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Original Article

TXNIP/NLRP3 Inflammasome Pathway in the Organismal Inflammatory Response of Elderly Patients with Severe Pneumonia Combined with Sepsis

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SUMMARY

Background: This study aimed to investigate the role of the thioredoxin-interacting protein (TXNIP) and the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome pathway in the inflammatory response of elderly patients with severe pneumonia and sepsis.
Methods: We conducted a retrospective analysis on the clinical data of 119 patients with severe pneumonia and sepsis treated at our hospital. Patients were categorized into two groups based on 28-day survival rate: the survival group (n = 89) and the death group (n = 30). Additionally, data from 39 healthy individuals who underwent medical checkups during the same period were collected to serve as controls.
Results: The levels of serum C-reactive protein, tumor necrosis factor-alpha, and procalcitonin at 24 h post-admission were significantly higher in the death group compared to both the survival and control groups, with higher levels also observed in the survival group relative to controls ($p < 0.05$). TXNIP and NLRP3 mRNA expression levels were significantly increased in the death group than in the survival and control groups, and were also higher in the survival group compared to the control group ($p < 0.05$). The death group exhibited higher respiratory rates and mean arterial pressures compared to those of the survival group ($p < 0.05$). Additionally, the Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment, and Charlson Comorbidity Index scores were significantly higher in the death group than in the survival group ($p < 0.05$).
Conclusion: The TXNIP/NLRP3 inflammasome pathway was implicated in the inflammatory response in elderly patients with severe pneumonia and sepsis, and was closely associated with patient prognosis.

1. Introduction

Pneumonia is a prevalent respiratory disease primarily induced by physicochemical factors, microorganisms, immune injury, and other factors that lead to varying degrees of alveolar and interstitial inflammation within the lungs. The incidence of pneumonia is notably high, and without timely treatment and control, it can escalate into severe pneumonia.[1] Severe pneumonia is characterized by a rapid onset and severe clinical manifestations. The elderly population, which is the most affected by severe pneumonia, exhibits a markedly reduced physical function and compromised immunity, making the progression to a systemic inflammatory response and sepsis more likely. Severe pneumonia is one of the primary underlying causes of sepsis, which exacerbates disease severity and significantly increases morbidity and mortality rates.[2,3] Therefore, early diagnosis and assessment of patients with severe pneumonia combined with sepsis are crucial for timely treatment adjustments and improved prognostic outcomes.[4]

In recent years, extensive research has highlighted the critical roles of inflammatory response and oxidative stress in the pathogenesis of severe pneumonia with sepsis.[5,6] Thioredoxin-interacting protein (TXNIP), a pro-inflammatory and pro-oxidative factor, has emerged as a key regulator of these processes. TXNIP can activate nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3), upregulate the expression of inflammatory cytokines and pro-apoptotic proteins, and alter intracellular calcium and reactive oxygen species levels. These actions collectively exacerbate the inflammatory response and induce apoptosis.[7,8] Despite these insights, the involvement of the TXNIP/NLRP3 inflammasome pathway in the inflammatory response of patients with severe pneumonia and sepsis remains unclear. Moreover, relevant reports on the relationship between the TXNIP/NLRP3 inflammasome pathway and the condition and prognosis of patients with severe pneumonia complicated by sepsisare lacking.

Considering this knowledge gap, we investigated the role of the TXNIP/NLRP3 inflammasome pathway in the inflammatory response in elderly patients with severe pneumonia and sepsis.

2. Material and methods

2.1. Clinical data

The clinical data of 119 patients with severe pneumonia and sepsis, treated at our hospital between May 2020 and December 2022, were retrospectively collected. The inclusion criteria were as

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follows: patients who met the diagnostic criteria for severe pneumonia[9] and sepsis;[10] patients aged 60–85 years; and patients with complete clinical data. Conversely, exclusion criteria included patients with an expected survival time of less than 24 h; those with malignant tumors, severe cardiovascular diseases, immunodeficiency, and infectious diseases; those with pulmonary diseases such as pulmonary embolism and pulmonary tuberculosis; and those with severe hepatic and renal diseases requiring long-term hemodialysis. The 119 patients were divided into survival (n = 89) and death (n = 30) groups based on their prognosis (28-day survival rate). In addition, clinical data from 39 healthy individuals who underwent medical checkups during the same period were collected and used as controls. This study was approved by the Medical Ethics Committee of The Third Hospital of Changsha (No. KY-EC-2022-012).

2.2. Sample size calculation

The null hypothesis (H0) was set as no significant difference in the TXNIP and NLRP3 levels between the survival and death groups, whereas the alternative hypothesis (H1) posited a significant difference in the TXNIP and NLRP3 levels between the two groups. Based on the literature and previous studies, TXNIP and NLRP3 levels were expected to differ between groups; thus, we opted for a two-sided t-test to assess intergroup differences. The effect size (Cohen's d) was set at 0.5, indicating a medium effect. The significance level (α) was set at 0.05, accepting a 5% risk of a Type I error. The statistical power ($1 - \beta$) was set at 0.8, indicating a desire to detect a true effect with 80% probability. The G*Power statistical software was used to calculate the required sample size. Considering a possible dropout rate of 10%, the final sample size was calculated as follows: n_{final} = n1, dropout rate = 119/0.9 ≈ 132. Ultimately, the study included 119 patients to ensure an adequate sample size and the reliability of the results.

2.3. Methods

2.3.1. Serum inflammatory factor levels

Peripheral venous blood samples (3-5 mL) were collected from all patients on the day of admission. The samples were centrifuged using a high-speed centrifuge (rotor radius of 6 cm), at 3500 r/min for 7-10 min. The obtained serum samples were then stored at -80 °C. The levels of C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and procalcitonin (PCT) were measured using enzyme-linked immunosorbent assay (ELISA). The CRP ELISA kit was purchased from Assaypro (Catalog No.: EC7501-1, USA), while the TNF-α ELISA kit was acquired from Biomatik (Catalog No.: EKA51882, Canada). The human PCT ELISA kit was obtained from Wuhan Giled Biotechnology Co., Ltd. (Catalog No.: J20690, China).

2.3.2. Detection of TXNIP and NLRP3 mRNA expression

Peripheral blood mononuclear cells (PBMCs) were isolated using Ficoll density gradient centrifugation. PBMCs were then divided into two portions: one portion was stored at -80 °C for subsequent protein extraction, while the other portion was treated with 1 mL of TRIzol reagent (Takara Bio., Catalog No.: 9108, Japan) and mixed thoroughly to extract total RNA. The purity and concentration of total RNA were determined using UV spectrophotometry. The primers for TXNIP were 5′-AATTGGCAGCAGATCAGGTCTAAGC-3′ (forward) and 5′-CATGTCATCTAGCAGAGGAGTGGTTG-3′ (reverse), and the primers for NLRP3 were 5′-TGGCTGTAACATTCGGAGATTGTGG-3′ (forward) and 5′-GCTTCTGGTTGCTGCTGAGGAC-3′ (reverse). A total of 1 μL of cDNA obtained from reverse transcription was used for quantitative fluorescence PCR amplification. Gene expression levels were quantified using the $2^{-\Delta\Delta Ct}$ method.

2.3.3. Clinical data collection

Clinical data, including temperature, heart rate, respiratory rate, and mean arterial pressure, were collected.

2.3.4. Relevant scores

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was used to assess the severity of illness.[11] This scoring system has a total score of 71 points, divided into three components: age, chronic health status, and acute physiology. Higher scores indicate greater severity of illness. The Sequential Organ Failure Assessment (SOFA) score includes evaluations of six organ systems (e.g., coagulation and respiration), with each system scored from 0 to 4.[12] Scores of 3–4 indicate organ failure, while scores of 1–2 indicate organ dysfunction. The Charlson Comorbidity Index (CCI) score was used to quantify comorbidities, with higher scores indicating a greater number of comorbidities.[13]

2.4. Observation indicators

The observation indicators included the following:

Comparison of serum CRP, TNF-α, and PCT levels among the three groups.

Comparison of TXNIP and NLRP3 mRNA expression levels among the three groups.

Comparison of clinical indices between the death group and the survival group.

Comparison of APACHE II, SOFA, and CCI scores between the death and survival groups.

Correlation between TXNIP and NLRP3 mRNA levels and APACHE II scores.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 23.0. Measurement data were expressed as mean ± standard deviation ($\overline{\chi} \pm S$), and comparisons were made using the t-test. Correlations were determined using Pearson correlation analysis. Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1. Comparison of baseline data

Age and chronic obstructive pulmonary disease (COPD) and diabetes mellitus comorbidity rates were significantly higher in the death group than in the survival and control groups ($p < 0.05$). This indicated that age and COPD and diabetes may be associated with the prognosis of patients with severe pneumonia (Table 1).

3.2. Comparison of serum CRP, TNF-α, and PCT Levels

At 24 h post-admission, serum levels of CRP, TNF-α, and PCT were significantly higher in the death group than in the survival group, and higher in the survival group compared to the control group ($p < 0.05$). This indicated that patients with severe pneumonia who succumb to illness may exhibit higher inflammatory responses (Figure 1).

3.3. Comparison of TXNIP and NLRP3 mRNA expression levels

The TXNIP and NLRP3 mRNA levels were significantly higher in

Table 1
Comparison of baseline data.

Item	Death group (n = 30)	Survival group (n = 89)	Control group (n = 39)
Male/female	22/8	49/40	19/20
Age (years)	70.8 ± 8.1	61.2 ± 8.9	56.7 ± 9.4
Smoking history [cases (%)]	14 (46.67)	31 (34.83)	13 (33.33)
Bronchial dilatation [cases (%)]	4 (13.33)	6 (6.74)	3 (7.69)
Bronchial asthma [cases (%)]	0 (0.00)	1 (1.12)	0 (0.00)
COPD [cases (%)]	8 (26.67)	4 (4.49)	3 (7.69)
Hypertension [cases (%)]	13 (33.33)	32 (35.96)	12 (30.77)
Diabetes mellitus [cases (%)]	13 (33.33)	10 (11.24)	4 (4.49)
BMI (kg/m^2)	22.19 ± 4.49	23.34 ± 4.22	22.94 ± 1.03

Note: BMI: body mass index; COPD: chronic obstructive pulmonary disease. Data are expressed as number of cases [n (%)] or mean ± standard deviation. * $p < 0.05$ compared with the death group; # $p < 0.05$ compared with the survival group.

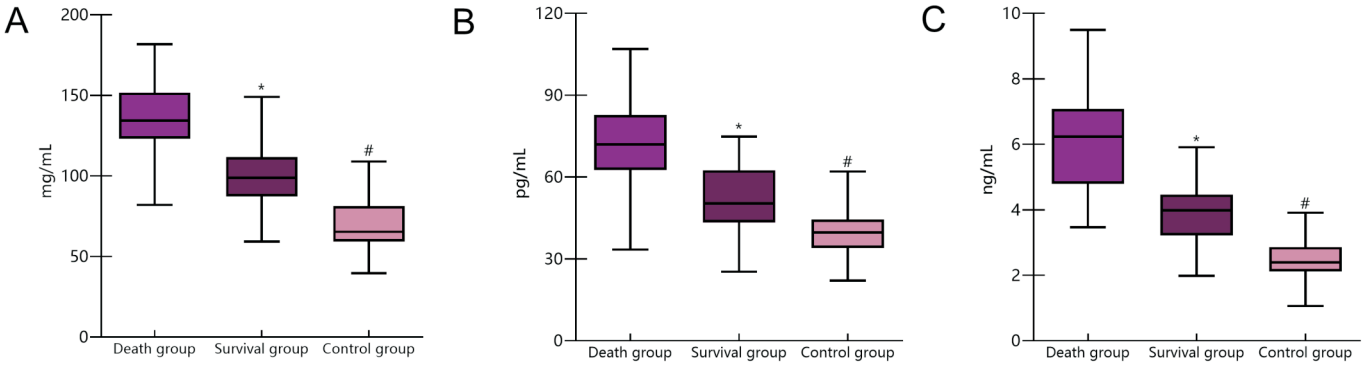

Figure 1. Comparison of serum CRP, TNF-α, and PCT levels at 24 h of admission in the three groups. A: The 24 h admission serum CRP levels of patients in the death group were significantly higher than those in the survival and control groups; B: The 24 h admission serum TNF-α levels of patients in the death group were significantly higher than those in the survival and control groups; C: The 24 h admission serum PCT levels of patients in the death group were significantly higher than those in the survival and control groups. Note: CRP: C-reactive protein; PCT: procalcitonin; TNF-α: tumor necrosis factor-alpha. * $p < 0.05$ compared with the death group; # $p < 0.05$ compared with the survival group.

the death group than in the survival and control groups. Similarly, the mRNA levels of TXNIP and NLRP3 mRNA in the survival group were significantly higher than those in the control group ($p < 0.05$). This suggested that serum TXNIP and NLRP3 mRNA levels might be elevated in patients with severe pneumonia complicated by sepsis (Figure 2).

3.4. Comparison of clinical index levels

There were no statistically significant differences in body temperature or heart rate between the death and survival groups ($p > 0.05$). However, respiratory rate and mean arterial pressure were significantly higher in the death group than in the survival group ($p < 0.05$). This indicated that patients with severe pneumonia often exhibited elevated respiratory rates and blood pressure during their clinical presentation (Figure 3).

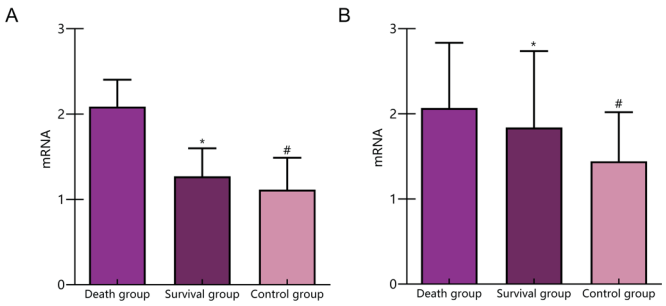

Figure 2. Comparison of serum TXNIP and NLRP3 levels at 24 h of admission in the three groups. A: The levels of TXNIP mRNA in patients in the death group were significantly higher than those in the survival and control groups; B: The levels of NLRP3 mRNA in patients in the death group were significantly higher than those in the survival and control groups. Note: NLRP3: nucleotide-binding oligomerization domain-like receptor protein 3; TXNIP: thioredoxin-interacting protein. * $p < 0.05$ compared with the death group; # $p < 0.05$ compared with the survival group.

3.5. Comparison of APACHE II, SOFA, and CCI scores

The APACHE II, SOFA, and CCI scores were significantly higher in the death group than in the survival group ($p < 0.05$). This suggestd that the higher the APACHE II, SOFA, and CCI scores in cases of severe

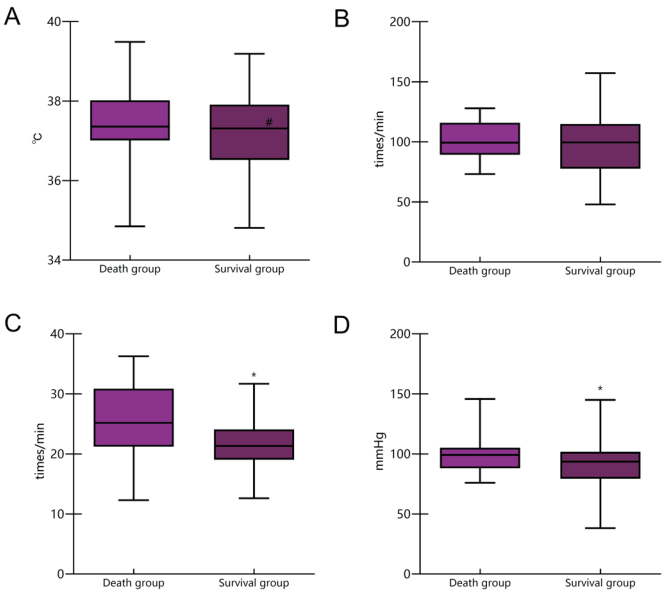

Figure 3. Comparison of clinical indicators. A: Body temperature; B: Heart rate; C: Respiratory rate; D: Mean arterial pressure. Note: * $p < 0.05$ when compared with the death group.

pneumonia complicated by sepsis, the poorer the prognosis (Figure 4).

3.6. Correlation between serum TXNIP and NLRP3 mRNA levels and APACHE II scores

Pearson correlation analysis demonstrated that serum TXNIP and NLRP3 mRNA levels positively correlated with APACHE II scores ($p < 0.001$). This suggests that the levels of serum TXNIP and NLRP3 mRNA closely associated with the severity of the patients' condition, providing a basis for early assessment of the disease (Figure 5).

4. Discussion

Severe pneumonia is a prevalent respiratory disease characterized by rapid progression, poor prognosis, and high morbidity and mortality rates, predominantly affecting the elderly. Its clinical manifestations often include respiratory failure, coma, and impaired consciousness. If not promptly controlled, severe pneumonia can compromise other organ systems, induce hypoperfusion and organ dysfunction, and lead to sepsis, thereby leading to the increase of morbidity and mortality.[14] Currently, the pathogenesis of severe pneumonia combined with sepsis remains poorly understood, but it is believed to be associated with systemic inflammatory responses and oxidative stress.[15,16] Severe pneumonia is typically accompanied by a significant impairment of the lung function. In this context, the release of inflammatory mediators and activation of cytokines play crucial roles in lung injury and the systemic response. Recent studies have indicated that TXNIP, an important regulatory factor, is closely associated with the activation of the NLRP3 inflammasome.[17] TXNIP is upregulated during the pathological process of severe pneumonia, facilitating the assembly and activation of the inflammasome through interaction with the NLRP3, thereby exacerbating the inflammatory response and resulting in cellular damage. Therefore, investigating the mechanisms underlying the TXNIP/NLRP3 inflammasome pathway may enhance our understanding of the pathogenesis of severe pneumonia and potentially identify novel therapeutic targets.

The excessive release of reactive oxygen species and pro-inflammatory cytokines triggers oxidative stress and an inflammatory cascade, playing a crucial role in the pathological process of severe pneumonia complicated by sepsis.[18] Wang L et al. demonstrated that upregulation of the TXNIP/NLRP3 inflammasome pathway exacerbates the inflammatory response and oxidative stress, contributing to the pathogenesis of severe pneumonia and sepsis.[19] The present study corroborated these findings, showing that serum levels of CRP, TNF-α, and PCT, as well as TXNIP and NLRP3 mRNA levels, were highest in the death group, followed by the survival group, and lowest in the control group. Additionally, the respiratory rate and mean arterial pressure were higher in the death group than in the survival group. Lu Y et al. found that serum PCT levels were significantly elevated in patients with severe pneumonia combined with sepsis compared with healthy individuals,[20] which is consistent with the results of this study. These findings suggested an inflammatory response in elderly patients with severe pneumonia combined with sepsis, and that TXNIP and NLRP3 mRNA levels may be prognostic indicators.

Analysis of the underlying mechanisms revealed that TXNIP is a thioredoxin (Trx)-binding and inhibiting protein. Trx functions as a free-radical scavenger during oxidative stress. Under normal conditions, TXNIP and Trx exist in a bound form. However, upon exposure to external stimuli, TXNIP dissociates from Trx, thereby inducing and exacerbating oxidative stress by inhibiting Trx.[21] NLRP3 inflammasomes, protein complexes composed of NLRP3, pro-caspase-1, and apoptosis-associated speck-like protein (ASC), are pivotal in the inflammatory response.[22] TXNIP can activate NLRP3 inflam-

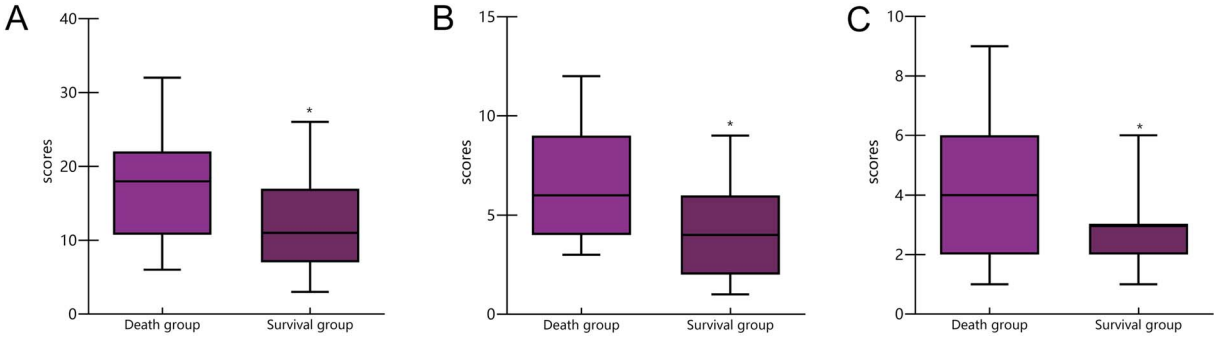

Figure 4. Comparison of APACHE II score, SOFA score and CCI score. A: APACHE II score; B: SOFA score; C: CCI score. Note: APACHE II: Acute Physiology and Chronic Health Evaluation II; CCI: Charlson Comorbidity Index; SOFA: Sequential Organ Failure Assessment. Compared with the death group, * $p < 0.05$.

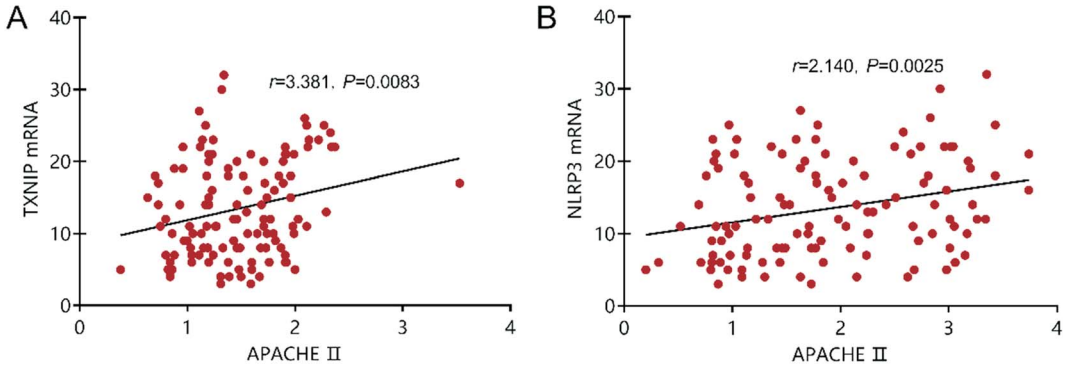

Figure 5. Correlation of serum TXNIP mRNA and NLRP3 mRNA levels with APACHE II scores. A: TXNIP mRNA was positively correlated with APACHE II scores; B: NLRP3 mRNA was positively correlated with APACHE II scores.

masomes by dissociating from Trx and binding to NLRP3 proteins, thereby triggering the inflammatory signaling pathway. This activation leads to the production of numerous inflammatory mediators, such as CRP, TNF-α, and PCT, which exacerbate the inflammatory response and promote apoptosis.[23] Iwasa M et al. found that oxidative stress enhances the interaction between TXNIP and NLRP3 inflammasomes,[24] which plays a significant role in the systemic inflammatory response.

APACHE II, SOFA, and CCI scores are recognized indicators for assessing the severity of severe pneumonia combined with sepsis. However, the complexity and comprehensive nature of these scoring systems limit their clinical application.[25] This study demonstrated that the APACHE II, SOFA, and CCI scores were significantly higher in the death group than in the survival group. Furthermore, serum levels of TXNIP and NLRP3 mRNA were positively correlated with the APACHE II score. These findings suggested that serum TXNIP and NLRP3 mRNA levels may be closely associated with disease severity and may provide a basis for early disease assessment.

The combined detection of serum TXNIP and NLRP3 mRNA levels appears to be an effective prognostic tool. This combined detection can help clinicians adjust their treatment plans in a timely manner to improve patient outcomes. The rationale is that serum TXNIP and NLRP3 mRNA levels reflect the degree of oxidative stress and inflammatory response, which are critical in the pathological process of severe pneumonia combined with sepsis. By measuring both markers, clinicians can have a more comprehensive view of the oxidative stress and inflammatory response, thereby enhancing the accuracy of prognosis prediction.[26] Research findings indicate that elevated levels of TXNIP and reduced levels of NRP1 in septic patients are closely associated with the occurrence and severity of acute kidney injury (AKI), and that the combined detection of these two markers can more effectively identify the risk of AKI in septic individuals.[27] Additionally, research has shown that miR-223-3p derived from platelet exosomes negatively regulates NLRP3-dependent inflammasomes to inhibit endothelial cell pyroptosis.[28] This is similar to the results regarding TXNIP in this study, suggesting that the combined detection of TXNIP and NLRP3 may serve as an effective prognostic indicator. It can be used as a valuable biological marker for risk assessment upon patient admission to guide the development of personalized treatment plans.

Although this study revealed prognostic factors associated with severe pneumonia, it has several limitations that may affect the reliability of the results. The small sample size and retrospective design may have led to data loss and selection bias, thereby affecting the statistical significance and generalizability of the findings. Additionally, the constraints of a single-center study may diminish the representativeness of the results. Future research should focus on large-sample, multicenter prospective designs to delve into the mechanisms of the TXNIP/NLRP3 inflammasome, along with long-term follow-up to comprehensively assess the influence of various clinical and laboratory indicators on patient prognosis.

In conclusion, the TXNIP/NLRP3 inflammasome pathway may play a significant role in the inflammatory response in elderly patients with severe pneumonia and sepsis, and may be closely related to patient prognosis.

Authorship

Mi Huang and Shengdao Dai designed experiments. Hui Yu and Wei Li carried out experiments, analyzed experimental results. Mi Huang wrote the manuscript. Shengdao Dai revised the manuscript. All authors approved the final manuscript.

Conflicts of interest statement

The authors declare that they have no competing interests.

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Ethics statement

This study was approved by the Medical Ethics Committee of The Third Hospital of Changsha (No. KY-EC-2022-012).

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