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ORIGINAL RESEARCH

Associations of Serum Legumain with Severity and Prognosis Among Acute Exacerbation of Chronic Obstructive Pulmonary Disease Patients

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Background: A number of studies have demonstrated that legumain is engaged in the pulmonary diseases. Nevertheless, the role of legumain is indistinct in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). The aim is to identify the correlation of serum legumain with AECOPD patients through a prospective cohort study.

Methods: All 202 patients with AECOPD were enrolled. Fasting venous blood was collected. Serum legumain was detected by ELISA.

Results: On admission, serum legumain concentration was gradually elevated in line with AECOPD severity scores. Additionally, serum legumain was closely associated with clinical characteristics. Linear regression analysis confirmed the positive relationships of serum legumain with COPD severity scores. Moreover, the poor prognoses were tracked in patients of AECOPD. Serum higher legumain at admission increased the risks of death and acute exacerbation during hospitalization.

Conclusion: Serum legumain at admission was positively correlated with the severity and adverse prognosis in AECOPD patients, indicating that legumain plays a vital role in the initiation and development of AECOPD. As a result, serum legumain can become a biomarker in the disease assessment and prognosis prediction for AECOPD.

Keywords: AECOPD, legumain, inflammatory cytokines, COPD severity scores, biomarker

Introduction

Chronic obstructive pulmonary disease (COPD) was typified with long-term respiratory symptoms brought on by abnormalities in alveolar or airflow that leading to a persistent and frequently growing blockage of airflow.[1,2] A growing amount of research pointed out that COPD was the primary cause of chronic respiratory fatalities worldwide.[3] In 2015, around three million people died from COPD.[4] Moreover, for the individual family and the community, COPD was an enormous financial burden, and it also was a significant and expanding global health issue.[5] An exacerbation of cough, sputum, and dyspnea in COPD patients within 14 days was defined as acute exacerbation of COPD (AECOPD).[6] Several studies had shown that AECOPD could lead to lung function decrease,[7] reduced quality of life,[8] and increased probability of death.[9] Thus, the early detection and prevention of AECOPD was a very important and difficult task in the clinical practice.

Legumain was a newly identified lysosomal cysteine,[10,11] which was expressed predominantly in CD68-positive macrophages.[12,13] Macrophages played a crucial role in the inflammatory cell penetration associated with COPD.[14,15] Accumulation and activation of macrophages promoted generation of cytokines,[13,16] which has been linked to pulmonary inflammatory response.[17–19] Research indicated that serum legumain was elevated in atherosclerosis and pancreatitis.[20–22]

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Further, serum legumain had also been shown to be raised in a few lung diseases consisting of lung cancer and pulmonary fibrosis.[13,23,24] Thus, the above evidence suggested that legumain was concerned in a variety of inflammatory diseases. Nevertheless, the relationships between serum legumain and AECOPD remained inconclusive.

The goal was to investigate the relationships of serum legumain with disease condition and various prognostic outcomes of AECOPD. AECOPD patients were recruited, and AECOPD-related adverse outcomes were followed up. Serum legumain level had been proven to have direct associations with the severity of AECOPD and its consequences.

Methods

Designing and Collecting Data

All participants were enrolled from the Affiliated Bozhou Hospital of Anhui Medical University between September 2022 and August 2023. Altogether, 202 individuals diagnosed with AECOPD were recruited. The criteria for recruitment were as follows: the hospitalized patients with a definitive diagnosis of COPD based on the GOLD criteria.[25,26] Participants were not accepted if they had other respiratory diseases, malignant tumors or severe cardiovascular and cerebrovascular diseases. All individuals agreed with and gave informed consent for participation in this research. Then, demographic and clinical dates were recorded. In addition, the prognoses of AECOPD patients were followed up in the next three years.

Specimen Collection

Fasting blood samples were taken from patients with AECOPD. The specimens were gathered and numbered. Blood samples were then centrifuged at low temperature (3600 rpm for 10 min) and placed in super cold refrigerator spare until detection.[27] Simultaneously, a respiratory questionnaire was completed under medical supervision during hospitalization. Questionnaires included the modified Medical Research Council (mMRC), COPD Assessment Test (CAT), and Clinical COPD Questionnaire (CCQ).[28–30]

Enzyme-Linked Immunosorbent Assay (ELISA)

The legumain ELISA kits were bought from CUSABIO (CSB-EL012903HU, https://www.cusabio.com/). Serum legumain was determined by following the earlier investigation.[31]

Statistical Analysis

The statistical analysis and chart generation were processed by GraphPad Prism 8 and SPSS 26.0 software. Continuous variables were repressed as mean or median. Categorical variables were repressed as frequencies. The continuous variables were compared through one-way ANOVA or non-parametric test. The categorical variables were compared with Fisher's exact test or Chi-squared test. The associations of serum legumain with clinical characteristics were explored by Spearman correlation analysis. The values of serum legumain concentration were log-transformed. The relationships of serum legumain with the severity scores were estimated via linear regression analysis and stratified analysis. The correlations of serum legumain with prognosis were evaluated using Chi-squared test and logistic regression analysis. The predictive efficiencies of serum legumain and general inflammatory cytokines for poor outcomes were explored by receiver operating characteristic (ROC) curve. *P* value less than 0.05 showed statistical significance.

Results

Demographic Information and Clinical Parameters

As shown in Table 1, serum legumain concentrations were classified as low (<2167.2 ng/mL), medium (2167.2~3258.3 ng/mL) and high (>3258.3 ng/mL). Based on the tertiles of serum legumain concentrations, the populations of AECOPD were split into three groups, and the numbers of AECOPD patients were 67, 68, and 67 in the low, middle, and high segments, respectively. In three groups, the average ages were 72.8, 74.7, and 75.6 years old. In general, males made up 76.1% of the low, 73.5% of the medium, and 77.6% of the high comparisons. Although there was no difference of age and sex in three subgroups, the recruited seasons were obviously different ($P<0.05$). Additionally, no difference in

Table 1 Demographic Characteristics of Participants at Baseline

Characteristics	Serum Legumain			*P*
	Low (<2167.2 ng/mL)	Medium (2167.2~3258.3 ng/mL)	High (>3258.3 ng/mL)	
N	67	68	67	
Age, year	72.8±8.86	74.7±8.66	75.6±8.88	0.174
Male, n (%)	51 (76.1)	50 (73.5)	52 (77.6)	0.877
Season, n (%)				**0.022**
Spring	28 (41.8)	27 (39.7)	20 (29.9)	
Summer	6 (9.0)	2 (2.9)	8 (11.9)	
Autumn	11 (16.4)	14 (20.6)	25 (37.3)	
Winter	22 (32.8)	25 (36.8)	14 (20.9)	
Smoking status, n (%)				0.269
Former	26 (38.8)	28 (41.2)	18 (26.9)	
Current	14 (20.9)	11 (16.2)	20 (29.9)	
None	27 (40.3)	29 (42.6)	29 (43.3)	
Comorbidities, n (%)				
Hypertension	33 (49.3)	34 (50.0)	33 (49.3)	1.000
Coronary heart disease	7 (10.4)	9 (13.2)	21 (31.3)	**0.005**
Diabetes mellitus	6 (6.0)	7 (10.3)	9 (13.4)	0.722
Cerebrovascular disease	7 (10.4)	9 (13.2)	16 (23.9)	0.085
Inhaled therapy, n (%)				
SABA	25 (37.3)	25 (36.8)	53 (79.1)	**<0.001**
SAMA	3 (4.5)	6 (8.8)	6 (9.0)	0.566
ICS	56 (83.6)	60 (88.2)	59 (88.1)	0.710
LABA	20 (29.9)	17 (25.0)	32 (47.8)	0.098
LAMA	15 (22.4)	10 (14.7)	14 (20.9)	0.377
LABA+LAMA	6 (9.0)	4 (5.9)	0	**0.031**
ICS+LABA	13 (19.4)	19 (27.9)	31 (46.3)	**0.003**
ICS+LABA+LAMA	10 (14.9)	13 (19.1)	13 (19.4)	0.308
White blood cell (10^9/L)	7.1±2.97	7.2±3.68	7.5±2.73	0.814
Neutrophil (10^9/L)	5.3±2.81	5.2±3.57	5.4±2.60	0.917
Lymphocyte (10^9/L)	1.1 (0.7, 1.5)	1.2 (0.9, 1.7)	1.2 (0.9, 1.6)	0.356
Monocyte (10^9/L)	0.5 (0.3, 0.7)	0.5 (0.4, 0.7)	0.6 (0.4, 0.9)	0.068
Eosinophil (10^9/L)	0.08 (0.01, 0.16)	0.11 (0.04, 0.20)	0.09 (0.02, 0.16)	0.273
Basophil (10^9/L)	0.02 (0.01, 0.04)	0.02 (0.01, 0.04)	0.02 (0.01, 0.04)	0.608
ALT (U/L)	16.5 (12.0, 23.3)	15.0 (12.0, 24.0)	16.0 (11.0, 28.0)	0.892
AST (U/L)	20.5 (17.0, 24.0)	21.0 (16.3, 25.0)	20.0 (16.0, 24.0)	0.482
Uric acid (μmol/L)	267.0 (227.0, 374.0)	305.5 (251.5, 364.8)	285.5 (243.5, 347.5)	0.238
Urea nitrogen (mmol/L)	5.8 (4.9, 6.8)	6.3 (4.7, 8.2)	5.3 (4.0, 7.7)	0.335
Creatinine (μmol/L)	64.0 (54.0, 78.0)	66.5 (53.0, 86.9)	60.0 (49.0, 78.0)	0.404
Creatine kinase (U/L)	56.5 (44.0, 93.5)	64.0 (42.0, 85.0)	64.5 (42.8, 99.0)	0.863
Creatine kinase isoenzyme (U/L)	14.0 (11.0, 18.0)	12.0 (9.0, 14.0)	12.5 (9.0, 18.3)	0.151
D-dimer (mg/L)	0.49 (0.27, 0.97)	0.52 (0.37, 1.13)	0.44 (0.30, 0.82)	0.193
C-reactive protein (mg/L)	30.3 (9.9, 110.5)	40.5 (6.0, 115.5)	87.8 (17.4, 154.6)	**<0.001**
Interleukin-6 (pg/mL)	10.0 (1.6, 19.0)	30.0 (10.3, 65.1)	51.0 (29.0, 84.3)	**0.033**

Note: Data in bold denote statistically significant results.

smoking status was discovered among three subgroups. Additionally, there was no difference of hypertension, and diabetes mellitus, cerebrovascular disease in three subgroups, the number of coronary heart disease was gradually increased in line with the elevated serum legumain. Furthermore, there was obvious differences in the pharmacological therapy of short-acting beta agonists (SABA), and inhaled corticosteroids (ICS), long-acting beta agonists (LABA)

combined with long-acting muscarinic antagonists (LAMA), ICS+LABA in three groups of AECOPD patients. Besides, that contents of C-reactive protein (CRP), interleukin-6 (IL-6) and D-dimer were consistently elevated in line with serum legumain levels (Table 1).

Serum Legumain Concentrations Predict Disease Severity in AECOPD Patients

As illustrated in Figure 1A, the levels of serum legumain were highest in ≥27 scores of CAT. Moreover, serum legumain level was elevated in 2~3 scores than ≤2 scores of mMRC (Figure 1B). Besides, according to CCQ score, serum legumain concentration was higher in ≥35 scores compared with the scores of ≤30 and 30~35 (Figure 1C). In addition, serum legumain level was further compared in AECOPD cases with different characteristics. As indicated in Table 2, serum legumain level was higher in patients with older age, enrolling in autumn, combining with coronary heart disease, diabetes mellitus, and cerebrovascular disease, as well as the usages of SABA, LABA, and ICS+LABA.

Associations of Serum Legumain with Clinical Characteristics in AECOPD Patients

Although there were no associations of serum legumain with white blood cells (WBC), neutrophils, lymphocytes, eosinophils and basophils, serum legumain were weakly and positively correlated with monocytes (r=0.161; *P*=0.022) (Figure 2). Additionally, we also evaluated the correlations of serum legumain with cardiac, renal, and hepatic function indicators. No obvious relationships of serum legumain with urea nitrogen, creatinine, aspartate aminotransferase (AST), creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and D-dimer were observed in AECOPD patients (Figure 2). However, serum legumain was positively related to IL-6 (r=0.497; *P*<0.001) and CRP (r=0.273; *P* <0.001) in AECOPD patients (Figure 2).

Correlations of Serum Legumain with Severity Scores in AECOPD Patients

In the univariate linear regression analysis, we found that every 1 unit increase in serum legumain in AECOPD patients, CAT score increased by 3.605, mMRC score increased by 0.558, and CCQ score increased by 8.541 (Table 3). To rule out any potential confounding factors, age, season, coronary heart disease, diabetes mellitus, cerebrovascular disease, the usage of SABA, LABA, and ICS+LABA were adjusted (Table 3). In the multivariate linear regression analysis, we still discovered that serum legumain had a positive correlation with the score of CAT (β=3.438; 95% CI: 0.334~6.541) and CCQ (β=9.109; 95% CI: 5.633~12.585) in AECOPD patients (Table 3). In addition, the relationships between serum legumain and severity scores were evulgated using stratified analysis. The results indicated that the confounding factors including age, smoking status, enrolled season, accompanied with diabetes mellitus can affect the associations between serum legumain and severity scores of AECOPD patients (Supplemental Table 1).

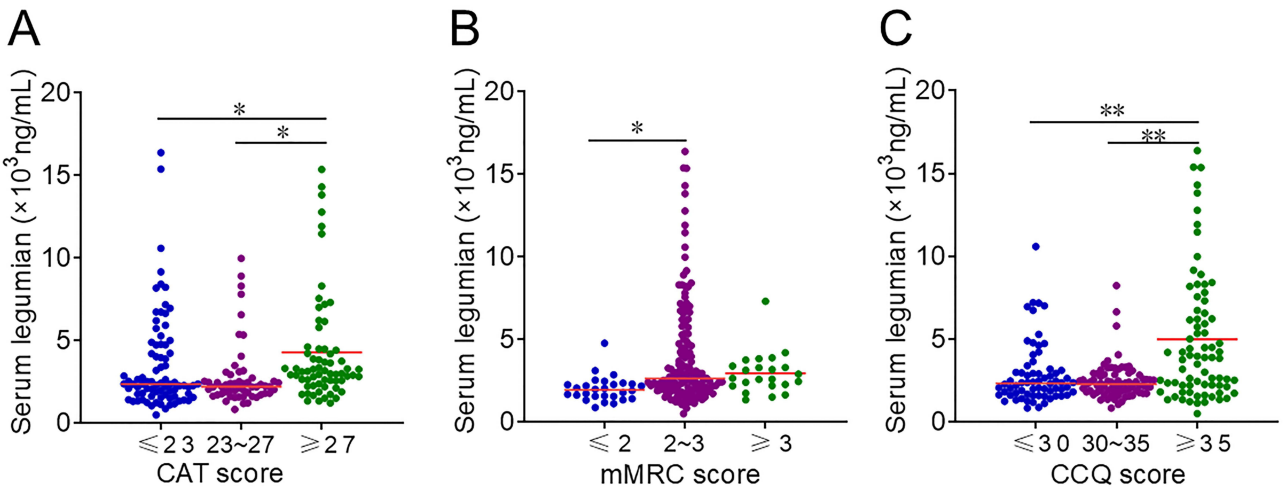

Figure 1 Serum legumain concentration was detected by through ELISA in AECOPD patients with different severity scores. (**A–C**) Serum legumain concentration was compared in AECOPD patients with different severity scores; (**A**) CAT score; (**B**) mMRC score; (**C**) CCQ score. * *P* < 0.05, ** *P*<0.01.

Table 2 The Level of Serum Legumain in COPD Patients

Variables	N	Legumain ($\times 10^3$ ng/mL)	t/Z/F	*P*
Age (Year)			−3.521	**<0.001**
≤74.0	106	2.3 (1.6, 3.3)		
>74.0	96	2.8 (2.2, 4.8)		
Gender			−0.201	0.841
Male	149	2.5 (1.9, 4.1)		
Female	53	2.5 (1.8, 4.4)		
Season			11.064	**0.011**
Spring	75	2.4 (1.7, 3.5)		
Summer	16	2.9 (1.8, 6.4)		
Autumn	50	3.3 (2.3, 6.0)		
Winter	61	2.4 (1.9, 3.1)		
Smoking status			2.559	0.080
Former	72	2.4 (2.0, 3.3)		
Current	45	3.0 (1.8, 5.8)		
None	85	2.5 (1.8, 4.5)		
Hypertension			0.131	0.896
Yes	100	2.6 (1.9, 4.0)		
No	102	2.4 (1.8, 4.2)		
Coronary heart disease			3.517	**0.001**
Yes	37	3.8 (2.4, 7.3)		
No	165	2.4 (1.8, 3.5)		
Diabetes mellitus			2.202	**0.029**
Yes	20	3.1 (2.3, 7.1)		
No	182	2.5 (1.9, 3.9)		
Cerebrovascular disease			2.617	**0.010**
Yes	32	3.2 (2.3, 7.2)		
No	170	2.4 (1.8, 3.8)		
SABA			5.604	**<0.001**
Yes	103	3.4 (2.2, 6.6)		
No	99	2.3 (1.7, 2.9)		
SAMA			1.074	0.284
Yes	15	3.0 (2.2, 6.2)		
No	187	2.5 (1.9, 4.0)		
ICS			0.818	0.414
Yes	175	2.5 (1.9, 4.2)		
No	27	2.5 (1.7, 3.6)		
LABA			3.081	**0.002**
Yes	69	3.0 (2.1, 6.1)		
No	133	2.4 (1.8, 3.4)		
LAMA			−0.465	0.643
Yes	39	2.6 (1.8, 4.2)		
No	163	2.5 (1.9, 4.1)		

(*Continued*)

Table 2 (Continued).

Variables	N	Legumain (×10^3 ng/mL)	t/Z/F	*P*
LABA+LAMA			−1.689	0.093
Yes	10	2.1 (1.6, 2.6)		
No	192	2.5 (1.9, 4.2)		
ICS+LABA			3.464	**0.001**
Yes	63	3.3 (2.2, 6.2)		
No	139	2.4 (1.8, 3.3)		
ICS+LABA+LAMA			−0.127	0.899
Yes	36	2.6 (1.8, 4.2)		
No	166	2.5 (1.9, 4.1)		

Note: Data in bold denote statistically significant results.

Associations of Serum Legumain with the Prognostic Outcomes in AECOPD Patients

As demonstrated in Table 4, with the increased serum legumain, the numbers of AECOPD patients with death, acute exacerbation in first year, and acute exacerbation in third year were elevated. Compared with the lower serum legumain group, the numbers of death, acute exacerbation in first and third years were gradually risen among AECOPD patients

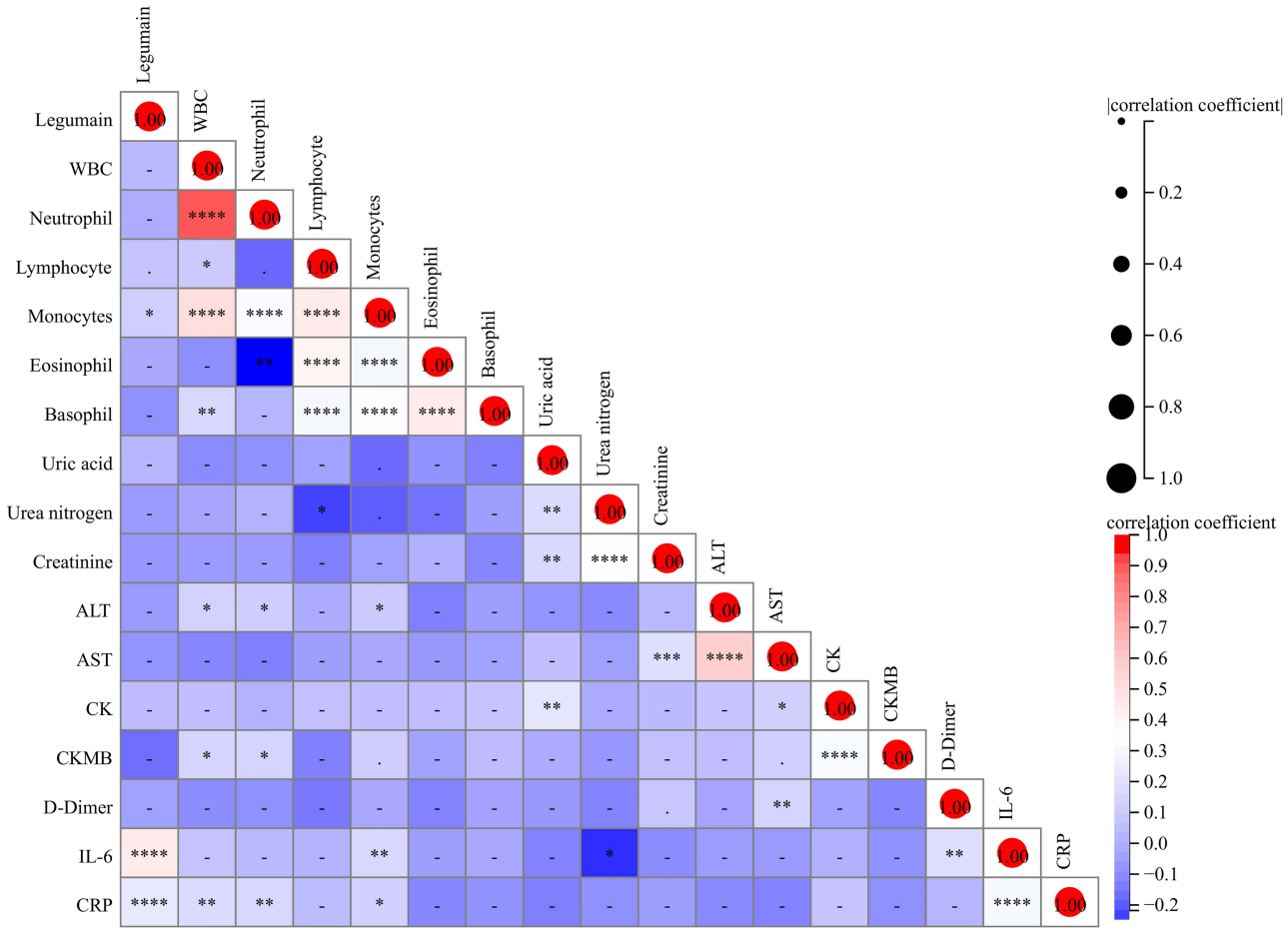

Figure 2 Correlations between serum legumain concentration and clinical characteristics were explored by Spearman correlation analysis in AECOPD patients. Different colors represented different correlation coefficients. Red color represented the positive association, and blue color represented the negative association. The darker the color, the stronger the association. * *P*<0.05, ** *P*<0.01, *** *P*<0.001, **** *P*<0.0001.

Table 3 Associations Between Serum Legumain and Severity Scores in AECOPD Patients

Models	Variables	Estimated Changes by Continues Serum Legumain	*P*
Unadjusted	N	202	
	CAT	**3.605 (0.871, 6.339)**	**0.010**
	mMRC	**0.558 (0.121, 0.994)**	**0.013**
	CCQ	**8.541 (5.569, 11.514)**	**<0.001**
Adjusted	CAT	**3.438 (0.334, 6.541)**	**0.030**
	mMRC	0.443 (−0.064, 0.950)	0.086
	CCQ	**9.109 (5.633, 12.585)**	**<0.001**

Notes: Adjusted for age, season, coronary heart disease, diabetes mellitus, cerebrovascular disease, SABA, LABA, and ICS+LABA. Data in bold denote statistically significant results.

Table 4 Associations Between Serum Legumain and Prognostic Outcomes in AECOPD Patients

Variables	Serum Legumain			*P*
	Low (<2167.2 ng/mL)	Medium (2167.2~3258.3 ng/mL)	High (>3258.3 ng/mL)	
N	67	68	67	
Death				
N, (%)	9 (13.4)	21 (30.9)	28 (41.8)	**0.001**
Unadjusted RR (95% CI)	Ref (1.0)	**2.891 (1.209, 6.916)**	**4.667 (1.983, 10.983)**	**0.006**
Adjusted RR (95% CI)	Ref (1.0)	**3.761 (1.150, 16.660)**	**3.915 (1.046, 14.658)**	**0.046**
Acute exacerbation in first year				
N, (%)	27 (40.3)	39 (57.4)	41 (61.2)	**0.036**
Unadjusted RR (95% CI)	Ref (1.0)	**1.992 (1.004, 3.952)**	**2.336 (1.169, 4.670)**	**0.015**
Adjusted RR (95% CI)	Ref (1.0)	1.905 (0.936, 3.878)	**2.331 (1.034, 5.254)**	**0.012**
Acute exacerbation in second year				
N, (%)	42 (40.1)	48 (70.6)	48 (71.6)	0.491
Unadjusted RR (95% CI)	Ref (1.0)	1.429 (0.696, 2.933)	1.504 (0.727, 3.109)	0.267
Adjusted RR (95% CI)	Ref (1.0)	1.583 (0.733, 3.422)	2.193 (0.875, 5.498)	0.080
Acute exacerbation in third year				
N, (%)	26 (39.4)	22 (32.8)	36 (54.5)	**0.036**
Unadjusted RR (95% CI)	Ref (1.0)	**2.696 (1.274, 5.707)**	**4.350 (1.901, 9.953)**	**0.001**
Adjusted RR (95% CI)	Ref (1.0)	**4.207 (1.825, 9.695)**	**5.514 (2.010, 15.132)**	**0.001**
Higher CAT score				
N, (%)	16 (23.9)	18 (26.5)	23 (34.3)	0.384
Unadjusted RR (95% CI)	Ref (1.0)	1.147 (0.527, 2.499)	1.666 (0.783, 3.544)	0.181
Adjusted RR (95% CI)	Ref (1.0)	1.186 (0.530, 2.652)	1.187 (0.493, 2.862)	0.582

Notes: Adjusted for age, season, coronary heart disease, diabetes mellitus, cerebrovascular disease, SABA, LABA, and ICS+LABA. Data in bold denote statistically significant results.
Abbreviation: RR, Relative risk.

(Table 4). Compared with AECOPD patients with lowest serum legumain, multivariate logistic regression analysis still observed that the highest serum legumain concentration on admission elevated the relative risks (RRs) of death (RR=3.915; 95% CI: 1.046~14.658), acute exacerbation in first year (RR=2.331; 95% CI: 1.034~5.254) and acute exacerbation in third year (RR=5.514; 95% CI: 2.010~15.132) within 3 years during hospitalization (Table 4). Kaplan–Meier survival curve indicated that the survival rate was lowest in AECOPD patients with highest serum legumain within

3 years (Supplemental Figure 1A). In order to explore the predictive efficiencies of serum legumain for poorer outcomes, ROC curve was carried out. The results suggested that the predictive efficiencies of serum legumain for the death, the numbers of acute exacerbation in first and third years were higher than those in IL-6 and CRP. However, the combination of serum legumain with the above inflammatory cytokines did not elevate the predictive powers for poor prognosis (Supplemental Figure 1B-D).

Discussion

This goal was to assess the associations of serum legumain levels with the severity and prognoses of AECOPD patients within 3 years. The following were the main findings: (1) Serum legumain concentration at admission was progressively upregulated in pace with the severity scores among AECOPD patients; (2) There were positive correlations of serum legumain with the severity scores in AECOPD patients; (3) Higher serum legumain concentration at admission elevated the probability of unfavorable prognosis in AECOPD subjects.

Legumain belonged to the C13 peptidase family.[10] Under normal physiological conditions, legumain was not expressed or low expression in human tissues.[22,32] Previous studies have shown that the pulmonary microenvironment in the lung can promote the progression of inflammatory response by inducing phenotypic activation of macrophages among AECOPD patients.[33,34] Legumain could modify the polarization of anti-inflammatory macrophages.[35,36] Past reports had revealed that serum legumain was elevated in inflammatory diseases such as acute pancreatitis, myocardial infarction, atherosclerosis, renal fibrosis, and hypertension.[22,37–39] Furthermore, an animal experiment discovered that pulmonary legumain was increased in mice model with pulmonary arterial hypertension.[24] In addition, legumain had also been shown to be involved in pulmonary fibrosis and lung cancer.[23,40] In fact, COPD was a chronically inflammatory disease. Consequently, we speculated that legumain might be implicated in the pathophysiological process of AECOPD. Subsequently, serum legumain level was tested. We discovered that serum legumain concentration was risen in tandem with the scores CAT, mMRC and CCQ of AECOPD patients. Moreover, serum legumain concentration was positively linked with severity scores. Stratified analysis indicated that age, smoking status, enrolled season, companied with diabetes mellitus affected the correlations of serum legumain with severity scores of AECOPD patients. The results highlighted a positive relationship between serum legumain and the severity of AECOPD. Inflammation was known to be one of the main mechanisms causing COPD. Spearman correlation analysis found that the level of serum legumain was significantly positively associated with inflammatory cytokines. Based on the above results, these findings manifested that serum legumain concentration can be used to evaluate the severity of AECOPD.

Several studies demonstrated that the frequency of exacerbation, severity, and CRP level existed an association with mortality of AECOPD.[41,42] Besides, a growing number of research had discovered the correlations between serum legumain and prognostic outcomes for a variety of diseases. A recent survey had shown that the higher expression of serum legumain was negatively connected with poor prognosis in patients with atherosclerosis.[43] An in vivo and in vitro experiment revealed that the rise of legumain in cardiac tissue predicted a high risk of death in myocardial infarction patients.[44] In addition, relevant studies found that the elevated levels of legumain were related to a higher mortality risk and short survival period in glioblastoma patients.[45,46] Thus, the relationships of serum legumain with the prognoses were estimated in AECOPD patients. We observed that the numbers of patients with death, acute exacerbations in the first and third years were gradually upregulated in pace with the elevated concentration of serum legumain among AECOPD patients. In addition, our results suggested that serum legumain level at admission was positively correlated with inflammatory cytokines of AECOPD patients. The previous studies revealed that activating macrophage can secrete legumain and legumain deficiency promoted proinflammatory cytokines production after myocardial infarction.[22] On the contrary, legumain inhibition reduced inflammatory reaction and macrophage activation.[47] In addition, other research found that legumain elevation in T cells repressed the immunosuppressive function and evoked inflammatory response.[39] So, the exact mechanism of the increased legumain-mediated poor prognosis of AECOPD patients was unclear. Moreover, the causal association between inflammatory response and legumain elevation cannot be demonstrated via the current cohort study. These findings confirmed the usefulness of serum legumain in predicting adverse prognoses for patients with AECOPD.

Although this study has improved our knowledge about the role of legumain in AECOPD. However, the current research included lots of limitations. First, this was a single-center and small sample study. The current results were needed to be verified by large-sample, multicenter trials. Second, the concentration of legumain was only measured in serum samples. The next stage would be to examine the expressions of legumain in the lung tissues and bronchoalveolar lavage fluid. Third, this study was only a clinical epidemiological study, the underlying mechanism of legumain upregulation had not been clarified in this research. Further animal and cellular studies were necessary to determine the mechanism of legumain elevation in COPD patients. Fourth, the severity score of CAT, CCQ, and mMRC were only used to evaluate the clinical symptoms and survival quality of AECOPD patients. The gold standard of severity was to detect pulmonary function among COPD patients. However, lung function could not be tested among AECOPD patients. Therefore, these scores could not fully represent the severity of AECOPD.

Conclusion

Based on this prospective cohort study, this research primarily illustrates the relationships of serum legumain at admission with the severity and poor prognosis among AECOPD patients. Our study showed that serum legumain is progressively upregulated in pace with the severity scores. Serum legumain concentration at admission shows the positive associations with the severity and poor prognosis among AECOPD patients. Based on the above findings, we think that legumain participates in the pathophysiology of AECOPD. Consequently, serum legumain detection may be beneficial in the evaluations and management of AECOPD patients in the clinical work.

Data Sharing Statement

The raw data used during the current research are available from the corresponding author on reasonable request.

Ethical Approval

The study was complied with the Declaration of Helsinki. The current study was supported by the Ethics Committee of the Affiliated Bozhou Hospital of Anhui Medical University (2021-10).

Consent to Participate

All research participants gave informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this study.

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