Journal of Inflammation Research Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Cross-Sectional and Longitudinal Associations of Serum LRG1 with Severity and Prognosis Among Adult Community-Acquired Pneumonia Patients

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Background: Leucine-rich α-2 glycoprotein 1 (LRG1) is associated with various inflammatory lung diseases. Nevertheless, the connection between LRG1 and adult community-acquired pneumonia (CAP) individuals was still not well understood. Through a prospective cohort study, the correlations of serum LRG1 with severity and prognosis were evaluated in CAP patients.

Methods: The study encompassed 327 patients who received the diagnosis of CAP. We collected fasting venous blood and clinical features. Serum LRG1 was detected by ELISA. CAP severity was assessed using various scoring systems. The prognostic outcomes were observed through follow-up visits.

Results: The level of serum LRG1 at admission was gradually increased with CAP severity scores. Serum LRG1 level shown positive associations with inflammatory indices, including C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6). Linear and logistic regression analyses suggested that serum LRG1 at admission was positively associated with severity scores and the risk of death in CAP patients. Serum LRG1 in combination with CAP severity scores significantly increased the predictive powers for severity and death compared with single serum LRG1 or severity scores.

Conclusion: The study revealed positive connections of serum LRG1 levels with severity and poor prognosis in CAP patients, suggesting LRG1 partakes into the physiological processes of CAP. Serum LRG1 may be regarded as a potential biomarker in predicting the severity and death among CAP patients.

Keywords: community-acquired pneumonia, LRG1, severity, outcomes, cohort study

Introduction

Community-acquired pneumonia (CAP) is a prevalently infectious disease that ranks as the fourth largest cause of mortality globally and the second highest cause of death in low-income nations. [1] CAP is a major contributor to mortality in both kids under five and older people.[2–4] Furthermore, it contributes to the high number of hospitalizations per year.[5] Despite the rapid advances in the treatment and detection of CAP, mortality remains high worldwide.[6,7] Therefore, we need early diagnosis and treatment of CAP to promote rational use of clinical drugs, reduce hospitalization time and poorly prognostic risks, and lower treatment costs.

Evaluating the severity and predicting severe CAP early are helpful for alleviating mortality risk but is fraught with complexity. The previous investigation has proposed that severity scores systems can assist in determining the severity

Received: 9 July 2024
Accepted: 28 October 2024
Published: 1 November 2024

and predict the risk of death in the clinical work.[8] However, CAP severity scoring systems need many clinical parameters and take very long time.[9] In addition, more and more investigations found that serum biomarkers may be able to assess the severity and prognosis of CAP in clinical practice, such as C-reactive protein (CRP), interleukin 6 (IL-6), and procalcitonin (PCT).[10,11] Although the single indicator is simple to obtain, these biomarkers have different limitations. For example, CRP has a low sensitivity for lung infections, while IL-6 has poor specificity.[12] Besides, a study found that IL-6 fails to predict mortality.[13] CRP and PCT have no clear advantage over CAP severity scores for predicting mortality.[14] Therefore, we need efficient biomarkers with greater sensitivity and specificity for evaluating the severity and poor prognosis among CAP patients.

Leucine-rich α-2 glycoprotein 1 (LRG1) is an essential member of the protein family containing leucine-rich repeats. It is recently discovered to mediate multiple processes, including inflammatory diseases, cardiovascular diseases, diabetes, tumors, and neurological diseases.[15] Serum LRG1 has been identified as a useful biomarker for monitoring disease in patients with psoriasis, lupus nephritis, rheumatoid arthritis and vasculitis.[16–19] Moreover, LRG1 levels are increased in patients with sepsis and severe colitis.[20] Additionally, there has been a rise in attention to the possible link between LRG1 and lung diseases. Research has demonstrated the upregulated LRG1 expressions in chronic obstructive pulmonary disease (COPD) and emphysema.[21] Besides, LRG1 is found to be implicated in the process of lung fibrosis.[22] Elevated level of LRG1 is reported in patients with non-small cell lung cancer (NSCLC), which correlates with the survival period after radiation treatment.[23,24] Several investigations have shown that LRG1 levels are elevated in respiratory disorders such as active tuberculosis, asthma, and severe acute respiratory syndrome (SARS).[25–27] Not only that, the expression of LRG1 is increased in various inflammatory diseases.[28] Meanwhile, CAP is a significantly inflammatory and contagiously respiratory disease.[29] However, up to now, there was no relative reports about the role of LRG1 in CAP. Yet, the association between LRG1 expression and CAP patients remained unclear.

Consequently, we hypothesized that LRG1 may have a crucial function in the pathophysiological progression of CAP. Furthermore, the role of LRG1 in CAP has not been thoroughly explored. The current experiment was the first study to evaluate the connections between serum LRG1 with severity and prognosis in CAP patients through a prospective study. Our results provided epidemiological evidence about the function of LRG1 in the process of CAP.

Materials and Methods

Subjects

The study was conducted at the Affiliated Bozhou Hospital of Anhui Medical University and the Second Affiliated Hospital of Anhui Medical University, Anhui Province, China. We obtained blood samples from CAP patients between November 2023 and May 2024. The inclusion criteria were: (1) CAP patients who corresponded to diagnosis and treatment of adults with CAP;[30] (2) participants who voluntarily joined this study and completed the follow-up research; and (3) patients who had not received any prior therapy or intervention. The exclusion standards encompassed: (1) individuals under 18 years old; (2) pregnant women; (3) those who had used antibiotics, antiviral medications, glucocorticoids, or other drugs within the past week; (4) CAP patients with co-existing autoimmune diseases, lung malignant tumors, COPD, various respiratory infections, asthma, or bronchiectasis, or other pulmonary diseases. The study obtained permission from the Ethics Committee of two hospitals. This research was in accordance with the Declaration of Helsinki. All participators offered informed consent.

Research Methodology and Data Acquisition

This investigation was a perspective cohort study. The sample size was calculated by PASS software. The results indicated that 250 samples could satisfy the need of research. Considering certain lost follow-up rate, the final sample size was more than 250. A total of 376 patients were recruited, among which 26 patients had incomplete information, 9 serum samples had hemolysis, and 14 patients dropped out. At last, 327 adult patients diagnosed with CAP were selected in the current research. Serum LRG1 was detected among all CAP patients. CAP patients were divided into three subgroups based on the tertiles of serum LRG1 content, T1 group (<7.61 μg/mL); T2 group (7.61–18.80 μg/mL); T3 group (>18.80 μg/mL). We also extracted biographical data and clinical features from the hospital's electronic healthcare

records, including comorbidities and indicators of routine blood, liver function, kidney function, myocardial function, inflammatory indices. CAP severity was assessed on admission using various scoring systems, including CURB-65, CRB-65, CURXO, SMART-COP, PSI, and APACHE II.[31,32] According to Diagnosis and Treatment of Adults with Community-acquired Pneumonia, CAP patients were classified into mild patients and severe patients by IDSA/ATS Criteria.[30] The relationships between serum LRG1 on admission and severity scores were assessed through a cross-sectional study. Then, the follow-up study was conducted and the prognostic outcomes were observed using a longitudinal study.

Enzyme-Linked Immunosorbent Assay (ELISA)

The peripheral blood samples were obtained before any intervention or therapy after admission and stored in an EDTA anticoagulant tube. The samples were allowed to stand in refrigerator at 4°C for 2 hours and then were centrifuged for 10 minutes at 3500 rpm and 4°C. After this process, we carefully packaged and stored the serum specimens at −80°C. We purchased commercial ELISA kits (CSB-E12962h) to detect the concentrations of serum LRG1. These kits were sourced from Cusabio (http://www.cusabio.cn/). Serum LRG1 detection was conducted in accordance with the protocols from the previous studies with minor modifications.[33,34] Serum samples were diluted by 10 times. The equivalent of standards, serum samples, and blank samples were added to the appropriate microtiter plate wells with specific antibody for LRG1 and horseradish peroxidase (HRP) conjugated goat-anti-mouse antibody. After the reaction completion, the absorbance values were read at 450 nm within 15 minutes. Then, the concentration was calculated based on the standard curves. The detection range of human LRG1 ELISA Kit was from 0.156 μg/mL to 40 μg/mL, and the sensitivity was 0.156 μg/mL. In addition, internal controls were used in the detection.

Statistical Analysis

Statistics was analyzed using SPSS 26.0. The normality was evaluated by Kolmogorov–Smirnov test. For normally distributed continuous variables, means and standard errors were shown. We represented non-normally distributed continuous variables using medians. Frequencies and percentages were shown with categorical variables. The *t*-test and ANOVA were used to compare the difference of continuous factors. In order to further compare the level of serum LRG1 in CAP patients with different severity, Bonferroni multiple comparison was conducted. Number of comparisons was from 2 to 5. The maximum number of comparisons was 5. Therefore, the new p-value thresholds should be less than 0.01 (0.05/5 = 0.01). The chi-square ($\chi 2$) test was used to analyze the categories variable. Spearman correlation coefficient was used to explore the relationships between serum LRG1 and inflammatory parameters in CAP patients. In order to assess the accuracy and reliability of regression models, variance inflation factor (VIF) was detected. Due to the values of VIF were less than 5, there was no obvious collinearity. The levels of serum LRG1 and CAP severity scores were continuous variables, the relationships between serum LRG1 level and CAP severity scores were examined by linear regression model. Moreover, statistical power was calculated by "1-β" and more than 80%. The prognostic outcomes were categorical variables. Then, we examined the correlations of serum LRG1 with prognostic outcomes by chi-square test and logistic regression model. Besides, binary logistical regression analysis and multinomial logistical regression analysis were used to analyze the relationships between serum LRG1 and CAP severity scores with or without adjustment for age, smoker, heart rate, respiratory rate, oxygen saturation, hypertension, white blood cell, neutrophil, lymphocyte, monocyte, ALT, AST, uric acid, urea nitrogen, creatinine, CK, CKMB, myoglobin, LDH, PCT, D-dimer, CRP, and IL-6. In addition, very few missing data or outliers were replaced with median or mean. Statistical significance for ordinal regression was assessed at a p-value of less than 0.05 (two-tailed) or a 95% confidence interval (CI) that does not include 1.

Results

Characteristics of the Populations

This study encompassed 327 patients diagnosed with CAP. The characteristics of the research population were compared and assessed. The baseline characteristics of the participants were shown in Table 1. We discovered that age, hypertension, blood

Table 1 Demographic Information and Clinical Characteristics

Characteristic	All Participators	Tertile of Serum LRG1			*P*
		T1 (<7.41 μg/mL)	T2 (7.41~18.64 μg/mL)	T3 (>18.64 μg/mL)	
N	327	109	109	109	
Age, years	59.5±1.01	55.7±1.74	58.3±1.82	64.6±1.56	**0.001**
Male, n (%)	179 (54.7)	54 (49.5)	61 (56.0)	64 (58.7)	0.377
Body mass index	22.0±0.24	21.8±0.37	22.0±0.39	22.1±0.50	0.819
Smoker, n (%)	59 (18.0)	24 (22.0)	20 (18.3)	15 (13.8)	0.309
Heart rate (beats per min)	89.8±0.97	89.5±1.51	89.5±1.93	90.6±1.62	0.627
Respiratory rate (breaths per min)	19.5±0.14	19.1±0.10	19.5±0.27	19.8±0.30	0.203
Oxygen saturation (%)	96.1±0.19	96.5±0.21	96.2±0.29	95.5±0.46	0.091
Temperature (°C)	36.7±0.04	36.7±0.06	36.7±0.06	36.8±0.07	0.456
Systolic pressure (mmHg)	125.3±1.14	123.5±2.00	125.5±1.97	126.7±1.94	0.608
Diastolic pressure (mmHg)	75.7±0.65	75.4±1.13	76.0±1.18	75.7±1.09	0.925
Hypertension, n (%)	89 (27.2)	23 (21.1)	26 (23.9)	40 (36.7)	**0.025**
Diabetes mellitus, n (%)	28 (8.6)	6 (5.5)	10 (9.2)	12 (11.0)	0.385
Cerebral infarction, n (%)	31 (9.5)	7 (6.4)	13 (11.9)	11 (10.1)	0.418
Coronary heart disease, n (%)	14 (4.3)	6 (5.5)	5 (4.6)	3 (2.8)	0.699
Bronchitis, n (%)	6 (1.8)	3 (2.8)	1 (0.9)	2 (1.8)	0.874
White blood cell (10^9/L)	7.9±0.24	7.8±0.34	7.7±0.42	8.1±0.47	0.734
Neutrophil (10^9/L)	6.6±0.49	5.8±0.33	6.4±0.93	7.5±1.09	0.331
Lymphocyte (10^9/L)	1.3±0.06	1.3±0.06	1.4±0.07	1.3±0.14	0.938
Monocyte (10^9/L)	0.48 (0.34, 0.75)	0.49 (0.36, 0.78)	0.50 (0.34, 0.69)	0.47 (0.32, 0.75)	0.569
Alanine aminotransferase (U/L)	20.0 (13.0, 35.0)	20.0 (12.0, 34.0)	19.0 (12.0, 32.0)	21.0 (13.0, 42.0)	0.543
Aspartate aminotransferase (U/L)	23.0 (17.0, 34.0)	22.0 (17.0, 30.0)	22.0 (17.0, 33.8)	26.0 (18.0, 39.0)	0.058
Uric acid (μmol/L)	284.3±7.18	260.9±8.45	290.7±11.76	301.3±15.79	0.084
Urea nitrogen (mmol/L)	6.5±0.42	5.2±0.23	5.5±0.29	8.7±1.16	**<0.001**
Creatinine (μmol/L)	72.3±3.50	63.1±2.36	69.1±3.53	84.6±9.49	**0.018**
Creatine kinase (U/L)	62.0 (39.0, 98.5)	63.0 (51.0, 85.0)	59.0 (32.0, 102.8)	61.5 (34.8, 110.8)	0.660
Creatine kinase isoenzyme (U/L)	12.0 (9.0, 17.0)	12.0 (9.0, 17.0)	12.5 (8.0, 16.0)	12.0 (8.8, 18.3)	0.691
Myoglobin (ng/mL)	32.3 (22.4, 74.0)	25.5 (16.9, 40.2)	31.0 (21.3, 53.0)	36.8 (29.8, 86.9)	0.301
Lactate dehydrogenase (U/L)	196.0 (162.0, 256.0)	188.0 (162.0, 231.0)	202.0 (163.0, 269.0)	202.0 (161.0, 270.0)	0.339
Procalcitonin (ng/L)	0.8±0.17	0.5±0.28	0.9±0.37	1.0±0.22	0.072
D-dimer (mg/L)	1.5±0.11	1.3±0.19	1.6±0.19	1.7±0.21	0.060
C-reactive protein (mg/L)	40.6 (15.2, 149.4)	29.9 (13.4, 73.7)	35.9 (12.1, 138.8)	136.3 (28.3, 210.2)	**0.043**
Interleukin-6 (pg/mL)	14.4 (4.4, 41.5)	9.1 (3.7, 32.4)	15.2 (3.7, 59.3)	18.9 (8.4, 72.0)	**0.040**

Notes: Bold values indicate statistical significance.

urea nitrogen, creatinine, CRP, and IL-6 exhibited a progressive increase in CAP patients with the increase of serum LRG1 (Table 1). Microbiological diagnosis was analyzed. Among all CAP patients, 102 (31.2%) cases exposed with Gram-positive coccus, 6 (1.8%) cases with Klebsiella pneumoniae, 10 (3.0%) cases with Pseudomonas aeruginosa, 4 (1.2%) cases with Legionella pneumophila, 44 (13.5%) cases with other atypical pathogens. Moreover, 5 (1.5%) subjects with Respiratory virus, 35 (10.7%) subjects with Enterobacteriaceae, 28 (8.6%) subjects with Fungi, and 93 (28.4%) with negative pathogenetic results.

Serum LRG1 Levels in CAP with Different Scoring Systems

CAP patients were categorized into three grades according to CRB-65 scores. The highest concentration of serum LRG1 was in grades ≥3 scores (Figure 1A). According to CURB-65 scores, CAP patients had higher serum LRG1 levels at grades of 3–5 and 2 than 0–1 (Figure 1B). Furthermore, serum LRG1 levels gradually increased with SMART-COP scores. The highest serum LRG1 concentration was found with 7–8 scores of SMART-COP in CAP patients (Figure 1C). Based on CURXO scores, serum LRG1 was substantially higher in severe patients than those in moderate patients (Figure 1D). Compared with II grades of PSI, V grades had higher serum LRG1 level in CAP patients. Similarly, serum LRG1 was higher in IV grades of PSI than I grade (Figure 1E).

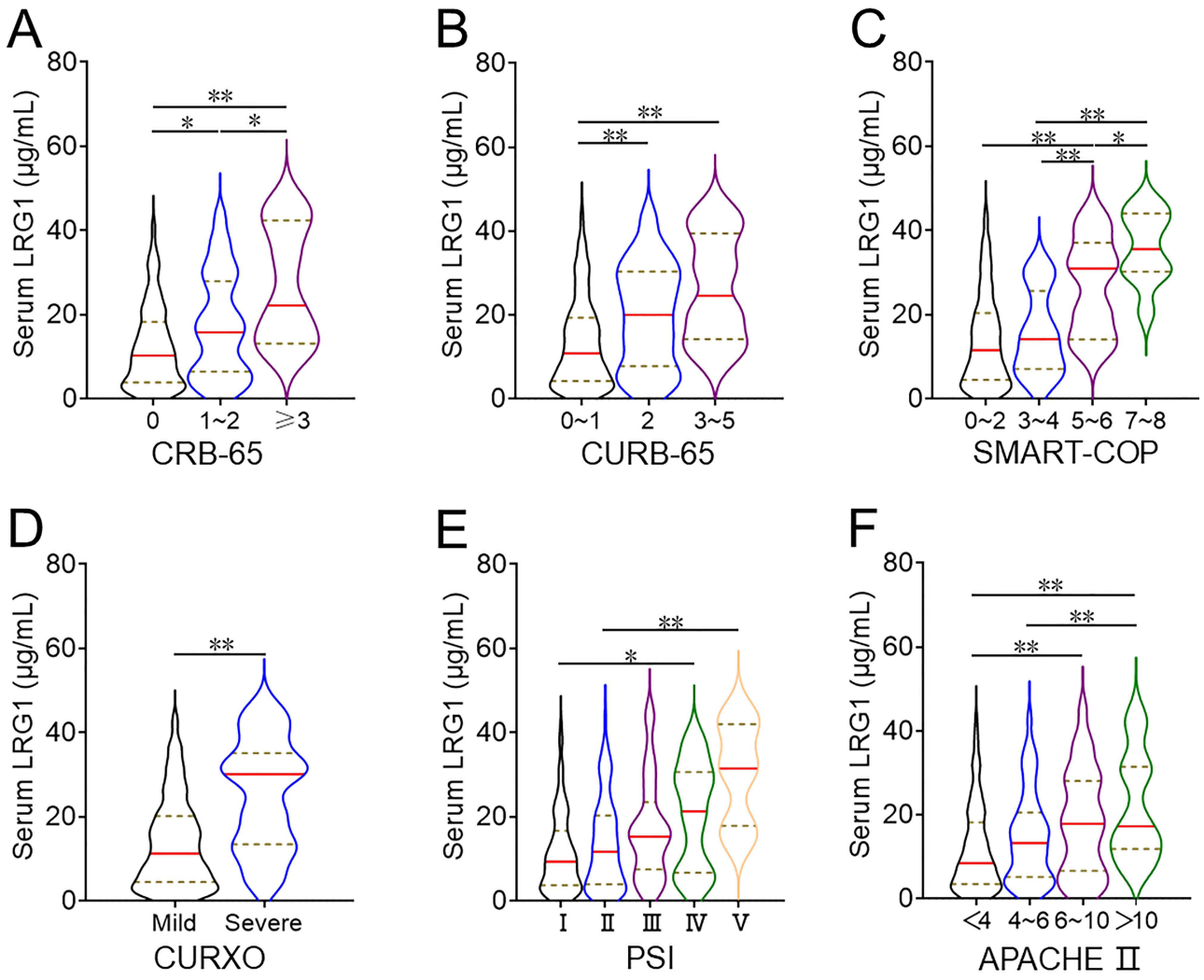

Figure 1 Serum LRG1 in CAP patients. (**A**–**F**) ELISA was used to analyze serum LRG1 levels with various severity scores. (**A**) CRB-65. (**B**) CURB-65. (**C**) SMART-COP. (**D**) CURXO. (**E**) PSI. (**F**) APACHE II. *P<0.05, **P<0.01.

Additionally, CAP patients with APACHE II scores above 6 also exhibited higher serum LRG1 levels than those with scores below 6 (Figure 1F).

Relationships Between Serum LRG1 Levels and Inflammatory Biomarkers

As depicted in Figure 2, serum LRG1 was weakly and positively associated with CRP (R = 0.345; $P < 0.001$), PCT (R = 0.229; $P < 0.001$), IL-6 (R = 0.208; $P = 0.001$), and D-dimer (R = 0.181; $P = 0.001$) in CAP patients.

Correlations Between Serum LRG1 and Severity Scores

In CAP patients, we used multivariate linear and logistic regression models to examine the correlations between serum LRG1 and CAP severity scores. Multivariate linear regression showed that the scores for PSI, CURXO (Severe), SMART-COP, and APACHE II went up by 0.789, 0.005, 0.079, and 0.152 with every 1 ng/mL increase in serum LRG1. Moreover, multivariate logistic regression found positive correlations between serum LRG1 level and scores for CURXO and APACHE II in CAP patients (Table 2).

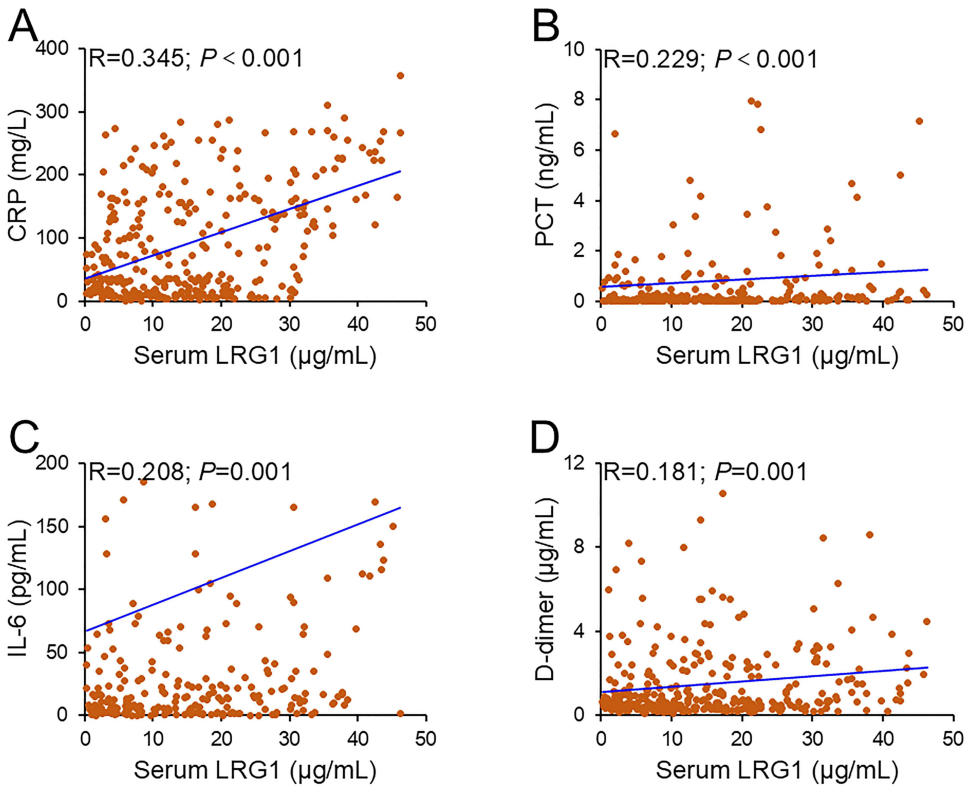

Figure 2 The correlation between serum LRG1 and inflammatory indices in CAP patients. The relationships between serum LRG1 and inflammatory indices were evaluated by Spearman Correlative analyses. (**A**) Serum LRG1 vs PCT. (**B**) Serum LRG1 vs CRP. (**C**) Serum LRG1 vs IL-6. (**D**) Serum LRG1 vs D-dimer.

Correlation Between Serum LRG1 and Prognosis

The predictive power of serum LRG1 for prognosis was observed in CAP patients during hospitalization. It mostly included mechanical ventilation, usage of vasoactive agents, ICU admission, mortality, and extended hospitalization. Among 327 CAP patients, there were 3 (2.8%) cases with mechanical ventilation in tertile 1, 7 (6.5%) cases with mechanical ventilation in tertile 2, 18 (16.5%) cases with mechanical ventilation in tertile 3, respectively. In the model 1, the relative risk (RR = 6.041; 95% CI: 1.692–21.566) of mechanical ventilation was obviously elevated in tertile 3 (Table 3). Furthermore, there was 1 case (0.9%) with vasopressors use in tertile 1, 3 cases (2.8%) in tertile 2, and 14 cases (12.8%) in tertile 3. The RR of vasopressors in the tertile 3 group was 14.299 (95% CI: 1.815–112.655). The RR of ICU admission (5.363; 95% CI: 1.744–16.493) in tertile 3 was significantly higher than that in tertile 1. In addition,

Table 2 Associations Between Serum LRG1 and CAP Severity Scores

Variables	Estimated Changes by Continues Serum LRG1	Estimated Changes (95% CI) by Tertiles of Serum LRG1			*P* trend
		T1 (<7.41 μg/mL)	T2 (7.41~18.64 μg/mL)	T3 (>18.64 μg/mL)	
N	327	109	109	109	
CURB-65	0.015 (−0.002, 0.033)	0 (Ref)	0.215 (−0.216, 0.365)	0.376 (−0.007, 0.133)	0.236
CRB-65	0.013 (−0.002, 0.028)	0 (Ref)	0.033 (−0.125, 0.235)	**0.062 (0.001, 0.124)**	0.211
PSI	**0.789 (0.174, 1.404)**	0 (Ref)	−5.999 (−8.365, 4.256)	1.728 (−0.721, 4.177)	0.136
CURXO (Severe)	**0.005 (0.007, 0.022)**	0 (Ref)	**0.021 (−0.002, 0.011)**	**0.038 (0.008, 0.068)**	**0.012**
SMART-COP	**0.079 (0.042, 0.115)**	0 (Ref)	**0.088 (0.012, 0.265)**	**0.197 (0.030, 0.364)**	**0.045**
APACHE II	**0.152 (0.035, 0.268)**	0 (Ref)	−1.063 (−3.254, 1.362)	0.385 (−0.020, 0.789)	0.328

Notes: Models were adjusted for age, smoker, heart rate, respiratory rate, oxygen saturation, hypertension, white blood cell, neutrophil, lymphocyte, monocyte, ALT, AST, uric acid, urea nitrogen, creatinine, CK, CKMB, myoglobin, LDH, PCT, D-dimer, CRP, and IL-6. Bold values indicate statistical significance.

Table 3 Associations Between Serum LRG1 and Prognostic Outcomes

Variables	Serum LRG1			*P*trend
	T1 (<7.41 μg/mL)	T2 (7.41~18.64 μg/mL)	T3 (>18.64 μg/mL)	
N	**109**	**109**	**109**	
Mechanical ventilation				
N, (%)	3 (2.8)	7 (6.4)	18 (16.5)	**0.001**
RR (Model 1)	Ref (1.0)	2.264 (0.561, 9.136)	**6.041 (1.692, 21.566)**	**0.029**
RR (Model 2)	Ref (1.0)	1.108 (0.158, 7.747)	2.072 (0.376, 11.428)	0.252
Usage of vasoactive agents				
N, (%)	1 (0.9)	3 (2.8)	14 (12.8)	**<0.001**
RR (Model 1)	Ref (1.0)	2.839 (0.287, 28.080)	**14.299 (1.815, 112.655)**	**0.038**
RR (Model 2)	Ref (1.0)	0.251 (0.002, 26.917)	8.864 (0.358, 219.353)	0.113
ICU admission				
N, (%)	4 (3.7)	6 (5.6)	22 (20.2)	**<0.001**
RR (Model 1)	Ref (1.0)	1.373 (0.368, 5.117)	**5.363 (1.744, 16.493)**	**0.033**
RR (Model 2)	Ref (1.0)	2.955 (0.182, 48.095)	5.937 (0.532, 66.276)	0.245
Death				
N, (%)	1 (0.9)	2 (1.8)	10 (9.2)	**0.006**
RR (Model 1)	Ref (1.0)	1.794 (0.157, 20.499)	**9.182 (1.130, 74.637)**	**0.024**
RR (Model 2)	Ref (1.0)	0.835 (0.026, 26.445)	**3.194 (1.216, 47.165)**	**0.045**
Longer hospital stays				
N, (%)	16 (14.7)	33 (30.3)	40 (36.7)	**0.001**
RR (Model 1)	Ref (1.0)	**2.700 (1.369, 5.323)**	**2.994 (1.524, 5.881)**	**0.008**
RR (Model 2)	Ref (1.0)	**0.712 (0.144, 3.528)**	**1.349 (0.302, 6.016)**	**0.674**

Notes: The length of hospital stay was divided into two groups: longer hospital stays, ≥13 days; lower hospital stays,<13 days. Model 1: Age and hypertension were adjusted. Model 2: Age, smoker, heart rate, respiratory rate, oxygen saturation, hypertension, white blood cell, neutrophil, lymphocyte, monocyte, ALT, AST, uric acid, urea nitrogen, creatinine, CK, CKMB, myoglobin, LDH, PCT, D-dimer, CRP, and IL-6 were adjusted. Bold values indicate statistical significance.
Abbreviation: RR, Relative risk.

multivariate logistic regression analyses demonstrated that the RRs of death in tertile 3 was obviously increased in model 1 (RR = 9.182; 95% CI: 1.130–74.637) and model 2 (RR = 3.194; 95% CI: 1.216–47.165) compared with tertile 1 (Table 3). Lastly, the relationship of serum LRG1 with extended hospitalization was explored in CAP patients. Multivariate logistic regression in model found that the RRs were upregulated in tertile 2 (RR = 2.700; 95% CI: 1.369–5.323) and tertile 3 (RR = 2.994; 95% CI: 1.524–5.881) than those in tertile 1 (Table 3).

The Predictive Powers for Severity and Death

We assessed the predictive abilities of serum LRG1 and clinical characteristics in the evaluation of severity by the receiver operating characteristic (ROC) curve area under the curve (AUC). As depicted in Figure 3A, these were the AUCs of severity: CURB-65, 0.882; CRB-65, 0.895; PSI, 0.799; SMART-COP, 0.979; APACHE II, 0.897; CURXO, 0.862; LRG1, 0.766; CRP, 0582; IL-6, 0.687; PCT, 0.746; LRG1+CURB-65, 0.877; LRG1+CRB-65, 0.899; LRG1+PSI, 0.828; LRG1+SMART-COP, 0.966; LRG1+APACHE II, 0.891; LRG1+CURXO, 0.854. The optimal threshold density, specificity and sensitivity of serum LRG1 in severe patients were 19.52 ng/mL, 72.20% and 75.63%, respectively. Furthermore, the AUCs of mortality were as follows: CURB-65, 0.861; CRB-65, 0.856; PSI, 0.842; SMART-COP, 0.947; APACHE II, 0.870; CURXO, 0.961; LRG1, 0.809; CRP, 0.582; IL-6, 0.692; PCT, 0.677; LRG1+CURB-65, 0.859; LRG1 +CRB-65, 0.869; LRG1+PSI, 0.845; LRG1+SMART-COP, 0.922; LRG1+APACHE II, 0.851; LRG1+CURXO, 0.890 (Figure 3B). The optimal cut-off value, specificity and sensitivity of serum LRG1 for death were 30.60 ng/mL, 87.90% and 71.53%, respectively.

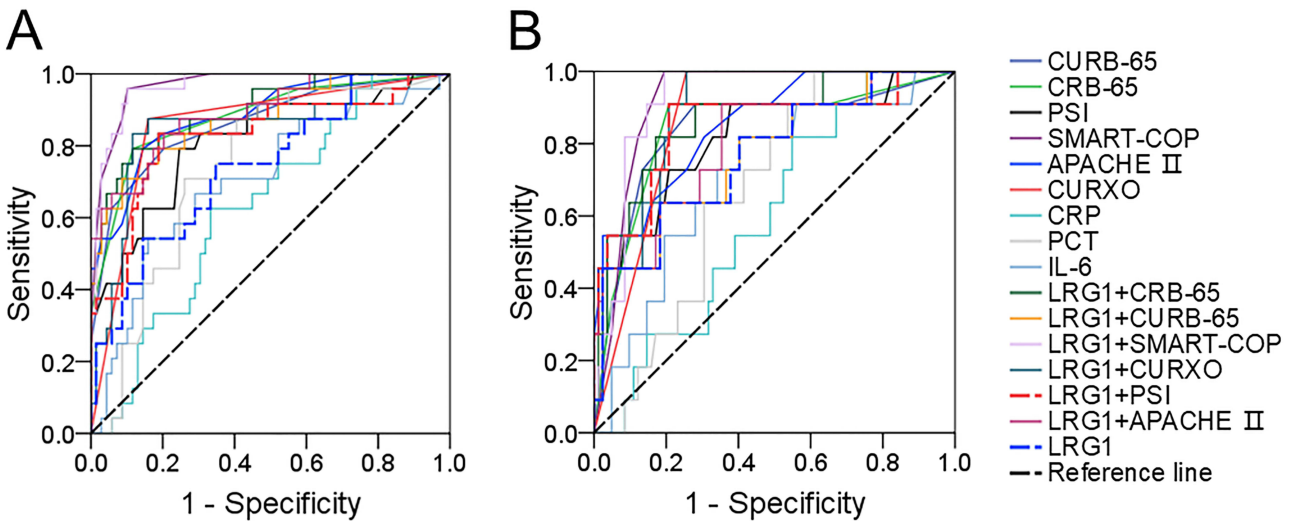

Figure 3 The powers to predict severity and mortality of cap patients. (**A** and **B**) The prognostic power for severity and mortality of CAP patients were assessed among serum LRG1 levels, inflammatory indicators, and severity scores. (**A**) The predictive capacity for severity. (**B**) The predictive ability for death.

Discussion

This study primarily assessed the correlations of serum LRG1 level with severity and prognosis among CAP patients. This study found that serum LRG1 at admission had positive correlations with CAP severity scores and unfavorable prognosis. The predictive capacities of serum LRG1 at admission for severity and mortality were similar with CAP severity scores, and obviously higher than inflammatory cytokines. Interestingly, the predicative capacities of serum LRG1 in combination with CAP severity scores for severity and death were elevated compared with single serum LRG1 or severity scores among CAP patients. These results indicated that LRG1 may involve in the initiation and development of CAP.

LRG1 is an essential member of the protein family containing leucine-rich repeats. LRG1 can be produced systemically and/or locally in response to many triggers, such as inflammation, infection, injury, autoimmune illness, and inflammation associated with tumors.[15] A previous study found that a large number of inflammatory factors are released under infections and inflammatory stimuli, which upregulates the protein expression of LRG1 in hepatocytes.[35] There is strong evidence that the expression of LRG1 is strongly raised in lung ailments, such as COPD, idiopathic pulmonary fibrosis, active tuberculosis, asthma, SARS, and sepsis.[21,23,25–28,36,37] Given that CAP is also an inflammatory and infectious disease, we hypothesized that LRG1 has implicated in the pathological processes of CAP. We found that serum LRG1 levels showed a steady increase as CAP severity scores elevation. In addition, serum LRG1 level was closely associated with several inflammatory indices in CAP patients. Furthermore, multivariate linear regression models have confirmed the positive correlations between serum LRG1 and CAP severity scores. Therefore, our results indicated positive correlations between serum LRG1 at admission and CAP severity scores.

Previous studies have found that LRG1 level is correlated with many prognostic outcomes across various diseases, such as dermatomyositis-related interstitial pneumonitis, cancer, diabetes, atherosclerosis, chronic inflammation, and immune senescence.[23,38–49] In patients with NSCLC, LRG1 expression is significantly elevated and strongly linked to survival time following radiotherapy.[23,24] A study found that LRG1 enhances the growth and spread of pancreatic ductal adenocarcinoma.[11] Besides, serum LRG1 level is strongly correlated with tumor size in colorectal cancer and glioblastoma.[45,50] Furthermore, elevated expression of LRG1 is related to the survival of interstitial pneumonia among individuals with dermatomyositis.[51] There is compelling evidence hinted that LRG1 can predict the risk of death among patients with diabetes.[42] Therefore, we explored the prognostic efficiencies of serum LRG1 content in CAP patients. Our findings indicated that serum LRG1 was positively correlated with death. Furthermore, the predictive value of serum LRG1 for severity and mortality were explored. These findings indicated that the predictive capacities of serum LRG1 at admission for assessing severity and mortality were similar with CAP severity scores, and obviously higher than

inflammatory biomarkers. Amusingly, serum LRG1 in combination with CAP severity scores significantly increased the predictive powers for severity and death compared with single serum LRG1 or severity scores among CAP patients. Thus, these results showed that serum LRG1 is positively correlated with poor outcomes in CAP patients.

It is now generally accepted that when lung inflammation occurs, most inflammatory cells release large amounts of pro-inflammatory factors, such as IL-1, IL-6, and tumor necrosis factor-α (TNF-α), which can mediate inflammation, and further promote inflammatory cells accumulation and infiltration in the lung tissue.[52,53] Under normal physiological conditions, LRG1 is primarily produced in hepatocytes and neutrophils, and it has a crucial function in maintaining vascular integrity and innate immune response.[54,55] Elevated LRG1 induces inflammatory reaction and immune cells accumulation at the inflammatory sites by promoting the extravasation and activation of neutrophils.[15] When the cells suffer inflammatory stimuli, LRG1 is secreted and released in response to inflammation by neutrophils, endothelium, epithelial, and fibroblasts.[56] LRG1 can enhance immune cells accumulation in the stimulated cell site and induce neutrophil extravasation and activation.[15] Moreover, TNF-α and other inflammatory mediators such as IL-6, IL-1β, and IL-22, also elevate the expression of LRG1.[57–59] Molecular experiments found that the mRNA expression of LRG1 ascends to the peak in 6 hours after IL-6 stimulation, which is 5 times higher than those in IL-1β and TNF-α. IL-6 and TNF-α have a synergistic effect on LRG1 production.[35] When inflammation occurs, concentrations of IL-6 peaks at 2 hours and rapidly decreased to one-third of its peak at 6 hours, falling to undetectable levels within approximately 24 hours in most patients.[60,61] Maybe, this was the reason for the weak correlation between serum LRG1 and IL-6. Previous studies from our laboratory found that inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, are elevated in CAP patients.[62,63] In addition, this research indicated that serum LRG1 was slightly and positively related to several inflammatory cytokines. Therefore, we speculate that inflammatory stimulation promotes the production and secretion of LRG1 in CAP, indicating that LRG1 partakes into the pathogenesis of CAP.

While this work enhanced our comprehension of the function of LRG1 in CAP, it did have certain constraints. First, the total amount of the sample was modest. To validate these findings, it is imperative to conduct subsequent research with more samples from multicenter. Second, only serum LRG1 was tested in CAP patients. Nonetheless, the contents of LRG1 in pulmonary tissue and bronchoalveolar lavage fluid remain unclear. Third, the study did not clarify the mechanism for the increase of serum LRG1 in CAP patients. Animal and cellular experiments are required to discover its biochemical mechanisms. Our research team intends to carry out these experiments as the next phase of our study. Fourth, this study was only a clinical epidemiological study. This study merely indicated that serum LRG level was positively correlated with severity and poor prognosis in CAP patients. However, the exact role of LRG1 was obscure in the process of pneumonia. The effects of pulmonary LRG1 knockdown or inhibition on the progression of CAP are needed to explore in animal experiments. Only when all issues have been addressed, the results can reveal whether serum LRG1 level can be used as a biomarker for the diagnosis and prognosis in CAP patients. Fifth, serum LRG1 is not the only CAP indicator. Serum LRG1 level at admission can assess the severity of the disease and the poor prognosis. However, serum LRG1 cannot accurately differentiate CAP from other inflammatory diseases. Finally, it is unclear whether LRG1 can be used as a therapeutic target for CAP. Perhaps conducting additional tests both in vitro and in vivo could provide a definitive answer to this question in the future.

Conclusion

Through this prospective cohort research, we explored the correlations between serum LRG1 at admission with severity and prognosis among CAP patients. Our study showed that serum LRG1 is consistently raised with the elevated severity scores. Serum LRG1 level at admission shows strongly positive correlations with severity and death among CAP patients. Based on the current findings, these results prompting that LRG1 may involve in the pathophysiologic progression of CAP. Therefore, serum LRG1 may be regarded as a potential biomarker in predicting severity and death among CAP patients.

Data Sharing Statement

The raw data used to draw the results in this article is available upon request from the corresponding authors.

Ethics Statement

The ethical boards of the Affiliated Bozhou Hospital and the Second Affiliated Hospital of Anhui Medical University granted approval for human subject research. Participants gave written consent to participate in this investigation. These individuals gave informed consent for the distribution of potentially identifying photos or data in this article.

Acknowledgments

We sincerely thank every patient and family member who took part in this study. We also extend our gratitude to the personnel of this study.

Funding

This study was supported by National Natural Science Foundation of China (82100078), Anhui Provincial Clinical Research Transformation Project (202204295107020056), Research Funds of Center for Big Data and Population Health of IHM (JKS2023010), Anhui Province Scientific Research of Health Commission (AHWJ2023A20189), and Bozhou Scientific Research of Health Commission (BZWJ2023a0002, BZWJ2022b008).

Disclosure

The authors report no conflicts of interest in this work.

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