ORIGINAL ARTICLE

Annals of Agricultural and Environmental Medicine
www.aaem.pl

LINC00861 protects against sepsis-associated acute kidney injury by regulating apoptosis and inflammation via miR-151a-3p/PDHA1 Axis

Xinghua Li[1+,A-D,F], Debiao Yu[2+,A-D,F], Dongqin Shen[3,A-D,F], Yeting Zhang[4,A-C,E-F], Wei Wang[5,B-C,E-F] ✉

[1] *Intensive Care Unit, Jinan Zhangqiu District People's Hospital, Jinan 250200, China*
[2] *Department of Medicine, Dongxihu Hospital of TCM, Wuhan 430040, China*
[3] *ICU, Jiangsu Provincial Hospital of Chinese Medicine Chongqing Hospital (Chongqing Yongchuan District Traditional Chinese Medicine Hospital), Chongqing 402160, China*
[4] *Department of Clinical Laboratory, No.215 Hospital of Shaanxi Nuclear Industry, Xianyang 712000, China*
[5] *Department of Emergency, The People's Hospital of Tongnan District, Chongqing City, Chongqing 402660, China*
A – Research concept and design, B – Collection and/or assembly of data, C – Data analysis and interpretation, D – Writing the article, E – Critical revision of the article, F – Final approval of the article

[+]Xinghua Li and Debiao Yu contributed equally to the study.

Xinghua Li, Debiao Yu, Dongqin Shen, Yeting Zhang, Wei Wang. LINC00861 protects against sepsis-associated acute kidney injury by regulating apoptosis and inflammation via miR-151a-3p/PDHA1 Axis. Ann Agric Environ Med. doi:10.26444/aaem/219991

Abstract

Introduction and Objective. Sepsis-associated acute kidney injury (SA-AKI) is a critical complication of sepsis marked by high morbidity and mortality. The aim of the study is to investigate the role of LINC00861 and its downstream regulatory axis in SA-AKI.

Materials and Method. 220 SA-AKI patients were enrolled and stratified according to survival outcomes. The levels of LINC00861, miR-151a-3p, and PDHA1 were detected in peripheral blood, and correlations with clinical parameters and prognosis were analyzed. *In vitro,* HK-2 cells were subjected to LPS to establish an SA-AKI model. Functional assays, including flow cytometry, ELISA, and qRT-PCR, were performed to evaluate apoptosis and inflammatory cytokines (IL-6, IL-18, TNF-α). Dual-luciferase assays and rescue experiments were conducted to elucidate the regulatory relationship among LINC00861, miR-151a-3p, and PDHA1.

Results. LINC00861 expression was reduced in SA-AKI non-survivor patients and was associated with higher SOFA and APACHE II scores, elevated PCT, SCr, and lactate levels. ROC analysis demonstrated good diagnostic performance (AUC = 0.835). LINC00861 (HR = 0.31, 95% CI: 0.16–0.58) was recognized as an independent prognostic factor for SA-AKI. Overexpression of LINC00861 suppressed LPS-induced apoptosis and reduced pro-inflammatory cytokine release in HK-2 cells. LINC00861 functioned as a sponge for miR-151a-3p, showing a negative correlation. miR-151a-3p directly targeted PDHA1, which was downregulated in non-survivors and positively correlated with LINC00861. Mechanistic analyses revealed that LINC00861 manages apoptosis and inflammation response by the miR-151a-3p/PDHA1 axis.

Conclusions. Reduced LINC00861 was independently associated with poor prognosis in SA-AKI. In vitro, LINC00861 was shown to regulate apoptosis and inflammation through the miR-151a-3p/PDHA1 axis.

Key words

apoptosis, inflammation, PDHA1, sepsis-associated acute kidney injury, LINC00861, miR-151a-3p

INTRODUCTION

Sepsis is a critical syndrome defined by multi-organ failure arising from the invasion of pathogenic microorganisms and the subsequent uncontrolled inflammatory response [1]. It is marked by rapid disease progression and severe systemic effects, often leading to multi-organ failure and death if not treated promptly [2]. Sepsis-associated acute kidney injury (SA-AKI) has become a major clinical problem in critically ill patients, yet its underlying pathophysiology remains incompletely understood. Inflammation and immune dysregulation, haemodynamic alterations, microcirculatory dysfunction, and metabolic reprogramming have all been implicated [3]. Clinically, AKI diagnosis relies on serum creatinine (SCr) and urine output, but these markers often lag behind actual injury due to renal compensatory capacity, delaying timely intervention [4]. Importantly, the high mortality of SA-AKI is not only related to disease severity but also to the timeliness of early prevention and intervention [5]. Thus, identifying high-risk prognostic factors and intervening at an early stage are crucial for improving patient outcomes, representing a current research hotspot.

Recent advances in RNA sequencing have revealed critical regulatory roles of lncRNAs, in disease progression [6]. Several lncRNAs, including NEAT1 and SNHG14, have been linked to SA-AKI pathogenesis and proposed as potential biomarkers [6]. LncRNAs often function through cross-regulation with microRNAs (miRNAs) to form complex molecular networks. For instance, SNHG14 modulates apoptosis and autophagy in LPS-induced AKI models via miR-373-3p [7], while the GAS6-AS2/miR-136-5p axis regulates oxidative stress and apoptosis to alleviate SA-AKI [8].

LINC00861, a newly-identified lncRNA located on chromosome 8q24.13, has emerged as a candidate regulator in multiple diseases. LINC00861 plays a vital role in sepsis onset

✉ Address for correspondence: Wei Wang, Department of Emergency, The People's Hospital of Tongnan District, Chongqing City, Chongqing 402660, China
E-mail: weiwangdr189@163.com

Received: 29.01.2026; accepted: 25.03.2026; first published: 06.05.2026

and progression [9]. Transcriptomic analyses have shown that LINC00861 is downregulated in sepsis patients and is closely associated with altered immune cell proportions [10]. However, its expression profile and functional role in SA-AKI remain unclear. Notably, earlier bioinformatics analysis predicted a direct binding interaction between LINC00861 and miR-151a-3p, a miRNA found to be elevated in SA-AKI [11]. This raises the hypothesis that LINC00861 may modulate SA-AKI progression via regulation of miR-151a-3p, a possibility that requires experimental validation.

The study explores the role of the LINC00861/miR-151a-3p regulatory axis in SA-AKI. Using clinical blood specimens from SA-AKI patients and an *in vitro* LPS-stimulated HK-2 cell model, the expression pattern of LINC00861 and functional mechanisms were analyzed. The findings provide novel insights into the molecular pathogenesis of SA-AKI and establish a theoretical basis for future diagnostic strategies and mechanistic investigations.

MATERIALS AND METHOD

Study subjects. Between January 2020 – January 2023, 220 patients were admitted to No. 215 Hospital of Shaanxi Nuclear Industry who met the Sepsis 3.0 criteria and KDIGO criteria for AKI, and were enrolled. Based on 30-day survival after sepsis diagnosis, participants were stratified into survival (110 cases) and mortality groups (110 cases). Causes of mortality were confirmed from medical records and were primarily attributed to sepsis-related multiple organ dysfunction; patients with deaths clearly unrelated to sepsis or AKI were excluded. During recruitment, patients were matched for age and gender between groups. Baseline demographic and clinical characteristics are summarized in Table 1 to demonstrate group comparability. Furthermore, age and gender were included as covariates in regression analyses to control for potential confounding effects, and the results are presented in Table 2.

Sepsis was defined as suspected or confirmed infection with a SOFA score ≥2. AKI was diagnosed based on one or more of the following criteria: an absolute increase in SCr of ≥26.5 μmol/L within 48 hours; a ≥1.5-fold increase in SCr compared with baseline within 7 days; or urine output <0.5 mL/kg/h for more than 6 hours.

Exclusion criteria: age <18 years; severe hypothermia; malignant tumours; chronic kidney disease; receipt of renal replacement therapy prior to enrollment; and voluntary discharge or death within 24 hours of admission.

To minimize confounding, detailed clinical parameters were collected and included in univariate and multivariate logistic regression models. These analyses were performed to determine whether LINC00861 was independently associated with prognosis after adjustment for established clinical predictors.

Fasting blood samples from SA-AKI patients were collected in the morning, allowed to stand at room temperature for 2 hours, and centrifuged at 3,500 rpm for 5 minutes at 4 °C. The resulting serum was isolated and stored at −80 °C until use.

This study was approved by the Ethics Committee of No. 215 Hospital of Shaanxi Nuclear Industry. Written informed consent was obtained from participants or their legal guardians before enrollment.

Cell culture. The human renal proximal tubular epithelial cell line HK-2 was obtained from ATCC (USA). Cells were cultured in DMEM (Gibco, USA) supplemented with 10% FBS (Gibco) in an incubator. To establish the *in vitro* SA-AKI model, HK-2 cells were stimulated with lipopolysaccharide (LPS; Sigma, USA) at a concentration of 5 μg/mL for 8 hours. Untreated cells cultured under the same conditions served as the control group.

Cell transfection. HK-2 cells were seeded into 6-well plates (2×10^5 cells/well) and cultured until they reached ~70% confluence. Transfections were performed using Lipofectamine 3000 (Invitrogen, USA). The following plasmids and oligonucleotides were used: overexpression vector for LINC00861 (oe-LINC00861), miR-151a-3p mimic (miR-mimic), small interfering RNA targeting PDHA1 (si-PDHA1), and their respective negative controls (oe-NC, miR-NC, and si-NC). Transfections were performed using a final concentration of 50 nM for the mimic/siRNA and 2 μg plasmid DNA per well in 6-well plates. All constructs were synthesized by GenePharma (Shanghai, China). After 6 hours of transfection, the medium was replaced with fresh complete medium, and cells were cultured.

qRT-PCR. RNA was extracted from LPS-treated HK-2 cells and clinical specimens using TRIzol (Invitrogen). PrimeScript RT reagent kit (Takara, Japan)/Mir-X miRNA First-Strand Synthesis Kit (Takara) were purchased to perform the reverse transcription of mRNA and lncRNA/miRNA. qRT-PCR was carried out using TB Green Premix Ex Taq II (Takara). GAPDH/U6 served as the internal control for mRNA and lncRNA/miRNA. Relative expression levels were calculated using the $2^{-\Delta\Delta Ct}$. All experiments were performed with at least 3 independent biological replicates, and each sample was analyzed in technical triplicates.

Dual-luciferase reporter assay. The wild-type sequences of LINC00861 and PDHA1 containing the putative miR-151a-3p binding sites were cloned into the pmirGLO (Promega, USA). Cells were co-transfected with 200 ng of wild-type or mutant reporter plasmid and 50 nM of miR-151a-3p mimic or miR-NC using Lipofectamine 3000 (Invitrogen). After 48 hours, luciferase activities were quantified using the Dual-Luciferase Reporter Assay System (Promega, USA).

Flow cytometry. Apoptotic cells were stained using the Annexin V-FITC/Propidium Iodide (PI) Apoptosis Detection Kit (BD Biosciences, USA). Briefly, 5 μL Annexin V-FITC and 5 μL PI were added to each sample and incubated. Samples were monitored on flow cytometer (BD Biosciences, USA).

ELISA. The concentrations of interleukin-6 (IL-6), interleukin-18 (IL-18), and tumour necrosis factor-alpha (TNF-α) in the supernatants were measured using commercially available ELISA kits (Beyotime, China; IL-6: PI325; IL-18: PI558; TNF-α: PT518).

Statistical analysis. GraphPad Prism 9.0 and R 4.0.0 were used. Continuous data are presented as mean ± SD. A *post hoc* power analysis was performed using R software, assuming a medium effect size (d = 0.5), a significance level of 0.05, and a desired power of 0.85 (two-tailed). The available clinical sample size met the calculated requirement. Comparisons were conducted using Student's t-test or one-way ANOVA followed by Bonferroni's *post hoc* test or chi-square test.

ROC curves were used to evaluate diagnostic performance. To evaluate the robustness of the diagnostic model, internal validation was performed using a 5-fold cross-validation approach. Pearson correlation and logistic regression were constructed to assess linear relationships between variables and independent risk factors. P-value < 0.05 was statistically significant.

RESULTS

Baseline characteristics of SA-AKI. The clinical profiles of SA-AKI survivors and non-survivors are summarized in Table 1. SOFA score, APACHE II score, PCT, Lactate, and Scr levels were higher in the non-survivor patients compared with survivors (Tab. 1). SOFA, APACHE II, and LINC00861 were independent risk factors for SA-AKI mortality (Tab. 2). Notably, LINC00861 retained its significance after adjustment, suggesting that it provides independent prognostic information beyond established clinical indicators.

Table 1. SA-AKI baseline characteristic

Parameters	Survival (n = 110)	Death (n = 110)	P-value
Age, years	60.68±9.47	62.20±9.24	0.227
Male, n (%)	63 (57.27)	68 (61.81)	0.582
Smoking, n (%)	52 (47.27)	57 (51.81)	0.589
Drinking, n (%)	49 (44.54)	43 (39.09)	0.494
Comorbidities			
Hypertension, n (%)	55 (50.00)	52 (47.27)	0.787
Diabetes, n (%)	31 (28.18)	38 (34.54)	0.383
Cardiovascular disease, n (%)	29 (26.36)	38 (34.54)	0.241
Cardiovascular disease, n (%)	37 (33.63)	49 (44.54)	0.128
Infection site			
Lung, n (%)	47 (42.72)	41 (37.27)	0.491
Urinary system, n (%)	16 (14.54)	23 (20.91)	0.289
Digestive system, n (%)	31 (28.18)	39 (35.45)	0.310
Other, n (%)	8 (7.27)	11 (10.00)	0.631
Scoring system			
SOFA	7.47±1.69	9.30±2.27	< 0.001
APACHE	24.61±5.44	27.75±7.16	< 0.001
Laboratory parameters			
ALT, U/L	35.02±11.52	36.43±12.19	0.380
AST, U/L	51.53±18.56	55.46±19.74	0.129
ALB, g/L	28.79±5.23	28.25±5.70	0.466
TBIL, μmol/L	24.72±6.66	25.83±8.75	0.290
DBIL, μmol/L	7.78±3.10	8.35±3.43	0.201
BUN, mmol/L	9.12±2.23	9.60±2.84	0.160
WBC, ´10^9	10.41±2.52	11.03±2.51	0.072
CRP, mg/L	140.61±52.11	152.52±57.96	0.110
PCT, ng/mL	12.04±12.17	15.44±13.13	0.047
LAC, mmol/L	2.49±0.51	2.66±0.55	0.019
SCr, μmol/L	88.54±25.44	96.94±24.44	0.013

ALB – Albumin; **ALT** – Alanine transaminase; **APACHE** – Acute physiology and chronic health evaluation; **AST** – Aspartate transferase; **BUN** – Blood urea nitrogen; **CRP** – C-reactive protein; **DBIL** – Direct bilirubin; **LAC** – Lactate; **PCT** – Procalcitonin; **SA-AKI** – Sepsis-associated acute kidney injury; **SCr** – Serum creatinine; **SOFA** – Sequential organ failure assessment; **TBIL** – Total bilirubin; **WBC** – White blood cell

Table 2. Logistic regression analysis

Parameters	Univariate		Multiple	
	OR value (95% CI)	P value	OR value (95% CI)	P value
Age, years	1.29 (0.76, 2.19)	0.345		
Male, n (%)	1.20 (0.70, 2.07)	0.492		
Smoking, n (%)	1.19 (0.70, 2.03)	0.500		
Drinking, n (%)	0.82 (0.48, 1.41)	0.495		
Comorbidities				
Hypertension, n (%)	0.89 (0.52, 1.52)	0.685		
Diabetes, n (%)	1.34 (0.76, 2.39)	0.309		
Cardiovascular disease, n (%)	1.47 (0.82, 2.64)	0.188		
Cardiovascular disease, n (%)	1.58 (0.92, 2.74)	0.098		
Infection site				
Lung, n (%)	0.79 (0.46, 1.36)	0.409		
Urinary system, n (%)	1.55 (0.77, 3.17)	0.218		
Digestive system, n (%)	1.39 (0.79, 2.48)	0.247		
Other, n (%)	1.41 (0.55, 3.79)	0.473		
Scoring system				
SOFA	2.69 (1.54, 4.78)	< 0.001	1.59 (1.35, 1.92)	< 0.001
APACHE	1.93 (1.13, 3.32)	0.01	1.09 (1.03,1.15)	< 0.001
Laboratory parameters				
ALT, U/L	0.92 (0.54, 1.57)	0.787		
AST, U/L	1.24 (0.73, 2.11)	0.418		
ALB, g/L	0.69 (0.41, 1.18)	0.178		
TBIL, μmol/L	1.15 (0.68, 1.96)	0.589		
DBIL, μmol/L	1.07 (0.63, 1.82)	0.787		
BUN, mmol/L	1.29 (0.76, 2.19)	0.345		
WBC, ´10^9	1.33 (0.78, 2.27)	0.281		
CRP, mg/L	1.44 (0.84, 2.45)	0.178		
PCT, ng/mL	2.42 (1.41, 4.19)	0.001	1.75 (0.92, 1.34)	0.085
LAC, mmol/L	1.54 (0.91, 2.64)	0.106		
SCr, μmol/L	1.60 (0.94, 2.78)	0.080		
LINC00861	0.22 (0.12,0.39)	< 0.001	0.31 (0.16, 0.58)	< 0.001

ALB – Albumin; **ALT** – Alanine transaminase; **APACHE** – Acute physiology and chronic health evaluation; **AST** – Aspartate transferase; **BUN** – Blood urea nitrogen; **CRP** – C-reactive protein; **DBIL** – Direct bilirubin; **LAC** – Lactate; **PCT** – Procalcitonin; **SA-AKI** – Sepsis-associated acute kidney injury; **SCr** – Serum creatinine; **SOFA** – Sequential organ failure assessment; **TBIL** – Total bilirubin; **WBC** – White blood cell

Clinical value of LINC00861. As shown in Figure 1A, LINC00861 levels were significantly lower in patients who died compared with those who survived. LINC00861 exhibited good predictive accuracy for survival outcomes in SA-AKI patients, with an AUC of 0.835 (95% CI: 0.781–0.890), a sensitivity of 86.3%, and a specificity of 71.8% (Fig. 1B). Internal validation demonstrated that the AUC values remained sTab. (Fig. S1). LINC00861 expression was inversely associated with several clinical severity indices, including SOFA score, APACHE II score, procalcitonin (PCT), lactate (LAC), and SCr (Fig. 1C).

LINC00861 overexpression attenuates LPS-induced apoptosis and inflammatory responses. As shown in Figure 2A, LPS stimulation significantly downregulated LINC00861 expression compared with control, whereas LINC00861 expression was

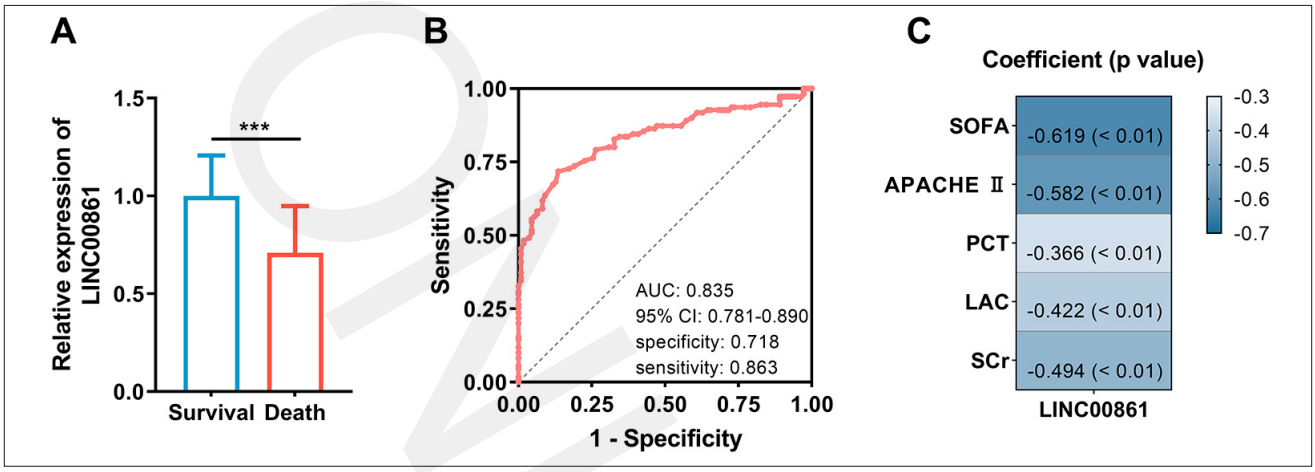

Figure 1. Expression pattern and clinical significance of LINC00861. (**A**) LINC00861 expression was reduced in non-survivors (n = 110) compared with survivors (n =110). (**B**) ROC analysis showed good diagnostic accuracy of LINC00861 for SA-AKI. (**C**) LINC00861 expression was negatively correlated with SOFA, APACHE II, PCT, LAC, and SCr. ***P < 0.001

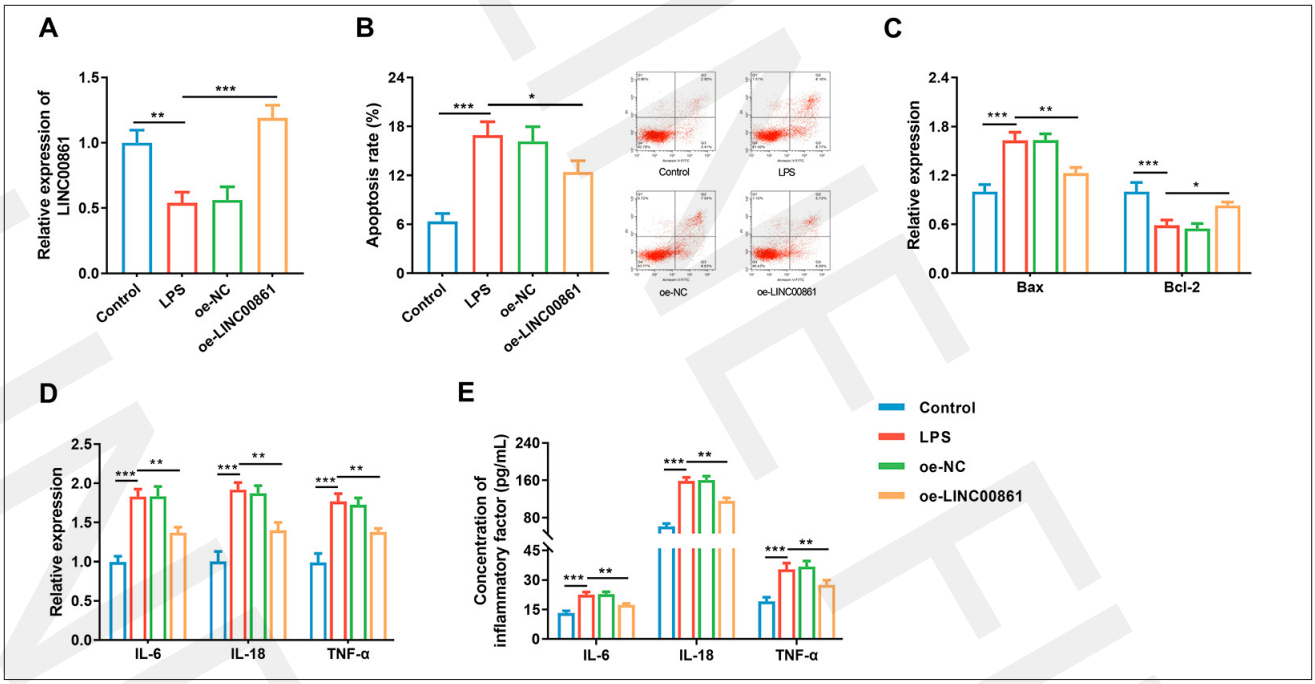

Figure 2. Overexpression of LINC00861 mitigates HK-2 cell apoptosis and inflammation under LPS treatment (n =3). (**A**) Relative expression of LINC00861. (**B**) Apoptosis rate. (**C**) Bax and Bcl-2 expression. (**D-E**) mRNA (**D**) and cytokine secretion (**E**) levels of IL-6, IL-18, and TNF-α.
*P < 0.05; **P < 0.01; ***P < 0.001.

markedly restored following plasmid overexpression. LPS markedly increased HK-2 cell apoptosis level, and elevated the abundance of the Bax and reduced the Bcl-2, while oe-LINC00861 reversed these effects (Fig. 2B and 2C). Inflammatory responses were markedly induced by LPS, as indicated by elevated mRNA levels of IL-6, IL-18, and TNF-α (Fig. 2D). oe-LINC00861 suppressed the LPS-induced upregulation of these inflammatory cytokines (Fig. 2D). LINC00861 overexpression reduced the secretion of three pro-inflammatory cytokines in the culture supernatants (Fig. 2E).

LINC00861 regulated cell apoptosis and inflammation through sponging miR-151a-3p. As shown in Figure 3A, bioinformatic analysis predicted a complementary binding sequence between LINC00861 and miR-151a-3p. Luciferase activity was downregulated in the wild-type LINC00861 construct, but not with the mutant construct (Fig. 3B). miR-151a-3p expression was markedly upregulated in LPS-treated HK-2 cells and in patients who succumbed to SA-AKI, whereas overexpression of LINC00861 suppressed miR-151a-3p expression in the cell model (Fig. 3C and 3D). Pearson correlation analysis further revealed an opposite association between LINC00861 and miR-151a-3p (Fig. 3E).

Functionally, miR-mimic significantly promoted apoptosis, as evidenced by an increased apoptosis rate and dysregulated levels of Bax and Bcl-2 (increased Bax and decreased Bcl-2 (Fig. 3F-G). Co-transfection with LINC00861 overexpression plasmid mitigated these pro-apoptotic effects (Fig. 3F-G). miR-151a-3p overexpression elevated the concentration of inflammatory cytokines IL-6, IL-18, and TNF-α, while LINC00861 overexpression counteracted this effect (P < 0.0) (Fig. 3H-I).

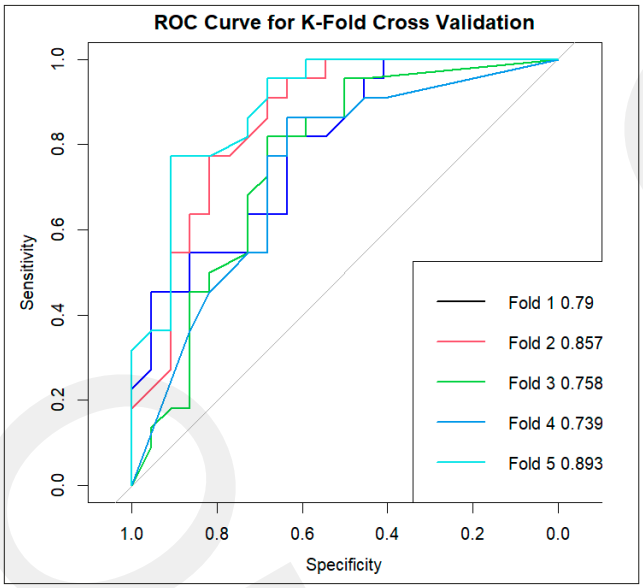

Figure S1. ROC curve from 5-fold cross-validation in the internal dataset

PDHA1 is a confirmed target of miR-151a-3p, and LINC00861 regulated apoptosis and inflammation via the miR-151a-3p/PDHA1 axis. Figure 4A shows the predicted binding sequence involving miR-151a-3p and PDHA1. Luciferase activity was inhibited in the wild-type PDHA1 construct, but not with the mutant construct (Fig. 4B). An anti-correlation between miR-151a-3p and PDHA1 expression was observed (Fig. 4C). PDHA1 expression was markedly decreased in non-survivors, consistent with the expression pattern of LINC00861 (Fig. 4D). Conversely, a positive correlation between LINC00861 and PDHA1 expression was identified (Fig. 4E).

PDHA1 silencing increased apoptosis rates, upregulated Bax, and downregulated Bcl-2 compared with oe-LINC00861 alone (Fig. 4F-G). Inflammatory cytokine assays further showed that PDHA1 knockdown elevated cytokine levels, while LINC00861 overexpression suppressed these responses (Fig. 4H-I). Combined treatment with oe-LINC00861 and si-PDHA1 partially enhanced cytokine expression compared with oe-LINC00861 alone (Fig. 4H-I).

DISCUSSION

Sepsis is one of the foremost causes of multiple organ dysfunction and mortality, with AKI being its most common and severe complication. SA-AKI patients typically experience more profound renal impairment, increased complications, and higher mortality [4]. In this study, SOFA and APACHE II scores were significantly elevated in patients who did not survive. As widely used scoring systems, both SOFA and APACHE II are valuable for predicting organ dysfunction, illness severity, and mortality risk. Higher scores consistently reflect more severe disease and worse outcomes, which is in line with the findings [12]. Biochemical markers such as PCT, SCr, and lactate are also central to SA-

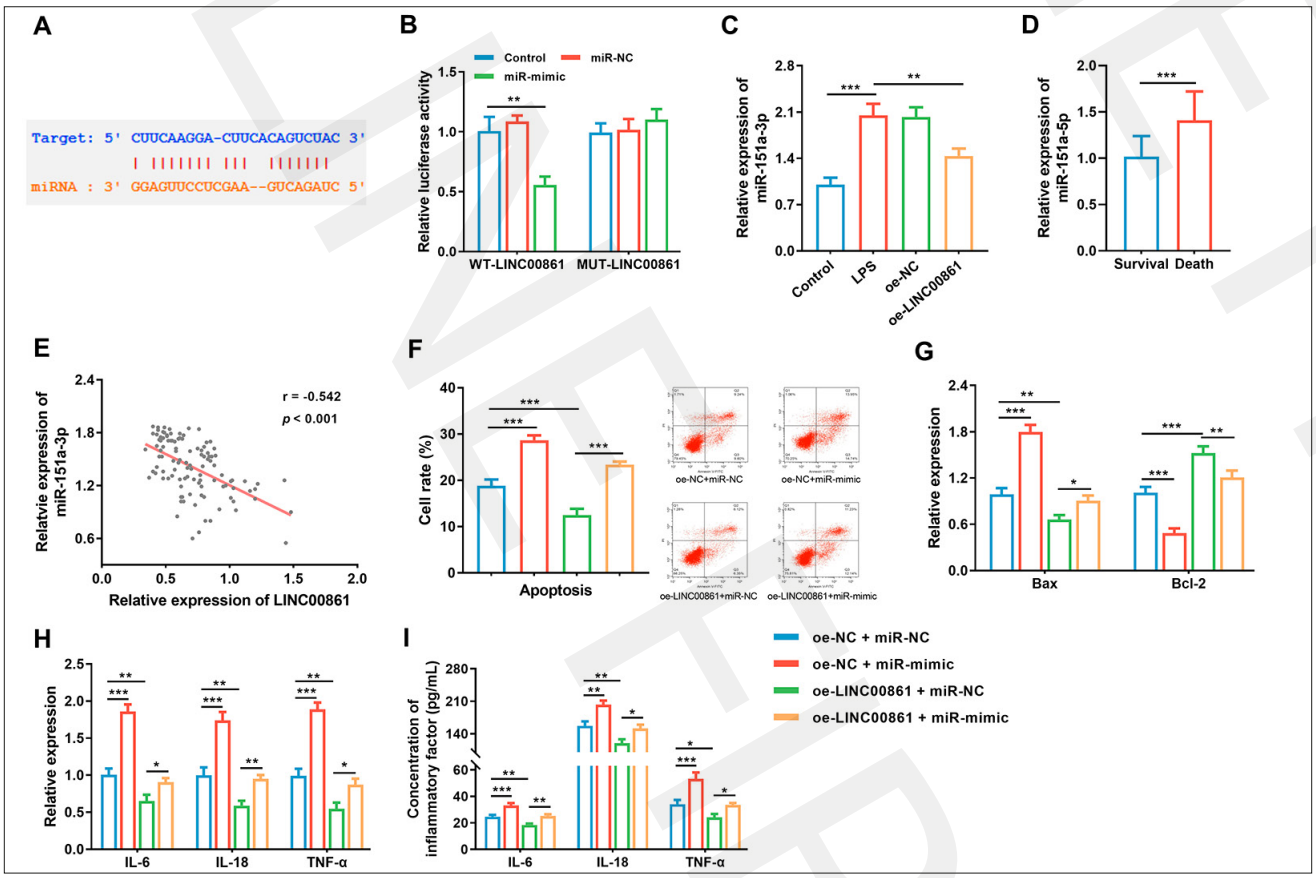

Figure 3. LINC00861 sponges miR-151a-3p to regulate apoptosis and inflammation. (**A**) Predicted binding site connecting LINC00861 and miR-151a-3p. (**B**) Luciferase activity assay (n =3). (**C**) miR-151a-3p expression in response to LPS stimulation (n =3). (**D**) miR-151a-3p was elevated in non-survivors (n = 110) compared with survivors (n =110) (**E**) Negative correlation between LINC00861 and miR-151a-3p (n = 110). (**F-G**) Apoptosis rate (**F**), Bax, and Bcl-2 expression (**G**) are affected by the LINC00861/miR-151a-3p axis (n =3). (**H-I**) Inflammatory cytokine levels measured by qRT-PCR (**H**) and ELISA (**I**), modulated by LINC00861 and miR-151a-3p (n =3). *P < 0.05; **P < 0.01; ***P < 0.001

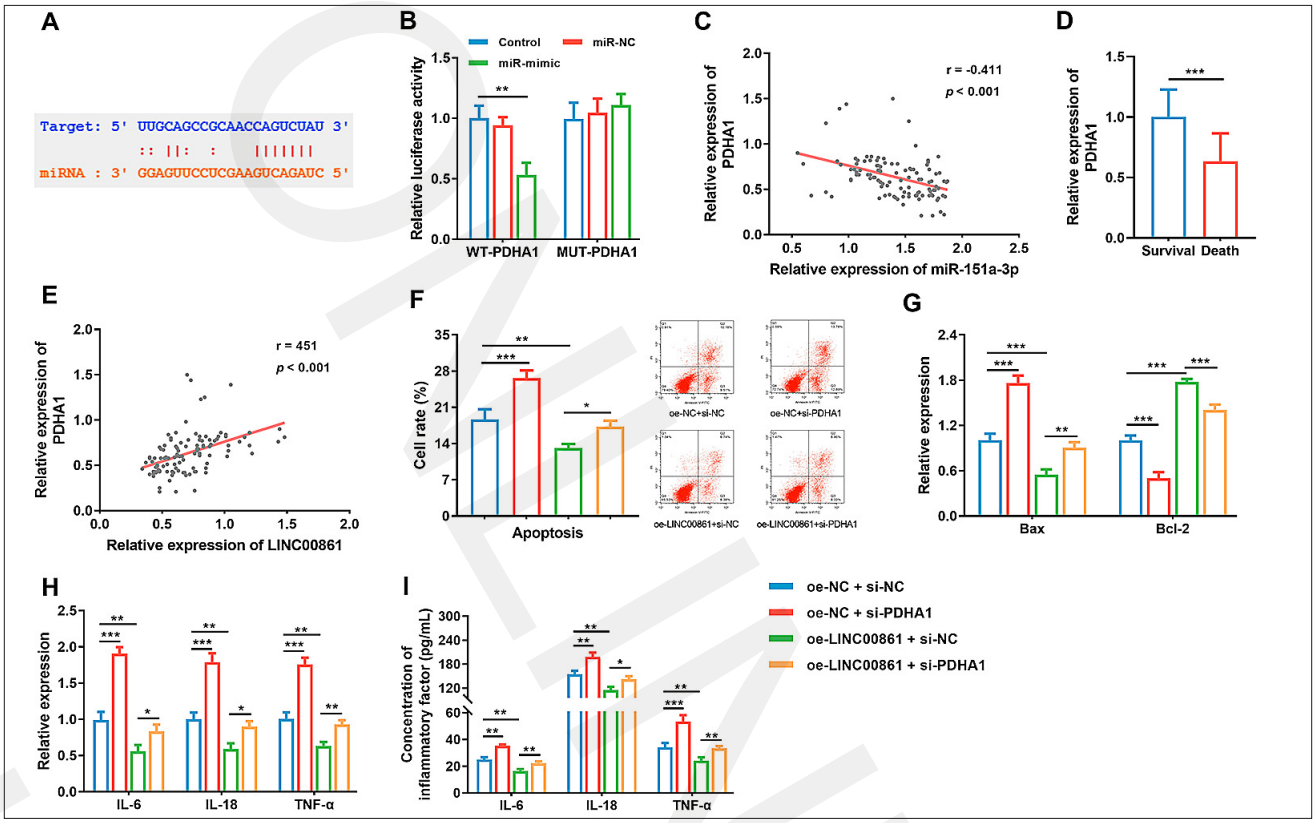

Figure 4. PDHA1 is a direct target of miR-151a-3p, and LINC00861 modulates apoptosis and inflammation via the miR-151a-3p/PDHA1 axis. (**A-B**) Putative binding site of miR-151a-3p with PDHA1 (**A**), experimentally validated by dual-luciferase reporter assay (**B**) (n =3). (**C**) Negative correlation between miR-151a-3p and PDHA1 expression (n = 110). (**D**) PDHA1 was lowered in SA-AKI non-survivor cohort (n = 110). (**E**) Positive correlation between LINC00861 and PDHA1 expression. (**F-G**) Effects of LINC00861 overexpression and PDHA1 knockdown on apoptosis (**F**) and Bax/Bcl-2 expression (**G**) (n =3). (**H-I**) IL-6, IL-18, and TNF-α levels measured by qRT-PCR (**H**) and ELISA (**I**) following LINC00861 overexpression and PDHA1 knockdown (n =3).
*P < 0.05; **P < 0.01; ***P < 0.001

AKI management. PCT elevation reflects infection severity and systemic inflammatory activation, and persistently high levels may exacerbate kidney injury and worsen prognosis [13]. SCr, a traditional marker of glomerular filtration, when persistently elevated, suggests impaired renal recovery and increased mortality risk [14].

Similarly, lactate, a marker of tissue hypoxia and anaerobic metabolism, is an indicator of septic shock. Sustained hyperlactataemia denotes microcirculatory dysfunction and tissue hypoperfusion, further aggravating renal tubular injury and promoting AKI progression [15]. The results confirm these markers as prognostic risk factors in SA-AKI. Notably, LINC00861 expression correlated significantly with these clinical parameters, implying that LINC00861 may be mechanistically involved in SA-AKI progression. Together with ROC analysis and its altered expression pattern, LINC00861 may serve as a potential prognostic biomarker.

Growing evidence highlights the involvement of lncRNAs in AKI pathogenesis. Given that SA-AKI manifests as inflammation, apoptosis, and oxidative stress, an LPS-induced HK-2 cell injury model was employed, which closely mimics sepsis-related renal pathology [16].

The findings underscore the dual roles of inflammation and apoptosis in SA-AKI. Circulating inflammatory mediators such as IL-6 and TNF-α are well-established predictors of poor prognosis. TNF-α acts as an early initiator of renal inflammation [17], while IL-6 amplifies the inflammatory cascade by stimulating tubular cells to release additional mediators [18]. IL-18, secreted by tubular epithelial cells and macrophages, further drives inflammation and apoptosis [19]. Overexpression of LINC00861 significantly reduces LPS-induced cytokine production, supporting its role in dampening inflammation. Apoptosis is a hallmark of SA-AKI pathophysiology, often intertwined with inflammatory processes. Systemic inflammation disrupts the renal microenvironment, triggering apoptosis of tubular epithelial cells [20]. The data show that LINC00861 regulates apoptosis by modulating Bax and Bcl-2, key members of the mitochondrial apoptosis pathway, thereby reducing apoptotic cell numbers. Collectively, these results suggest that LINC00861 exerts renoprotective effects by suppressing both inflammation and apoptosis.

Mechanistically, lncRNAs frequently function as ceRNA, sequestering miRNAs to control mRNA stability or translation [21]. In this study, LINC00861, which was downregulated in SA-AKI, directly sponged miR-151a-3p. Consistently, miR-151a-3p was upregulated in patients with poor prognosis, and functional assays revealed that its overexpression aggravated apoptosis and inflammation in HK-2 cells. miR-151a-3p was upregulated in diabetic nephropathy and immune disorders [22], supporting its dysregulation in pathological conditions.

PDHA1, a direct target of miR-151a-3p, was further identified. PDHA1 expression was suppressed in the SA-AKI poor prognosis, and its knockdown significantly enhanced apoptosis and inflammation. These results suggest that the protective effects of LINC00861 were mediated through the LINC00861/miR-151a-3p/PDHA1 axis. Previous studies have implicated PDHA1 in sepsis and immune regulation

[23], and its inhibition is associated with excessive lactate production, particularly in tumours [24]. As PDHA1 encodes the α-subunit of pyruvate dehydrogenase, the rate-limiting enzyme that converts pyruvate into acetyl-CoA, its downregulation disrupts energy metabolism and favours lactate accumulation [25]. This mechanistic link may help explain the elevated lactate levels observed in SA-AKI patients, although further validation is required.

From a clinical perspective, LINC00861 detection may be feasible in routine practice, as its expression can be readily quantified using qRT-PCR–based methods in clinical samples. However, further large-scale and multicentre studies are required to validate its diagnostic and prognostic performance before clinical application.

Limitations of the study. This study has several limitations. Although internal validation supported the stability of the diagnostic model, the study still lacks external validation from independent cohorts. Therefore, future multicentre studies with larger sample sizes are warranted to further confirm the clinical applicability of LINC00861. Only HK-2 cells were used for *in vitro* experiments. Although HK-2 cells are a widely accepted model of human proximal tubular epithelial cells, they may not fully recapitulate the complex cellular interactions and microenvironment present *in vivo*. Validation in primary renal tubular cells would further enhance the translational relevance. The functional role of LINC00861 was only investigated *in vitro*, and no *in vivo* gain- or loss-of-function experiments were performed. Although preliminary plans for animal experiments were considered, they could not be implemented due to constraints in funding and technical resources. Future research will aim to include animal models to elucidate the in vivo mechanisms of LINC00861 in SA-AKI progression.

CONCLUSION

LINC00861 is associated with SA-AKI progression and emerged as an independent predictor of adverse prognosis in SA-AKI. Mechanistically, *in vitro* experiments demonstrated that LINC00861 regulates LPS-induced apoptosis and inflammation in HK-2 cells via the miR-151a-3p/PDHA1 axis. Given its correlation with established clinical indicators and its regulatory effects observed in cellular models, LINC00861 may serve as a potential prognostic biomarker for SA-AKI; however, causal relationships in clinical settings require further validation.

REFERENCES

1. Zhang L, Lin Y, Zhang Z, et al. Immune regulation and organ damage link adiponectin to sepsis. Front Immunol. 2024;15:1444884. http://doi.org/10.3389/fimmu.2024.1444884
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10. http://doi.org/10.1001/jama.2016.0287
3. Kuwabara S, Goggins E, Okusa MD. The Pathophysiology of Sepsis-Associated AKI. Clinical Journal of the American Society of Nephrology: CJASN. 2022;17(7):1050–69. http://doi.org/10.2215/CJN.00850122
4. Peerapornratana S, Manrique-Caballero CL, Gómez H, Kellum JA. Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment. Kidney Inter. 2019;96(5):1083–99. http://doi.org/10.1016/j.kint.2019.05.026
5. Tsai H-S, Tsai F-C, Chen Y-C, et al. Impact of acute kidney injury on one-year survival after surgery for aortic dissection. Ann Thoracic Surg. 2012;94(5):1407–12. http://doi.org/10.1016/j.athoracsur.2012.05.104
6. Xue K, Wu K, Luo H, et al. Identification of hub genes and prediction of the ceRNA network in adult sepsis. Peer J. 2025;13:e19619. http://doi.org/10.7717/peerj.19619
7. Yang N, Yan N, Bai Z, et al. FTO attenuates LPS-induced acute kidney injury by inhibiting autophagy via regulating SNHG14/miR-373-3p/ATG7 axis. Inter Immunopharmacol. 2024;128:111483. http://doi.org/10.1016/j.intimp.2023.111483
8. Cui H, Ren G, Hu X, et al. Suppression of lncRNA GAS6-AS2 alleviates sepsis-related acute kidney injury through regulating the miR-136-5p/OXSR1 axis in vitro and in vivo. Renal Failure. 2022;44(1):1070–82. http://doi.org/10.1080/0886022X.2022.2092001
9. Cheng Y, Cao X, Zhang J, et al. Dysregulated lncRNAs are Involved in the Progress of Sepsis by Constructing Regulatory Networks in Whole Blood Cells. Front Pharmacol. 2021;12:678256. http://doi.org/10.3389/fphar.2021.678256
10. Cheng Y, Xu L, Wang J, et al. Analysis of bulk RNA-seq data from sepsis patients reveals sepsis-associated lncRNAs and targeted cell death-related genes contributing to immune microenvironment regulation. Front Immunol. 2023;14:1026086. http://doi.org/10.3389/fimmu.2023.1026086
11. Han R, Li W, Tian H, et al. Urinary microRNAs in sepsis function as a novel prognostic marker. Exp Therapeutic Med. 2023;26(1):346. http://doi.org/10.3892/etm.2023.12045
12. Chen J-J, Kuo G, Hung C-C, et al. Risk factors and prognosis assessment for acute kidney injury: The 2020 consensus of the Taiwan AKI Task Force. J Formosan Med Assoc. 2021;120(7):1424–33. http://doi.org/10.1016/j.jfma.2021.02.013
13. Yunus I, Fasih A, Wang Y. The use of procalcitonin in the determination of severity of sepsis, patient outcomes and infection characteristics. PloS One. 2018;13(11):e0206527. http://doi.org/10.1371/journal.pone.0206527
14. Makris K, Spanou L. Acute Kidney Injury: Definition, Pathophysiology and Clinical Phenotypes. Clin Biochem Rev. 2016;37(2):85–98.
15. Baser MR, Ganta R, Neeradi C, Varatharajan S. Serum Lactate Levels and Their Correlation With Hospital Outcomes in ICU Patients With Shock: A Cross-Sectional Study at a Tertiary Care Center. Cureus. 2025;17(6):e86564. http://doi.org/10.7759/cureus.86564
16. Xu S, Cui M, Wang R. Rs9839776 Genetic Variant of lncRNA SOX2OT Contributes to Susceptibility of Acute Kidney Injury in Sepsis Patients via Regulating SOX2OT/miR-9-5p Axis. J Inflammation Res. 2025;18:6077–89. http://doi.org/10.2147/JIR.S508476
17. Moreno JA, Izquierdo MC, Sanchez-Niño MD, et al. The inflammatory cytokines TWEAK and TNFα reduce renal klotho expression through NFκB. J Am Soc Nephrol. 2011;22(7):1315–25. http://doi.org/10.1681/ASN.2010101073
18. Su H, Lei C-T, Zhang C. Interleukin-6 Signaling Pathway and Its Role in Kidney Disease: An Update. Front Immunol. 2017;8:405. http://doi.org/10.3389/fimmu.2017.00405
19. Thomas JM, Ling YH, Huuskes B, et al. IL-18 (Interleukin-18) Produced by Renal Tubular Epithelial Cells Promotes Renal Inflammation and Injury During Deoxycorticosterone/Salt-Induced Hypertension in Mice. Hypertension (Dallas, Tex: 1979). 2021;78(5):1296–309. http://doi.org/10.1161/HYPERTENSIONAHA.120.16437
20. Gomez H, Ince C, De Backer D, et al. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics, and the tubular cell adaptation to injury. Shock (Augusta, Ga). 2014;41(1). http://doi.org/10.1097/SHK.0000000000000052
21. Zhang X, Wang W, Zhu W, et al. Mechanisms and Functions of Long Non-Coding RNAs at Multiple Regulatory Levels. Inter J Molecular Sci. 2019;20(22). http://doi.org/10.3390/ijms20225573
22. Ali H, Malik MZ, Abu-Farha M, et al. Dysregulated Urinary Extracellular Vesicle Small RNAs in Diabetic Nephropathy: Implications for Diagnosis and Therapy. J Endocrine Soc. 2024;8(8):bvae114. http://doi.org/10.1210/jendso/bvae114
23. Zhang J, Wu Y, Du Y, et al. Cuproptosis-Related Genes as Prognostic Biomarkers for Sepsis: Insights into Immune Function and Personalized Immunotherapy. J Inflamm Res. 2024;17:4229–45. http://doi.org/10.2147/JIR.S461766
24. Fan J, Shan C, Kang H-B, et al. Tyr phosphorylation of PDP1 toggles recruitment between ACAT1 and SIRT3 to regulate the pyruvate dehydrogenase complex. Molecular Cell. 2014;53(4):534–48. http://doi.org/10.1016/j.molcel.2013.12.026
25. Zhu H, Ma X, Ye T, et al. Esophageal cancer in China: Practice and research in the new era. Int J Cancer. 2023;152(9):1741–51. http://doi.org/10.1002/ijc.34301