

IL-10 Combined with NGAL Has Diagnostic Value for AECOPD Combined with AKI

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Background: In patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) complicated by acute kidney injury (AKI) has an acute onset and seriously affects the prognosis of patients. The inflammatory factors are still in doubt in the diagnosis of AECOPD with AKI.

Material and Methods: This study is a retrospective study. By collecting the plasma concentrations of inflammatory factors IFN- γ , IL-2, IL-4, IL-10, IL-17, and NGAL in patients with AECOPD group, AECOPD plus AKI group, and control group. The expression level of each factor among the three different groups was analyzed, and the correlation of each factor was analyzed. The diagnostic value of each factor in patients with AECOPD combined with AKI was tested.

Results: A total of 245 cases of AECOPD, 69 cases of AECOPD with AKI, and 50 healthy control group were included in this study. IFN- γ and IL-4 were differentially expressed among the three groups ($P < 0.001$). However, there was no difference between the AECOPD group and the AECOPD + AKI group ($P = 0.153$, and 0.070 , respectively). The expression of IL-2, IL-10, IL-17, and NGAL in the three groups were different, and there are statistical differences in pairwise comparisons. (all P values are < 0.001). The univariate analysis showed that NGAL and IL-10 with the best correlation ($r = 0.696$). The ROC curve shows that IL-10 and NGAL have better diagnostic value for AECOPD with AKI.

Conclusion: The inflammatory factor IL-10 combined with NGAL has a better diagnostic value for AECOPD with AKI.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, acute kidney injury, inflammatory factors, diagnosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and frequently-occurring disease that seriously endangers human health, ranking fourth in the world as the cause of death.¹ The preventable and treatable diseases, COPD, which characterized by persistent respiratory symptoms and restricted airflow. The course of the disease is divided into stable phase (SCOPD) and acute exacerbation phase (AECOPD).² Studies have found that the pathogenesis of COPD is related to airway and systemic inflammation.³ AECOPD is a significant cause of death in patients with COPD.^{4,5} The AECOPD patients have continued to worsen their daily condition in a short period, and they need to change the conventional medication of COPD. The AECOPD patients have cough, shortness of breath or wheezing in a short period, which can be accompanied by fever and other symptoms.⁶

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Acute kidney injury (AKI) is a group of clinical syndromes that refers to sudden (within 1-7d) and sustained (>24h) sudden declines in renal function. The defined of AKI is an increase in serum creatinine (SCr) of at least 0.5mg/dl and manifested as nitrogen, plasmaemia, water-electrolyte, and acid-base balance and systemic symptoms can be accompanied by oliguria (<400mL/24h or 17mL/h) or anuria (<100mL/24h).⁷ When AKI occurs, multiple organ functions of the human body will be impaired. The AKI patients, interaction between organs will accelerate the disease process and lead to increased mortality.⁸ Studies have shown that patients with AECOPD and AKI are more common in clinical.⁹ AECOPD severe infection can cause a significant increase in endotoxin in the body blood.¹⁰ A large amount of endotoxin can promote the rise of the expression of inflammatory molecules, producing tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), Inflammatory factors, and adhesion molecules, such as interleukin-17 (IL-17), serum soluble intercellular adhesion factor-1 (sICAM-1), and gamma-interferon (IFN- γ).¹¹⁻¹⁴ Inflammatory mediators lead to vasodilation, increased vascular permeability and serum protein exudation, resulting in reduced blood vessel content, lower blood pressure, and decreased renal perfusion, which directly damage kidney function. The hypercapnia caused by CO₂ retention causes respiratory acidosis and renal vasospasm, which results in a reduction of renal blood flow. Due to the loss of body fluids such as sweating, AECOPD blood volume decreases, resulting in insufficient renal perfusion. Renal ischemia/reperfusion injury promotes the development of AKI.¹⁵ However, AECOPD is mostly elderly patients with reduced renal reserve function, so it is more common for AECOPD patients to have AKI.¹⁶

At present, the diagnosis of AKI is delayed and missed by using increased SCr and decreased urine output. Therefore, a variety of markers related to AKI diagnosis have been clinically developed, mainly divided into two categories:¹ Physiological indicators of the disease: including renal blood perfusion, oxygen combined state, glomerular filtration rate, urinary flow rate, etc.;² Structural damage indicators: including urine related to renal tubular structure damage, immune inflammation, oxidative stress, abnormal cell metabolism, detection of protein, enzyme, nucleic acid, sediment, etc. The purpose of testing the above indicators is to assist the AKI risk assessment, early diagnosis, and judgment of the etiology, course progression and prognosis. However, the clinical application value of these biomarkers is still being evaluated.¹⁷⁻¹⁹

In this study, inflammatory biomarkers IFN- γ , IL-2, IL-4, IL-10, IL-17, and “kidney injury” biomarker neutrophil

gelatinase-associated lipocalin (NGAL) were tested. Based on this, the diagnostic value of the above inflammation markers in AECOPD combined with AKI was verified.

Materials and Methods

The Patients' Information

The study was performed at the “Emergency Department of Beijing Chaoyang Hospital, Capital Medical University” from November 2014 to November 2015. The study protocol was approved by the Human Research Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University (approval number: 2014-KE-124). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki.

Diagnostic Criteria

The inclusion criteria of AECOPD are following the revised Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Diseases in China in 2007. Patients who have continued bad daily condition need to change the routine medication of fundamental COPD. Usually, during the disease, patients have a cough, Sputum, shortness of breath, and/or wheezing increase, sputum volume increases, purulent or sticky purulent, and inflammation with fever and other symptoms can be significantly worsened. A total of 245 AECOPDs were included in this study, according to this criterion. The diagnosis of AKI was based on the KDIGO guidelines published in 2012.²⁰ That is, the increase of blood creatinine (Scr) $\geq 26.5 \mu\text{mol/L}$ within 48 hrs; or the rise of Scr to ≥ 1.5 times the underlying value, and it is apparent or inferred that it occurred within the previous 7 days, or the urine output is less than 0.5 mL/kg (for 6 hrs). According to the diagnostic criteria of AECOPD and AKI, a total of 69 patients with AECOPD + AKI were included in this study. At the same time, 50 healthy people from the physical examination centre were collected as the control group. Exclusion criteria were as follows: patients without complete medical records, patients with urinary tract infections, patients with chronic kidney disease (CKD) grade 5 history, and patients receiving dialysis before admission.

The Characteristics of Patient

The patients' age, gender, history, complications were collected, and non-invasive mechanical ventilation, invasive mechanical ventilation, and automatic ventilation time were recorded. At the same time, ICU admission, ICU

hospitalization time and length of hospitalization, and detailed diagnosis and treatment were recorded.

Statistical Analysis

In this study, the data were processed using statistical software SPSS25.0. At the same time, the data were plotted using Graphpad prism 8 software. The continuity data that conform to the normal distribution are expressed by mean \pm standard deviation, the pairwise comparison is performed by *t*-test, and the analysis of data from three groups or more uses single-factor analysis of variance. Bonferroni *t*-test was applied to the pairwise correlation between the three groups. The area under the ROC curve is calculated using the Area Under Curve (AUC). When $P < 0.05$, the difference is statistically significant.

Results

The Included Patients

A total of 245 cases of AECOPD were included in this study; 69 cases of AECOPD combined with AKI group, and 50 healthy subjects were included as the control group.

Comparative Analysis of Factors in the Three Groups

IFN- γ and IL-4 were differentially expressed among the three groups ($P < 0.001$). Although the expressions of IFN- γ and IL-4 were higher in the AECOPD group and the AECOPD + AKI group than in the control group (both P values < 0.001). However, there was no difference in the expression of IFN- γ and IL-4 between the AECOPD group and the AECOPD + AKI group (P values were 0.153 and 0.070, respectively).

The expression of IL-2, IL-10, IL-17 and NGAL in the three groups was different ($P < 0.001$). The expression of IL-10 in the AECOPD + AKI group was higher than that in the

AECOPD group, and the expression of IL-10 in the AECOPD group was higher than that in the control group (all P values are < 0.005). See Table 1 and Figure 1 for detailed results.

Correlation Analysis

The univariate analysis showed that the IFN- γ , IL-2, IL-4, IL-10, and IL-17 were positive correlation ($P < 0.05$) with NGAL. NGAL and IL-10 with the best correlation ($r = 0.696$, $P < 0.05$). Although the other factors are related to NGAL, the correlation coefficients are lower. More details are shown in Table 2.

Diagnostic Effects of the Factors

We tested the ROC curve of the diagnostic utility of each factor in the AECOPD group and the AECOPD with the AKI group to distinguish the two diseases. The ROC curve results show that IL-10 and IL-17 have a better AUC region. More details are shown in Table 3 and Figure 2.

Discussion

Since the 21st century, the majors of Nephrology and Critical Care Medicine have proposed the concept of acute kidney injury (AKI) and put forward the risk, damage, failure, loss, end-stage renal disease standard (RIFLE standard) and AKI network according to the severity of the disease.¹⁹ The recommended (AKIN) stratified diagnosis is based on early diagnosis and early treatment of AKI.²¹ AKI is widely distributed in various clinical departments. It is a common complication of acute, severe and complex cases. The hospital mortality rate is high, medical resources are consumed, and the long-term mortality and chronic kidney disease rate of survivors are significantly increased. The studies show that the incidence of AKI in hospitalized patients is 7%

Table 1 Factor Expression Levels and Comparison Results in Different Groups

Factor	IFN- γ (pg/mL)	IL-17 (pg/mL)	NGAL (μ g/L)	IL-10 (ng/L)	IL-2 (pg/mL)	IL-4 (ng/L)
AECOPD (A, 245)	1102.314 \pm 206.384	413.246 \pm 87.236	6.525 \pm 1.201	284.546 \pm 56.246	1169.182 \pm 204.087	342.414 \pm 59.593
Control group (B, 50)	562.354 \pm 172.838	213.311 \pm 69.849	5.719 \pm 1.653	183.524 \pm 75.669	549.467 \pm 207.385	170.948 \pm 56.948
AECOPD+AKI (C, 69)	1141.331 \pm 192.605	440.962 \pm 88.959	7.586 \pm 0.616	314.271 \pm 32.619	1230.979 \pm 163.400	356.090 \pm 33.859
P1 (A vs B)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
P2 (A vs C)	0.459	0.019	< 0.001	< 0.001	0.067	0.211
P3 (B vs C)	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
F	163.452	93.09	37.818	87.7	224.3	216.427
P	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Notes: Bonferroni *t*-test was applied to the pairwise correlation between the three groups. The normal value: IFN- γ , 1.21–5.51 μ g/L; IL-17: 0.7–20ng/L; NGAL, 3–106 ng/mL; IL-10, 38.6 \pm 10.6 ng/mL; IL-2, 7.25–42.63pg/mL; IL-4, 0.78 \pm 0.33ng/mL.

Abbreviations: A, AECOPD group; B, Control group; C, AECOPD+AKI group; P1, the value of group A vs group B; P2, the value of group A vs group C; P3, the value of group B vs group C.

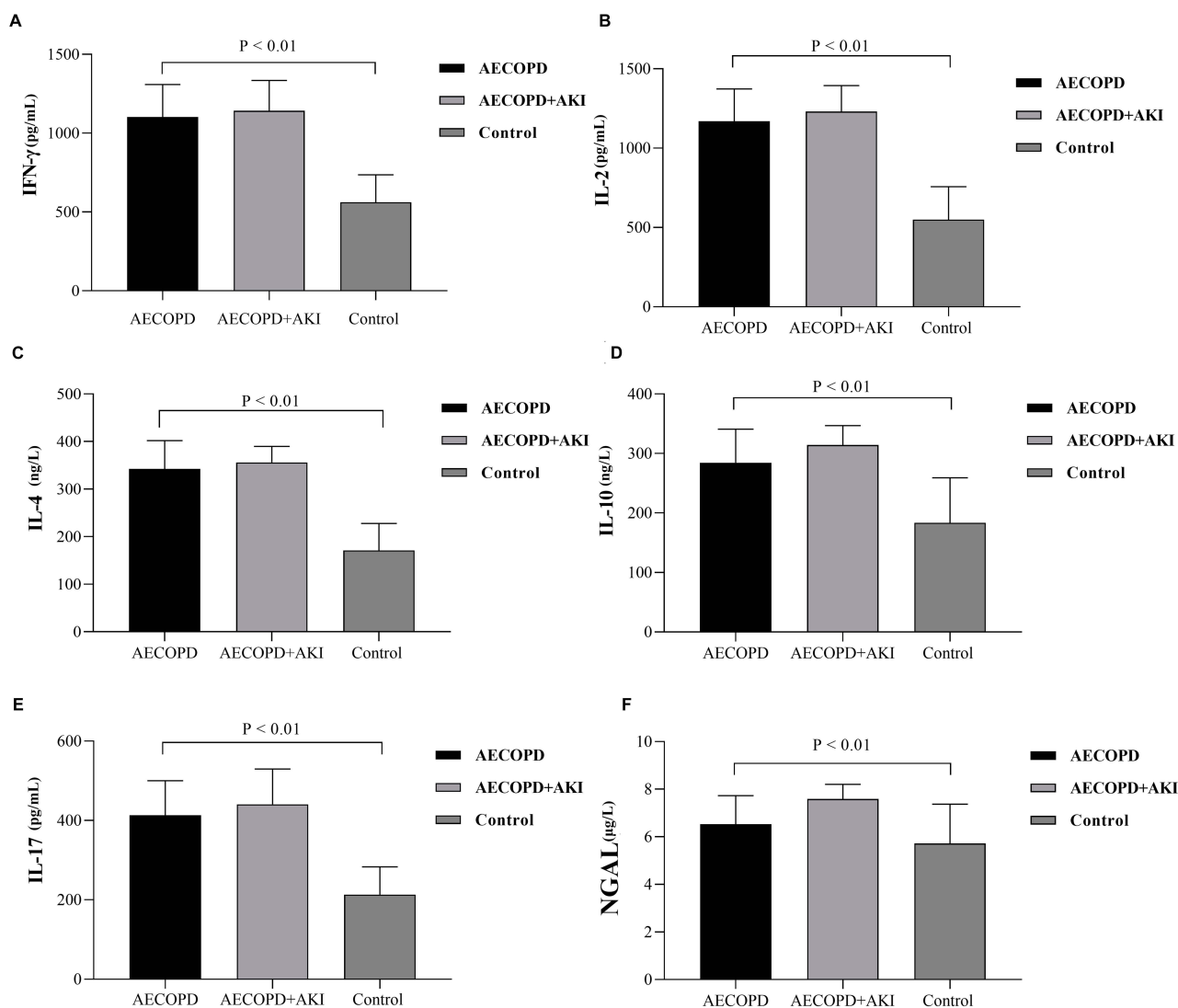


Figure 1 The expression levels of inflammatory factors in AECOPD group, AECOPD with AKI group, and control group. (A) IFN- γ ; (B) IL-2; (C) IL-4; (D) IL-10; (E) IL-17; (F) NGAL

to 18%, and that of high-risk patients (such as ICU) is 30% to 70%.^{22,23} Studies have shown that nearly one in five AECOPD patients who require hospitalization have evidence of combined AKI.²⁴ The key to determining the prognosis of AKI is early detection, early diagnosis and early intervention. Studies have shown that even a small degree of renal dysfunction can increase mortality.

In this study, we selected 245 AECOPD and 69 AECOPD patients with AKI. At the same time, 50 healthy subjects were selected as the control group to study related inflammatory factors. The results showed that the inflammatory factors IFN- γ , IL-2, IL-4, IL-10, IL-17, and NGAL were statistically different in the three groups as a whole (all P values were < 0.01). However, the AECOPD group and AECOPD + There was no

difference in the expression of IFN- γ and IL-4 in the AKI group. Therefore, we believe that IFN- γ and IL-4 are not good inflammatory factors that distinguish AECOPD with AKI. The inflammatory factors IL-2, IL-10, IL-17 and NGAL were statistically different in the two groups of two comparisons (all P values were < 0.01). NGAL is also called human lipocalin 2, Lin2 or siderocalin.²⁵ Because NGAL can be used as a new carrier to mediate the transport of iron ions into cells, it can be used as an acute disease response protein. In the early diagnosis of AKI, the blood and urine NGAL concentrations usually rise rapidly, and the 2h is most obvious. The rise is usually tens to hundreds of times higher than the critical value. However, traditional serum creatinine (sCr), urinary enzymes and other indicators often take 24–72 hrs to increase

Table 2 The Univariate Analysis in Different Factor

Control Variable		IFN	IL-2	IL-4	IL-10	IL-17	NGAL	Group
IFN	Correlation	1.000	0.438	0.431	0.316	0.407	0.188	-0.077
	Sig.	.	0.000	0.000	0.000	0.000	0.000	0.151
IL2	Correlation	0.438	1.000	0.484	0.313	0.395	0.240	-0.060
	Sig.	0.000	.	0.000	0.000	0.000	0.000	0.266
IL4	Correlation	0.431	0.484	1.000	0.368	0.406	0.281	-0.070
	Sig.	0.000	0.000	.	0.000	0.000	0.000	0.195
IL10	Correlation	0.316	0.313	0.368	1.000	0.311	0.696	0.067
	Sig.	0.000	0.000	0.000	.	0.000	0.000	0.209
IL17	Correlation	0.407	0.395	0.406	0.311	1.000	0.226	-0.022
	Sig.	0.000	0.000	0.000	0.000	.	0.000	0.684
NGAL	Correlation	0.188	0.240	0.281	0.696	0.226	1.000	0.252
	Sig.	0.000	0.000	0.000	0.000	0.000	.	0.000
Group	Correlation	-0.077	-0.060	-0.070	0.067	-0.022	0.252	1.000
	Sig.	0.151	0.266	0.195	0.209	0.684	0.000	.

Abbreviation: Sig, Significant.

Table 3 Comparison of ROC Curve Results Between AECOPD Group and AECOPD + AKI Group

Variable Test	Region	Standard Error ^a	Asymptotic Significance ^b	95% CI	
				LL	UL
IFN	0.541	0.039	0.305	0.465	0.616
IL-2	0.584	0.036	0.034	0.514	0.654
IL-4	0.588	0.034	0.027	0.520	0.655
IL-10	0.664	0.033	0.000	0.600	0.729
IL-17	0.604	0.039	0.009	0.528	0.680
NGAL	0.766	0.026	0.000	0.714	0.818

Notes: The test result variables IFN, IL2, IL4, IL10, IL17, and NGAL have at least one binding value between the positive real-time state group and the negative real-time state group, and the statistics may be biased. ^aAssumed by non-parameters; ^bNull hypothesis: true region = 0.5. 95%

Abbreviations: CI, Confidence interval; LL, Lower limit; UL, upper limit; AUC, Area Under Curve.

significantly, so NGAL can be used as a new kidney injury marker for early diagnosis of AKI.²⁶ Majhi et al Found in a cohort study of children with AKI who were undergoing cardiopulmonary bypass surgery.²⁷ The area under the AUC-ROC curve for the diagnosis of AKI in 2h urine NGAL was 0.998, and its critical value was 50 µg/L (ELISA method), 100% and 98%, respectively. The area under the ROC curve for serum NGAL diagnosis of AKI was 0.906, the critical value was 25 µg/L, and the sensitivity and specificity were 70%, and 94%, respectively. The diagnosis of NGAL as AECOPD combined with AKI in this study showed that the area under the ROC curve was 0.766. Compared with other

inflammatory factors, NGAL can still be used as the best diagnostic indicator. IL-2 can affect T cell development, differentiation and functional expression by inducing T cell kinase (Itk).²⁸ Because it is mainly expressed in human T cells, it plays an important role in T cell receptor (TCR) and chemokine receptor signal transduction pathways.²⁹ Based on the above mechanism, IL-2 can regulate the expression of Itk in the prognosis of inflammatory and immune diseases such as parasitic infection, viral infection, allergic dermatitis, bronchial asthma (asthma for short). However, the correlation between IL-2 and NGAL and the diagnosis of AECOPD with AKI disease (area under the AUC curve is 0.584) and correlation

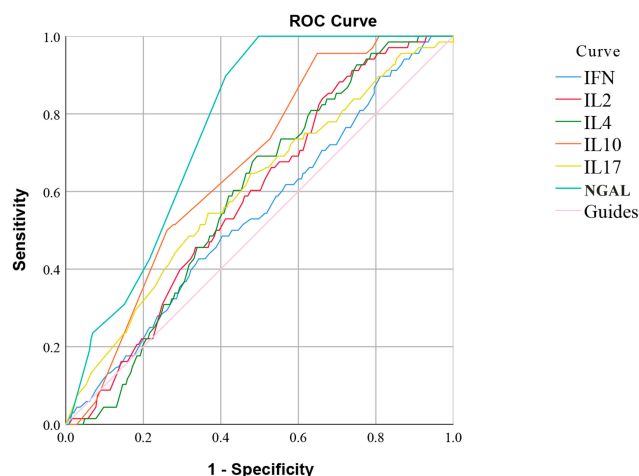


Figure 2 The ROC curve results for different inflammatory factors.

($r = 0.240$, $P < 0.001$) were not very good in this study. IL-10 is a multi-cell source and multi-functional cytokine.³⁰ It is not only involved in regulating cell growth and differentiation but also in inflammatory and immune responses. It is a recognized inflammatory and immune suppressive factor. Recent studies have found that helper T lymphocytes (CD4 + CD25 + FoxP3 +, Treg) inhibit the innate immune inflammatory response by secreting IL-10, thus protecting the mouse model of acute ischemia/reperfusion kidney injury.^{31,32} The study found that within the first 48 hrs of acute kidney injury, iNos-positive pro-inflammatory (M1) macrophages first chemotactically recruited to local tissues, secreting inflammatory mediators leading to the amplification of inflammatory responses and further tissue damage; Arginase 1 and mannose receptor-positive non-inflammatory (M2) macrophages appeared in local kidney tissues 3 days after acute kidney injury, and increased significantly 5–7 days. These cells expressed IL-10, and it has the effects of anti-inflammatory and promoting repair. Studies have shown that IL-17A/F and Th17 cells cause kidney damage.³³ The IL-17 family, including IL-17A (CTLA-8), IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. IL-17 cytokine family uses an unusual cysteine knot-folding structure, similar to nerve growth factor (NGF) and platelet-derived growth factor (PDGF), but different from other immune cytokine subclasses. Experimental studies in animals that damage glomerular disease have shown that they are involved in the initial inflammatory response in the kidney.³⁴ Studies of patients with autoimmune diseases such as systemic lupus erythematosus found that elevated levels of IL-17A in the blood circulation and a higher proportion of Th17 cells were associated with the severity of the disease.³⁵ Animal models of acute kidney injury have demonstrated that the

administration of antibodies against IL-17A can reduce kidney injury.³⁶ Therefore, blocking the IL-17A/F signaling pathway may be an enthusiastic approach in clinical trials to explore new therapies for the treatment and prevention of immune-mediated kidney disease. In this study, compared with IL-17 ($r = 0.226$, $P < 0.001$), IL-10 ($r = 0.696$, $P < 0.001$) had a better correlation with NGAL. Therefore, IL-10, combined with NGAL, has a better diagnostic effect on AECOPD combined with AKI.

Limitations

The sample size of the AECOPD + AKI group (245) and the control group (50) can achieve 90% test efficiency. Still, the unequal proportion of the samples in the two groups affects the test efficiency to a certain extent. The experimental method used in this study is an enzyme-linked immunosorbent assay. Although enzyme-linked immunosorbent assays have been widely used in clinical practice due to its high sensitivity and specificity, the choice of reagents, hemolysis, contamination of specimens, and various steps in operation may affect the results. Therefore, in the next step, we need more rigorous experimental design and experimental methods to verify this conclusion.

Conclusion

In short, the tissue damage and repair process of AECOPD combined with AKI involves a variety of complex mechanisms. Early detection, early diagnosis, and early intervention of the disease can significantly improve renal function and reduce patient mortality. In the detection of inflammatory factors, we found that IL-10 combined with NGAL has a better diagnostic effect on the disease. More research is needed to confirm our findings.

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Disclosure

The authors report no conflicts of interest in this work.

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