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Original Article

Clinical and prognostic significance of long non-coding RNA CRNDE expression in severe pneumonia and its correlation with inflammatory factor levels

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Abstract: Objective: To investigate the clinical and prognostic significance of long non-coding RNA (lncRNA) CRNDE expression in severe pneumonia and its correlation with the levels of inflammatory factors. Methods: In this retrospective study, 86 patients with severe pneumonia were selected as the observation group (OG), and 70 patients with non-severe pneumonia were selected as the control group (CG). The expression of lncRNA CRNDE was measured by real-time fluorescence quantitative reverse transcription polymerase chain reaction. The relationship between lncRNA CRNDE expression and clinical characteristics and prognosis of patients was analyzed. The correlation between lncRNA CRNDE expression and the levels of inflammatory factors related to severe pneumonia was also analyzed. Results: Relative expression of lncRNA CRNDE in OG was significantly higher than that in CG ($P<0.05$). The receiver operator characteristic (ROC) curve analysis revealed that lncRNA CRNDE expression could be used for the detection of severe pneumonia. The expression of lncRNA CRNDE was not related to gender, age, or smoking history (all $P>0.05$), but related to the pneumonia severity index (PSI) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and procalcitonin (PCT), C-reactive protein (CRP), and D-dimer (DD) expression ($P<0.05$). Spearman correlation analysis revealed that lncRNA CRNDE expression was positively correlated with the expressions of PCT, CRP, and DD ($r=0.908$, 0.898, and 0.951, respectively, $P<0.001$). Conclusions: lncRNA CRNDE is highly expressed in the serum of patients with severe pneumonia and is an independent risk factor for the poor prognosis of these patients. The expression of lncRNA CRNDE is also positively correlated with the levels of inflammatory factors in such patients, which can be used for the clinical detection of severe pneumonia.

Keywords: lncRNA CRNDE, severe pneumonia, clinical, prognosis, inflammatory factor

Introduction

Pneumonia is a rapid-onset inflammatory disease that affects the terminal airways, alveoli, and pulmonary interstitium [1]. The condition of some patients can be controlled by early intervention and standardized treatment; however, if pneumonia is not effectively controlled and the condition persists, it can develop into severe pneumonia, leading to increased mortality [2, 3]. Severe pneumonia is a common infectious disease in intensive care units (ICUs), usually caused by fungal, bacterial, viral, or parasitic infections. Pneumonia can also be caused by a combination of pathogenic microorganisms and physical factors. Common symptoms of pneumonia include dyspnea, fever, chest pain, and hypotension [4, 5]. The risk of poor prognosis in most patients with severe pneumonia cannot be reduced by antibiotic treatment, which may be related to the degree of pulmonary infection [6]. Currently, there is no unified standard for the severity of pulmonary infection, and inflammation is the main feature and evaluation approach of the disease. However, a non-specific assessment of a patient's condition by evaluating the levels of inflammatory factors alone cannot provide effective guidance for the treatment of the condition, and may prolong the condition and aggravate persistent extrapulmonary tissue lesions, thus delaying recovery [7, 8]. Therefore, it is essential to identify indicators that specifically reflect the severity of pneumonia.

With the continuous development and improvement of clinical testing technology, biomarkers are gradually becoming widely used in the treatment and prognosis of diseases. Long non-coding RNAs (lncRNAs) are a group of RNAs

with a length of more than 200 nucleotides that can be transcribed but cannot be translated. LncRNAs can act as the main components of nucleoprotein complexes to regulate downstream genes, and the mutations of related genes are involved in the development of many diseases [9, 10]. In recent years, clinical studies have confirmed the association between lncRNA expression and various cancers, and abnormal expression of lncRNAs has been observed in various tumor tissues [11-13]. LncRNA CRNDE is a cancer regulatory gene that is highly expressed in non-small cell lung cancer [14]. However, only a few studies have investigated the relationship between lncRNA CRNDE expression and severe pneumonia. In this study, the expression of lncRNA CRNDE in the serum of patients with severe pneumonia was detected, and the relationship between lncRNA CRNDE expression and the clinicopathologic features of these patients were analyzed. In addition, the significance of lncRNA CRNDE expression in evaluating the prognosis of severe pneumonia and its relationship with the levels of inflammatory factors was investigated.

Materials and methods

Baseline data

In this retrospective study, 86 patients with severe pneumonia admitted to the ICU of Zibo Central Hospital from January 2016 to January 2017 were assigned as the observation group (OG). Another 70 patients with non-severe pneumonia were selected as the control group (CG). This study was approved by the Medical Ethics Committee of Zibo Central Hospital.

Inclusion criteria

The inclusion criteria were as follows: (1) patients diagnosed with severe pneumonia according to the criteria in the diagnostic and treatment guidelines for severe pneumonia [15], (2) patients requiring mechanical ventilation by endotracheal intubation, (3) patients with consciousness or orientation disorder, and (4) patients who had not been treated with antibiotics, hormones, or immunosuppressants recently.

Exclusion criteria

The exclusion criteria were as follows: (1) patients with malignant solid tumors, (2) patients with active pulmonary tuberculosis or a history of pulmonary tuberculosis, (3) patients with severe liver and kidney failure and pulmonary embolism, (4) patients with autoimmune disease-induced lung diseases, (5) patients with incomplete pathologic data.

Outcome measurements

In the early morning of the day of admission, 5 mL of venous blood was taken from the elbow of each patient, placed in a non-anticoagulation test tube, and centrifuged at 3000 rpm for 10 min, and the serum was stored at -70°C for later use. Total RNA was extracted with Trizol reagent, and the integrity of RNA was detected by agarose gel electrophoresis. cDNA was synthesized by reverse transcription following the instructions of the reverse transcription kit (BIOMIGA). GAPDH was used as an internal control, and qRT-PCR was performed under the following conditions: 95°C for 30 s, 95°C for 5 s, and 58°C for 34 s, for a total of 45 cycles. The cycle threshold (Ct) value of lncRNA CRNDE and the internal control was measured, and the relative expression of lncRNA CRNDE in each sample was assessed using the $2^{-\Delta\Delta Ct}$ method. The primer sequences used were as follows: CRNDE: forward primer 5'-ACGCTAACTGGCACCTTGTT-3'; reverse primer 5'-TGGGGATTACTGGGGTAGGG-3'; GAPDH: forward primer 5'-GAAGGTGAAGGTCGGAGTC-3'; reverse primer 5'-GAAGATGGTGATGGGATTTC-3'.

Venous blood was collected as described in the preceding subsection. Procalcitonin (PCT) was detected by chemiluminescence immunoassay (Wuhan Easy Diagnosis Biomedicine Co., Ltd., model: SMART 300). C-reactive protein (CRP) was detected using an automatic microprotein creatinine analyzer (Shanghai Jumu Medical Equipment Co., Ltd., model: PA-900) by nephelometry. D-dimer (DD) was detected using an automatic coagulation analyzer (Beijing Jiuqiang Biotechnology Co., Ltd., model: 3-500).

All patients were administered symptomatic treatments such as breathing support by ventilator, antibiotics, sputum atomization, and maintenance of liquid and acid-base balance. After discharge, patients were followed up for 3 years by outpatient visit or telephone until February 1, 2020. The numbers of survivors and deaths were recorded, and all respondents completed the follow-up.

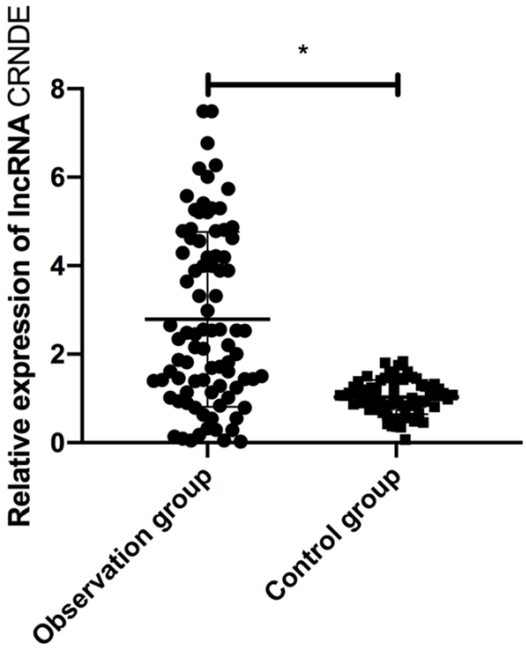

Figure 1. Comparison of serum lncRNA CRNDE expression between two groups. The relative expression of lncRNA CRNDE in the observation group (3.01±1.90) was significantly higher than in the control group (1.12±0.40). Note: lncRNA: long non-coding RNA. * indicates *P*<0.05.

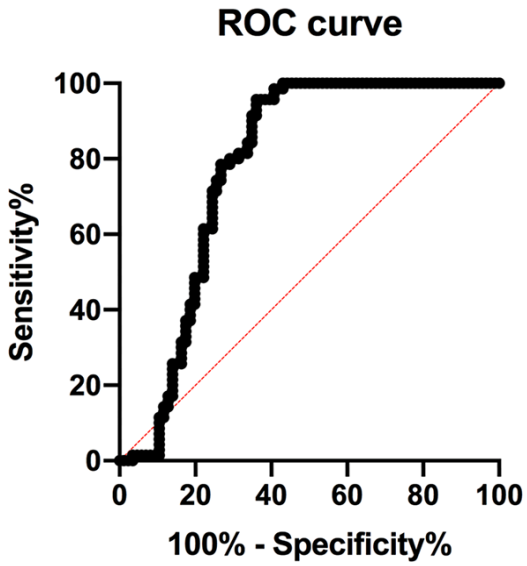

Figure 2. Diagnostic value of lncRNA CRNDE in severe pneumonia. ROC curve analysis showed that the AUC of lncRNA CRNDE in severe pneumonia was 0.781, and the 95% CI was 0.704-0.858. Note: lncRNA: long non-coding RNA; ROC: Receiver Operator Characteristic; AUC: Area Under the Curve; 95% CI: 95% Confidence Interval.

Statistical analysis

The Statistical Package for Social Science (SPSS) 22.0 was used to process the data. Counted data were described by n (%) and analyzed using a χ^2 test. Measured data were represented by ($\bar{x} \pm s$) and analyzed using a t test. Kaplan-Meier analysis was used for survival analysis, and the Log-rank method was used to make comparisons between groups. The receiver operator characteristic (ROC) curve was constructed to analyze the diagnostic value of lncRNA CRNDE expression in severe pneumonia. Cox regression analysis was used to analyze the risk factors affecting the prognosis of patients with severe pneumonia. Spearman's correlation was used for correlation analysis. A difference was considered significant at *P*<0.05.

Results

Comparison of baseline data

The OG had 48 males and 38 females, aged 40-90 years, with an average age of (68.64±9.35) years, while the CG had 41 males and 29 females, aged 40-90 years, with an average age of (68.83±10.25) years. There was no significant difference in gender or age between the two groups (*P*>0.05).

Comparison of relative expression of lncRNA CRNDE

The relative expression of lncRNA CRNDE in the serum of patients in the OG (3.01±1.90) was significantly higher than that in the CG (1.12±0.40) (*P*<0.05), as shown in **Figure 1**.

Diagnostic value of lncRNA CRNDE in severe pneumonia

ROC curve analysis revealed that the area under the curve (AUC) for lncRNA CRNDE in severe pneumonia was 0.781, and the 95% confidence interval (95% CI) was 0.704-0.858 (**Figure 2**).

Relationship between lncRNA CRNDE expression and clinicopathologic features

Using the average expression of lncRNA CRNDE in the serum as the cut-off value, 86 patients were divided into low and high lncRNA CRNDE

Table 1. Relationship between the expression level of lncRNA CRNDE in serum and clinicopathologic data in patients with severe pneumonia

Baseline data	n	LncRNA CRNDE		X^2	*P*
		Low expression	High expression		
Gender				0.506	0.477
Male	48	23 (53.49)	25 (58.14)		
Female	38	20 (46.51)	18 (41.86)		
Age				0.080	0.777
>68	43	21 (48.84)	22 (51.16)		
≤68	43	22 (51.16)	21 (48.84)		
BMI	86	25.34 (22.87, 26.27)	24.38 (22.82, 26.43)		0.682
History of smoking				0.182	0.670
Yes	39	19 (44.19)	20 (46.51)		
No	47	24 (55.81)	23 (53.49)		
Diabetes					
Yes	7	3 (42.85)	4 (57.15)	23.471	<0.001
No	79	38 (48.11)	41 (51.89)		
PSI score				18.601	<0.001
>140	51	19 (44.19)	32 (74.42)		
≤140	35	24 (55.81)	11 (25.58)		
APACHE II score				14.651	<0.001
>22	48	17 (39.53)	29 (67.44)		
≤22	40	26 (60.47)	14 (32.56)		
PCT (μg/L)				18.031	<0.001
>1.70	45	16 (37.21)	29 (67.44)		
≤1.70	41	27 (62.79)	14 (32.56)		
CRP (mg/L)				18.001	<0.001
>130	43	15 (34.88)	28 (65.12)		
≤130	43	28 (65.12)	15 (34.88)		
DD (mg/L)				27.401	<0.001
>3.40	42	13 (30.23)	29 (67.44)		
≤3.40	44	30 (69.77)	14 (32.56)		

Note: lncRNA: long non-coding RNA; PSI: Pneumonia Severity Index; APACHE: Acute Physiology and Chronic Health Evaluation; PCT: Procalcitonin; CRP: C-Reactive Protein; DD: D-Dimer.

expression groups. The results showed that the expression of lncRNA CRNDE was not related to the gender, age, or smoking history of patients (all *P*>0.05), but was related to the pneumonia severity index (PSI) score, Physiology and Chronic Health Evaluation (APACHE) II score, and expressions of PCT, CRP, and DD (all *P*<0.05) (**Table 1**).

Relationship between lncRNA CRNDE expression and prognosis of patients with severe pneumonia

At the end of the follow-up period, the 3-year survival rate of the high lncRNA CRNDE expression group was (20.93%, 9/43), which was significantly lower than that of the low lncRNA CRNDE expression group (58.14%, 25/43) (*P*<0.05) (**Figure 3**).

Multivariate analysis of risk factors affecting poor prognosis of patients with severe pneumonia

Multivariate analysis showed that the PSI score, APACHE II score, and expression of PCT, CRP, DD, and lncRNA CRNDE were independent risk factors favoring a poor prognosis in patients with severe pneumonia (*P*<0.05 for all) (**Tables 2** and **3**).

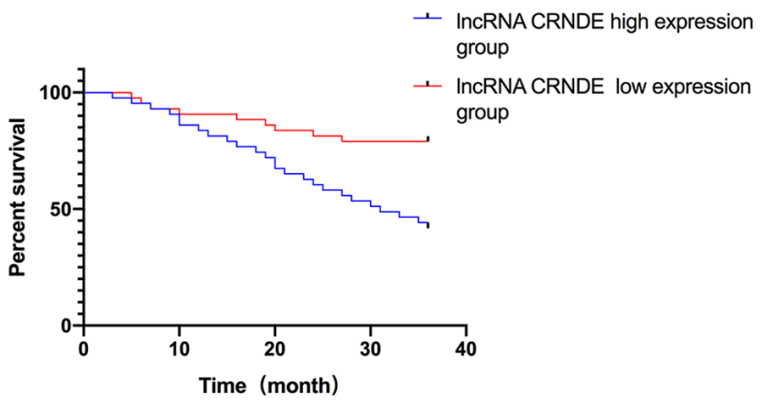

Figure 3. Relationship between lncRNA CRNDE expression and prognosis of patients with severe pneumonia. By the end of the follow-up period, the 3-year survival rate of the lncRNA CRNDE high expression group was significantly lower than that of the lncRNA CRNDE low expression group. Note: lncRNA: long non-coding RNA.

Table 2. Analysis of risk factors affecting adverse prognosis in patients with severe pneumonia

Indicator	B value	χ^2 value	*P* value	OR value	95% CI
PSI score	0.418	6.021	<0.001	0.362	0.263-0.493
APACHE II score	0.305	4.564	<0.001	0.532	0.343-0.803
PCT	0.378	5.827	<0.001	2.486	1.540-4.002
CRP	0.394	4.094	<0.001	2.208	1.273-3.813
DD	0.459	7.167	<0.001	3.399	2.025-5.708
lncRNA CRNDE	0.247	4.337	<0.001	0.598	0.387-0.914

Note: PSI: Pneumonia Severity Index; APACHE: Acute Physiology and Chronic Health Evaluation; PCT: Procalcitonin; CRP: C-Reactive Protein; DD: D-Dimer; lncRNA: long non-coding RNA; OR: Odd Ratio; 95% CI: 95% Confidence Interval.

Comparison of the levels of inflammatory factors

The levels of the inflammatory factors, PCT, CRP, and DD, in the OG were higher than those in the CG (all $P<0.05$) (**Figure 4**).

Correlation between lncRNA CRNDE expression and severe pneumonia-related inflammatory factor levels

Spearman correlation analysis revealed that the expression of lncRNA CRNDE was positively correlated with the expression of PCT, CRP, and DD ($r=0.908$, 0.898, 0.951, respectively; $P<0.001$ for all) in the serum of patients with severe pneumonia (**Figure 5**).

Discussion

Severe pneumonia is a common critical respiratory disease with a particular high incidence in elderly patients. The acute onset and severity of pneumonia lead to high mortality. If left untreated, severe pneumonia can induce systemic inflammatory response syndrome, multiple organ dysfunction syndromes, severe sepsis, and an increased risk of death [16, 17]. Commonly used organ support techniques and anti-infection treatments fail to fundamentally control the mortality of patients with severe pneumonia [18]. Early detection and treatment are essential to prevent severe illness and poor prognosis. By analyzing the specific indicators of severe pneumonia, anti-infection treatment for patients with lung infection can be strengthened, providing a basis for improving prognosis and evaluating severity. LncRNAs are transcribed by RNA polymerase II as transcription by-products. They lack open reading frames and have limited or no protein-coding function; therefore, lncRNAs were initially considered to have no biological function [19]. However, recent studies have demonstrated that lncRNAs not only participate in the functioning of genes that encode regulatory proteins, but also regulate signaling pathways and target genes by affecting physiologic processes such as chromosome reconstruction, X chromosome silencing, and transcriptional interference activation. LncRNAs also play an important role in the progression of tumors, cardiovascular diseases, and immune system diseases [20, 21]. LncRNA MALAT1 is highly expressed in patients with lung inflammatory injury and pulmonary fibrosis, and is closely related to prognosis [22]. It is speculated that lncRNAs may be used as specific markers and novel therapeutic targets for inflammatory diseases. Therefore, in the present study, the relationship between lncRNA CRNDE expression and the clinical prognosis of severe pneumonia was explored, so as to provide a novel approach for diagnosis and treatment.

Table 3. Assignment table

Factor	Assignment
PSI score	>140=1, ≤140=0
APACHE II score	>22=1, ≤22=0
PCT	>1.70=1, ≤1.70=0
CRP	>130=1, ≤130=0
DD	>3.40=1, ≤3.40=0
LncRNA CRNDE	Data belong to continuous variables and were analyzed as raw data
Death	Death =1, survival =0

Note: PSI: Pneumonia Severity Index; APACHE: Acute Physiology and Chronic Health Evaluation; PCT: Procalcitonin; CRP: C-Reactive Protein; DD: D-Dimer; lncRNA: long non-coding RNA.

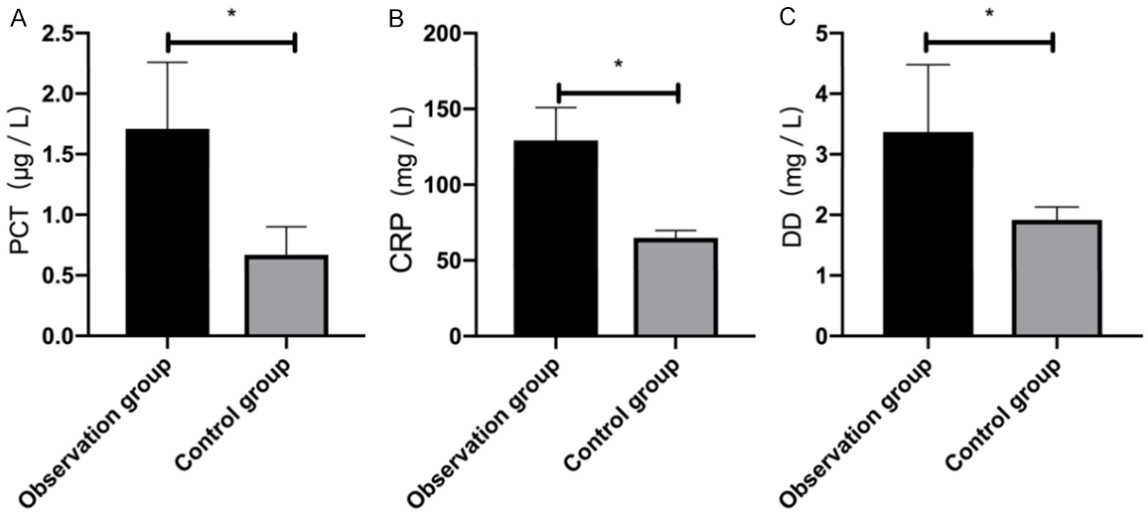

Figure 4. Comparison of the levels of the inflammatory factors PCT, CRP, and DD between the two groups. A: PCT; B: CRP; C: DD. Note: PCT: Procalcitonin; CRP: C-Reactive Protein; DD: D-Dimer. * indicates comparison between the two groups, $P<0.05$.

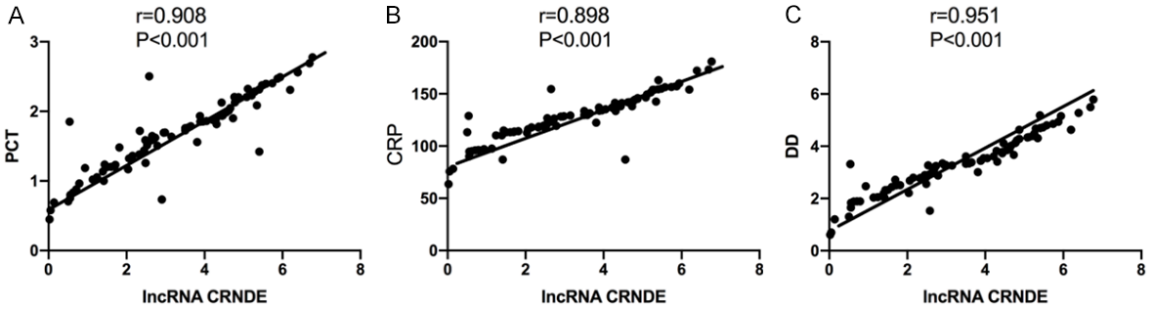

Figure 5. Correlation between lncRNA CRNDE expression and severe pneumonia-related inflammatory factor levels. A: Spearman correlation analysis indicated a positive correlation between the expression of lncRNA CRNDE and PCT in patients with severe pneumonia ($r=0.908$, $P<0.001$); B: Spearman correlation analysis showed that lncRNA CRNDE expression was positively correlated with that of CRP in patients with severe pneumonia ($r=0.898$, $P<0.001$); C: Spearman correlation analysis indicated a positive correlation between the expression of lncRNA CRNDE and DD in patients with severe pneumonia (r=0.951, $P<0.001$). Note: lncRNA: long non-coding RNA; PCT: Procalcitonin; CRP: C-Reactive Protein; DD: D-Dimer.

First, the expression of lncRNA CRNDE in patients was measured, and lncRNA CRNDE expression in the OG was found to be higher than in the CG. This indicated that lncRNA

CRNDE was highly expressed in patients with severe pneumonia. To further understand the diagnostic value of lncRNA CRNDE in severe pneumonia, ROC curve analysis was performed, and the results revealed that lncRNA CRNDE expression could be used for detection of severe pneumonia. LncRNA CRNDE expression is involved in severe pneumonia progression and can be used to assess the severity of pneumonia. To further understand the influence of lncRNA CRNDE expression on the progression of severe pneumonia, the relationship between lncRNA CRNDE and the clinicopathologic data of patients with severe pneumonia was analyzed. It revealed that the expression of lncRNA CRNDE was related to the PSI score, APACHE II score, and expression levels of PCT, CRP, and DD. The PSI score is used to predict the death risk of patients with severe pneumonia within 28 days through a series of examinations including demography, underlying diseases, blood tests, and imaging; however, this approach is highly subjective [23]. The APACHE II score is widely used to evaluate the prognosis of patients with inflammation and sepsis, but its calculation process is relatively complex [24]. Generally, PCT originates from the thyroid gland and is decreased in the serum, serving as a specific marker of non-inflammatory cascade reaction. During bacterial infection, PCT levels change within 4 h, and the increased PCT levels are positively correlated with the severity of infection. At the same time, these levels are not affected by hormones and the immune system [25]. CRP, an acute phase reaction protein, serves as a sensitive index with a relatively short half-life that can effectively reflect infection in the body. When patients get better, CRP levels can rapidly return to normal. Elevated CRP levels are closely related to the degree of infection [26]. DD is specifically produced by the fibrinolytic enzyme hydrolysis of cross-linked fibrin and indicates hypercoagulable state and hyperfibrinolysis *in vivo*. When coagulation disorders and inflammatory reactions occur in the body, DD levels increase [27]. Our results suggested that changes in clinical indicator levels commonly used to detect severe pneumonia were correlated with the expression of lncRNA CRNDE, and that lncRNA CRNDE may be a marker for severe pneumonia. A follow-up study revealed that the 3-year survival rate of the lncRNA CRNDE high expression group was lower than that of the low expression group, suggesting that lncRNA CRNDE may be an adverse prognostic factor for severe pneumonia. Multivariate analysis showed that the PSI score, APACHE II score, and the expression levels of PCT, CRP, DD, and lncRNA CRNDE were independent risk factors for poor prognosis, which. verified our hypothesis. Previously, a study [28] suggested that lncRNA may be an important regulator of the inflammatory response by mediating the transcription of inflammation-related mediators. The levels of inflammatory factors in patients with severe pneumonia were higher than in normal subjects, and the expression of lncRNA CRNDE was positively correlated with the expression levels of PCT, CRP, and DD. It can be concluded that lncRNA CRND regulates the levels of inflammatory factors that directly affect severe pneumonia, based on the present study. It was previously reported that lncRNA CRNDE triggers inflammation through the TLR3-NF-κB-cytokine signaling pathway [29]. The current analysis indicated that increased expression of lncRNA CRNDE could aggravate the inflammatory reaction in patients with severe pneumonia, leading to poor prognosis.

However, this study has some limitations. The sample size of this study was small, and the relationship between lncRNA CRNDE expression and severe pneumonia requires further study. In addition, the selected inflammatory factors were not comprehensive. Therefore, other inflammatory markers that reflect the degree of inflammation in severe pneumonia could also be included in future studies to comprehensively explore the mechanisms of inflammatory changes. In the next step, we will continue to investigate these topics to provide more effective detection techniques for severe pneumonia.

In summary, high expression of lncRNA CRNDE in the serum of patients with severe pneumonia is an independent risk factor for poor prognosis. It is speculated that the high expression of lncRNA CRNDE may be involved in occurrence and development of severe pneumonia.

Disclosure of conflict of interest

None.

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