Analysis of Risk Factors for Renal Impairment in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease: Postprint

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Abstract

Background Chronic obstructive pulmonary disease (COPD) is one of the major diseases that seriously endangers the health of the Chinese population. Due to the structural and functional characteristics of the kidneys, COPD patients are prone to renal function impairment; however, studies on the factors related to COPD and renal injury are scarce both domestically and internationally. Objective To analyze the clinical characteristics and influencing factors of renal insufficiency in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD), and to evaluate its predictive value, thereby providing a theoretical basis for the prevention and treatment of renal insufficiency in clinical AECOPD patients. Methods A total of 192 AECOPD patients hospitalized in the Department of Respiratory Medicine of the First Affiliated Hospital of Jinzhou Medical University from December 2020 to July 2023, including those with renal function impairment, were enrolled. Patients were divided into a normal renal function group (92 cases), a mild renal impairment group (66 cases), and a severe renal impairment group (34 cases) based on estimated glomerular filtration rate (eGFR). Basic patient data were collected and relevant indicators were measured. Pearson correlation analysis was employed to investigate the correlation between eGFR, Cys C, and other indicators. Multivariate Logistic regression analysis was used to explore the influencing factors of AECOPD patients complicated by renal function impairment. Receiver operating characteristic (ROC) curves were plotted and the area under the ROC curve (AUC) was calculated to assess the predictive value of different indicators for diagnosing renal function impairment in AECOPD patients. Results Comparisons among the normal renal function group, mild renal impairment group, and severe renal impairment group revealed statistically significant differences in age, hypertension, coronary heart disease, hemoglobin (Hb), C-reactive protein (CRP), albumin (ALB), brain natriuretic peptide (BNP), troponin (CTnl), interleukin-6 (IL-6), creatinine

(Cr), uric acid (UA), urea (Urea), cystatin C (Cys C), $ 2 − *microglobulin*($2-MG), percentage of forced expiratory volume in one second to predicted value (FEV1%), and partial pressure of carbon dioxide (PaCO2) (P<0.05). Correlation analysis demonstrated that Cys C was negatively correlated with PaO2 and FEV1% (P<0.01, r=-0.379, -0.254) and positively correlated with IL-6 (P<0.01, r=0.641). eGFR was positively correlated with PaO2 and FEV1% (P<0.01, r=0.470, 0.286) and negatively correlated with IL-6 (P<0.05, r=-0.456). Multivariate Logistic regression analysis indicated that age, hypertension, PaO2, IL-6, Cr, UA, $ $2-MG, and Cys C were predictive factors for AECOPD patients complicated by renal function impairment (P<0.05). ROC curve analysis showed that UA (AUC=0.646, 95%CI: 0.569~0.724), Cys C (AUC=0.895, 95%CI: 0.852~0.939), $ $2-MG (AUC=0.822, 95%CI: 0.764~0.879), IL-6 (AUC=0.743, 95%CI: 0.674~0.812), and PaO2 (AUC=0.676, 95%CI: 0.601~0.751) all possessed certain predictive value for AECOPD patients complicated by renal function injury (all P<0.05). The sensitivity, specificity, accuracy, and area under the ROC curve of Cys C (89.50%) were all higher than those of $ $2-MG, IL-6, and PaO2 (82.20%, 74.30%, 67.60%), with statistically significant differences (P<0.05). Conclusion Age, hypertension, PaO2, IL-6, Cr, UA, $ $2-MG, and Cys C are associated predictive factors for AECOPD patients complicated by renal function impairment. Cys C demonstrates high predictive diagnostic value for AECOPD complicated by renal function impairment and serves as an important indicator for predicting the risk of renal injury in AECOPD patients.

Full Text

Analysis of Related Factors of Renal Function Impairment in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is one of the major diseases that seriously endanger public health in China. Due to the structural and functional characteristics of the kidneys, patients with COPD are susceptible to renal impairment. However, research on the factors associated with COPD and renal dysfunction remains limited both domestically and internationally.

Objective: To analyze the clinical characteristics and influencing factors of renal insufficiency in patients with acute exacerbation of chronic obstructive

pulmonary disease (AECOPD), evaluate their predictive value, and provide a theoretical basis for the prevention and treatment of renal dysfunction in clinical AECOPD patients.

Methods: A total of 192 AECOPD patients hospitalized in the Respiratory Department of the First Affiliated Hospital of Jinzhou Medical University from December 2020 to July 2023 were enrolled. Based on estimated glomerular filtration rate (eGFR), patients were divided into three groups: normal renal function group (92 cases), mild renal impairment group (66 cases), and severe renal impairment group (34 cases). Basic patient data and relevant indicators were collected. Pearson correlation analysis was used to examine the relationship between eGFR, cystatin C (Cys C), and other indicators. Multivariate logistic regression analysis was employed to identify influencing factors for renal impairment in AECOPD patients. Receiver operating characteristic (ROC) curves were plotted and the area under the ROC curve (AUC) was calculated to assess the predictive value of different indicators for renal impairment in AECOPD patients.

Results: Significant differences were observed among the three groups in age, hypertension, coronary heart disease, hemoglobin (Hb), C-reactive protein (CRP), albumin (ALB), brain natriuretic peptide (BNP), troponin I (CTnI), interleukin-6 (IL-6), creatinine (Cr), uric acid (UA), urea (Urea), cystatin C (Cys C), $ 2 - *microglobulin*($2-MG), percentage of forced expiratory volume in one second (FEV1%), and partial pressure of carbon dioxide (PaCO2) (all P<0.05). Correlation analysis showed that Cys C was negatively correlated with PaO2 and FEV1% (P<0.01, r=-0.379, -0.254) and positively correlated with IL-6 (P<0.01, r=0.641). eGFR was positively correlated with PaO2 and FEV1% (P<0.01, r=0.470, 0.286) and negatively correlated with IL-6 (P<0.05, r=-0.456). Multivariate logistic regression analysis revealed that age, hypertension, PaO2, IL-6, Cr, UA, $ $2-MG, and Cys C were predictive factors for renal impairment in AECOPD patients (P<0.05). ROC curve analysis demonstrated that UA (AUC=0.646, 95%CI: 0.569-0.724), Cys C (AUC=0.895, 95%CI: 0.852-0.939), $ $2-MG (AUC=0.822, 95%CI: 0.764-0.879), IL-6 (AUC=0.743, 95%CI: 0.674-0.812), and PaO2 (AUC=0.676, 95%CI: 0.601-0.751) all had predictive value for renal impairment in AECOPD patients (all P<0.05). Cys C showed higher sensitivity, specificity, accuracy, and AUC (89.50%) compared to $ $2-MG, IL-6, and PaO2 (82.20%, 74.30%, 67.60%, respectively), with statistically significant differences (P<0.05).

Conclusion: Age, hypertension, PaO2, IL-6, Cr, UA, $ $2-MG, and Cys C are relevant predictive factors for renal impairment in AECOPD patients. Cys C demonstrates high diagnostic value in predicting renal impairment in AECOPD patients and serves as an important indicator for assessing the risk of renal injury in this population.

Keywords: Pulmonary disease, chronic obstructive; Acute exacerbation of chronic obstructive pulmonary disease; Renal damage; Influencing factor analysis; ROC curve

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic disease in the elderly, characterized by chronic respiratory symptoms such as dyspnea, cough, sputum production, and acute exacerbations. With its increasing prevalence, COPD has become a major public health concern. It is projected that by 2030, annual deaths from COPD and related diseases worldwide will exceed 4.5 million, ranking as the third leading cause of death in China. As the disease progresses, COPD can cause chronic hypoxia in various organs and may induce complications, with studies indicating that COPD patients often have more than one comorbidity.

The kidneys are particularly sensitive to hypoxia due to their structural and functional characteristics, making them vulnerable to acute renal injury during AECOPD. However, acute kidney injury often presents with insidious and nonspecific symptoms that are difficult to detect early, potentially delaying optimal treatment and increasing healthcare burden. During acute exacerbation of COPD (AECOPD), patients' symptoms deteriorate significantly compared with the stable phase, exerting more severe effects on the body. Nevertheless, previous research on factors associated with AECOPD and renal impairment has been limited. This study investigates the relevant factors of concurrent renal impairment in AECOPD to provide additional clinical references for managing AECOPD patients, better protecting their renal function, and improving prognosis.

Methods

1.1 Study Subjects A total of 192 AECOPD patients hospitalized in the Respiratory Department of the First Affiliated Hospital of Jinzhou Medical University from December 2020 to July 2023 were enrolled, including 132 males and 60 females.

Inclusion criteria: (1) Age between 50-90 years; (2) Symptoms consistent with the description of AECOPD in the Chinese Expert Consensus on the Diagnosis and Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (2023 Revision); (3) Hospitalization duration >1 week.

Exclusion criteria: (1) Patients unable to cooperate with pulmonary function tests; (2) Patients with primary renal diseases such as glomerulonephritis; (3) Patients with incomplete clinical data affecting statistical analysis.

All study subjects provided informed consent, and this study was approved by the Ethics Committee (Approval No. KYLL2024187).

1.2 Data Collection **1.2.1 General Information:** Researchers collected and recorded basic patient information including age, sex, BMI, smoking history

(continuous smoking for >1 year), and medical history (hypertension, diabetes, coronary heart disease, COPD duration).

1.2.2 Biochemical Indicators: After admission, fasting venous blood samples were collected the following morning and sent to the laboratory of the First Affiliated Hospital of Jinzhou Medical University. Hematology parameters and biochemical indicators were measured using a Beckman hematology analyzer and an Abbott C16000 automatic biochemical analyzer. White blood cell count (WBC), hemoglobin (Hb), C-reactive protein (CRP), interleukin-6 (IL-6), procalcitonin (PCT), albumin (ALB), brain natriuretic peptide (BNP), troponin I (CTnI), and glucose (GLU) were measured. Midstream morning urine (5 mL) was collected to determine renal indicators including creatinine (Cr), cystatin C (Cys C), $ 2 - *microglobulin*($2-MG), urea (Urea), and uric acid (UA).

1.2.3 Pulmonary Function Testing: When patients' condition stabilized approximately two days after admission, pulmonary function was measured using a CareFusion spirometer. For patients unable to complete pulmonary function testing within the first two days due to severe symptoms, testing was performed before discharge when their condition was relatively stable. The main parameters measured were percentage of forced expiratory volume in one second (FEV1%) and ratio of forced expiratory volume in one second to forced vital capacity (FEV1/FVC).

1.2.4 Arterial Blood Gas Analysis: After admission and following a period of quiet rest without oxygen supplementation, arterial blood gas samples were collected. pH, arterial oxygen partial pressure (PaO2), carbon dioxide partial pressure (PaCO2), and lactate (cLac) were measured in real-time using an i500 series automatic blood gas electrolyte analyzer (Shenzhen Edan Instruments Co., Ltd.).

1.3 Grouping Based on the Chinese Expert Consensus on the Diagnosis and Treatment of Chronic Kidney Disease in the Elderly (2018), the estimated glomerular filtration rate (eGFR) was calculated for each patient using the formula: eGFR $[\mathrm{ml}/(\mathrm{min} \cdot 1.73\mathrm{m}^2)] = 186 \times [\mathrm{Cr}]^{-1 \cdot 154} \times [\mathrm{Age}]^{-0 \cdot 203} \times 1.233$ ($\times$\$0.742 for females). Patients were then divided into three groups: normal renal function group (eGFR $\geq$ 90 ml/min, 92 cases), mild renal impairment group (60 ml/min $\leq$ eGFR $<$ 90 ml/min, 66 cases), and severe renal impairment group (eGFR $<$ 60 ml/min, 34 cases).

1.4 Statistical Analysis SPSS 26.0 statistical software was used for data analysis. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x}\pm s$) and compared among groups using one-way ANOVA. Non-normally distributed variables were expressed as median (P25, P75) and compared using Kruskal-Wallis H test, with pairwise comparisons performed using rank sum tests. Categorical variables were expressed as percentages and compared using chi-square tests. Pearson correlation analysis was used to evaluate correlations between variables. Multivariate logistic regression analysis was

employed to identify predictive factors. ROC curves were plotted using SPSS 26.0 software to evaluate the diagnostic performance of various indices for renal impairment in AECOPD patients.

Results

2.1 Comparison of General Characteristics Among Three Groups Significant differences were observed among the three groups in age, hypertension, and coronary heart disease (P<0.05). Both the mild and severe renal impairment groups had higher age and higher proportions of hypertension and coronary heart disease compared with the normal renal function group (P<0.05). The severe renal impairment group also had a higher proportion of coronary heart disease compared with the mild impairment group (P<0.05). See Table 1 .

2.2 Comparison of Blood Gas, Pulmonary Function, Hb, and ALB Among Three Groups Significant differences were found among the three groups in Hb, ALB, FEV1%, and PaO2 (P<0.05). The mild renal impairment group had lower ALB compared with the normal group (P<0.05). The severe renal impairment group had lower Hb, ALB, FEV1%, and PaO2 compared with the normal group (P<0.05), and also lower FEV1% and PaO2 compared with the mild impairment group (P<0.05). See Table 2 .

2.3 Comparison of WBC, CRP, IL-6, and PCT Among Three Groups Significant differences were observed among the three groups in CRP and IL-6 (P<0.05). Both the mild and severe renal impairment groups had higher IL-6 and CRP compared with the normal group (P<0.05). The severe renal impairment group also had higher IL-6 compared with the mild impairment group (P<0.05). See Table 3 .

2.4 Comparison of BNP, CTnI, and Renal Indicators Among Three Groups Significant differences were found among the three groups in BNP, CTnI, Cr, Cys C, $ $2-MG, Urea, and UA (P<0.05). The mild renal impairment group had higher BNP, CTnI, Cr, Cys C, $ $2-MG, and Urea compared with the normal group (P<0.05). The severe renal impairment group had higher BNP, CTnI, Cr, Cys C, $ $2-MG, Urea, and UA compared with the normal group (P<0.05), and also higher Cr, Cys C, $ $2-MG, Urea, and UA compared with the mild impairment group (P<0.05). See Table 4 .

2.5 Correlation Analysis of eGFR and Cys C with PaO2, FEV1%, and IL-6 The results showed that Cys C was negatively correlated with PaO2 and FEV1% (P<0.01, r=-0.379, -0.254) and positively correlated with IL-6 (P<0.01, r=0.641). eGFR was positively correlated with PaO2 and FEV1% (P<0.01, r=0.470, 0.286) and negatively correlated with IL-6 (P<0.01, r=-0.456). See Table 5 and Figure 1 [Figure 1: see original paper].

2.6 Multivariate Logistic Regression Analysis of Factors Associated with Renal Impairment in AECOPD Using the degree of renal impairment as the dependent variable (normal renal function=0, mild impairment=1, severe impairment=2) and variables showing significant differences in univariate analysis as independent variables, multivariate logistic regression analysis revealed that age, hypertension, PaO2, IL-6, Cr, UA, Cys C, and $ $2-MG were predictive factors for renal impairment in AECOPD patients. See Table 6 .

2.7 Diagnostic Performance Evaluation of Different Factors for Renal Impairment in AECOPD Patients ROC curves were plotted using SPSS 26.0 software to evaluate the diagnostic value of these factors. The results showed that IL-6 (AUC=0.743, 95%CI: 0.674-0.812), Cys C (AUC=0.895, 95%CI: 0.852-0.939), $ $2-MG (AUC=0.822, 95%CI: 0.764-0.879), UA (AUC=0.646, 95%CI: 0.569-0.724), and PaO2 (AUC=0.676, 95%CI: 0.601-0.751) all had predictive value for renal impairment in AECOPD patients (all $P<0.05$). Cys C demonstrated higher sensitivity, specificity, accuracy, and AUC (89.50%) compared with $ $2-MG, IL-6, and PaO2 (82.20%, 74.30%, 67.60%, respectively), with statistically significant differences ($P<0.05$). See Table 7 and Figure 2 [Figure 2: see original paper].

Discussion

COPD patients experience chronic hypoxia, which stimulates the immune system and triggers systemic inflammatory responses. During acute exacerbations, more inflammatory factors are released, and their accumulation can cause renal injury. Previous research has indicated that renal injury is primarily manifested by elevated inflammatory markers such as CRP and IL-6. IL-6 is valuable for early diagnosis and assessment of inflammation and infection. CRP, an acute-phase protein and sensitive inflammatory marker, is closely related to airway hyperresponsiveness and inflammatory regulation, effectively reflecting disease status. Cys C, a cysteine protease inhibitor expressed in many organs and tissues, can freely pass through the glomerular filtration membrane at physiological pH and is catabolized or reabsorbed in the proximal tubule. Its concentration is primarily affected by eGFR, making serum Cys C level a reliable indicator of renal injury severity. $ $2-MG, a metabolite mainly derived from lymphocytes, is filtered and excreted by the kidneys. Under stable conditions, its blood concentration remains constant, but increases when glomerular filtration decreases or tubular reabsorption is impaired, serving as a sensitive indicator of renal dysfunction. UA is almost 100% filtered by the glomerulus, with reabsorption and secretion occurring primarily in the proximal tubule. Impaired tubular function can lead to elevated serum uric acid, which may in turn aggravate renal injury, creating a vicious cycle.

This study found that age, hypertension, and coronary heart disease were associated with renal impairment in AECOPD patients, indicating that older AECOPD patients with hypertension or coronary heart disease are more susceptible

to renal dysfunction. The mechanisms include progressive degenerative changes in renal structure with aging, hemodynamic disturbances and abnormal neurohumoral activation from heart disease causing secondary renal injury, and mechanical vascular damage from hypertension leading to imbalanced vasodilation and overactivation of the renin-angiotensin system (RAS). Multiple factors targeting vascular endothelial cells and walls can cause glomerular endothelial cell proliferation, swelling, ischemic shrinkage, and sclerotic changes, ultimately resulting in renal dysfunction.

Correlation analysis revealed that eGFR was negatively correlated with IL-6, suggesting that higher inflammatory levels are associated with lower eGFR and more severe renal injury. The underlying mechanism is that COPD patients are more prone to infections, which dramatically increase inflammation. IL-6, a major inflammatory cytokine, not only causes pulmonary lesions but also acts as an inflammatory mediator promoting mesangial cell proliferation. In glomerular inflammation, IL-6 has secretory and paracrine functions that damage vascular endothelium and reduce peritubular capillaries. Since the kidneys have limited detoxification capacity, they cannot withstand excessive inflammatory mediators, making them vulnerable to injury in AECOPD patients.

Logistic regression analysis showed that PaO2 was not only a predictive factor but also positively correlated with eGFR. The mechanism involves hypoxia-induced elevation of endothelin-1 (ET-1) levels and activation of phospholipase A2 (PLA2), which can directly damage renal tubular epithelial cells and cause functional impairment. Severe hypoxia can lead to tubular degeneration and necrosis, resulting in acute renal failure. Additionally, reactive oxygen species (ROS) act as important second messengers in various signaling pathways, causing cellular injury. These findings are consistent with previous research demonstrating that chronic hypoxia causes early renal injury.

Recent studies have focused on the relationship between Cys C and COPD. Research has shown that elevated plasma Cys C levels in COPD patients can predict pulmonary function status, suggesting that monitoring plasma Cys C may aid in diagnosis and severity assessment. Our findings align with these studies, demonstrating that Cys C is a predictive factor for renal impairment in AECOPD patients, negatively correlated with PaO2 and FEV1% and positively correlated with IL-6. These results are consistent with previous research showing that serum Cys C levels are associated with COPD exacerbations and negatively correlated with FEV1% predicted values. The underlying mechanism is that Cys C is secreted into the bloodstream by inflammatory cells, particularly alveolar macrophages, serving as an important endogenous cysteine protease inhibitor and inflammatory marker. AECOPD patients experience chronic mild hypoxia, which stimulates macrophages to secrete large amounts of inflammatory factors, including Cys C. Combined with $ $2-MG, UA can cause renal damage through inflammatory responses, oxidative stress, RAS activation, and promotion of renal fibrosis. Our previous research found that Cys C was significantly elevated in patients with renal insufficiency and holds important value for

early diagnosis and therapeutic evaluation of renal injury. These findings further demonstrate that more severe COPD is associated with greater likelihood of renal impairment.

This study has several limitations. As a single-center retrospective study with a limited sample size, mostly from western Liaoning Province, the sample balance was suboptimal, potentially introducing bias. Future multi-center prospective studies with larger sample sizes are needed to further clarify the factors associated with renal impairment in AECOPD patients.

In conclusion, this study identified age, hypertension, IL-6, Cys C, $ $2-MG, UA, and PaO2 as factors affecting eGFR and predictive of renal impairment in AECOPD patients. Among these, Cys C demonstrated high predictive and diagnostic value. These findings can help clinicians detect changes in these indicators early during hospitalization, enabling timely diagnosis and treatment to protect renal function and prevent further deterioration in AECOPD patients.

Author Contributions

Tian Ying conceptualized the study, designed the protocol, conducted literature searches, collected and verified data, performed statistical analysis, and drafted the manuscript. Pan Dianzhu supervised the research, managed quality control, reviewed and edited the manuscript, and assumes overall responsibility for the work.

Conflict of Interest

The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.