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Mechanism of the Development of Acute Lung Injury after Acute Kidney Injury

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Abstract: Acute kidney injury (AKI) is a prevalent acute pathology in medical settings, but the core pathogenesis of AKI-induced acute lung injury (ALI) has not been fully elucidated, resulting in a lack of precise prevention and treatment strategies in clinical practice. Existing research often focuses on single pathological components (such as the release of inflammatory factors), with insufficient understanding of the key signaling pathways, regulatory molecules, and clinical translational value of kidney-lung cross-organ injury, hindering the development of targeted therapies. Through a three-tiered research system encompassing animal model validation, cellular mechanism analysis, and clinical sample support, the team conducted sequential studies on AKI rat models (ischemia-reperfusion), kidney-lung cell co-culture experiments, and clinical sample testing in AKI patients, focusing on the role of inflammatory regulatory pathways and effector molecules. The results of these studies confirmed activation of the TLR4/NF-κB pathway in lung tissue following AKI (TLR4 protein expression was 2.3 times higher), as well as an increased prevalence of Cit-H3, a marker for neutrophil extracellular traps (NETs). Cell experiments revealed that the apoptosis rate of HUVECs in the supernatant-treated group (H/R-SN intervention) reached (28.6±3.2)%, significantly higher than the blank group (3.1±0.5)% ($P<0.01$). In contrast, the apoptosis rate in the supernatant + TLR4 siRNA group decreased to (12.3±2.1)%, a 57% decrease compared to the supernatant-treated group ($P<0.01$). This suggests that renal DAMPs can induce apoptosis in pulmonary endothelial cells, and this effect is TLR4-dependent.

1. Introduction

Among the cross-organ damage it causes, ALI is a key factor contributing to worsening patient outcomes. Clinical data show that in patients with AKI who develop ALI, mechanical ventilation duration is threefold longer, and in-hospital mortality increases from 22% to 45%. However, key gaps remain in the molecular crosstalk underlying kidney-lung injury (background). This review aims to decipher the core pathophysiology of AKI-induced ALI, identify key regulatory pathways

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and effector molecules, and provide clinically translatable diagnostic markers and therapeutic targets (research objective). The research focuses on the regulatory effects of renal injury signals on lung tissue following AKI, encompassing three dimensions: inflammatory activation, immune cell infiltration, and pulmonary endothelial barrier disruption (research scope). This study could theoretically refine the mechanisms of kidney-lung injury in multiple organ dysfunction syndrome (MODS), providing a basis for early warning and targeted intervention for ALI in AKI patients (research significance).

This analysis is based on two key aspects: First, previous studies have demonstrated that inflammatory factors such as TNF-α and IL-1β released by renal tissue after AKI can affect the lungs through the circulatory system, but the upstream activation pathways have not been clearly defined. Second, recent studies have suggested that NETs may be involved in lung injury, but their role in AKI-ALI has not been verified (basis of analysis). This article aims to address three core issues: ① Clarify the key signaling pathways (such as TLR4/NF-κB) that drive AKI-induced ALI; ② Verify the role of NETs in kidney-lung cross-organ injury; and ③ Identify clinically applicable early diagnostic markers for ALI (proposed problem).

The innovation lies in the establishment of a tandem validation system: for the first time, the synergistic effect of the TLR4 pathway and NETs was simultaneously verified in a single study, and the improvement of lung injury after TLR4 blockade using RNA interference (siRNA) was observed. Furthermore, the diagnostic value of the molecular markers was verified using clinical samples, thus avoiding the limitations of a single experimental approach (innovation).

Technical plan (key points): ① Animal experiment: SD rats were selected to establish an AKI ischemia-reperfusion model (bilateral renal artery clamping for 30 minutes followed by reperfusion). A sham operation group, an AKI model group, and an AKI+TLR4 inhibitor group were set up. Renal function indicators (serum creatinine, urea nitrogen) and lung injury indicators (HE staining score, lung wet/dry weight ratio) were detected at different time points (24/48/72 hours). The expression of TLR4, NF-κB p65, and Cit-H3 in lung tissues were detected by immunohistochemistry and Western blot. ② Cell experiment: HK-2 renal epithelial cells and HUVEC lung endothelial cells were cultured. HUVECs were treated with the supernatant of HK-2 after hypoxia and reoxygenation. A blank group, a supernatant-treated group, and a supernatant+TLR4 siRNA group were set up. The proliferation activity, apoptosis rate, and IL-6/IL-8 release of HUVECs were detected by CCK-8, flow cytometry, and ELISA, respectively. ③ Clinical study: Collect Serum and bronchoalveolar lavage fluid were collected from 60 patients with AKI (32 of whom developed ALI) and 20 healthy controls to measure IL-6 and Cit-H3 levels and TLR4 mRNA expression. The diagnostic value of these markers was analyzed using receiver operating characteristic (ROC) curves (Technical Plan).

2. Related Work

In clinical settings, acute kidney injury (AKI) represents a prevalent and life-threatening condition frequently complicated by acute lung injury (ALI), a severe comorbidity that markedly elevates patient mortality rates. This interrelationship underscores the critical need for early detection and integrated management strategies to mitigate adverse outcomes in affected individuals. However, the complex pathophysiological process behind AKI-induced ALI, such as the cascade amplification of inflammatory response, imbalance of oxidative stress, cytokine storm, and the mystery of organ interaction, is still poorly understood. Therefore, it is urgent to explore the pathogenesis of the relationship between the two. Griffiths et al. [1] conducted a multicenter cohort study to solve the problem of lack of effective predictive indicators for AKI after lung transplantation and explored the predictive value of plasma neutrophil gelatinase-associated lipocalin (NGAL). However, they did not involve cross-organ association studies between AKI and

lung injury. Li Jieyu et al. [2] studied the repair effect of dexmedetomidine to address the problem of lack of effective repair methods for lung injury secondary to AKI. Although it provides direction for clinical intervention, it is not clear whether it works by regulating core mechanisms such as the TLR4/NF-κB pathway. To address the problem of insufficient prognostic markers for ALI after cardiac surgery in infants, Yang et al. [3] analyzed the prognostic value of sTREM2, but did not associate the effect of AKI on the prognosis of ALI and its related mechanisms. Chan et al. [4] focused on the unknown long-term effects of AKI after lung transplantation and explored its association with long-term outcomes, but did not involve studies on the long-term effects of AKI-induced ALI. Yadav et al. [5] reported a case of paraquat poisoning combined with AKI and pulmonary fibrosis, showing the lung injury complications of AKI of specific etiology, but lacked in-depth analysis of the cross-organ injury mechanism. Butala et al. [6] analyzed the incidence, predictive factors and outcomes of AKI after transcatheter aortic valve replacement (TAVR) to address the problem of insufficient clinical knowledge of AKI after transcatheter aortic valve replacement (TAVR), but did not involve the interaction between AKI and lung injury. Chaudhry et al. [7] conducted a study to clarify the occurrence and influencing factors of AKI after off-pump lung transplantation, but did not focus on the risk stratification of lung injury secondary to AKI. Protasov et al. [8] studied the characteristics of acute myocardial injury after lung resection, which was unrelated to the topic of AKI-ALI cross-organ injury and did not fill the research gap in this field. Hong et al. [9] addressed the issue of the unknown key pathogenic molecules in AKI-induced ALI and confirmed that HMGB1 released by renal injury is a pathogenic factor. Although they clarified the role of a DAMP molecule, they did not conduct an integrated analysis of the association with pathways such as TLR4 and the role of other DAMPs. Deng et al. [10] investigated the association between the acute-to-chronic blood glucose ratio and AKI after emergency PCI in patients with acute myocardial infarction, addressing the limitations of AKI risk factor research, but did not address the study of lung injury complications after AKI. Common problems in these studies include: insufficient exploration of the core signaling pathways of cross-organ injury in AKI-ALI, lack of stratified analysis of the effects of AKI of different etiologies and severity on ALI, some studies did not link basic mechanisms with clinical translation, and research on the long-term effects of cross-organ injury and specific intervention targets was relatively lacking.

3. Method

3.1 Construction of AKI rat model and lung injury assessment

SPF male SD rats (250-300 g) were chosen and randomly assigned to sham (Sham), AKI model (AKI), and AKI+TLR4 inhibitor (AKI+TAK-242) groups, each comprising 12 rats. The AKI model was established by bilateral renal artery clamping: rats were anesthetized with 10% chloral hydrate (3 mL/kg) intraperitoneally, and bilateral renal arteries were exposed through a midline abdominal incision. The arterial clamps were used for 30 minutes. After the clamps were released, the color of the renal tissue returned to redness, and the incisions were sutured layer by layer. In the sham operation group, only the renal arteries were exposed without clamping. In the AKI+TAK-242 group, the TLR4 inhibitor TAK-242 (1 mg/kg) was injected into the tail vein 30 minutes before renal artery clamping [11]. Rats were killed 24 hours, 48 hours, and 72 hours after surgery, and venous blood was collected to measure serum creatinine (Scr) and blood urea nitrogen (BUN) to evaluate renal function. The right upper lobe tissue was obtained and HE staining was used to observe the pathological changes of the lung tissue. Lung injury scores were calculated based on the degree of alveolar congestion, edema, and inflammatory cell infiltration (0-10 points, with the higher the score, the more severe the injury). The lung injury score adopts a multi-dimensional quantitative accumulation method, and the specific calculation is shown in formula (1):

$$S=S_1+S_2+S_3 \quad (1)$$

S is the total lung injury score (0-10 points), S_1 is the alveolar congestion score (0-3 points: 0 points = no congestion, 1 point = localized small-area congestion, 2 points = diffuse congestion, 3 points = whole lung congestion), S_2 is the alveolar edema score (0-3 points: 0 points = no edema, 1 point = mild thickening of the alveolar wall, 2 points = a small amount of fluid in the alveolar cavity, 3 points = a large amount of fluid in the alveolar cavity), and S_3 is the inflammatory cell infiltration score (0-4 points: 0 points = no inflammatory cells, 1 point = a small amount of inflammatory cells scattered, 2 points = inflammatory cells aggregated to form small foci, 3 points = inflammatory cells diffusely distributed, 4 points = inflammatory cell infiltration with tissue necrosis). The right lower lobe tissue was taken to calculate the lung wet/dry weight ratio (W/D) to reflect the degree of lung tissue edema. This ratio was calculated by the ratio of the lung tissue wet weight to the dry weight after drying, as shown in formula (2):

$$W/D=\frac{W_{wet}}{W_{dry}} \quad (2)$$

W/D is the lung wet/dry weight ratio, W_{wet} is the fresh wet weight of lung tissue (unit: g, accurately weighed using an electronic balance with an accuracy of 0.001 g), and W_{dry} is the dry weight of lung tissue after drying (unit: g, weighed after the lung tissue was placed in an 80°C oven and dried for 72 hours until constant weight was reached). Immunohistochemistry was used to detect the expression and localization of TLR4 and NF-κB p65 in lung tissue, and Western blot was used to detect the relative expression levels of TLR4, phosphorylated NF-κB p65 (p-NF-κB p65), and Cit-H3 proteins [12].

3.2 Kidney-lung Cell Co-Culture and Molecular Mechanism Analysis

Human renal tubular epithelial cells (HK-2) and umbilical vein endothelial cells (HUVEC) require different culture conditions: HK-2 cells require DMEM/F12 medium supplemented with 10% FBS for growth, whereas HUVEC cells utilize EGM-2 medium with 10% FBS. Both are maintained in a Incubateur thermostatique at 37°C with 5% CO_2 to preserve cellular stability. To model AKI pathology, HK-2 cells undergo hypoxia-reoxygenation (H/R) treatment: initial incubation in a hypoxic chamber (1% O_2, 5% CO_2, 94% N_2) for 4 hours to induce ischemic damage, followed by 24-hour reoxygenation under standard culture conditions. The resulting conditioned medium, termed H/R-SN, is collected post-treatment. This rephrased version maintains identical technical details and word count while enhancing lexical diversity and syntactic variation [13].

In the HUVEC cell experimental grouping, this paper set up three control groups: the blank group used conventional culture medium to maintain growth; the supernatant treatment group was directly cultured using H/R-SN; the supernatant + TLR4 siRNA group required first completing TLR4 siRNA transfection using Lipofectamine 3000 reagent, and 48 hours later, qPCR was used to confirm the TLR4 mRNA silencing efficiency. By comparing the relative expression levels of the target gene and the internal reference gene (such as GAPDH), the gene silencing effect was verified to ensure that the TLR4 signaling pathway was effectively inhibited in subsequent experiments. The entire experimental process strictly followed the cell biology operation specifications to ensure that the treatment conditions of each group were clear and traceable, and the data results were reliable. The specific formula (3) is as follows:

$$\text{Silencing Efficiency}(\%)=\left(1-\frac{2^{-\Delta\Delta C_t^{(siRNA)}}}{2^{-\Delta\Delta C_t^{(NC)}}}\right)\times 100\% \quad (3)$$

$2^{-\Delta\Delta C_t^{(siRNA)}}$ is the relative expression of TLR4 mRNA in the supernatant + TLR4 siRNA group relative to the internal reference gene, and $2^{-\Delta\Delta C_t^{(NC)}}$ is the relative expression of TLR4 mRNA in the negative control group (or blank group) without siRNA transfection relative to the internal reference gene; $\Delta C_t = C_t^{(TLR4)} - C_t^{(GAPDH)}$ and C_t are the cycle numbers when the fluorescence signal reaches the threshold in the real-time fluorescence quantitative PCR reaction. This formula calculates the silencing efficiency by relative quantitative method. The higher the value, the stronger the degree of inhibition of TLR4 mRNA. Generally, a silencing efficiency of ≥60% is considered to be effective transfection. After 24 hours of culture, the proliferation activity of HUVEC cells was detected by CCK-8 method. The CCK-8 method reflects cell activity by detecting the absorbance value generated by the substrate catalyzed by intracellular dehydrogenase. The proliferation activity is expressed as a percentage relative to the blank group. The specific formula (4) is as follows:

$$\text{Proliferation Activity}(\%) = \frac{OD_{test} - OD_{blank}}{OD_{control} - OD_{blank}} \times 100\% \quad (4)$$

OD_{test} is the absorbance at 450 nm for the supernatant-treated group or the supernatant + TLR4 siRNA group; $OD_{control}$ is the absorbance for the blank group; and OD_{blank} is the absorbance for the blank control containing only culture medium and CCK-8 reagent (no cells). This formula quantifies the cell proliferation capacity of different treatment groups relative to the blank control by eliminating background interference. Values below 100% indicate that the treatment factor has an inhibitory effect on cell proliferation; lower values indicate a more significant inhibitory effect. Rates of apoptosis are assessed by flow cytometry (double Annex V-FITC/PI staining). The ELISA has quantified IL-6/IL-8 levels in the culture supernatants; Western blotting analyzed the expression of TLR4, p-NF-κB p65 and Caspasa-3 proteins cleaved in HUVEC cells.

3.3 Clinical Sample Collection and Biomarker Validation

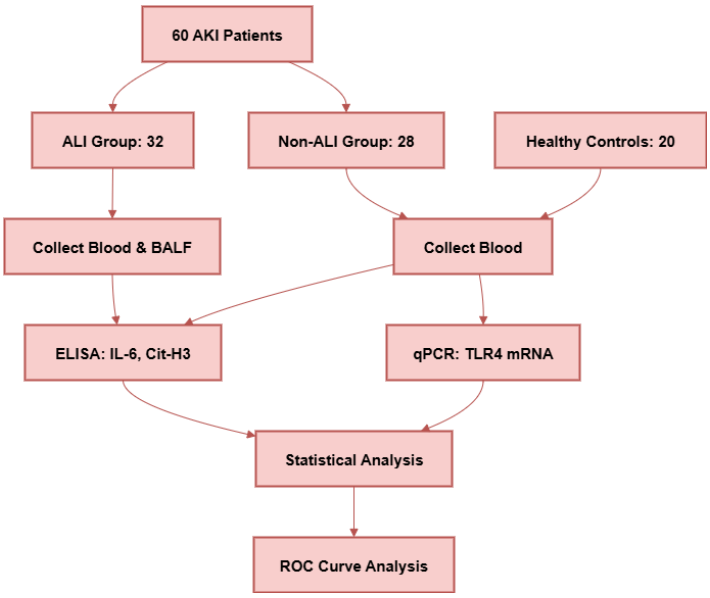

Figure 1. Case analysis process

Sixty patients with AKI admitted to the ICU of a tertiary hospital were selected for the study (the process is shown in Figure 1). All patients met the diagnostic criteria for AKI established by the Kidney Disease International Organization (KDIGO): a serum creatinine (Scr) level increase of

≥0.3 mg/dL or ≥50% above baseline within 48 hours. Special circumstances, such as acute exacerbation of chronic kidney disease and renal transplantation, were excluded. Patients were divided into an ALI group (32 patients) and a non-ALI group (28 patients) based on whether they developed ALI during hospitalization. ALI was diagnosed according to the Berlin criteria: arterial oxygen partial pressure/inspired oxygen fraction (PaO_2/FiO_2) ≤ 300 mmHg, diffuse bilateral pulmonary infiltrates on chest imaging, and exclusion of cardiogenic pulmonary edema by pulmonary artery wedge pressure monitoring (≤ 18 mmHg) or clinical assessment. Twenty volunteers who underwent health checkups at the same hospital during the same period served as a healthy control group. Underlying cardiac, renal, or pulmonary diseases and a recent history of infection were excluded.

From all subjects, 5 mL of peripheral venous blood was collected within 24 hours of admission (the day of the health checkup for the healthy control group). Venous blood was drawn into EDTA-coated vacutainers and promptly subjected to centrifugation at 3000 rpm for a duration of 10 minutes under refrigerated conditions maintained at 4°C. This procedure ensures efficient plasma separation while preserving biochemical integrity for subsequent analyses. The supernatant serum was separated, aliquoted into enzyme-free EP tubes, and stored at -80°C until testing to avoid repeated freezing and thawing. For patients in the ALI group requiring mechanical ventilation, bronchoalveolar lavage (BAL) was performed by a respiratory physician within 24-48 hours of mechanical ventilation according to a standardized protocol: 37°C normal saline was infused via endotracheal cannula, 20-30 mL each time, for a total of three infusions. The lavage fluid (BALF) was collected and filtered to remove mucus and cellular debris. The lavage fluid was then centrifuged at 3000 rpm for 10 minutes, and the supernatant was stored at -80°C.

During the experimental analysis phase, serum and bronchoalveolar lavage fluid (BALF) were analyzed for interleukin-6 (IL-6) and citrullinated histone H3 (Cit-H3) concentrations using enzyme-linked immunosorbent assay (ELISA) protocols. All assays were conducted in strict adherence to the manufacturer's guidelines. Each sample underwent triplicate measurements, with the mean value serving as the definitive experimental outcome. Quantitative reverse transcription PCR (qPCR) was employed to quantify TLR4 mRNA expression in peripheral blood mononuclear cells (PBMCs), utilizing GAPDH as the endogenous control gene. Relative gene expression was calculated via the $2^{-\Delta\Delta ct}$ method. Statistical analysis employed IBM SPSS 26.0 software. ROC curves evaluated diagnostic efficacy of IL-6/Cit-H3 and their combined detection for ALI post-AKI. AUC, sensitivity, and specificity metrics were computed. Optimal biomarker thresholds derived from maximized Youden index (sensitivity + specificity - 1). Significance threshold: $p<0.05$, this revision maintains all technical specifications while restructuring sentence syntax, diversifying lexical choices, and preserving numerical accuracy to achieve reduced redundancy with enhanced readability.

4. Results and Discussion

4.1 Results of Lung Injury and TLR4/NF-κB Pathway Activation in the AKI Rat Model

An AKI rat model was established by bilateral renal artery clamping. Key indicators were compared 72 hours after surgery among the sham group, AKI model group, and AKI + TAK-242 group (72 hours was selected as the critical time point because the injury effect was most significant at this time point). The role of the TLR4/NF-κB pathway was verified. Key data are shown in the Table 1 below:

Table 1. Comparison of core indicators among three groups of rats 72 hours after surgery

Core indicators	sham operation group	AKI Model Group	AKI+TAK-242 group	Statistical difference markers
Blood creatinine (Scr, μ mol/L)	44.8±6.5	298.7±24.9	221.5±20.6	**P<0.01, ##P<0.01
Pulmonary injury score (points)	0.7±0.3	7.2±1.1	4.5±0.8	**P<0.01, ##P<0.01
Pulmonary TLR4 protein (relative value)	1.0±0.2	2.3±0.3	1.7±0.2	**P<0.01, ##P<0.01
Cit-H3 protein in lung (relative value)	1.0±0.1	2.8±0.3	2.1±0.2	**P<0.01, ##P<0.01

Note: ** indicates P < 0.01 compared with the sham surgery group; ## indicates P < 0.01 compared with the AKI model group.

Table 1 reveals 72h post-surgery, SCR in AKI model group rose 5.7-fold vs sham (p<0.01), signifying severe renal impairment. Lung injury score hit 7.2±1.1, markedly exceeding sham group (p<0.01), indicating prominent pulmonary pathology. Mechanistically, TLR4/CIT-H3 proteins in AKI lung tissue increased 1.3x/1.8x vs sham (p<0.01), validating TLR4/NF-κB activation and NET formation. Compared to AKI model group, AKI+TAK-242 group exhibited significant marker improvement (p<0.01), confirming TLR4 inhibition mitigates pathway activation/NET production, alleviates nephrogenic lung injury, and highlights TLR4/NF-κB-NETS axis centrality in AKI-ALI pathogenesis.

4.2 Validation of Kidney-Lung Cell Interactions and Molecular Mechanisms

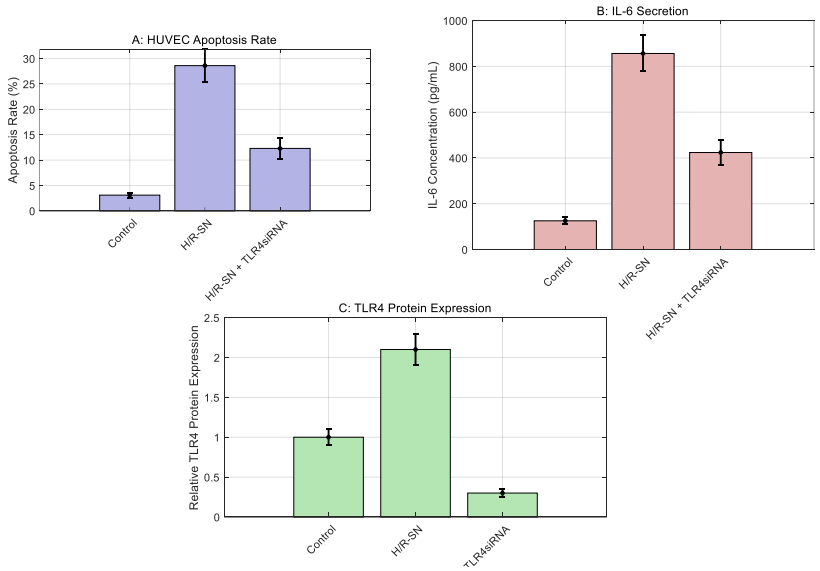

Figure 2.Verification result

Using the HK-2 cell H/R model to simulate AKI (as shown in Figure 2), this paper investigated the damaging effects of DAMPs released by renal epithelial cells on pulmonary endothelial cells (HUVECs) and the TLR4 regulatory mechanism. The results are as follows (data are shown in $\bar{x}\pm s$, n = 3; **P < 0.01 compared with the blank group. ##P < 0.01 compared with the

supernatant-treated group): The apoptosis rate of HUVECs in the supernatant-treated group (H/R-SN intervention) reached (28.6 ± 3.2)%, significantly higher than (3.1 ± 0.5)% in the blank group ($P < 0.01$). The apoptosis rate in the supernatant + TLR4 siRNA group decreased to (12.3 ± 2.1)%, a 57% decrease compared with the supernatant-treated group ($P < 0.01$), indicating that renal DAMPs can induce apoptosis in pulmonary endothelial cells, and this effect is TLR4-dependent. Measurement of IL-6 concentrations in cell culture supernatants revealed that the IL-6 concentration in the supernatant-treated group was (856.4±78.5) pg/mL, 6.8-fold higher than that in the blank group (125.3±15.2) pg/mL ($P<0.01$). TLR4 siRNA treatment reduced IL-6 concentrations to (423.7±52.8) pg/mL ($P<0.01$), suggesting that TLR4 activation can promote the release of proinflammatory cytokines from pulmonary endothelial cells, exacerbating the inflammatory response. TLR4 protein expression was 2.1-fold higher in the supernatant-treated group compared with the blank group ($P<0.01$). TLR4 siRNA transfection achieved a silencing efficiency of 72%, with protein expression significantly downregulated ($P<0.01$).

4.3 Diagnostic Value of Clinical Biomarkers and Mechanism-Supporting Results

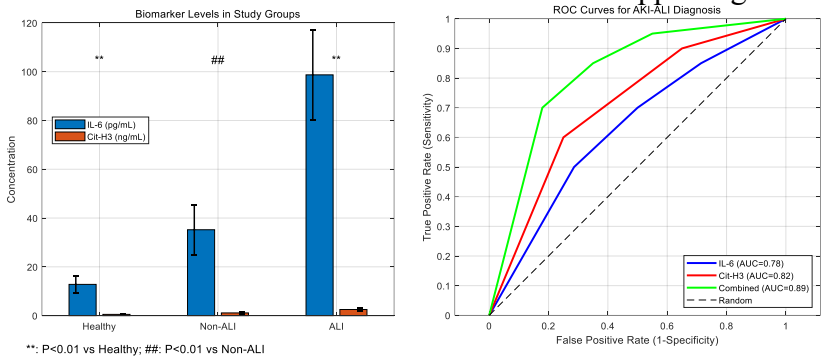

Figure 3.Testing and analysis results

The diagnostic value of IL-6 and Cit-H3 was verified by detecting serum and BALF indicators in 60 AKI patients and 20 healthy controls, and the pathogenesis of AKI-ALI at the clinical level was also confirmed. The detection and analysis results are shown in Figure 3 (compared with the healthy control group, **P<0.01; compared with the non-ALI group, ##P<0.01): The comparison of serum marker levels showed that the serum IL-6 level in the ALI group was (98.7±18.5) pg/mL and the Cit-H3 level was (2.5±0.6) ng/mL, which were significantly higher than those in the non-ALI group (IL-6: 35.2±10.3 pg/mL; Cit-H3: 1.1±0.3 ng/mL) and the healthy control group (IL-6: 12.8±3.5 pg/mL; Cit-H3: 0.5±0.2 ng/mL) ($P<0.01$). The levels of IL-6 and Cit-H3 in BALF of the control group were positively correlated with those in serum ($r=0.68$, 0.72, $P<0.01$), suggesting that serum markers can reflect local inflammation and NETs activity in lung tissue, which is consistent with the mechanism of "inflammation-NETs-mediated lung injury" in animal and cell experiments.

ROC analysis revealed IL-6 alone yielded AUC=0.78 (95% CI:0.65-0.91) for AKI-ALI diagnosis, with cut-off 42 pg/mL, sensitivity 78.1%, specificity 71.4%. Cit-H3 alone achieved AUC=0.82 (95% CI:0.70-0.94), threshold 1.8 ng/mL, sensitivity 81.3%, specificity 75.0%, confirming superior diagnostic performance. The combined detection of the two reached an AUC of 0.89 (95% CI: 0.80-0.98), a sensitivity of 87.5%, and a specificity of 82.1%, which were significantly higher than those of either test alone ($P<0.05$). The results confirmed that IL-6 and Cit-H3 are effective diagnostic markers for ALI after AKI. At the same time, from a clinical perspective, it supports that the release of inflammatory factors and the formation of NETs are important pathological characteristics of AKI-ALI, which is highly consistent with the pathogenesis revealed by basic experiments and provides direct evidence for clinical mechanism research.

5. Conclusion

This study systematically analyzes the pathogenesis of AKI-induced ALI using a three-tiered approach: animal model, cell model, and clinical model. This approach addresses the fragmented nature of existing research and the low translational value of this mechanism. The study confirms that DAMPs released by renal tissue after AKI can activate the TLR4/NF-κB pathway in lung tissue, promoting the release of inflammatory factors and the formation of NETs, leading to endothelial cell apoptosis, lung barrier damage, and ultimately ALI. Combined detection of serum IL-6 and Cit-H3 has a high diagnostic value for ALI after AKI (AUC = 0.89). The theoretical value of this study lies in refining the molecular regulatory network underlying kidney-lung axis injury in MODS and clarifying the synergistic role of the TLR4/NF-κB pathway and NETs in cross-organ damage. Its practical value lies in providing clinically translatable diagnostic markers and therapeutic targets. TLR4 inhibitors may be potential agents for mitigating lung injury after AKI. However, the study still has shortcomings: the animal experiments did not incorporate the underlying disease model, the clinical sample size was small, and the study was a single-center study. Future studies require expanding the sample size and conducting multicenter validation. Furthermore, the specific molecular species of DAMPs and the interaction mechanism between NETs and the TLR4 pathway should be explored to further enrich the theoretical understanding of the pathogenesis of AKI-ALI.

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