Tohoku J. Exp. Med., 2025, **265**, 21-27

Clinical Significance of lncRNA NNT-AS1 in the Diagnosis, Deterioration and Prognosis of Sepsis

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Sepsis is a serious infectious disease that may lead to a systemic inflammatory and life-threatening condition. Early diagnosis and treatment of sepsis is important to prevent organ failure and reduce mortality. This paper investigated the expression of long non-coding RNA NNT-AS1 (lncRNA NNT-AS1) in sepsis and its relationship the development of the disease, and revealed the clinical potential of NNT-AS1 in the diagnosis and prognosis of sepsis. Clinical data of the included individuals were collected and analyzed. Acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score were performed based on the severity of the patient's condition. Inflammatory factors were measured by enzyme-linked immunosorbent assay (ELISA). NNT-AS1 expression was quantified by real-time quantitative polymerase chain reaction (RT-qPCR). The ability of NNT-AS1 to identify sepsis was evaluated using receiver operating characteristic (ROC) curve. The prognostic value of NNT-AS1 was confirmed by the Kaplan-Meier method and Cox regression analysis. Biochemical indicators, inflammatory factors, APACHE II score and SOFA score were higher in sepsis patients than in healthy individuals. Serum NNT-AS1 was actively expressed in sepsis and had a high diagnostic value. NNT-AS1 levels were positively correlated with APACHEII score, SOFA score, and inflammatory factor levels. Meanwhile, high expression of NNT-AS1 predicted shorter survival of patients. NNT-AS1 was highly expressed in sepsis and was closely related to the development of patients' conditions. By monitoring the changes of NNT-AS1 may be of key value for the diagnosis, prognosis and therapeutic prognosis of patients.

Keywords: diagnosis; inflammatory factor; lncRNA NNT-AS1; prognosis; sepsis
Tohoku J. Exp. Med., 2025 January, **265** (1), 21-27.
doi: 10.1620/tjem.2024.J053

Introduction

Sepsis is an organ dysfunction syndrome caused by a dysregulated response to infection, triggered by a variety of infections (Chen et al. 2022). The latest data show that sepsis affects more than 30 million people globally each year, with a mortality rate of about 1/5 (Tocu et al. 2023). The fundamental pathogenesis of sepsis is still unclear, involving complex systemic inflammatory response, immune dysfunction, tissue damage and gene polymorphism (Feng et al. 2023; Han et al. 2023). In addition to factors such as the patient's overall health and the type of infection, mortality in sepsis patients depends on the timeliness of diagnosis and treatment (Wang et al. 2021). Meanwhile, the occurrence of sepsis may also be accompanied by complications such as acute lung injury, and easily lead to poor prognosis or death (Jan et al. 2019). If sepsis is recognized at an early stage and prognostic outcomes are monitored in time, the mortality rate of patients is significantly reduced.

LncRNA has no ability to encode proteins, while have been shown to be involved in the regulation of gene expression and cellular processes (Liu et al. 2021). The role of lncRNA in diseases is very complex, and there are still many unknown mechanisms and modes of action to be further studied, which has become a research hotspot in recent years. It has been claimed that lncRNA influence the development of sepsis by regulating the inflammatory response and cellular function (Gao and Huang 2021). For instance,

Received January 17, 2024; revised and accepted June 18, 2024; J-STAGE Advance online publication June 27, 2024
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lncRNA UCA1 mediated the prognosis of sepsis and was strongly associated with inflammatory factors (Wang et al. 2022a). Recent evidence also described the regulatory capacity of the lncRNA NEAT-2 in septic endothelial histiocytes (Yin et al. 2023). LncRNA NEAT1 acted as a therapeutic factor to suppress the activity of sepsis cells by regulating the miR-31-5p/POU2F1 axis (Yang et al. 2021). LncRNA NNT-AS1 (NNT-AS1) is transcribed from the antisense strand of the NNT gene in the human genome and is located in the chromosome 5q12 region (Wang et al. 2020a). Zhou and Duan (2020) summarized the diagnostic and prognostic value of NNT-AS1 in cancer, and explored the potential mechanism in targeting downstream microRNA (miRNA) and drug resistance of NNT-AS1. Chen et al. (2021b) stated that as an indicator factor predicting disease production, NNT-AS1 was consistent with the trend of expression of C-reactive protein (CRP) and procalcitonin (PCT) levels in patients with refractory mycoplasma pneumoniae pneumonia. In addition, NNT-AS1 has been noted to be involved in the development of diabetic nephropathy and chronic obstructive pulmonary disease, which may cause cellular inflammatory responses (Mei et al. 2020; Geng et al. 2021). Based on this, this study speculated that NNT-AS1 may also have some clinical value in the sepsis.

Herein, we investigated the NNT-AS1 level in sepsis serum and analyzed the potential clinical value of NNT-AS1 in the diagnosis, disease development and prognosis of sepsis by combining the clinical indicators, general data and prognostic outcomes of the included samples.

Materials and Methods

Study subjects

Among the sepsis patients attending The First People's Hospital of Neijiang between March 2022 and June 2023, 115 cases meeting the requirements were selected as the experimental group for this experiment. Inclusion criteria included: patients met the diagnostic criteria for sepsis jointly developed by the Society of Critical Care Medicine and the American College of Chest Physicians in 2016. All patients underwent systematic surgery and antibiotic treatment at our hospital. Patients had complete clinical data and agreed to participate in the study. Exclusion criteria: patients with malignant tumor, immune disease or liver and kidney insufficiency. Patients with cognitive dysfunction or psychiatric disorders. Patients who had taken immunosuppressive agents and associated sepsis medications within the 3 months prior to the study. In addition, 115 healthy individuals were named as the control group. All participants were informed of the purpose of the study and volunteered to participate, providing written consent. The study was approved by the Hospital Ethics Committee.

Collection and detection of clinical indicators

Fasting venous blood (5 mL) was collected from patients with sepsis and healthy people, and serum samples were separated after centrifugation at 3,000 r/min for 10 min.

The white blood cell count (WBC) was measured by an automatic blood cell counter (Mindray BC-6800, China). The levels of C-reactive protein (CRP), procalcitonin (PCT), fibrinogen (FB) and inflammatory factors (TNF-α, IL-1β, IL-6 and IL-22) were evaluated by enzyme-linked immunosorbent assay (ELISA). ELISA kits were purchased from Abcam (Cambridge, MA, USA), and the procedures were performed according to the manufacturer's instructions.

Table 1. Clinical information of included individuals.

Characteristics	Healthy controls	Sepsis patients	*P* value
Age (years)	53.76 ± 10.34	53.93 ± 6.50	0.877
Gender (Male/Female)	49/66	55/60	0.429
BMI (kg/m^2)	22.23 ± 3.82	21.93 ± 3.12	0.513
CRP (mg/L)	8.91 ± 1.74	19.85 ± 3.54	< 0.001
PCT (ng/mL)	0.03 ± 0.01	2.04 ± 0.96	< 0.001
FB (g/L)	2.67 ± 1.00	5.24 ± 1.29	< 0.001
WBC (× 10^9/L)	7.29 ± 2.17	12.96 ± 5.03	< 0.001
TNF-α (μg/L)	4.97 ± 0.89	15.10 ± 3.36	< 0.001
IL-1β (μg/L)	1.21 ± 0.47	6.07 ± 2.46	< 0.001
IL-6 (μg/L)	24.15 ± 6.56	91.47 ± 12.05	< 0.001
IL-22 (μg/L)	20.04 ± 4.17	30.43 ± 3.20	< 0.001
APACHE II score	-	13.07 ± 3.58	-
SOFA score	-	7.15 ± 1.70	-

body mass index: BMI; acute physiology and chronic health evaluation II score: APACHE II score; sequential organ failure assessment score: SOFA score; C-reactive protein: CRP; procalcitonin: PCT; fibrinogen: FB; white blood cells: WBC; including tumor necrosis factor α: TNF-α; interleukin-1β: IL-1β; interleukin-6: IL-6; interleukin-22: IL-22

Processing of general information

According to the clinical characteristics of the experimental group 24 h after admission, acute physiology and chronic health evaluation (APACHE) II score and sequential organ failure assessment (SOFA) score were performed. The general information of the enrolled persons was recorded in Table 1, and the patients were followed up for 28 days after treatment to grasp the recovery or death of the patients in time.

Quantification of NNT-AS1 expression

RNA was isolated from serum samples using the TRIzol (Invitrogen, Carlsbad, CA, USA) method, and then reverse transcription and PCR assays were performed sequentially with the participation of Prime Script RT Reagent Kit (Takara, China) and SYBR Premix Ex Taq TM Kit (Takara, China). Amplification assays were performed in a CFX96 real-time PCR system (Bio-Rad, Spain). The levels of NNT-AS1 were normalized to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and calculated by the $2^{-\Delta\Delta ct}$ method. The primer sequences were: NNT-AS1 F-5′-CTGGAATCCCTGCTACTCAGGA-3′ and R-5′-GCCATGTGATATGCCTGCTC-3′; GAPDH F-5′-GGGCTCTCCAGAACATC-3′ and R-5′-CCATGTGATATGCCTGCT-3′.

Statistical analysis

SPSS 22.0 and GraphPad Prism 9.0 software were applied to process. The potential of NNT-AS1 for the diagnosis of sepsis was evaluated by ROC curves. The correlation between NNT-AS1 expression and clinical indicators of patients was analyzed by Pearson correlation method. The prognostic value of NNT-AS1 in sepsis was confirmed by Kaplan-Meier method and multivariate Cox regression analysis. Measurements were expressed as mean ± standard deviation, and *t*-test was used for comparison between two groups. Differences were considered statistically significant at $P < 0.05$.

Results

General information of subjects

CRP, PCT, FB and WBC levels were higher in the experimental group than in the control group. By measuring the levels of inflammatory cytokines, the concentration of TNF-α, IL-1β, IL-6, and IL-22 were significantly elevated in patients with sepsis. In addition, APACHE II scores and SOFA scores of septic patients were assessed with reference to clinical data. The differences of the above indicators were statistically significant ($P < 0.001$; Table 1).

Expression and diagnostic significance of NNT-AS1

The relatively elevated expression of NNT-AS1 in the serum of sepsis patients compared with healthy controls was known by RT-qPCR (Fig. 1a). The ROC curve results elaborated the high sensitivity and specificity of NNT-AS1 to differentiate between sepsis patients and healthy persons

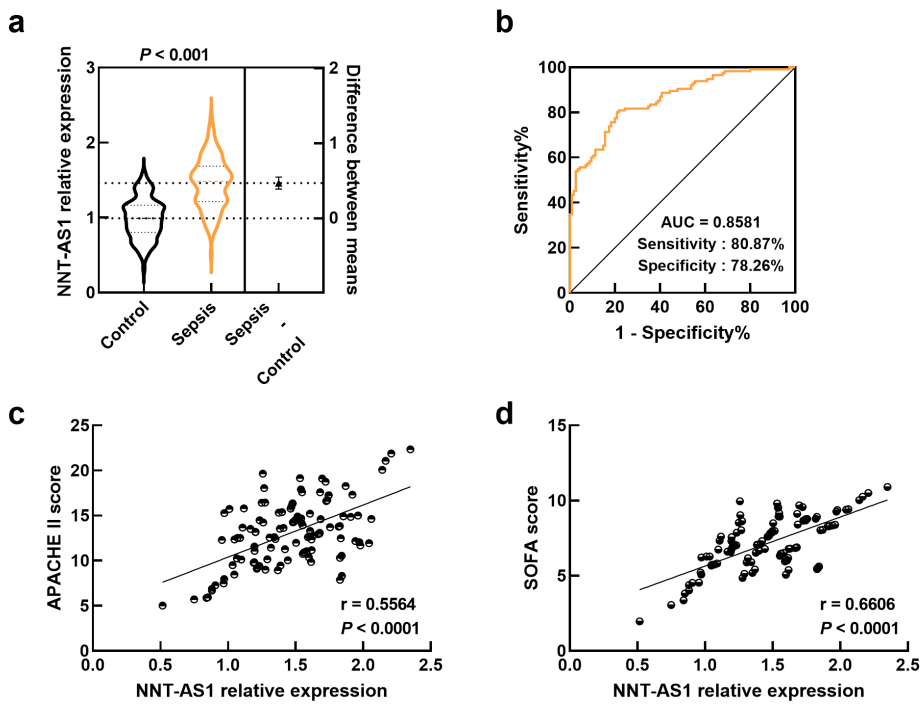

Fig. 1. Detection of NNT-AS1 expression in healthy and septic serum samples.
NNT-AS1 expression was upregulated in sepsis ($P < 0.001$; a). NNT-AS1 has high sensitivity and specificity for identifying patients with sepsis (AUC = 0.8581; b). NNT-AS1 levels were positively associated with APACHE II score (r = 0.5564, $P < 0.001$; c) and SOFA score (r = 0.6606, $P < 0.001$; d).

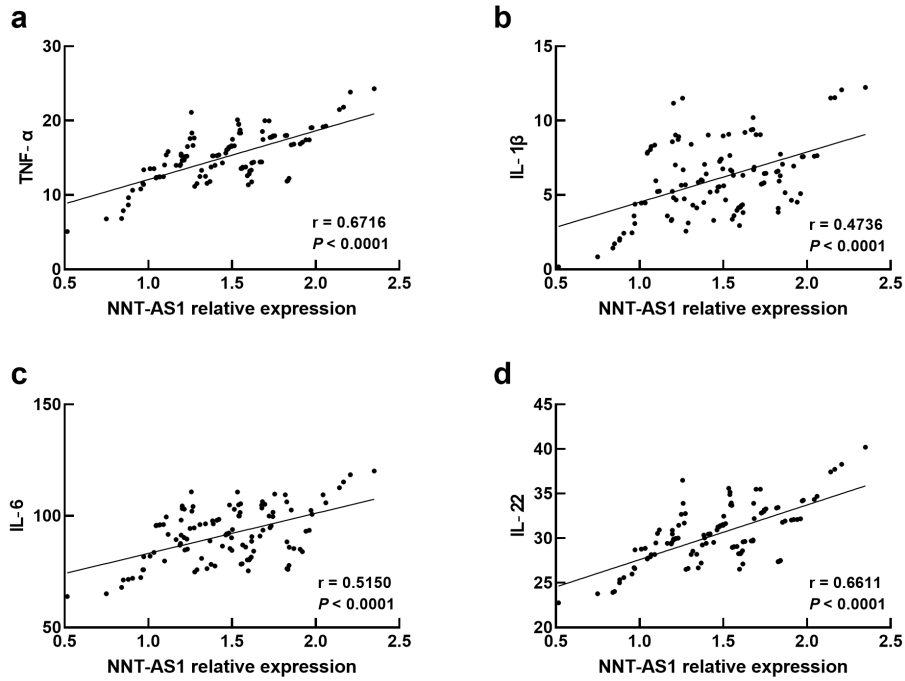

Fig. 2. Relationship between NNT-AS1 levels and inflammatory factor content.
TNF-α (r = 0.6716, $P < 0.001$; a), IL-1β (r = 0.4736, $P < 0.001$; b), IL-6 (r = 0.5150, $P < 0.001$; c) and IL-22 (r = 0.6611, $P < 0.001$; d) levels were all positively proportional to the NNT-AS1.

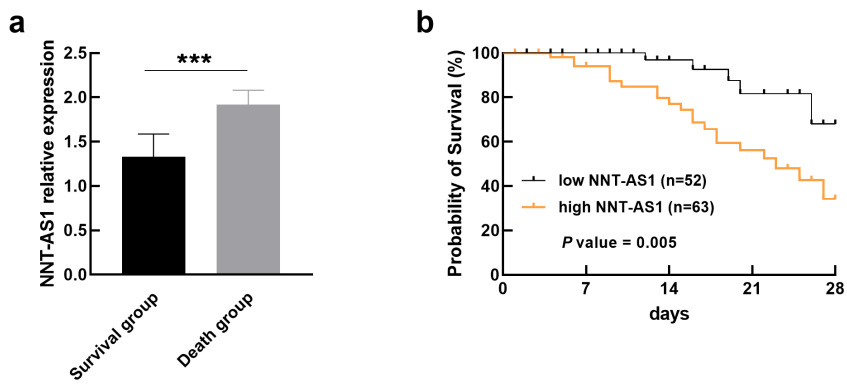

Fig. 3. Prognostic value of NNT-AS1 in sepsis.
NNT-AS1 expression was higher in the death group than in the survival group (***$P < 0.001$; a). The survival probability of patients in the high NNT-AS1 group was lower than that in the low NNT-AS1 group ($P = 0.001$; b).

(80.87% and 78.26%), and the area under the curve (AUC) was 0.8581 in Fig. 1b, suggesting that NNT-AS1 has the potential to be used as a diagnostic biomarker for sepsis.

Correlation between NNT-AS1 expression and APACHE II score, SOFA score

The results of Pearson correlation analysis showed that NNT-AS1 level was positively correlated with APACHE II score (r = 0.5564, $P < 0.001$; Fig. 1c). Similarly, NNT-AS1 levels were positively associated with SOFA score (r = 0.6606, $P < 0.001$; Fig. 1d), implying that NNT-AS1 may be related to the severity and prognosis of sepsis.

Relationship between NNT-AS1 level and inflammatory factors

Furthermore, NNT-AS1 with the levels of inflammatory factors in sepsis patients was assessed by Pearson's analysis as shown in Fig. 2a-d, the levels of TNF-α (r = 0.6716, $P < 0.001$), IL-1β (r = 0.4736, $P < 0.001$), IL-6 (r = 0.5150, $P < 0.001$) and IL-22 (r = 0.6611, $P < 0.001$) were all positively proportional to the NNT-AS1 level, which was up-regulated in sepsis patients.

Table 2. Analysis of factors affecting the cumulative survival of sepsis.

Characteristics	Multivariate Cox's regression	
	P value	HR (95% CI)
NNT-AS1	0.002	7.268 (2.136-24.731)
Age	0.639	1.265 (0.474-3.380)
Gender	0.908	1.059 (0.398-2.821)
BMI	0.569	1.316 (0.511-3.389)
CRP	0.177	1.945 (0.741-5.106)
PCT	0.168	1.943 (0.755-5.001)
FB	0.009	4.156 (1.434-12.040)
WBC	0.454	1.482 (0.530-4.148)
TNF-α	0.595	1.284 (0.512-3.222)
IL-1β	0.529	1.397 (0.494-3.953)
IL-6	0.349	1.726 (0.551-5.413)
IL-22	0.007	4.480 (1.509-13.302)
APACHE II score	0.364	1.621 (0.572-4.600)
SOFA score	0.141	2.083 (0.784-5.537)

body mass index: BMI; acute physiology and chronic health evaluation II score: APACHE II score; sequential organ failure assessment score: SOFA score; C-reactive protein: CRP; procalcitonin: PCT; fibrinogen: FB; white blood cells: WBC; including tumor necrosis factor α: TNF-α; interleukin-1β: IL-1β; interleukin-6: IL-6; interleukin-22: IL-22

Association of NNT-AS1 with prognosis in patients with sepsis

The patients were followed up after a 28-day post-treatment period and were categorized into survival group and death group based on their survival status. The expression level of NNT-AS1 was higher in the death group of sepsis patients than in the survival group using RT-qPCR method (Fig. 3a). Based on the mean value of serum NNT-AS1 expression in sepsis patients, the included patients were categorized into low NNT-AS1 group (n = 52) and high NNT-AS1 group (n = 63). Through Kaplan-Meier curve, it was observed that patients with low NNT-AS1 had a higher survival probability than those with high NNT-AS1 (Fig. 3b). In addition, multifactorial Cox's regression analysis confirmed that both NNT-AS1 (P = 0.002), FB (P = 0.009) and IL-22 (P = 0.007) may be independent prognostic factors for sepsis, as presented in Table 2. This implies that NNT-AS1 has the potential as a prognostic biomarker for sepsis.

Discussion

Sepsis is a common severe inflammatory reaction caused by infection, which can induce different degrees of organ dysfunction and a variety of complications, affecting the prognosis and survival outcome of patients (Su et al. 2021). Although the current clinical methods have made progress in the treatment of patients, the morbidity and mortality of sepsis have not been significantly improved in recent years, endangering the life safety of patients.

Common markers of inflammation and infection, including CRP and PCT, are often elevated in sepsis and are used to assist in determining whether patients are ill (Lee et al. 2022; Lin et al. 2023). Many studies have pointed out that sepsis patients have elevated levels of biochemical indicators compared to healthy persons (Zhang et al. 2021; Miao et al. 2022; Olinder et al. 2022). In the present study, it was elaborated that CRP, PCT, FB, and WBC indices were upregulated in sepsis and they were significantly different from healthy controls, which is similar to the existing evidence. Also, inflammatory factors TNF-α, IL-1β, IL-6, and IL-22 were prominently expressed in sepsis patients. It is noteworthy that APACHE II score and SOFA score can be used to reflect the severity of disease and the degree of organ function damage in patients with sepsis (Chen et al. 2021a). It has been reported that high APACHE II scores and SOFA scores are associated with poor prognosis and increased mortality in sepsis patients (Wang et al. 2020b). In this study, it was found that both APACHE II score and SOFA score were significantly higher in sepsis patients, suggesting that the condition of the patients was aggravated. The above results indicate that there are obvious differences between the included sepsis patients and healthy people, and the related inflammatory indicator factors are obviously upregulated.

On this basis, the clinical function of NNT-AS1 in sepsis was further discussed by taking NNT-AS1 as the research object. Among the available evidence, NNT-AS1 was found to be highly expressed in esophageal squamous cell carcinoma, lung cancer and pancreatic cancer (Huang et al. 2020; Pan et al. 2022; Lu et al. 2023). We also demonstrated an increasing trend of NNT-AS1 in the serum of sepsis patients. NNT-AS1 has high sensitivity and specificity in distinguishing patients from healthy persons, suggesting that NNT-AS1 has the potential to be a diagnostic marker for sepsis. In addition, NNT-AS1 level was positively correlated with APACHE II score and SOFA score, implying that the detection of NNT-AS1 combined with APACHE II score and SOFA score may be used for the diagnosis and evaluation of early sepsis. Moreover, NNT-AS1 expression was also positively correlated with inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-22), indicating that patients' condition may worsen with the increase of index levels.

In the studies on lncRNA in sepsis, ZFAS1, GSEC and SNHG7 were all confirmed to be associated with poor prognosis of patients (Xu and Shao 2019; Li et al. 2022; Xiao et al. 2022). Wang and colleagues (2022b) demonstrated that the lncRNA CASC2 was downregulated in sepsis patients and that CASC2 levels were lower in the death group than in the survival group. To explore the prognostic potential of NNT-AS1 in sepsis, we further performed statistics on the survival of patients. The results showed that the NNT-AS1 level was higher in the death group than in the survival group. Meanwhile, Kaplan-Meier curve and multi-

variate Cox regression analysis clarified the prognostic value of NNT-AS1 in the risk of death in patients with sepsis. These findings tell us that overexpression of NNT-AS1 indicates a poor prognosis and it may be an independent prognostic biomarker for sepsis.

This study proposed that upregulated NNT-AS1 may be associated with the identification and prognosis of sepsis patients, but there are inevitably has some limitations: (1) The limited sample size and single source included may cause the experimental results to be chance. (2) Single-center study, which may lead to selection bias. (3) The study of the molecular mechanism of NNT-AS1 in sepsis needs more in-depth discussion.

In summary, NNT-AS1 was elevated in sepsis, which predicted exacerbation of the patient's condition, increased levels of inflammation and poorer prognostic outcomes. NNT-AS1 may serve as a new diagnostic and prognostic biomarker for sepsis and provide new ideas for the treatment of patients with sepsis.

Author Contributions

Xin Liu: Conceptualization; Data curation; Formal analysis; Investigation; Resources; Writing - original draft. Jianyuan Huang: Conceptualization; Methodology; Project administration; Supervision; Writing - review & editing.

Conflict of Interest

The authors declare no conflict of interest.

References

Chen, H., Li, T., Yan, S., Liu, M., Liu, K., Zhang, H., Gao, M. & Xiao, X. (2021a) Pentraxin-3 Is a Strong Biomarker of Sepsis Severity Identification and Predictor of 90-Day Mortality in Intensive Care Units via Sepsis 3.0 Definitions. *Diagnostics* (*Basel*), **11**, 1906.

Chen, P., Huang, Z., Chen, L., Zhuang, S., Lin, H., Xie, J. & Zheng, K. (2021b) The relationships between LncRNA NNT-AS1, CRP, PCT and their interactions and the refractory mycoplasma pneumoniae pneumonia in children. *Sci. Rep.*, **11**, 2059.

Chen, Q., Liang, X., Wu, T., Jiang, J., Jiang, Y., Zhang, S., Ruan, Y., Zhang, H., Zhang, C., Chen, P., Lv, Y., Xin, J., Shi, D., Chen, X., Li, J., et al. (2022) Integrative analysis of metabolomics and proteomics reveals amino acid metabolism disorder in sepsis. *J. Transl. Med.*, **20**, 123.

Feng, F., Yang, H., Yang, W. & Chen, Y. (2023) Metabolic resuscitation therapy in critically ill patients with sepsis and septic shock: A pilot prospective randomized controlled trial. *Open Med.* (*Wars*), **18**, 20230637.

Gao, Z. & Huang, D. (2021) lncRNA GAS5-mediated miR-23a-3p promotes inflammation and cell apoptosis by targeting TLR4 in a cell model of sepsis. *Mol. Med. Rep.*, **24**, 510.

Geng, Z., Wang, X., Hao, S., Dong, B., Huang, Y., Wang, Y. & Xu, L. (2021) LncRNA NNT-AS1 regulates proliferation, ECM accumulation and inflammation of human mesangial cells induced by high glucose through miR-214-5p/smad4. *BMC Nephrol.*, **22**, 368.

Han, R., Li, W., Tian, H., Zhao, Y., Zhang, H., Pan, W., Wang, X., Xu, L., Ma, Z. & Bao, Z. (2023) Urinary microRNAs in sepsis function as a novel prognostic marker. *Exp. Ther. Med.*, **26**, 346.

Huang, J.W., Luo, X.Y., Li, Z.H. & Lang, B.P. (2020) LncRNA NNT-AS1 regulates the progression of lung cancer through the NNT-AS1/miR-3666/E2F2 axis. *Eur. Rev. Med. Pharmacol. Sci.*, **24**, 238-248.

Jan, J.S., Yang, C.H., Wang, M.H., Lin, F.L., Yen, J.L., Hsieh, I., Khotimchenko, M., Lee, T.H. & Hsiao, G. (2019) Hirsutanol A Attenuates Lipopolysaccharide-Mediated Matrix Metalloproteinase 9 Expression and Cytokines Production and Improves Endotoxemia-Induced Acute Sickness Behavior and Acute Lung Injury. *Mar. Drugs*, **17**, 360.

Lee, E.H., Lee, K.H., Song, Y.G. & Han, S.H. (2022) Discrepancy of C-Reactive Protein, Procalcitonin and Interleukin-6 at Hospitalization: Infection in Patients with Normal C-Reactive Protein, Procalcitonin and High Interleukin-6 Values. *J. Clin. Med.*, **11**, 7324.

Li, L., Zhang, S., Liu, J. & Luo, Y. (2022) Abnormal Expression of SNHG7 Is a Biomarker for the Diagnosis and Prognosis of Neonatal Sepsis. *Tohoku J. Exp. Med.*, **258**, 257-263.

Lin, S., Li, P., Yang, J., Liu, S., Huang, S., Huang, Z., Zhou, C. & Liu, Y. (2023) An immune genes signature for predicting mortality in sepsis patients. *Front. Immunol.*, **14**, 1000431.

Liu, Y., Liang, L., Ji, L., Zhang, F., Chen, D., Duan, S., Shen, H., Liang, Y. & Chen, Y. (2021) Potentiated lung adenocarcinoma (LUAD) cell growth, migration and invasion by lncRNA DARS-AS1 via miR-188-5p/ KLF12 axis. *Aging* (*Albany N. Y.*), **13**, 23376-23392.

Lu, Y., Chen, Q., Zhu, S. & Gong, X. (2023) Hypoxia promotes immune escape of pancreatic cancer cells by lncRNA NNT-AS1/METTL3-HuR-mediated ITGB1 m(6)A modification. *Exp. Cell Res.*, **432**, 113764.

Mei, J., Zhang, Y., Lu, S. & Wang, J. (2020) Long non-coding RNA NNT-AS1 regulates proliferation, apoptosis, inflammation and airway remodeling of chronic obstructive pulmonary disease via targeting miR-582-5p/FBXO11 axis. *Biomed. Pharmacother.*, **129**, 110326.

Miao, J., Ren, Z., Zhong, Z., Xu, F., Wang, J. & Yang, J. (2022) The Correlation of Antibacterial Peptides Concentration in Umbilical Cord Blood and Early Onset Sepsis in Preterm Infants. *Front. Pediatr.*, **10**, 903319.

Olinder, J., Borjesson, A., Norrman, J., West, T., Carlstrom, J., Gustafsson, A., Annborn, M., Herwald, H. & Ryden, C. (2022) Hepcidin discriminates sepsis from other critical illness at admission to intensive care. *Sci. Rep.*, **12**, 14857.

Pan, X., Wang, Q., Yu, Y., Wu, W., Chen, L., Wang, W. & Li, Z. (2022) Antisense lncRNA NNT-AS1 promoted esophageal squamous cell carcinoma progression by regulating its sense gene NNT expression. *Cell Death Discov.*, **8**, 424.

Su, X., Li, Y., Zhang, Y. & Han, S. (2021) Efficacy of alanyl glutamine in nutritional support therapy for patients with sepsis: A protocol for systematic review and meta-analysis. *Medicine* (*Baltimore*), **100**, e24861.

Tocu, G., Mihailov, R., Serban, C., Stefanescu, B.I., Tutunaru, D. & Firescu, D. (2023) The Contribution of Procalcitonin, C-Reactive Protein and Interleukin-6 in the Diagnosis and Prognosis of Surgical Sepsis: An Observational and Statistical Study. *J. Multidiscip. Healthc.*, **16**, 2351-2359.

Wang, H., Feng, Q., Wu, Y., Feng, L., Yuan, H., Hou, L., Wei, P., Wang, C. & Wang, J. (2021) Association of circulating long non-coding RNA HULC expression with disease risk, inflammatory cytokines, biochemical index levels, severity-assessed scores, and mortality of sepsis. *J. Clin. Lab. Anal.*, **35**, e23656.

Wang, H., Guo, M., Ding, D., Yang, F. & Chen, Z. (2020a) Long Non-Coding RNA NNT-AS1 Contributes to Cisplatin Resistance via miR-1236-3p/ATG7 Axis in Lung Cancer Cells. *Onco. Targets Ther.*, **13**, 3641-3652.

Wang, J., Feng, Q., Wu, Y. & Wang, H. (2022a) Involvement of blood lncRNA UCA1 in sepsis development and prognosis, and its correlation with multiple inflammatory cytokines. *J. Clin. Lab. Anal.*, **36**, e24392.

Wang, R., Zhao, J., Wei, Q., Wang, H., Zhao, C., Hu, C., Han, Y., Hui, Z., Yang, L., Dai, Q. & Liu, C. (2022b) Potential of circulating lncRNA CASC2 as a biomarker in reflecting the inflammatory cytokines, multi-organ dysfunction, disease severity, and mortality in sepsis patients. *J. Clin. Lab. Anal.*, **36**, e24569.

Wang, Y., Xu, Z., Yue, D., Zeng, Z., Yuan, W. & Xu, K. (2020b) Linkage of lncRNA CRNDE sponging miR-181a-5p with aggravated inflammation underlying sepsis. *Innate Immun.*, **26**, 152-161.

Xiao, J., Wu, Y., Paranggan, P., Gao, W., Gao, Z., Liu, J. & Wu, L. (2022) Involvement of plasma lncRNA GSEC in sepsis discrimination and prognosis, and its correlation with macrophage cell inflammation and proliferation. *Immunobiology*, **227**, 152264.

Xu, Y. & Shao, B. (2019) Circulating long noncoding RNA ZNFX1 antisense RNA negatively correlates with disease risk, severity, inflammatory markers, and predicts poor prognosis in sepsis patients. *Medicine* (*Baltimore*), **98**, e14558.

Yang, Y., Xue, J., Qin, L., Zhang, J., Liu, J. & Yu, J. (2021) LncRNA NEAT1 Promotes Inflammatory Response in Sepsis via the miR-31-5p/POU2F1 Axis. *Inflammation*, **44**, 1518-1528.

Yin, X.Y., Liu, Y., Lu, Z.M., Pang, T., Cui, H.T., Xue, X.C., Fang, G.E. & Luo, T.H. (2023) LncRNA NEAT-2 regulate the function of endothelial progenitor cells in experimental Sepsis model. *Mol. Biol. Rep.*, **50**, 6643-6654.

Zhang, B., Yu, L. & Sheng, Y. (2021) Clinical value and role of microRNA-29c-3p in sepsis-induced inflammation and cardiac dysfunction. *Eur. J. Med. Res.*, **26**, 90.

Zhou, C. & Duan, S. (2020) The Role of Long Non-Coding RNA NNT-AS1 in Neoplastic Disease. *Cancers* (*Basel)*, **12**.