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Short communication

Clinical relevance of serum Krebs von den Lungen-6 levels in patients with coronavirus disease 2019

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ABSTRACT

The clinical relevance of Krebs von den Lungen-6 (KL-6) levels in patients with coronavirus disease 2019 (COVID-19) is unclear. This study aimed to evaluate the correlation between KL-6 levels, laboratory parameters, and clinical outcomes. We enrolled 364 patients with confirmed COVID-19 who were hospitalized within 1 week of symptom onset. Their serum KL-6 level was measured on admission. Demographic data, symptoms, comorbidities, and laboratory parameters were recorded at the time of admission. Days to nucleic acid conversion and days of hospitalization were defined as clinical outcomes for evaluating the clinical relevance of serum KL-6 levels in COVID-19. Patients with elevated KL-6 levels were significantly older; had more reported instances of fever, cough, fatigue, and wheezing; and a longer hospital stays than those with normal KL-6 levels; the difference was statistically significant ($p < 0.001$). Furthermore, KL-6 levels was associated with the days of hospitalization and various laboratory parameters that influence the severity and prognosis of COVID-19. Elevated KL-6 levels have also been shown to be an independent risk factor for prolonged hospitalization. Our data suggest that serum KL-6 levels on admission can serve as an indicator for assessing the clinical outcomes of COVID-19.

1. Introduction

Currently, the total number of patients with coronavirus disease 2019 (COVID-19) worldwide has surpassed 40 million, with more than one million deaths have been reported. The pandemic has caused incalculable damage to the world, and its impact is expected to continue. COVID-19 induces lung damage, mainly in alveolar cells, primarily by stimulating the production of proinflammatory factors and inducing oxidative stress [1]. Krebs von den Lungen-6 (KL-6) is a high-molecular-weight glycoprotein produced primarily by damaged or regenerating alveolar type II cells [2]. It is elevated in the serum of patients with interstitial lung diseases (ILDs), such as idiopathic pulmonary fibrosis and allergic pneumonia [2]. KL-6 can be used to evaluate prognosis in patients with ILDs and predict their response to anti-fibrotic therapies [3]. It is also used as a biomarker for evaluating prognosis of acute respiratory distress syndrome (ARDS) [4]. In a previous study, the serum KL-6 level was significantly higher in ILD patients than in those without ILD patients or healthy subjects and was positively correlated with computerized tomography scores [5]. In another study, among patients with ARDS, plasma KL-6 levels patients were higher in non-survivors than in survivors [4], and were the highest in patients with ARDS complicated with DIC [6]. Patients with critical ill COVID-19 often progress to ARDS and coagulation disorders; thus, it is possible that KL-6 may also play a role in patients with critical COVID-19. In general, KL-6 levels are the highest in patients with ILD, followed by patients with ARDS and the lowest in patients with COVID-19 [7]. However, these three diseases are not mutually exclusive and may overlap. Miriana et al. reported that elevated serum KL-6 levels in patients with severe COVID-19 could be useful in evaluating COVID-19 prognosis [8]. Xue et al. further suggested that KL-6 may be useful as an indicator of COVID-19 progression, correlating with the degree of lung injury, inflammation, and pulmonary ventilation [9]. However, the sample sizes of these

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studies [8,9] were small, and the studies predominantly included severe and critically ill patients, while most real-world COVID-19 cases are mild to moderate. The clinical relevance of serum KL-6 levels in patients with different severity of COVID-19 has not been investigated.

In this study, we investigated the clinical relevance of KL-6 levels in COVID-19 patients during hospitalization to provide clinical-based evidence on whether KL-6 should be considered a critical parameter applicable to clinical management.

2. Materials and methods

COVID-19 patients hospitalized at Wuhan Central Hospital between February 10 and March 26, 2020, were included in this study. They were considered to have suspected COVID-19 or confirmed COVID-19 based on etiological or serological evidence diagnosis according to the Guidelines of the Diagnosis and Treatment of New Coronavirus Pneumonia (version 7) published by the National Health Commission of China [10]. Patients were classified as having mild, moderate, or severe/critical COVID-19 according to the above guidelines [10]. All patients were hospitalized within 1 week of symptom onset, and tests for laboratory parameters (including hematological, biochemical, coagulation, inflammatory, and immunological tests) were performed on admission. The remaining serum was stored and served as a sample for KL-6 measurements. Serum KL-6 levels were estimated using the KL-6 reagent according to the manufacturer's instructions (SEKISUI Technology Co., Ltd.). Elevated KL-6 levels were defined using a cutoff value of 500 U/mL. Patients were discharged when they met all the following criteria [10]: (i) no fever for at least 3 days, (ii) significant improvement on chest computed tomography and respiratory symptoms, and (iii) negative viral RNA from two nasopharyngeal swabs obtained at least 24 h apart. In patients, nucleic acid conversion was confirmed by three negative results in a row; the first time point of the negative test result was defined as the time point of nucleic acid conversion. Time to nucleic acid conversion and the days of hospitalization were the primary clinical outcomes. This study was approved by the Ethics Committee of Wuhan Central Hospital (Research Ethics No. 1, 2020), which waived the requirement for informed consent considering the infectivity of COVID-19.

2.1. Statistical analysis

Normally distributed continuous data are expressed as means with standard deviations. Non-normally distributed continuous data are expressed as medians with quartile intervals. The χ^2 test or Fisher's exact probability test was used to compare qualitative data. Independent sample comparisons between two sets of nonparametric data were made using the Mann-Whitney U test and comparisons between multiple groups were made using the Kruskal-Wallis H test. Spearman correlation or Pearson correlation analysis was used to investigate the relationships between variables. Receiver operating characteristic (ROC) curves were constructed to determine the effectiveness of KL-6 in predicting clinical outcomes. Because there were very few critically ill patients in our sample, we classified severe and critical patients into one category for statistical purposes. Statistical significance was set at $p < 0.05$.

3. Results and discussion

A total of 364 patients were included in the final analysis. In total, 54 patients had elevated KL-6 levels and 310 patients had normal KL-6 levels, and their median age of 64.5 and 58 years, respectively. After two or three nucleic acid tests, 221 patients tested positive for nucleic acid and 143 patients tested negative for nucleic acid, but they tested positive on the specific immunoglobulin (Ig) A, IgM or IgG tests. The median KL-6 level was 259.0 U/mL (390.5–183.2U/mL). Patients with elevated KL-6 levels were significantly older than those with normal KL-6 levels ($p < 0.001$). Patients with elevated KL-6 levels also had a significantly higher degree of fever, cough, fatigue, and wheezing than those with normal KL-6 ($p < 0.001$) (Table 1). In addition, Patients with severe/critical COVID-19 had higher KL-6 levels compared to patients with mild and moderate COVID-19 ($p = 0.018$) (Supplement Table).

In terms of clinical outcomes, patients with elevated KL-6 levels had a significantly longer hospital stay than patients with normal KL-6 levels ($p < 0.001$). When comparing laboratory parameters, we found that patients with elevated KL-6 levels had significantly higher percentages of neutrophils ($p < 0.001$) and globulin ($p = 0.003$) and higher levels of alanine aminotransferase (ALT) ($p = 0.034$), aspartate aminotransferase (AST) ($p = 0.015$), glucose ($p = 0.009$), gamma-glutamyl transpeptidase ($p = 0.014$), hydroxybutyrate dehydrogenase ($p < 0.001$), lactate dehydrogenase (LDH) ($p < 0.001$), D-dimer ($p < 0.001$), C-reactive protein (CRP) ($p = 0.002$), procalcitonin (PCT) ($p = 0.002$), IgM ($p < 0.001$), IgG ($p < 0.001$), and IgA ($p < 0.001$) than those with normal KL-6 levels. These patients also had a significantly lower lymphocyte percentage ($p < 0.001$), albumin levels ($p = 0.001$), blood phosphorus levels ($p = 0.007$), and activated partial thromboplastin time ($p = 0.015$) than those with normal KL-6 levels. (Table 2).

Univariate analysis indicated that there was a strong correlation between days of hospitalization and laboratory parameters; KL-6 levels ($r = 0.410$), neutrophils ($r = 0.459$), LDH levels ($r = 0.467$), PCT levels ($r = 0.393$), CRP levels ($r = 0.553$), D-dimer levels ($r = 0.390$), and prothrombin time (PT) ($r = 0.269$) were all positively associated with days of hospitalization ($p < 0.001$). In contrast, eosinophil percentage ($r = -0.496$), lymphocyte counts ($r = -0.496$), and hemoglobin levels ($r = -0.221$) were negatively associated with days of hospitalization ($p < 0.001$). Multiple linear regression analysis adjusted for age, sex, smoking history, disease severity, symptoms, and comorbidities suggested that KL-6 was an independent risk factor for longer hospitalization (Table 3).

Our results revealed a correlation between KL-6 levels and laboratory parameters, which suggested that KL-6 levels were negatively

Table 1
Demographic and clinical characteristics of COVID-19 patients stratifying with a cut-off of KL-6 of 500 U/ml.

	Overall N = 364	KL-6 ≥ 500 (U/ml) N = 54	KL-6 < 500 (U/ml) N = 310	*p*-Value
Demographic				
Age	59.00 (46.00; 69.00)	64.50 (57.00; 70.00)	58.00 (43.00; 68.00)	<0.001
Male	155 (42.58)	26 (48.15)	129 (41.61)	0.370
Smoker	32 (8.79)	4 (7.41)	28 (9.03)	0.691
Severity				
Severe/critical	29 (7.97)	6 (11.11)	23 (7.41)	0.668
Moderate	298 (81.87)	43 (79.63)	255 (82.26)	
Mild	37(10.16)	5 (9.26)	32 (10.32)	
HR chest computed tomography	349(95.88)	53 (98.15)	296 (84.81)	0.708
Symptoms				
Fever	216 (59.34)	32 (59.26)	184 (59.34)	**<0.001**
Cough	196 (53.84)	37 (68.52)	159 (51.29)	
Fatigue	166 (45.60)	31 (57.41)	135 (43.54)	
Dyspnea	108 (29.67)	28 (51.85)	80 (25.81)	
Diarrhea	30 (8.24)	15 (27.78)	15 (4.84)	
Sore throat	17 (4.67)	6 (11.11)	9 (2.90)	
Muscle soreness	6 (1.64)	2 (3.73)	4 (1.29)	
Comorbidity				
Hypertension	131 (35.99)	24 (44.44)	107 (34.52)	0.808
Diabetes	60 (16.48)	10 (18.52)	50 (16.13)	
Heart related disease	53 (14.56)	8 (14.81)	45 (14.51)	
Hyperlipidemia	14 (3.85)	2 (3.70)	12 (3.87)	
Malignancy	34(9.34)	5 (9.26)	29 (9.35)	
Chronic gastritis	14(3.85)	2 (3.70)	12 (3.87)	
Chronic Obstructive Pulmonary Disease	17(4.67)	3 (5.56)	14 (4.56)	

Table 2
Clinical outcomes and laboratory parameters of COVID-19 patients stratifying with a cut-off of KL-6 of 500 U/ml.

	Overall N = 364	KL-6 ≥ 500 (U/ml) N = 54	KL-6 < 500 (U/ml) N = 310	*p*-Value
Clinical outcomes				
Days of hospitalization	22.00 (13.00–32.00)	31.50 (24.00–44.00)	20.00 (12.00–29.00)	**<0.001**
Days of nucleic acid conversion	25.00 (14.50–36.50)	26.00 (16.00–39.00)	25.00 (12.00–36.00)	0.266
Hematological parameters				
White blood cell counts	4.98 (2.24–7.07)	5.00 (2.75–7.59)	4.98 (2.13–7.00)	0.939
Red blood cell counts	4.25 (3.87–4.60)	4.18 (3.78–4.43)	4.26 (3.91–4.61)	0.234
Neutrophil (%)	63.40 (55.30–73.80)	70.80 (60.23–80.08)	62.30 (54.50–72.05)	**<0.001**
Lymphocyte (%)	26.50 (17.40–33.60)	20.60 (11.98–26.33)	28.00 (18.55–33.95)	**<0.001**
Eosinophil (%)	1.30 (0.30–2.30)	1.00 (0.20–1.83)	1.40 (0.40–2.40)	0.081
Basophil (%)	0.30 (0.20–0.50)	0.40 (0.20–0.60)	0.30 (0.20–0.50)	0.730
Monocytes (%)	6.90 (5.70–8.80)	6.95 (5.40–8.55)	6.90 (5.70–8.85)	0.786
Platelets	209.00 (165.00–257.00)	208.00 (153.00–241.00)	209.00 (167.00–259.00)	0.307
Hemoglobin	127.00 (117.00–138.00)	127.50 (117.00–136.00)	127.00 (117.00–138.00)	0.736
Biochemical parameters				
Albumin	38.90 (35.40–43.00)	37.05 (33.33–40.10)	39.50 (35.70–43.35)	**0.001**
Globulin	26.80 (24.00–30.50)	29.15 (25.50–33.73)	26.70 (23.90–30.00)	**0.003**
Alanine aminotransferase	19.60 (13.10–36.10)	28.65 (16.00–45.50)	19.10 (12.95–34.50)	**0.034**
Aspartate aminotransferase	26.80 (24.00–30.50)	22.80 (17.75–33.55)	18.50 (14.90–26.40)	**0.015**
Creatine kinase	61.00 (40.25–92.00)	56.00 (36.00–93.00)	62.00 (41.00–92.00)	0.451
Creatinine	63.90 (49.90–80.60)	65.85 (49.50–80.35)	63.20 (49.95–80.75)	0.993
Total bilirubin	10.30 (7.50–14.40)	10.55 (7.28–15.68)	10.20 (7.55–14.20)	0.700
Direct bilirubin	3.20 (1.70–4.60)	3.65 (1.88–5.63)	3.20 (1.70–4.60)	0.266
Indirect bilirubin	7.20 (5.40–9.90)	7.40 (5.43–10.48)	7.10 (5.40–9.90)	0.900
Glucose	5.08 (4.59–6.28)	5.60 (4.85–7.01)	5.03 (4.54–6.08)	**0.009**
Gamma-glutamyl transpeptidase	21.40 (14.20–38.20)	26.40 (19.08–48.43)	20.00 (13.85–37.95)	**0.014**
Hydroxybutyrate dehydrogenase	132.00 (111.00–168.20)	175.00 (141.00–231.00)	128.00 (108.00–154.50)	**<0.001**
Lactate dehydrogenase	165.50 (140.00–213.50)	219.00 (182.00–279.00)	161.00 (138.00–200.00)	**<0.001**
Total protein	66.60 (61.70–71.10)	66.50 (60.50–72.80)	66.60 (62.10–71.05)	0.727
Chloride	104.50 (102.45–106.30)	103.80 (99.73–106.03)	104.50 (102.60–106.30)	0.060
Potassium	4.21 (3.91–4.47)	4.12 (3.70–4.44)	4.22 (3.93–4.47)	0.087
Sodium	140.30 (138.30–142.33)	140.90 (138.40–142.65)	140.20 (138.30–142.28)	0.468
Phosphate	1.09 (0.94–1.21)	1.00 (0.88–1.14)	1.11 (0.95–1.23)	**0.007**
Coagulation parameters				
Prothrombin activity	105.00 (90.00–118.80)	99.00 (80.08–115.80)	105.00 (91.70–118.80)	0.066
Prothrombin time	11.50 (11.00–12.00)	11.70 (11.10–12.38)	11.40 (10.90–12.00)	0.074
Activated partial thromboplastin time	27.90 (25.30–31.10)	26.85 (22.63–30.73)	27.90 (25.80–31.10)	**0.015**
Prothrombin time ratio	0.97 (0.93–1.03)	0.99 (0.96–1.05)	0.97 (0.93–1.03)	0.051
Thrombin time	16.40 (15.70–17.15)	16.50 (15.70–17.10)	16.40 (15.70–17.20)	0.491
D-dimer	0.62 (0.24–1.55)	1.75 (0.75–8.84)	0.53 (0.23–1.32)	**<0.001**
Inflammatory parameters				
C-reactive protein	0.36 (0.09–2.45)	1.27 (0.18–3.90)	0.26 (0.08–1.99)	**0.002**
Procalcitonin	0.05 (0.04–0.07)	0.05 (0.04–0.09)	0.04 (0.04–0.06)	**0.002**
Immunological parameters				
$CD4^+$T lymphocyte % (N = 180)	43.28 (36.30–48.27)	36.71 (29.76–52.64)	43.70 (37.40–48.16)	0.128
$CD8^+$T lymphocyte % (N = 180)	24.69 (19.70–30.76)	24.41 (19.66–30.54)	25.26 (19.78–30.84)	0.740
$CD4^+$T lymphocyte/$CD8^+$T lymphocyte ratio(N = 180)	1.69 (1.25–2.35)	1.67 (1.18–2.36)	1.69 (1.29–2.36)	0.460
Immunoglobulin M	18.06 (5.77–46.06)	27.65 (15.60–69.54)	15.81 (5.22–40.26)	**0.004**
Immunoglobulin G	62.27 (20.49–99.77)	99.27 (73.27–118.95)	55.54 (14.61–89.63)	**<0.001**
Immunoglobulin A	9.64 (3.23–25.32)	25.29 (11.15–47.90)	7.83 (2.71–21.45)	**<0.001**

correlated with eosinophils ($r = -0.226$), lymphocytes ($r = -0.359$), albumin levels ($r = -0.364$), blood chloride ($r = -0.136$), blood sodium ($r = -0.120$), and $CD4^+$T lymphocytes ($r = -0.405$). We also found that KL-6 levels were positively correlated with neutrophils ($r = 0.320$), ALT ($r = 0.172$), AST ($r = 0.242$), glucose ($r = 0.291$), LDH ($r = 0.411$), CRP ($r = 0.344$), D-dimer ($r = 0.415$), IgM ($r = 0.190$), IgG ($r = 0.405$), and IgA ($r = 0.364$). (Fig. 1). Furthermore, a KL-6 level of 294.5 U/mL was found to be the best threshold to predict hospital stay of <4 weeks, with a sensitivity and specificity of 74.5% and 73.2%, respectively (Fig. 2).

COVID-19 is an acute infectious disease caused by the newly discovered severe acute respiratory syndrome coronavirus 2. It manifests as bilateral interstitial pneumonia on imaging. Approximately 30–60% patients exhibit some degree of pulmonary interstitial changes, and most patients have a good prognosis [11]. KL-6 is a mucus-like high-molecular-weight glycoprotein that is expressed in type II lung cells and respiratory bronchial epithelial cells of healthy human lungs [11] and is an indicator of the severity and prognosis of interstitial pneumonia [5,11]. The main manifestation of COVID-19 is diffuse alveolar injury, with significant lung epithelial cell hyperplasia, atrophy, shedding or squamous metaplasia in the acute phase, leading to the destruction of the alveolar epithelial barrier and release of a large amount of KL-6 [12,13]. In previous studies, the serum KL-6 level was significantly elevated in patients with severe COVID-19 compared to that in patients with mild-to-moderate disease, therefore, KL-6 could be used to assess the severity of COVID-19 [14,15] and predict the prognosis [8] of COVID-19. In the current study, we found that patients with elevated KL-6 levels were older and more likely to have symptoms such as fever, cough, and dyspnea. A previous study has demonstrated that advanced age and significant symptoms are considered risk factors for poor prognosis in COVID-19 patients [16]. In other studies, patients with elevated KL-6 levels concentration presented many abnormal laboratory parameters, including lower lymphocyte counts and albumin levels and, higher neutrophil counts, liver enzyme levels, blood glucose levels, D-dimer levels, inflammatory marker expression, and antibody levels,

Table 3
Univariate and multivariate analysis for times of hospitalization.

	Univariate analysis		Multivariate liner regression model	
Factors	Coefficient	*p*	Coefficient (95 CI %)	*p*
KL-6	0.410	<0.001	0.006 (0.001–0.010)	**0.013**
Eos%	−0.496	<0.001	−1.770 (−2.645–0.894)	**<0.001**
Lym%	−0.496	<0.001	−0.966 (−1.560–0.372)	**0.002**
Neu%	0.459	<0.001	−0.675 (−1.192–0.158)	**0.011**
Mono%	0.073	0.163		
WBC	0.053	0.310		
Hb	−0.211	<0.001	−0.078 (−0.161–0.006)	0.067
LDH	0.467	<0.001	0.014 (−0.004–0.032)	0.118
PCT	0.393	<0.001	−10.856 (−16.44–5.67)	**<0.001**
CRP	0.553	<0.001	1.843 (1.27–2.41)	**<0.001**
D-dimer	0.390	<0.001	−0.186 (−0.324–0.048)	**0.009**
APTT	0.096	0.074		
PT	0.269	<0.001	1.38 (0.54–2.23)	**0.001**

Multivariate liner regression model was adjusted by age, gender, smoking history, disease severity, symptoms, and comorbidity.

which have been proposed as risk factors related to a more severe case and poor prognosis of COVID-19 [17,18]. Additionally, KL-6 levels were found to correlate well with abnormalities in laboratory parameters. Thus, based on our data, KL-6 can be clinically index used to predict the severity and prognosis of COVID-19.

Similar to the abnormal parameters, including neutrophil counts, LDH levels, PCT levels, CRP levels, D-dimer levels, and PT, which have previously been found to correlate strongly correlated well with the days of hospitalization [17,19–21], higher KL-6 levels were positively correlated with the days of hospitalization in our study. After controlling for potential confounders, including age, sex, disease severity, and comorbidity, we found that elevated KL-6 levels were independently associated with prolonged hospitalization in COVID-19 patients. Furthermore, our ROC model showed that KL-6 presented a favorable ability to predict days of hospitalization of <4 weeks, with a cut-off value of 294.5 U/mL. A KL-6 cut-off value of 500 U/mL is considered a useful indicator of ILDs, even in early disease stages. However, given that our study included patients with a relatively short disease duration who were hospitalized within 1 week of symptom onset, it was not likely to rapidly develop into marked interstitial lung changes. Although the cutoff value for KL-6 in study was <500 U/mL, our data suggest that COVID-19 patients with higher KL-6 levels on admission have worse clinical features and outcomes. As we performed measurements at only one timepoint, we could not evaluate the changing pattern of KL-6 levels with disease development. It is possible that in patients with worse clinical outcomes, KL-6 levels might reach the 500 U/mL threshold at later timepoint measurements. A longitudinal study with dynamic data is needed to validate our hypotheses.

This study has some limitations. First, we included only serum KL-6 levels on admission and did not monitor KL-6 levels dynamically during the course of the disease. Second, KL-6 levels may be more reflective of the degree of lung injury in critically ill patients with COVID-19, especially those requiring intubation and mechanical ventilation. However, the number of critically ill COVID-19 patients included in our study was very small to effectively evaluate this possibility. Our study supports the use of serum KL-6 levels in COVID-19 patients in the clinical setting, especially because, according to the current data, the proportion of critically ill patients is very small (18.1%) [22]. Although these results are only preliminary, it is noteworthy that KL-6 is readily detected in the serum of COVID-19 patients and can be an independent risk factor for assessing COVID-19 hospitalization. Overall, our results suggest that KL-6 testing could play an important role in assessing COVID-19 prognosis.

4. Conclusion

KL-6 levels were found to be associated with the days of hospitalization and various laboratory parameters that influence the severity and prognosis of COVID-19. Elevated KL-6 levels were found to be an independent risk factor for prolonged hospitalization, and serum KL-6 levels on admission might be an indicator for assessing the clinical outcomes of COVID-19. However, longitudinal studies with dynamic data are needed to provide comprehensive evidence on the clinical relevance of serum KL-6 levels in COVID-19.

Author contributions

Baoqing Sun, Hui Wang and Hao Chen conceived and designed the project. Hao Chen and Hui Wang performed the experiments. Hao Chen and Rundong Qin designed the study and analyzed the data. Hao Chen

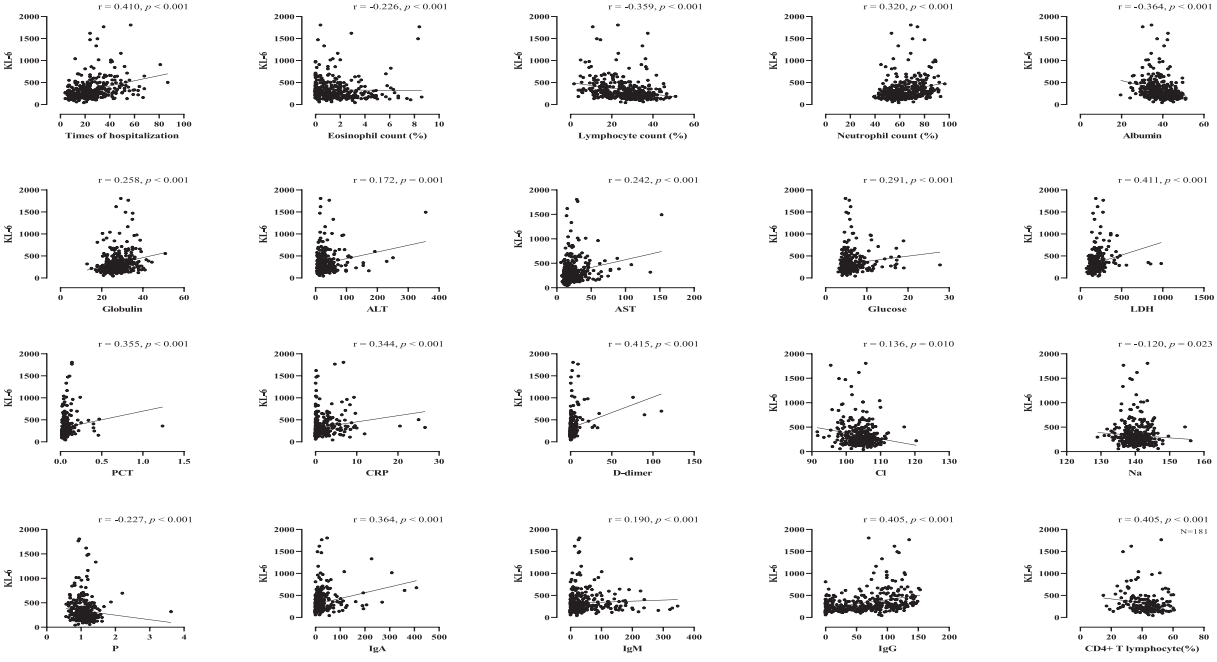

Fig. 1. The correlation between KL-6 and laboratory parameters.

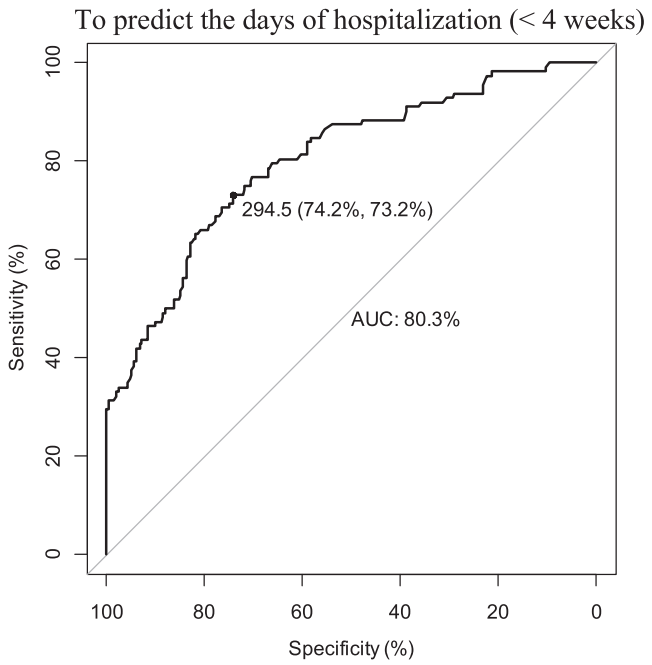

Fig. 2. Roc curve of KL-6 level to predict the days of hospitalization.

and Rundong Qin wrote and revised the manuscript. Zhifeng Huang, Wenting Luo, Peiyan Zheng, Huimin Huang and Haisheng Hu mainly collected the clinical data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2021.155513.

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