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Abnormal Expression of SNHG7 Is a Biomarker for the Diagnosis and Prognosis of Neonatal Sepsis

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Long non-coding RNA (lncRNA) is of great significance in diagnosing and prognosis of human diseases. This study aims to explore the expression of lncRNA SNHG7 in infants with neonatal sepsis and further evaluate the diagnostic and prognostic value of SNHG7 in neonatal sepsis. The expression levels of serum SNHG7 in 81 neonates were detected by quantitative real-time-PCR (qRT-PCR). The correlations between SNHG7 and clinicopathological indicators were estimated by the Pearson correlation coefficient. The receiver operating characteristic (ROC) curve was generated to assess the diagnostic value of SNHG7. Kaplan-Meier survival curve and multivariate Cox regression analysis were conducted to evaluate the prognostic value of SNHG7 in neonatal sepsis. The expression level of serum SNHG7 was significantly upregulated in the neonatal sepsis group compared to the controls, and overexpressed SNHG7 showed clinical diagnostic value for neonatal sepsis. It was observed that the SNHG7 levels were positively correlated with some indicators representing the degree of inflammation. Follow-up analysis and multivariate Cox regression revealed that the death probability of neonates with high SNHG7 level was higher than that with low SNHG7 levels, and SNHG7 was an independent factor of poor prognosis in neonates with neonatal sepsis. Together, our findings show that highly expressed SNHG7 has the potential to be a diagnostic biomarker for neonates with neonatal sepsis and was closely related to the poor prognosis of neonatal sepsis.

Keywords: diagnosis; neonatal sepsis; prognosis; SNHG7
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Introduction

Sepsis is characterized by the imbalance of immune response to infection (Cornelius et al. 2020). Neonatal sepsis (NS), a systemic disease caused by bacterial, fungal, or viral infections, is the third leading cause of neonatal death after premature infant and intrapartum-related complications (Pathirana et al. 2016; Eshetu et al. 2020). Globally, adult sepsis has higher morbidity and mortality rates, while neonatal sepsis has more severe long-term impacts on surviving children (Angus et al. 2001). In the past few decades, microbial culture, which was once the gold standard for diagnosis of neonatal septicemia, is no longer in the same diagnostic position with the increase of uncertain factors, such as small blood volume of newborns and exposure of the mothers to antibiotics during delivery (Schelonka et al. 1996; Connell et al. 2007). Since NS must be diagnosed as early as possible and treated promptly, there has been constant exploration to find effective and accurate biomarkers for NS diagnosis and prognosis.

Long non-coding RNA (lncRNA) is a non-coding RNA with more than 200 nucleotides (He et al. 2020). The efficacy of lncRNA on gene regulation is still unclear. The most widely accepted understanding is that lncRNA competes with microRNA (miRNA) for the same mRNA target or acts as an enticement or miRNA "sponge" to regulate the effect of miRNA on gene expression (Wang et al. 2016; Zhou et al. 2020). Several studies have reported the role of lncRNA in sepsis. For instance, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a highly conserved lncRNA widely distributed in human tissues, has shown prognosis value in adult sepsis (Chaleshi et al. 2020). In patient cohorts, abnormal MALAT1 differentiates sepsis survivors from non-survivors (Zhao et al. 2021). Song et al. (2021) reported that lncRNA CASC15 was elevated in NS patients and had the ability to distinguish

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between NS patients and neonatal pneumonia (NP) patients. LncRNA small nucleolar RNA host genes (SNHGs) have a vast family system, including 22 members from SNHG1 to SNHG22 (Qin et al. 2020). SNHG7 is an oncogene on chromosome 9q34.3 that plays a role in many human cancers (Cheng et al. 2019). Shan et al. (2018) reported that SNHG7 overexpression significantly promoted tumorigenesis and liver metastasis of SW480 cells. Recently, studies suggest that SNHG7 is involved in regulating the inflammatory responses. For example, Peng et al. (2021) showed that the increased SNHG7 aggravated the inflammation and apoptosis of cardiac fibroblasts. Zhang et al. (2021) found that SNHG7 promoted inflammation and oxidative stress through the NF-κB signaling pathway in Parkinson's disease models. The role of SNHG7 in regulating inflammatory response and oxidative stress in human diseases has gradually been widely recognized. Systemic inflammation of organisms is usually the primary manifestation of sepsis. However, the relationship among SNHG7, inflammation, and sepsis remains to be further explored.

With the passage of time and the deepening of research, the detection of lncRNA expression will achieve the diagnosis and prognosis of diseases, and as a potential target for disease treatment, it will show broad clinical application prospects. However, there are still many problems to be solved before lncRNA can be used as a biomarker in clinic, and our current study only preliminarily verified the association between SNHG7 and NS, and its role in NS. In the present study, we speculated that SNHG7 may play a role in NS. In the current study, the expression levels of SNHG7 in all subjects were detected and the diagnostic and prognostic value of SNHG7 for NS through ROC curve and follow-up studies were assessed. Our study may provide new ideas for the diagnosis and prognosis of NS.

Materials and Methods

Study population and sample collection

The Ethics Committee of Binzhou Medical University Hospital has approved the study, and guardians of all the neonates in the group have signed informed consent forms. Eighty one neonates with NS, admitted to this hospital from May 2020 to June 2021, were selected as the case group. Other 76 neonates clinically diagnosed with pneumonia without NS symptoms were selected as the control group. The diagnostic principles of NS are based on the criteria established by the Kunming Neonatal Sepsis Definition Conference in 2003, including abnormal clinical manifestations, disease history, laboratory examination, and positive blood pathogens. This study did not include premature infants, newborns with congenital malformations or chromosomal abnormalities, and newborns with autoimmune diseases. Peripheral venous blood of all subjects was collected for biochemical analysis on the day of enrollment. The routine blood test was performed by automatic blood analyzer (Sysmex Corporation, Kobe, Japan). CRP level was determined by a 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan). PCT level was tested by E170 electrochemiluminescence analyzer (Hitachi), and inflammatory factors were detected by ELISA.

Quantitative real-time PCR analysis

Total RNA was isolated by TRIzol reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. 2 μg RNA was reverse transcribed into the cDNA using the SuperScript II Reverse Transcriptase kit (Qiagen, Valencia, CA, USA). The cDNAs were amplified on ABI7300 real-time PCR machine (Applied Biosystems, Foster City, MA, USA) using SYBR® Premix Ex Taq™ (Takara, Dalian, China). The amplification conditions were arranged as follows: 95°C for 5 min, 45 cycles of 95°C for 10 s, 55°C for 15 s and 60°C for 15 s. The endogenous gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as the internal control and the relative expressions of SNHG7 were calculated by the $2^{-\Delta\Delta Ct}$ method. The primers used are as follows: SNHG7 (forward primer): 5'-GTCAGCCGCATCTTCTTTTG-3', SNHG7 (reverse primer): 5'-CGCCCAATACGACCAAATC-3'; GAPDH (forward primer): 5'-CACCGTCAAGGCTGAGAAC-3', GAPDH (reverse primer): 5'-TGGTGAAGACGCCAGTGGA-3'.

Follow-up analysis

After admission, the corresponding treatment plan was formulated according to the neonate's condition. For discharged patients, follow-up analysis is generally conducted by telephone follow-up, while for hospitalized patients, their hospital number is often recorded, and their examination and treatment status are tracked at any time. Subsequently, a 28-day follow-up survey recorded the deaths of neonates during the follow-up period. According to the median level of SNHG7 expression of all patients, the patients were divided into low expression group and high expression group. At the end of the follow-up analysis, the Kaplan-Meier survival curve of neonates with adverse events was generated to evaluate the interplay between the expression level of SNHG7 and the poor NS prognosis.

Statistical analysis

All statistical analyses were performed using SPSS software and GraphPad Prism 8.0 software. Data were presented as mean ± standard deviation (SD). Differences were evaluated by the Chi-square test, student t-test, and one-way ANOVA. The receiver operating characteristic (ROC) curve estimated the clinical diagnostic value of SNHG7 for NS. Pearson correlation coefficient was conducted to evaluate the correlation between SNHG7 and clinical parameters. Multivariate Cox regression analysis was performed to identify independent factors affecting overall survival, and a P value less than 0.05 was considered significant.

Results

Demographic data and clinicopathological characteristics

We compared the demographic data and the clinical characteristics between the NS and the control group. We found no significant differences between the two groups concerning age, sex, and body weight (Table 1, $P > 0.05$). However, significant differences were observed in the level of white blood cells (WBC), C-reactive protein (CRP), procalcitonin (PCT), neutrophil-lymphocyte ratio (NLR), interleukin (IL)-6, IL-8 and tumor necrosis factor-α (TNF-α) between control and NS groups ($P < 0.001$).

Serum SNHG7 expression levels and correlation analysis with clinical indicators

The expression levels of SNHG7 in the NS samples were analyzed by qRT-PCR. Our data showed that the expression levels of serum SNHG7 were significantly reduced in the NS group compared with the control group (Fig. 1, $P < 0.001$), indicating that SNHG7 might contribute to the pathogenic process of NS. Moreover, we used the Pearson correlation coefficient method to evaluate the correlation between SNHG7 and various clinicopathological features of NS neonatal. The results showed that SNHG7 expression levels positively correlated with WBC, CRP, PCT, NLR, IL-6, IL-8, and TNF-α levels of NS neonates (Table 2, $P < 0.05$), indicating that SNHG7 is directly related to the severity of inflammation in NS.

Diagnostic value of SNHG7 in NS

The ROC curve was used to evaluate the diagnostic significance of SNHG7 for NS. The AUC (area under the curve) value of this curve was 0.918, and the values of sensitivity and specificity were 80.2% and 92.1%, respectively, indicating potential clinical application value for NS diagnosis (Fig. 2).

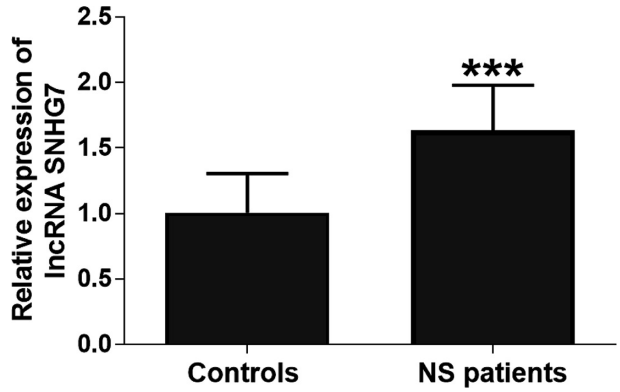

Fig. 1. The relative expression of serum SNHG7 in controls and neonatal sepsis (NS) patients.
The relative expression level was elevated in the NS group compared to the control group.
$^{***}P < 0.001$.

Predictive value of SNHG7 in NS neonatal with poor prognosis

According to the median level of serum SNHG7 in the NS group, we divided the neonates into two groups: the high SNHG7 expression group (n = 42) and the low SNHG7 expression group (n = 39). The Kaplan-Meier survival curve was plotted based on death events in neonates during the 28-day follow-up period. The prognostic value of SNHG7 for NS was evaluated by analyzing the relationship between SNHG7 levels and the death events. In Fig. 3, 4 deaths occurred in the low SNHG7 expression group,

Table 1. Comparison of clinical data between the two groups.

Indicators	Controls (n = 76)	Neonatal sepsis patients (n = 81)	*P*
Sex (n)			0.574
male	36	42	
female	40	39	
Body weight (kg)	3.43 ± 0.45	3.50 ± 0.52	0.335
Age (days)	11.91 ± 4.50	10.90 ± 5.25	0.2
WBC ($\times 10^9$/L)	10.15 ± 3.92	17.29 ± 5.75	< 0.001
CRP (mg/L)	7.34 ± 3.90	10.97 ± 5.37	< 0.001
PCT (ng/mL)	0.53 ± 0.26	3.63 ± 3.24	< 0.001
NLR ($\times 10^9$/L)	5.94 ± 2.83	8.77 ± 2.98	< 0.001
IL-6 (pg/mL)	308.57 ± 44.55	366.64 ± 70.56	< 0.001
IL-8 (pg/mL)	414.41 ± 45.82	458.37 ± 66.82	< 0.001
TNF-α (pg/mL)	313.18 ± 46.00	392.91 ± 66.36	< 0.001

Data are expressed as n or mean ± SD.
Controls, patients with pneumonia; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; NLR, neutrophil-lymphocyte ratio; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α.

Table 2. Correlation between lncRNA SNHG7 and clinical parameters.

Parameters	Correlation with lncRNA SNHG7 (r)
WBC	0.731**
CRP	0.470**
PCT	0.268*
NLR	0.331**
IL-6	0.373**
IL-8	0.267*
TNF-α	0.334**

WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; NLR, neutrophil-lymphocyte ratio; IL-6, interleukin-6; IL-8, interleukin-8; TNF-*α*, tumor necrosis factor-*α*.
**Significantly correlated at the 0.01 level (two-sided); *Significantly correlated at the 0.05 level (two-sided).

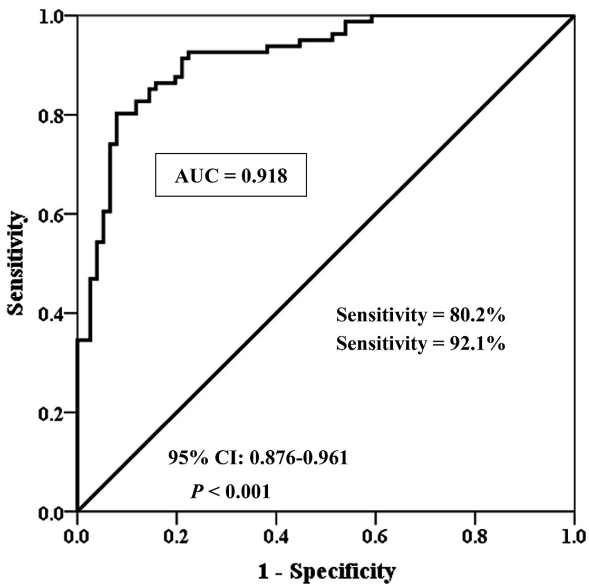

Fig. 2. The receiver operating characteristic (ROC) curve.
ROC curve showed that high expression of SNHG7 has clinical diagnostic value for NS.

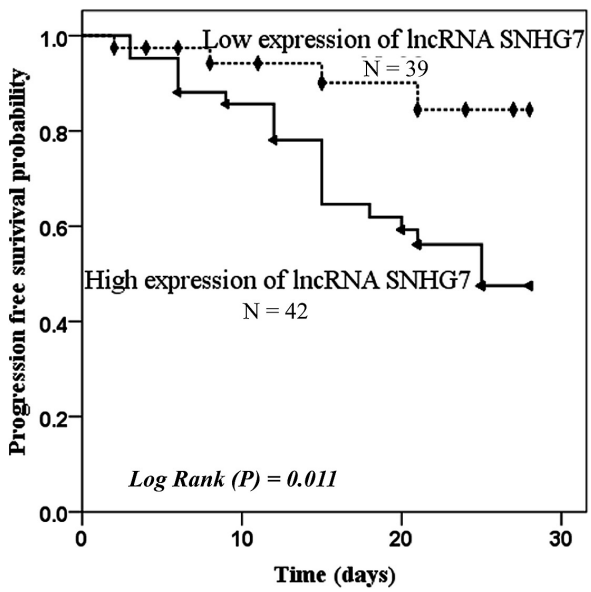

Fig. 3. Kaplan-Meier survival curve of NS neonates with different SNHG7 levels.
The overall survival rate was lower in the group with high SNHG7 expression than the group with low SNHG7 expression.

while 19 death cases occurred in the high SNHG7 expression group. The probability of death in the high SNHG7 expression group was significantly higher than that in the low SNHG7 expression group (log-rank $P = 0.011$). A multivariate Cox regression analysis was performed to verify the relationship between various clinical indicators and prognosis. Our data showed that SNHG7 might be an independent predictor of the poor prognosis of NS neonates (Table 3, HR = 3.413, 95% CI = 1.063-10.960, $P = 0.039$).

Discussion

NS is one of the acute diseases that severely endanger the life, health, and safety of neonates (Fleischmann et al. 2021). It is characterized by a lack of typical clinical manifestations in the early stage, rapid progress, and poor prognosis. Studies show that the incidence of NS in developed countries is about 1-8 per 1,000 live births, while the incidence in developing countries is about three times more (Satar et al. 2018). An early and effective diagnosis of NS is crucial and is also the key to reducing neonatal mortality. With increasing of relevant studies in recent years, more and more scholars have shown lncRNA to play a crucial role in regulating of immune functions. The abnormal expression of lncRNA might be the key to the occurrence and development of various diseases (Peng et al. 2018). Here, we found that the relative level of serum SNHG7 in the NS group was higher than that in the control group. Furthermore, abnormal expression of SNHG7 had diagnostic efficacy for NS, and its specificity is better than sensitivity, which is of clinical significance for the diagnosing NS. Moreover, SNHG7 also showed high prognostic value in the poor prognosis of NS.

Table 3. Multivariate Cox analysis of clinical characteristics concerning overall survival.

Characteristics	Multivariate analysis		
	HR	95% CI	*P*
LncRNA SNHG7	3.413	1.063-10.960	0.039
Age	1.584	0.604-4.151	0.350
Sex	1.400	0.556-3.528	0.476
Body weight	1.463	0.575-3.721	0.424
WBC	1.821	0.738-4.493	0.193
CRP	1.530	0.564-4.154	0.404
PCT	1.506	0.583-3.891	0.398
NLR	1.528	0.588-3.970	0.384
IL-6	1.433	0.539-3.809	0.471
IL-8	1.433	0.522-3.939	0.485
TNF-α	1.509	0.613-3.716	0.370

WBC, white blood cell; CRP, C-reactive protein; PCT, procalcitonin; NLR, neutrophil-lymphocyte ratio; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α; HR, hazard ratio; CI, confidence interval.

Sepsis is a manifestation of a severe systemic inflammatory reaction (Han et al. 2019). In the early stages of sepsis, monocytes, macrophages, and neutrophils are continuously activated under the stimulation of antigens. This leads to excessive release of various pro-inflammatory factors, further aggravating the inflammatory reaction (Zoso et al. 2016; Jedynak et al. 2019). At the same time, the pro-inflammatory factors can promote the expression of adhesion molecules and coagulation factors in endothelial cells, causing a systemic inflammatory reaction and abnormal coagulation function, and leading to multiple organ dysfunction or septic shock (Muresan et al. 2018). Inflammatory factors such as IL-6, IL-8, IL-1β and TNF-α are the earliest products of an inflammatory reaction and play an essential role in transmitting information, activating, and regulating immune cells (Khaertynov et al. 2017). Our data revealed that the levels of CRP, IL-6, IL-8 and TNF-α in the NS group were significantly enhanced compared to controls. Meanwhile, we also noted that SNHG7 expression levels were positively correlated with the levels of the above inflammatory indicators. Previously, it has been reported that SNHG7 expression is elevated in monocyte, macrophages, and unstable atherosclerotic plaques (Pan et al. 2019). These data suggested that for the inflammatory response of NS, high expression of SNHG7 is often closely associated with the degree of inflammation. These results were consistent with the reports by Peng et al. (2021) and Zhang et al. (2021) that showed SNHG7 to have a stimulating effect on inflammation.

Biomarkers are the indexes that can reflect the normal biological processes, pathological processes, or pharmacological results of therapeutic interventions, and can be objectively measured and estimated (Ziemssen et al. 2019). The diagnostic and prognostic value of lncRNA in sepsis has been extensively studied. For example, Huang et al. (2018) found that circulating lncRNA NEAT1 was associated with poor prognosis and increased expression of pro-inflammatory cytokines in sepsis. Correct diagnosis and accurate division of neonatal sepsis are crucial for guiding physicians to take timely and effective treatment measures (Rogers et al. 2016). Based on the difference in SNHG7 levels between the NS group and the control group, and the degree of inflammation of sepsis, our study suggested that SNHG7 might be used as a candidate biomarker for sepsis diagnosis. Likewise, the information provided by the ROC curve showed that SNHG7 has an excellent diagnostic value for NS. Therefore, our study established that the highly expressed SNHG7 is a potential new biomarker for the diagnosis of NS neonates. Also, a 28-day follow-up study revealed that neonates with high SNHG7 expression were more likely to die than those with low SNHG7 expression. Additionally, multivariate Cox regression analysis also suggested that SNHG7 is an independent prognostic factor in NS. Although we have experimentally proved a strong association between SNHG7 and NS, its specific role in disease pathogenesis is still unknown. Similarly, the molecular mechanism of SNHG7 regulating inflammation needs further exploration. Due to the lack of experimental data, the results require constant re-evaluation and clinical validation.

The limitations of this study are as follows: this study belongs to a single-center study with a small sample size. In a larger cohort and multi-center study with a large sample size, it is extremely important to evaluate the diagnostic and prognostic efficiency of SNHG7 for NS. Besides, the biological mechanism of SNHG7 regulating NS has always been a hot research topic. As for what causes the abnormal levels of SNHG7 in NS patients, more studies are needed to

detect it.

In summary, our study showed that the SNHG7 level is elevated in the serum of neonates with NS. The high expression of SNHG7 predicted the occurrence of NS and was related to the poor prognosis of neonates. According to current studies, lncRNA as a NS biomarker needs to be proved by many studies. As biomarkers, lncRNA is not only stable in nature, but also easy to obtain and with mature detection methods. Once such biomarkers are applied in clinical practice, they will contribute to the diagnosis of diseases and even the development of new therapeutic targets. Our study is the beginning of new research to explore the role of SNHG7 in NS, which has practical implications for the future diagnosis and treatment of NS.

Author Contributions

L.L. and Y.L. contributed to the study conception and design. Material preparation, data collection and analysis were performed by S.S.Z. and J.Y.L. The first draft of the manuscript was written by L.L. Y.L. contributed to interpretation of the results and critically revised the manuscript. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

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