cardiomyopathy, chronic kidney failure, and cirrhosis, respectively. As for the biochemical indexes, the median level of serum creatinine (Scr), albumin, white blood cell (WBC), and C-reactive protein (CRP) were 1.8 (1.2-2.5) mg/dL, 26.6 (22.3-36.5) g/L, 11.7 (3.1-26.2) $\times 10^9$/L, and 109.0 (56.0-155.1) mg/L, respectively. The patients had median APACHE II score of 15 (10.0-19.0) and SOFA score of 6.0 (4.8-8.0). And regarding their inflammatory cytokine levels, the median values of TNF-α, IL-1β, IL-6, and IL-8 were 208.2 (136.5-321.3) pg/mL, 9.6 (4.5-19.9) pg/mL, 89.0 (52.2-170.8) pg/mL, and 127.4 (66.0-191.0) pg/mL, respectively.

3.2 | LncRNA CRNDE expression in sepsis

LncRNA CRNDE expression was elevated in sepsis patients compared with HCs (P < .001) (Figure 1A), and ROC curve analysis disclosed its value in discriminating sepsis patients from HCs with an AUC of 0.885 (95%CI:0.849-0.921) (Figure 1B).

TABLE 1 Clinical characteristics of sepsis patients

Items	Sepsis patients (N = 146)
Demographics	
Age (years), Mean ± SD	57.1 ± 10.9
Gender (male/female), No. (%)	99/47
BMI (kg/m^2), Mean ± SD	22.5 ± 4.0
Current smoking, No. (%)	51 (34.9)
Chronic complications	
COPD, No. (%)	23 (15.8)
Cardiomyopathy, No. (%)	51 (34.9)
Chronic kidney failure, No. (%)	14 (9.6)
Cirrhosis, No. (%)	24 (16.4)
Biochemical indexes	
Scr (mg/dL), Median (IQR)	1.8 (1.2-2.5)
Albumin (g/L), Median (IQR)	26.6 (22.3-36.5)
WBC ($\times 10^9$/L), Median (IQR)	11.7 (3.1-26.2)
CRP (mg/L), Median (IQR)	109.0 (56.0-155.1)
Disease severity	
APACHE II score, Median (IQR)	15 (10.0-19.0)
SOFA score, Median (IQR)	6.0 (4.8-8.0)
Inflammatory cytokines	
TNF-α (pg/mL), Median (IQR)	208.2 (136.5-321.3)
IL-1β (pg/mL), Median (IQR)	9.6 (4.5-19.9)
IL-6 (pg/mL), Median (IQR)	89.0 (52.2-170.8)
IL-8 (pg/mL), Median (IQR)	127.4 (66.0-191.0)

Abbreviations: APACHE II, acute pathologic and chronic health evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; IL, interleukin; IQR, interquartile range; Scr, serum creatinine; SD, standard deviation; SOFA, sequential organ failure assessment; TNF-α, tumor necrosis factor-α; WBC, white blood cell.

3.3 | Correlation of lncRNA CRNDE with APACHE II score and SOFA score in sepsis patients

According to the percentile of lncRNA CRNDE expression in sepsis patients, lncRNA CRNDE expression was classified into four clusters for the followed analyses: Quantile 1 (0%-24%), Quantile 2 (25%-50%), Quantile 3 (50%-74%), and Quantile 4 (75%-100%). APACHE II score and SOFA score were compared among patients at 4 clusters of lncRNA CRNDE expression to evaluate the correlation of lncRNA CRNDE with APACHE II score and SOFA score, which presented that higher lncRNA CRNDE quantile was associated with increased APACHE II score (P < .001) (Figure 2A) and SOFA score (P < .001) (Figure 2B) in sepsis patients.

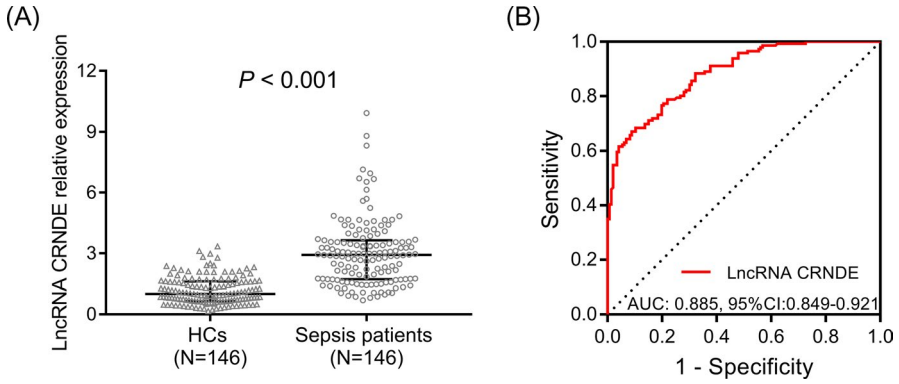

FIGURE 1 The expression of lncRNA CRNDE in sepsis and its value in predicting sepsis vulnerability. Comparison of lncRNA CRNDE expression between sepsis patients and HCs (A). The performance of lncRNA CRNDE in distinguishing sepsis patients from HCs (B). The triangles represented healthy controls, dots represented sepsis patients, the upper/lower line represented 25%/75% quantile, and the middle line represented median of lncRNA CRNDE relative expression. HCs, healthy controls; lncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed

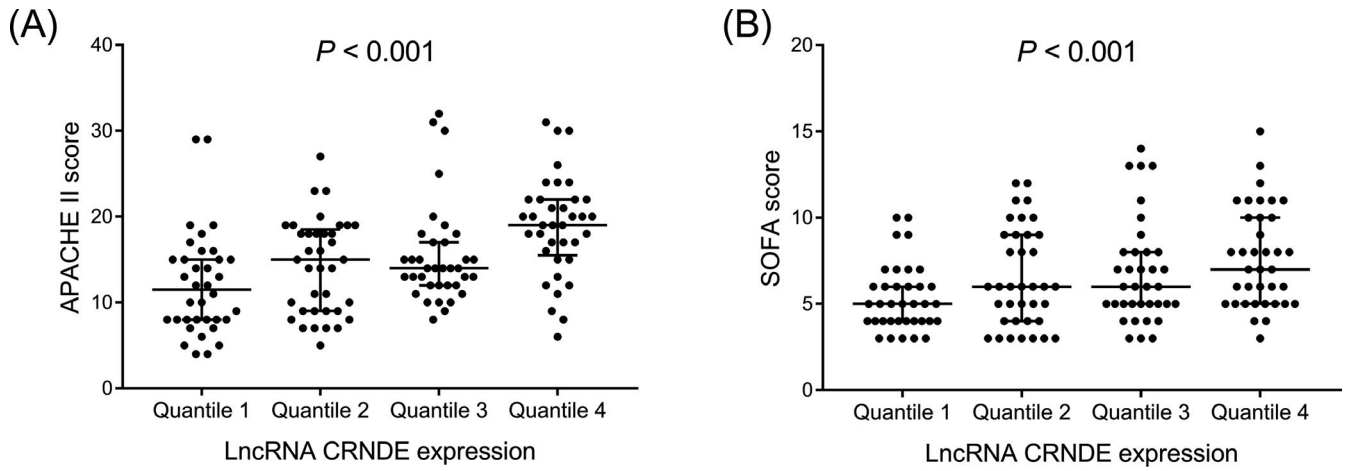

FIGURE 2 Positive correlation of lncRNA CRNDE with APACHE II score and SOFA score in sepsis patients. The correlation of lncRNA CRNDE quantile with APACHE II score (A). The correlation of lncRNA CRNDE quantiles with SOFA score (B). LncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed; APACHE II, acute pathologic and chronic health evaluation II; and SOFA, sequential organ failure assessment

3.4 | Correlation of lncRNA CRNDE with biochemical indexes in sepsis patients

Each biochemical index was compared among patients at 4 clusters of lncRNA CRNDE expression to assess the correlation of lncRNA CRNDE with the biochemical indexes, which showed that higher lncRNA CRNDE quantile was correlated with elevated Scr ($P < .001$) and CRP ($P < .001$), but not correlated with albumin ($P = .157$) or WBC ($P = .197$) in sepsis patients (Table 2).

TABLE 2 Correlation of lncRNA CRNDE with biochemical indexes in sepsis patients

Indexes	LncRNA CRNDE expression				*P* value
	Quantile 1	Quantile 2	Quantile 3	Quantile 4	
Scr (mg/dL), Median (IQR)	1.6 (0.8-2.0)	1.4 (0.9-2.2)	2.1 (1.3-3.1)	2.3 (1.3-3.2)	<.001
Albumin (g/L), Median (IQR)	27.4 (23.5-34.0)	26.2 (22.7-36.0)	26.8 (22.1-40.0)	25.7 (18.5-34.1)	.157
WBC ($\times 10^9$/L), Median (IQR)	11.9 (3.7-25.2)	11.8 (1.7-25.8)	11.6 (3.2-31.3)	14.0 (6.6-26.4)	.197
CRP (mg/L), Median (IQR)	69.8 (48.7-93.7)	93.2 (50.5-133.9)	153.2 (116.6-165.2)	129.7 (65.0-233.5)	<.001

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; lncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed; Scr, serum creatinine; WBC, white blood cell.

TABLE 3 Correlation of lncRNA CRNDE with inflammatory cytokines in sepsis patients

Indexes	LncRNA CRNDE expression				*P* value
	Quantile 1	Quantile 2	Quantile 3	Quantile 4	
TNF-α (pg/mL), Median (IQR)	145.4 (77.2-226.2)	155.6 (122.4-226.3)	301.3 (168.3-471.0)	311.2 (165.0-394.4)	<.001
IL-1β (pg/mL), Median (IQR)	8.8 (3.8-14.1)	7.2 (4.9-11.4)	15.1 (7.3-28.3)	13.9 (4.4-45.4)	.001
IL-6 (pg/mL), Median (IQR)	58.5 (42.7-126.0)	79.3 (51.3-127.7)	114.9 (73.2-176.6)	114.1 (62.6-226.4)	.003
IL-8 (pg/mL), Median (IQR)	66.0 (44.8-157.8)	133.5 (64.9-164.0)	186.7 (108.3-267.7)	125.1 (81.1-212.2)	.002

Abbreviations: IL, interleukin; IQR, interquartile range; lncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed; TNF-α, tumor necrosis factor-α.

3.5 | Correlation of lncRNA CRNDE with inflammatory cytokines in sepsis patients

Each inflammatory cytokine level was compared among patients at 4 clusters of lncRNA CRNDE expression to assess the correlation of lncRNA CRNDE with inflammatory cytokines (Table 3). It was shown that higher lncRNA CRNDE quantile was correlated with increased TNF-α ($P < .001$), IL-1β ($P = .001$), IL-6 ($P = .003$), and IL-8 ($P = .002$) levels in sepsis patients.

3.6 | Correlation of lncRNA CRNDE with 28-days mortality in sepsis patients

The 28-days mortality was 8.3%, 32.4%, 36.1%, and 45.9% in patients at Quantile 1, Quantile 2, Quantile 3, and Quantile 4 lncRNA CRNDE expression, respectively, and it was compared among patients at 4 clusters of lncRNA CRNDE expression to assess the correlation of lncRNA CRNDE with 28-days mortality. The analysis disclosed that higher lncRNA CRNDE quantile was associated with raised 28-days mortality ($P = .005$) (Figure 3) in sepsis patients.

3.7 | Correlation of lncRNA CRNDE with TLR3 in sepsis patients and HCs

LncRNA CRNDE was positively correlated with TLR3 in sepsis patients ($P < .001$, $r = .491$) (Figure 4A) and HCs ($P = .041$, $r = .169$) (Figure 4B). However, the correlation coefficient was smaller in HCs compared with that in sepsis patients, which indicated that lncRNA CRNDE was less correlated with TLR3 in HCs than that in sepsis patients.

3.8 | Correlation of TLR3 with disease severity, biochemical indexes, inflammatory cytokines, and 28-days mortality in sepsis patients

According to the percentile of TLR3 expression in sepsis patients, TLR3 expression was classified into four clusters: Quantile 1 (0%-24%), Quantile 2 (25%-50%), Quantile 3 (50%-74%), and Quantile 4 (75%-100%). Disease severity, biochemical indexes, inflammatory cytokines, and 28-days mortality were compared among patients with TLR3 expression at different quantiles (Table 4). TLR3 expression was positively correlated with APACHE II score ($P < .001$) and SOFA score ($P < .001$); positively correlated with Scr ($P < .001$), CRP ($P < .001$); negatively correlated with albumin ($P < .001$), but nor correlated with WBC ($P = .301$); positively associated with TNF-α ($P < .001$), IL-1β ($P < .001$), IL-6 ($P = .005$), and IL8 ($P = .001$); and positively correlated with 28-days mortality ($P = .004$) in sepsis patients.

4 | DISCUSSION

Our study revealed that: (a) LncRNA CRNDE was overexpressed in sepsis patients, and it distinguished sepsis patients from HCs. (b) In sepsis patients, lncRNA CRNDE was positively correlated with Scr, CRP, APACHE II score, SOFA score, TNF-α, IL-1β, IL-6, IL-8, and 28-days mortality. (c) LncRNA CRNDE was positively correlated with TLR3 in sepsis patients, and TLR3 was positively correlated with disease severity, inflammatory cytokines, and 28-days mortality as well.

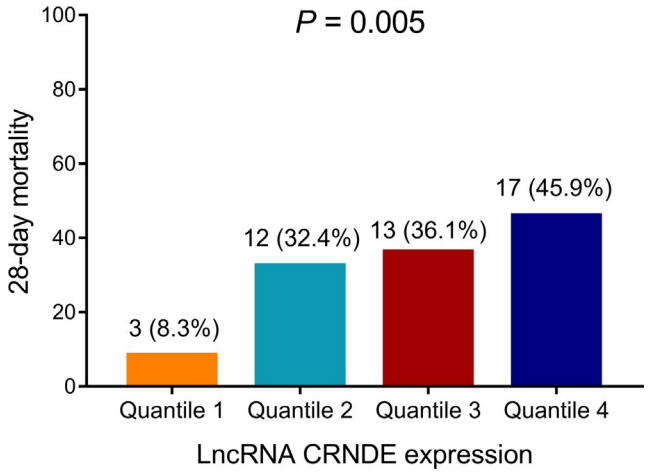

FIGURE 3 Positive correlation of lncRNA CRNDE with 28-days mortality in sepsis patients. Correlation of lncRNA CRNDE quantile with 28-days mortality. LncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed

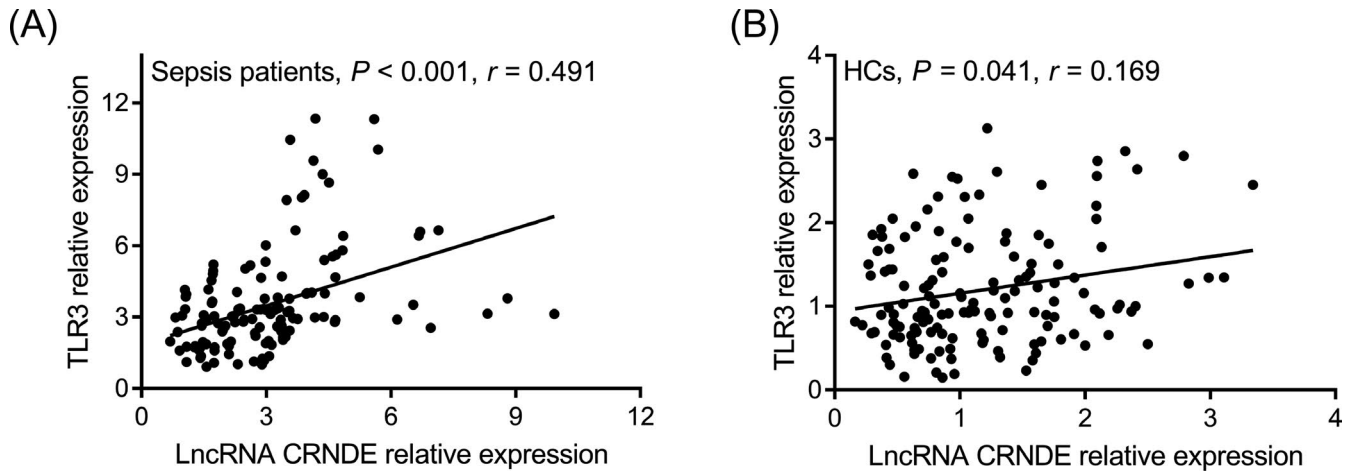

FIGURE 4 Positive correlation of lncRNA CRNDE with TLR3 in sepsis patients and HCs. The correlation of lncRNA CRNDE with TLR3 in sepsis patients (A). The correlation of lncRNA CRNDE with TLR3 in HCs (B). LncRNA CRNDE, long non-coding RNA colorectal neoplasia differentially expressed; TLR3, toll-like receptor 3; and HCs, healthy controls

TABLE 4 Correlation of TLR3 with disease severity, biochemical indexes, inflammatory cytokines, and 28-days mortality in sepsis patients

Indexes	TLR3 expression				*P* value
	Quantile 1	Quantile 2	Quantile 3	Quantile 4	
APACHE II score, Median (IQR)	9.0 (8.0-13.8)	14.0 (11.0-18.5)	15.0 (12.0-18.0)	20.0 (15.5-24.0)	<.001
SOFA score, Median (IQR)	4.0 (3.0-5.0)	6.0 (5.0-8.0)	7.0 (5.0-9.0)	8.0 (5.0-11.0)	<.001
Scr (mg/dL), Median (IQR)	1.4 (0.8-1.9)	1.7 (0.8-2.5)	2.1 (1.4-2.6)	2.0 (1.3-3.1)	<.001
Albumin (g/L), Median (IQR)	28.3 (25.6-40.6)	27.8 (23.5-44.5)	23.8 (19.0-34.9)	25.4 (18.6-31.0)	<.001
WBC ($\times 10^9$/L), Median (IQR)	10.3 (3.2-25.8)	7.3 (2.6-27.6)	18.9 (3.3-26.5)	18.3 (3.3-26.2)	.301
CRP (mg/L), Median (IQR)	71.0 (38.9-103.4)	124.9 (60.2-151.0)	140.1 (68.5-191.5)	114.0 (63.5-201.0)	<.001
TNF-α (pg/mL), Median (IQR)	157.0 (110.6-253.1)	161.5 (136.2-262.3)	202.7 (133.7-261.0)	327.6 (228.3-406.1)	<.001
IL-1β (pg/mL), Median (IQR)	7.2 (3.8-12.8)	8.5 (5.1-19.2)	9.5 (5.1-15.4)	22.1 (6.1-56.9)	<.001
IL-6 (pg/mL), Median (IQR)	54.7 (38.3-150.6)	91.6 (68.0-130.1)	91.7 (59.8-177.6)	119.7 (62.2-243.7)	.005
IL-8 (pg/mL), Median (IQR)	85.9 (35.8-166.6)	102.1 (76.5-176.0)	145.6 (91.5-189.9)	165.2 (93.8-220.0)	.001
28-days mortality, No. (%)	3 (8.3)	11 (29.7)	15 (41.7)	16 (43.2)	.004

Abbreviations: APACHE II, acute pathologic and chronic health evaluation II; CRP, C-reactive protein; IL, interleukin; IQR, interquartile range; Scr, serum creatinine; SOFA, sequential organ failure assessment; TLR3, toll-like receptor 3; TNF-α, tumor necrosis factor-α; WBC, white blood cell.

LncRNAs participate in pathological processes in various diseases including inflammatory diseases, and their roles in sepsis have been revealed in recent years. For instance, lncRNA MEG3 is overexpressed in sepsis, and it is correlated with increased disease risk, systemic inflammation, disease severity, and poor prognosis in sepsis patients.[17] In addition, lncRNA HOTAIR upregulates inflammatory cytokine levels in monocytes and promotes monocyte apoptosis, which accelerates disease progression in sepsis.[3] As for lncRNA CRNDE, it is reported that knockdown of lncRNA CRNDE reduced sepsis-induced kidney injury via inhibiting TLR3/NF-κB pathway.[11] Moreover, lncRNA CRNDE is correlated with shorter life span of sepsis patients probably via sponging microRNA-181a-5p.[18] This previous evidence discloses the molecular function of lncRNA CRNDE in sepsis, whereas there is limited information about its clinical implication, especially its correlation with disease severity or inflammation. Thus, we detected lncRNA CRNDE in sepsis patients and investigated its correlation with clinical characteristics. First of all, we found that lncRNA CRNDE was upregulated in sepsis patients compared with HCs, and it distinguished sepsis patients from HCs. This could be due to that lncRNA CRNDE might be positively correlated with inflammation as well as organ injury, which were significantly outstanding in sepsis patients. Thus, lncRNA CRNDE was overexpressed in sepsis patients. More importantly, in sepsis patients, lncRNA CRNDE was positively correlated with Scr, CRP,

APACHE II score, SOFA score, TNF-α, IL-1β, IL-6, and IL-8. Here were several reasons: (a) As shown previously, lncRNA CRNDE activated pro-inflammatory TLR3/NF-κB pathway in sepsis; therefore, it was correlated with increased inflammatory markers including CRP and inflammatory cytokines.[10] (b) In addition, lncRNA CRNDE has been reported to cause organ injury, especially kidney injury, via inducing inflammation, cell edema, and necrosis; thus, it might interfere with kidney function and positively correlate with Scr in sepsis patients.[11] (c) We observed that lncRNA CRNDE was positively correlated with inflammatory cytokines and Scr, which indicated that lncRNA CRNDE aggravated inflammation and organ injury in sepsis; thereby, it was positively associated with APACHE II score and SOFA score. As for the prognostic value of lncRNA CRNDE, it was observed to be positively correlated with 28-days mortality in sepsis patients. This could be explained by that lncRNA CRNDE facilitated the release of inflammatory cytokines via activating TLR3/NF-κB pathway,[10] causing damage to organs and contributing to increased disease severity, thereby, led to higher 28-days mortality in sepsis patients.

As shown by previous study, silencing lncRNA CRNDE inhibited the activation of TLR3 in a mouse model of sepsis and reduced sepsis-induced kidney injury.[11] Thus, we speculated that lncRNA CRNDE might be directly correlated with TLR3 in sepsis patients as well, and their interaction might be associated with disease severity, inflammation, and mortality in sepsis patients. It was observed that lncRNA CRNDE was positively correlated with TLR3 in sepsis patients and HCs, whereas the correlation coefficient was smaller in HCs compared with that in sepsis patients. This implied that lncRNA CRNDE presented a stronger correlation with TLR3 in sepsis patients than that in HCs. Furthermore, TLR3 was disclosed to be positively associated with disease severity, inflammation, and 28-days mortality in sepsis patients as well. The reasons included: (a) TLR3 was a key regulator of antiviral immune responses, and it controlled the expression of inflammatory cytokines via activating NF-κB.[19] (b) Additionally, TLR3 was shown to induce organ dysfunctions and decrease the survival rate in sepsis.[12-14,16,19] Thereby, TLR3 was positively correlated with disease severity, inflammation, and 28-days mortality of sepsis patients in our study.

There remained some limitations to our study. Firstly, although lncRNA CRNDE was shown to be correlated with several inflammatory cytokines in this study, further investigation about the influence of lncRNA CRNDE on more inflammation markers (including anti-inflammatory markers) could be added in future studies for validation. Secondly, only the correlation of lncRNA CRNDE with TLR3 was assessed in this study, while whether lncRNA CRNDE induced disease progression via directly regulating TLR3/NF-κB pathway was still unknown and needed further validation by functional experiments. Lastly, limited sample size might cause reduced statistical power; thus, further larger cohort from multiple centers might help improve the persuasiveness of the results.

In conclusion, lncRNA CRNDE interacts with TLR3 and correlates with advanced disease severity, inflammation, and higher 28-days mortality in sepsis patients, which suggests the potential of lncRNA CRNDE and TLR3 measurements in disease monitoring of sepsis.

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None.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

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