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RESEARCH ARTICLE

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Evaluating the potency of blood long noncoding RNA PVT1 as candidate biomarker reflecting inflammation, multiple organ dysfunction, and mortality risk in sepsis patients

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Abstract

Objective: Long noncoding RNA plasmacytoma variant translocation 1 (lnc-PVT1) promotes septic inflammation and organ injuries via multiple ways, while its clinical engagement in sepsis management is indistinct. This study aimed to investigate its relationship with inflammation, multiple organ dysfunction, and mortality risk in sepsis patients.

Methods: Sepsis patients and age-/gender-matched healthy controls were enrolled; their lnc-PVT1 expression in plasma were detected by RT-qPCR. For sepsis patients only, the inflammatory cytokine levels (tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-17A) in plasma were detected by ELISA. According to the survival data during 28-day follow-up, sepsis patients were divided into sepsis survivors and sepsis deaths.

Results: Lnc-PVT1 expression was increased in sepsis patients ($N = 157$) compared with healthy controls ($N = 80$) ($p < 0.001$). In sepsis patients, lnc-PVT1 was linked with higher acute physiology and chronic health evaluation II (APACHEII) score ($p = 0.001$), total sequential organ failure assessment (SOFA) score, and its most subitems (SOFA-respiratory system, SOFA-coagulation, SOFA-liver, SOFA-cardiovascular system, and SOFA-renal system scores) (all $p < 0.01$), but not SOFA-nervous system score ($p = 0.091$); it did not relate to primary infection sites either ($p = 0.204$). Furthermore, lnc-PVT1 correlated with increased C-reactive protein, TNF-α, IL-1β, and IL-17 in sepsis patients (all $p < 0.01$). Additionally, lnc-PVT1 expression was higher in sepsis deaths than that in sepsis survivors ($p < 0.001$), following receiver-operating characteristic curve disclosed that lnc-PVT1 predicted 28-day septic mortality risk (area under the curve: 0.789, 95% confidence interval: 0.702–0.875).

Conclusion: Circulating lnc-PVT1 exhibits the potential as a biomarker in sepsis patients to inform inflammation, multiple organ dysfunction, and mortality risk.

KEYWORDS
inflammation, long noncoding RNA PVT1, mortality risk, multiple organ dysfunction, sepsis

Jing Chen and Haibo Ren contributed equally to this work.

1 | INTRODUCTION

Sepsis, a common and potentially fatal systemic illness, develops from dysregulated systemic inflammatory and immune response to bacterial, fungal, and/or viral infections.[1,2] Sepsis rapidly progresses to multiple organ failure, acidosis, septic shock, and eventually deaths.[3] As a medical emergency, earlier identification and intervention (including appropriate antibiotic treatment and restoration of tissue perfusion via fluid resuscitation) have been considered as a priority in the management of sepsis.[4–7] However, in the absence of sensible and efficient biomarkers, underrecognition of sepsis and delayed assessment result in the emergency of drug-resistant pathogens, substantial long-term complications, prolonged hospitalization stay, and dismal prognosis.[8,9] To aid in the optimization of sepsis patient management and the improvement of prognosis, more emphasis should be placed on the explorations of novel and rapidly measurable biomarkers for reflecting disease development, progression, and prognosis of sepsis patients.

Long noncoding RNAs (lncRNAs) are highly stable and readily detectable in blood, implying that long noncoding RNAs might be rapidly measurable biomarkers for disease development and progression.[10] Among these identified lncRNAs, long noncoding RNA plasmacytoma variant translocation 1 (lnc-PVT1), a large long noncoding RNA, is located on chromosome 8 telomeric to the c-MYC gene, which is widely known as an oncogene in multiple cancers.[11] Besides its well-known role in cancers, the involvement of lnc-PVT1 in the pathophysiological processes of inflammation and organ dysfunction (including lung, heart, and kidney) has recently gained attention.[12–18] For instance, lnc-PVT1 is highly expressed in myocardial tissues, which enhances the release of inflammatory cytokines and induces myocardial injury through the activation of mitogen-activated protein kinase (MAPK)/nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) pathway in sepsis rats.[12] Another study reveals that overexpression of lnc-PVT1 inhibits cell viability while promotes cell apoptosis and the secretion of inflammation cytokines (including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-17 (IL-17), and interleukin-6 (IL-6)) via modulating c-Jun-N-terminal kinase (JNK)/NF-κB pathway in lipopolysaccharide-induced septic acute kidney injury model.[13] Considering that lnc-PVT1 is key in the inflammation and multiple organ dysfunction (such as lung, heart, and kidney) in sepsis, it was speculated that lnc-PVT1 might be implicated in reflecting organ failures and prognosis in sepsis patients. Nevertheless, the clinical implication of lnc-PVT1 in sepsis remains poorly investigated.

In the present study, we detected the lnc-PVT1 expression in sepsis patients and healthy controls, then explored the correlation of lnc-PVT1 with inflammation, organ dysfunction, and prognosis in sepsis patients.

2 | MATERIALS AND METHODS

2.1 | Subjects

This study consecutively enrolled 157 sepsis patients and 80 healthy controls. The sepsis patients were recruited from March 2017 to December 2019, and the healthy controls were recruited from November 2019 to December 2019. The inclusion criteria of sepsis patients were: (1) diagnosed as sepsis according to the sepsis definitions in the Third International Consensus[19]; (2) admitted to our department within 12 hr after onset of sepsis symptom; (3) no less than 18 years old; (4) not received immunosuppressive therapy within 6 months before admission; and (5) seronegative for human immunodeficiency virus (HIV). The exclusion criteria of sepsis patients were: (1) suffering from or had a history of hematological malignancies or other solid tumors; (2) complicated with congenital immunodeficiency or autoimmune diseases; and (3) pregnant or lactating woman. Healthy controls were recruited from the health examination centers. The inclusion criteria of healthy controls were: (1) age and gender matched with sepsis patients and (2) had no obvious abnormality in biochemical indexes, which was confirmed in the health examination. The exclusion criteria of healthy controls were: (1) history of sepsis or other severe infections; (2) history of hematological malignancies or other solid tumors; and (3) complicated with inflammatory disease. This study was approved by the Institutional Review Board. All subjects or their family members provided the written informed consents. Of note, since it was difficult to healthy controls who were willing to participate the study, fewer healthy controls were enrolled.

2.2 | Data and sample collection

Data of complete diagnostic workup for patients were recorded, which included age, gender, body mass index (BMI), primary infection site, primary organism, C-reactive protein (CRP) level, acute physiology and chronic health evaluation II (APACHE II) score, and sequential organ failure assessment (SOFA) score. The primary organism was cultured prior to initiating antimicrobial therapy, and APACHE II score and SOFA score were assessed within 24 hr after admission. Peripheral blood was drawn from sepsis patients within 24 hr after admission. For healthy controls, their peripheral blood was collected when they underwent health examination after providing informed consents. The plasma was centrifugated from peripheral blood at 3000 g for 20 min. The plasma was stored at −80°C until using.

2.3 | Lnc-PVT1 detection

For all subjects, the lnc-PVT1 relative expression in plasma was detected by reverse transcription quantitative polymerase chain reaction (RT-qPCR). Initially, QIAamp RNA Blood Mini Kit (Qiagen,

German) was used to extract total RNA from plasma samples. Following that, the reverse transcription reaction was performed to convert RNA to complementary DNA (cDNA) using PrimeScript™ RT reagent Kit (Takara, China), and the cDNA was amplified using TB Green™ Fast qPCR Mix (Takara, China). Lastly, the relative level of lnc-PVT1 was quantified using $2^{-\triangle\triangle Ct}$ method with GAPDH as internal reference. Primers were designed according to the previous study[20]: lnc-PVT1 forward primer: 5'-TGAGAACTGTCCTTACGTGACC-3'; reverse primer: 5'-AGAGCACCAAGACTGGCTCT-3'; GAPDH forward primer: 5'-TGACCACAGTCCATGCCATCAC-3'; and reverse primer: 5'-GCCTGCTTCACCACCTTCTTGA-3'.

2.4 | Inflammation cytokine detection

For sepsis patients, the level of inflammatory cytokine (TNF-α, IL-1β, and IL-17) in plasma was detected by enzyme-linked immunosorbent assay (ELISA). All ELISA kits used in this assay were purchased from Thermo Fisher Scientific. The standard procedures were carried out referring to the instructions of the kits. In brief, firstly, the standards and samples were added to the 96-well plate and banded to the immobilized antibody. A sandwich is then formed by the addition of the second antibody. After incubation, tetramethylbenzidine (TMB) substrate was added to generate blue coloration. Stop solution was then added, and the signal intensity was measured at 450-nm wavelengths on microplate reader (BioTek, USA).

2.5 | Follow-up data

After admission, all patients were continuedly followed up until death or finishing 28-day surveillance. During the 28-day follow-up, the survival status was recorded, and all sepsis patients were divided into sepsis survivors and sepsis deaths.

2.6 | Statistical analysis

SPSS 24.0 statistical software (IBM, USA) and GraphPad Prism 8.02 (GraphPad Software Inc., USA) were used for statistical analysis. Continuous variables were checked for normality by the Kolmogorov–Smirnov test. Normally distributed variables were displayed as mean ± standard deviation, and non-normal distributed variables were displayed as median (interquartile range (IQR)). The Wilcoxon rank-sum test was used to compare the difference of lnc-PVT1 between two subjects; the Kruskal–Wallis H rank-sum test was used to compare the difference of lnc-PVT1 among three or above subjects. The Spearman's rank correlation test was used in analyzing the correlation between two continuous variables. Receiver-operating characteristic (ROC) curve and the area under the curve (AUC) were used to assess the performance of lnc-PVT1 in predicting 28-day mortality risk of sepsis patients. p value <0.05 was considered as statistically significant.

TABLE 1 Sepsis patients' characteristics

Items	Sepsis patients ($N = 157$)
Age (years), mean ± SD	56.2 ± 12.3
Gender, no. (%)	
Female	63 (40.1)
Male	94 (59.9)
BMI (kg/m^2), mean ± SD	23.2 ± 3.7
Primary infection site, no. (%)	
Abdominal infection	65 (41.4)
Respiratory infection	33 (21.0)
Skin and soft-tissue infection	29 (18.5)
Others	30 (19.1)
Primary organism, no. (%)	
G-	83 (52.9)
G+	37 (23.6)
Others	80 (51.0)
CRP (mg/L), median (IQR)	106.7 (54.1–141.4)
APACHE II score, mean ± SD	12.5 ± 6.6
SOFA score, mean ± SD	5.6 ± 2.7

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; CNS, central nervous system; CRP, C-reactive protein; G−, Gram negative; G+, Gram positive; IQR, interquartile range; SOFA, sequential organ failure assessment; SD, standard deviation.

3 | RESULTS

3.1 | Clinical features of sepsis patients

In the analyzed sepsis patients ($N = 157$), there were 63 (40.1%) females and 94 (59.9%) males, with the mean age of 56.2 ± 12.3 years and the mean BMI of 23.2 ± 3.7 kg/m^2 (Table 1). As to primary infection site, 65 (41.4%), 33 (21.0%), 29 (18.5%), and 30 (19.1%) sepsis patients had abdominal infection, respiratory infection, skin and soft-tissue infection, and other infections, respectively. In terms of primary organism, 83 (52.9%), 37 (23.6%), and 80 (51.0%) sepsis patients had G-, G+, and other primary organisms, respectively. Additionally, the median CRP was 106.7 (54.1–141.4) mg/l; the mean APACHE II score was 12.5 ± 6.6; the mean SOFA score was 5.6 ± 2.7. In aspect of healthy controls, their mean age was 53.7 ± 11.9 year and mean BMI was 22.9 ± 2.9 kg/m^2, with 65% males and 35% females. By comparison, no difference of age ($p = 0.137$), gender ($p = 0.443$), or BMI ($p = 0.467$) was observed between sepsis patients and healthy controls.

3.2 | Comparison of lnc-PVT1 between sepsis patients and healthy controls

Lnc-PVT1 expression was increased in sepsis patients compared with healthy controls (median (IQR): 2.495 (1.822–3.475) vs. 1.000 (0.592–1.677), $p < 0.001$) (Figure 1).

3.3 | Correlation of lnc-PVT1 with total SOFA score and subitems of SOFA score in sepsis patients

Lnc-PVT1 was positively correlated with total SOFA score and APACHEII score ($p = 0.001$, $r = 0.282$) in sepsis patients ($p < 0.001$, $r = 0.373$) (Figure 2A, B). As for the correlation of lnc-PVT1 with subitems of SOFA score, lnc-PVT1 was positively correlated with SOFA-respiratory system score ($p < 0.001$, $r = 0.411$), SOFA-coagulation score ($p = 0.005$, $r = 0.223$), SOFA-liver score ($p < 0.001$, $r = 0.288$), SOFA-cardiovascular system score ($p < 0.001$, $r = 0.291$), and SOFA-renal system score ($p < 0.001$, $r = 0.298$), while it was not correlated with SOFA-nervous system score ($p = 0.091$, $r = 0.135$) in sepsis patients (Table 2). Besides, lnc-PVT1 did not relate to primary infection stie ($p = 0.204$, Figure S1). Collectively, these data indicated that lnc-PVT1 was positively correlated with multiple organ dysfunction in sepsis patients.

3.4 | Correlation of lnc-PVT1 with inflammation in sepsis patients

Lnc-PVT1 was positively correlated with CRP ($p < 0.001$, $r = 0.418$) (Figure 3A), TNF-α ($p < 0.001$, $r = 0.373$) (Figure 3B), IL-1β ($p = 0.002$, $r = 0.248$) (Figure 3C), and IL-17 ($p < 0.001$, $r = 0.316$) in sepsis patients (Figure 3D). Collectively, these data indicated that lnc-PVT1 was positively correlated with inflammation in sepsis patients.

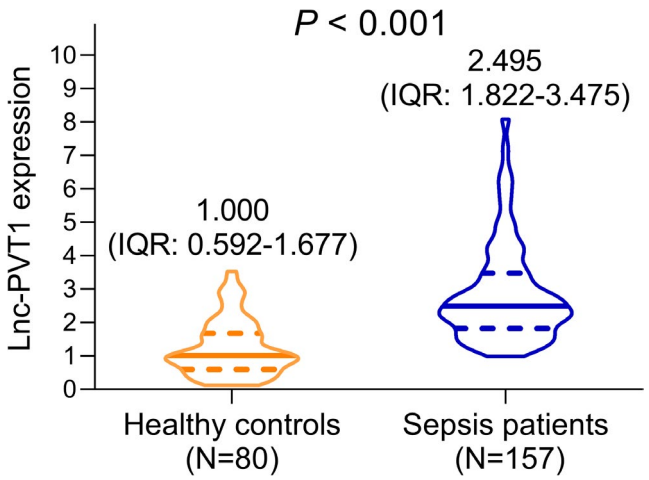

FIGURE 1 Comparison of lnc-PVT1 expression between health controls and sepsis patients. In violin graphs, full line represented median value, dotted line represented 25th percentile value and 75th percentile value, and cross width represented the distribution

3.5 | The value of lnc-PVT1 for predicting 28-day mortality risk in sepsis patients

Based on the survival status during the 28-day follow-up, sepsis patients were divided into sepsis survivors and sepsis deaths. There were 125 (79.6%) sepsis survivors and 32 (20.4%) sepsis deaths. Their lnc-PVT1 expression was then compared, which revealed that lnc-PVT1 expression was higher in sepsis deaths than that in sepsis survivors (median (IQR): 4.224 (2.707–4.967) vs. 2.254 (1.660–2.964), $p < 0.001$) (Figure 4A). The following ROC curve analysis exhibited that lnc-PVT1 (AUC: 0.789, 95%CI: 0.702–0.875) could predict 28-day mortality risk in sepsis patients (Figure 4B). At the best cut-off point (the point at which the sum of sensitivity and specificity was the largest; lnc-PVT1 = 2.670), the sensitivity was 84.4% and the specificity was 68.0%. However, after multivariate analysis, lnc-PVT1 was not an independent factor for predicting mortality (Table S1), indicating it might affect the prognosis via interaction of other factors such as inflammation and organ dysfunctions.

4 | DISCUSSION

LncRNA, as a novelly discovered group of noncoding RNAs, is closely engaged in the pathogenesis of many critically ill diseases including sepsis.[21,22] To take examples, a famous lncRNA, HOTAIR, enhances T cell exhaustion to promote septic immunosuppression[23]; then, another commonly studied lncRNA, UCA1, regulates EZH2/HOXA1 signaling to promote inflammation in sepsis-induced pneumonia[24]; what's more, TUG1 (also a famous lncRNA) attenuates sepsis caused lung injury via miR-494/PDK4 axis.[25]

Growing evidence elucidates the importance of lnc-PVT1 in regulating inflammation in multiple diseases including sepsis.[12,13,15–17] For instance, in asthma, lnc-PVT1 facilitates the expressions of IL-1β, IL-6, and TNF-α via the modulation of miR-149.[12] As to sepsis, lnc-PVT1 induces the secretion of inflammatory factors (including TNF-α, IL-1β, IL-6, intrelukin-10, IL-17, and interferon-γ) via down-regulating miR-143.[12] Meanwhile, the involvement of lnc-PVT1 in the organ dysfunction of sepsis is also elucidated.[12–15] For instance, one study based on the myocardial cell model of sepsis reveals that

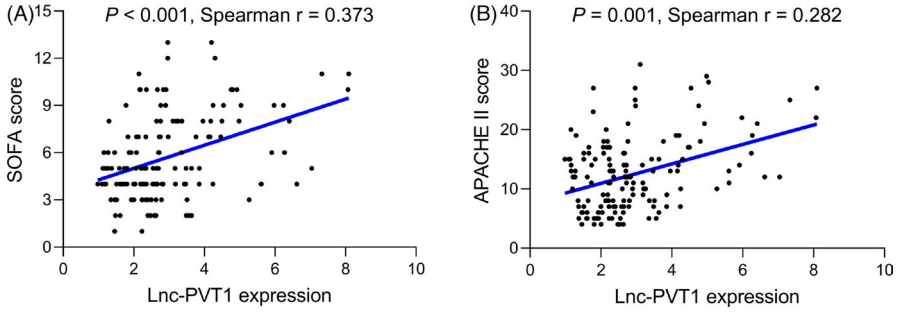

FIGURE 2 Lnc-PVT1 positively correlated with SOFA and APACHE II scores in sepsis patients. Correlation of lnc-PVT1 with SOFA score (A) and APACHE II score (B) in sepsis patients

lnc-PVT1 knockdown promotes cell apoptosis in lipopolysaccharide-induced heart cells via upregulating c-Myc, Bid, Bax, and caspase-3 expressions.[14] Furthermore, curcumin suppresses lnc-PVT1 expression in LPS-induced septic acute kidney tissues and mitigates LPS-induced septic acute kidney injury in mice.[18] Based on the critical role of lnc-PVT1 in the inflammation and multiple organ dysfunction (such as lung, heart, and kidney) in sepsis, lnc-PVT1 might serve as a possible biomarker of systematic inflammation, multiple organ dysfunction, and mortality risk in sepsis patients, while no study has been investigated yet.

In the present study, we detected the expression of lnc-PVT1 in sepsis patients and healthy controls; furthermore, we explored its potential role in indicating organ dysfunction in sepsis patients. It was found that lnc-PVT1 was increased in sepsis patients compared with healthy controls, which might be explained by that: Excessive inflammation and multiple organ dysfunction were key activities in the development and progression of sepsis; meanwhile, lnc-PVT1 could exaggerate inflammation, accelerate cell damage and multiple organ dysfunction (such as lung, heart, and kidney) through the mechanism of JNK/NF-κB and MAPK/NF-κB pathways; hence, lnc-PVT1 was highly expressed in sepsis patients.[1,12–14] Besides, it was observed that lnc-PVT1 was positively correlated with multiple organ dysfunction in sepsis patients, which were reflected by its positive correlation with SOFA-respiratory system, SOFA-coagulation, SOFA-liver, SOFA-cardiovascular system, and SOFA-renal system. Some possible explanations were as follow: (i) lnc-PVT1 probably enhanced the secretion of inflammatory factors (such as prostaglandin E2, IL-1β, IL-6, and TNF-α) via increasing PKC, MyD88, and NF-κB expressions, which contributed to the loss of barrier integrity, leakage of intravascular proteins/plasma into the extravascular space, and exposure of tissue factors to blood coagulation factors, edema formation and subsequently attenuated microvascular perfusion, thereby, leading to blood clotting multiple organ failure in sepsis patients[2,17,26]; (ii) lnc-PVT1 probably repressed cell viability but facilitated cell apoptosis in respiratory epithelial cells, cardiomyocytes, hepatocytes, and endothelial cells by the mechanisms of JNK/NF-κB and MAPK/NF-κB pathways during sepsis, which induced cell damage in vital organs (such as lung, heart, and kidney) and subsequent multiple organ dysfunction; hence, lnc-PVT1 was closely linked with multiple organ dysfunction in sepsis patients[2,12–14,16]; and (iii) lnc-PVT1 could regulate autophagy via multiple ways to induce organ dysfunction.[27,28] Furthermore, the present study disclosed that lnc-PVT1 was positively correlated with inflammation in sepsis patients (reflected by their correlation with CRP, TNF-α, IL-1β, and IL-17). Possible explanation was as follows: lnc-PVT1 could mediate the activation of several downstream signaling pathways (such as JNK, MAPK, and NF-κB), which triggered the transcription of multiple activation genes that were involved in the inflammation (such as TNF, IL-1, and IL-18), which mediated a cascade of other inflammatory cytokines and chemokines, devoting to persistent and uncontrolled inflammation, thereby, lnc-PVT1 was linked

TABLE 2 Correlation of lnc-PVT1 with subitems of SOFA score in sepsis patients

	Lnc-PVT1 relative expression	
Items	***p* value**	**Spearman *r***
SOFA-respiratory system	<0.001	0.411
SOFA-coagulation	0.005	0.223
SOFA-liver	<0.001	0.288
SOFA-cardiovascular system	<0.001	0.291
SOFA-nervous system	0.091	0.135
SOFA-renal system	<0.001	0.298

Note: Correlation was determined by the Spearman's rank correlation test. lnc-PVT1, long noncoding RNA PVT1; SOFA, sequential organ failure assessment.

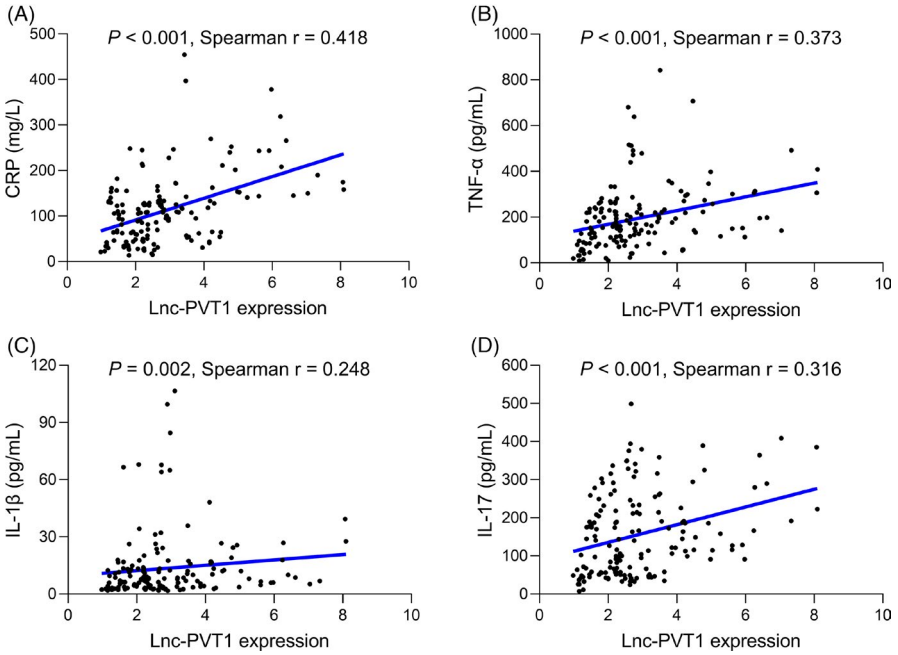

FIGURE 3 Lnc-PVT1 positively correlated with inflammatory indexes in sepsis patients. Correlation of lnc-PVT1 with CRP (A), TNF-α (B), IL-1β (C), and IL-17 (D) levels in sepsis patients

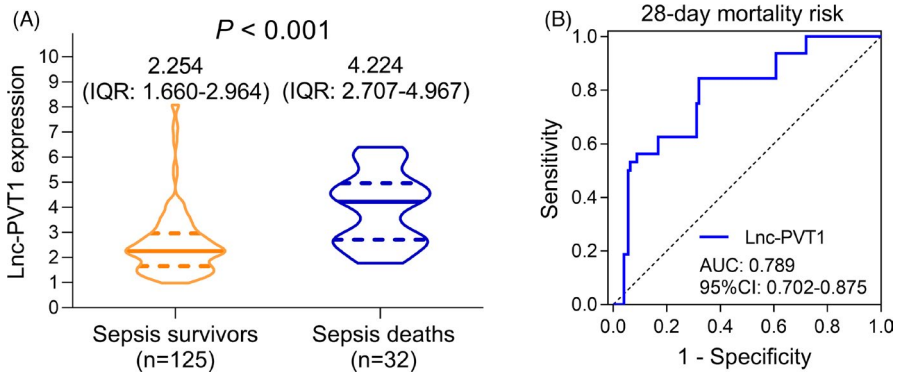

FIGURE 4 Lnc-PVT1 correlated with 28-day mortality risk in sepsis patients. Comparison of lnc-PVT1 between sepsis survivors and sepsis deaths (A). ROC curve analysis of lnc-PVT1 in predicting 28-day mortality risk in sepsis patients (B). In violin graphs, full line represented median value, dotted line represented 25th percentile value and 75th percentile value, and cross width represented the distribution

with inflammation in sepsis patients.[2,12,17] Interestedly, the present study exhibited that the most common infection site that resulted in sepsis was the abdominal infection (41.4%), followed by respiratory infection (21.0%). While from a review, the most common infection site that leads to sepsis was the lung infection, followed by abdominal infection.[1] The discripancy might be explained by that the relatively small sample size of enrolled sepsis patients might limit the generalizability of our finding.

Regarding the prognostic value of lnc-PVT1 in sepsis patients, no preceding evidence has been published yet. In the present study, it was exhibited that lnc-PVT1 could predict 28-day mortality risk in sepsis patients (AUC: 0.789, 95%CI: 0.702–0.875). The possible reasons might include that: (i) lnc-PVT1 probably prompted excessive inflammation, cell injury, and multiple organ dysfunction via the modulation of several pathways and genes (such as MyD88, JNK, and NF-κB), which exacerbated the disease activity and dismal prognosis in sepsis patients; therefore, lnc-PVT1 could predict 28-day mortality risk in sepsis patients[12–16]; (ii) based on aforementioned findings, lnc-PVT1 was related to exacerbated disease activity (amplified inflammation and multiple organ dysfunction); hence, lnc-PVT1 was indirectly associated with worse prognosis in sepsis patients.

It is interesting to discover the source of plasma lnc-PVT1 in sepsis, while no related detect is performed in our study; we think T lymphocytes are the main contributor to plasma lnc-PVT1. Besides, TNF-α, IL-1β, and IL-17 are common proinflammatory cytokines; meanwhile, they are reported to be regulated by lncRNA PVT1; therefore, they are detected in our study.

The present study initially unraveled the clinical role of lnc-PVT1 in sepsis patients regarding its correlation with inflammation, multiple organ dysfunction, and poor prognosis; however, the following were some limitations. First, with a relatively small sample size (only 157 sepsis patients), the statistic power of the analyses might be reduced. Second, the molecular mechanism regarding the effect of lnc-PVT1 on regulating inflammation and organ dysfunction was not explored, while some previous studies have been conducted to investigate this. Third, only four inflammatory indexes (CRP, TNF-α, IL-1β, and IL-17) were assessed and included in analyses; further studies were needed for detecting more inflammatory indexes (such as IL-6) in sepsis patients. Fourth, the lnc-PVT1 expression was only assessed at a single time point; further study investigating the longitudinal change of lnc-PVT1 during the follow-up and during the treatment of sepsis would be desirable. Fifth, anti-inflammation treatment would affect lnc-PVT1 level then caused bias to the findings. Sixth, enrollment of a cohort of disease controls to verify the diagnostic value of lnc-PVT1 for sepsis is needed.

To sum up, overexpressed lnc-PVT1 relates to exaggerated inflammation and multiple organ dysfunction to some extent; furthermore, it also displays the potential for predicting 28-day mortality risk in sepsis patients. These evidences would provide new information and may help to improve the management of sepsis.

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CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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