

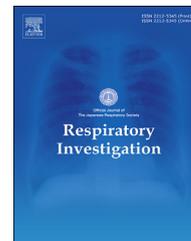


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## Original article

# Serum Krebs von den Lungen-6 levels are associated with mortality and severity in patients with coronavirus disease 2019



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## ABSTRACT

**Background:** The serum Krebs von den Lungen-6 (KL-6) level is a predictive factor for acute respiratory distress syndrome (ARDS). The development of ARDS has been reported in patients with coronavirus disease 2019 (COVID-19). This study aimed to determine whether serum KL-6 levels are associated with mortality and severity in patients with COVID-19.

**Methods:** Among 361 Japanese patients with COVID-19 who were hospitalized at Kanagawa Cardiovascular and Respiratory Center between February 2020 and December 2020, 356 patients with data on serum KL-6 levels were enrolled and their medical records were retrospectively analyzed.

**Results:** A negative correlation was observed between KL-6 levels and the ratio of the arterial partial pressure of oxygen to the fraction of inspired oxygen on admission. The KL-6 levels on admission and the maximal KL-6 levels were higher in patients with severe disease ( $n = 60$ ) than in those with nonsevere disease ( $n = 296$ ). Furthermore, the maximal KL-6 levels were higher in nonsurvivors ( $n = 6$ ) than in survivors ( $n = 350$ ). In nonsurvivors, the KL-6 levels increased as the disease progressed. The optimal cutoff value of the maximal KL-6 level for discriminating between survivors and nonsurvivors was 684 U/mL, with a sensitivity of 83.3%, a specificity of 90.5%, and an area under the curve of 0.89.

**Conclusions:** The serum KL-6 level was associated with disease severity. Patients with KL-6 levels  $\geq 684$  U/mL had a significantly poorer outcome than those with KL-6 levels  $< 684$  U/mL.

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**Abbreviations:** ARDS, acute respiratory distress syndrome; AUC, area under the curve; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation;  $\text{FiO}_2$ , fraction of inspired oxygen; ILD, interstitial lung disease; IPF, interstitial pulmonary fibrosis; KL-6, Krebs von den Lungen-6; ROC, receiver operating characteristic;  $\text{SpO}_2$ , saturation of percutaneous oxygen.

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## 1. Introduction

Coronavirus disease 2019 (COVID-19) has spread worldwide. As of December 2020, the numbers of patients with COVID-19 and associated deaths are still rapidly increasing. Some existing drugs have been reported to be effective in patients with COVID-19 [1–3]. However, many patients with COVID-19 become severe or critical despite treatment with antiviral or anti-inflammatory drugs.

Severe pneumonia in patients with COVID-19 results in acute respiratory distress syndrome (ARDS) [4]. A single-center, retrospective, observational study reported that older patients were more likely to develop ARDS and to require mechanical ventilation [4]. A systematic review and meta-analysis reported that 20.3% of patients with COVID-19 required admission to the intensive care unit and 32.8% presented with ARDS [5]. An autopsy series reported that the main pulmonary pathologic change in patients with COVID-19 was diffuse alveolar damage, accompanied by small-vessel thrombosis and hemorrhage [6]. These findings showed that the development of ARDS is a risk factor for death in patients with COVID-19.

Krebs von den Lungen-6 (KL-6) is a high-molecular-weight mucin-like glycoprotein [7]. This biomarker represents type II pneumocyte injury and/or permeability enhancement after the destruction of the alveolar–capillary barrier [7,8]. KL-6 is a biomarker for interstitial lung diseases (ILDs), including interstitial pulmonary fibrosis (IPF) and connective-tissue disease-associated ILD, and ARDS [9,10]. Elevation of serum KL-6 levels is also reported in pulmonary mycobacterial infection [11,12]. Furthermore, serum KL-6 is a prognostic marker in patients with IPF [13]. A study reported that patients with IPF with KL-6 levels <1000 U/mL showed a significantly more favorable prognosis than those with KL-6 levels  $\geq$ 1000 U/mL [13]. Similar to the study in patients with IPF, another study reported that patients with ARDS with serum KL-6 levels >530 U/mL had significantly lower survival rates [14].

KL-6 has been shown to be a useful marker for evaluating the severity of COVID-19 [15,16]. However, to our knowledge, the correlation between serum KL-6 levels and mortality in patients with COVID-19 has not yet been investigated. We hypothesized that this biomarker would be beneficial for predicting mortality in patients with COVID-19. If this hypothesis is confirmed, then measurements of serum KL-6 levels can enable medical providers to identify patients who are likely to develop severe disease and to intensify their treatment to prevent their deterioration. Thus, we performed this retrospective observational study to determine whether the serum KL-6 level is associated with the short-term prognosis of patients with COVID-19.

## 2. Patients and methods

### 2.1. Study population

We retrospectively enrolled 361 Japanese patients who were hospitalized at Kanagawa Cardiovascular and Respiratory

Center between February 1, 2020, and December 31, 2020. Five patients were excluded because they did not have data on KL-6 levels. All patients had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection confirmed by reverse transcription-polymerase chain reaction testing, and were diagnosed with COVID-19 pneumonia before admission based on the findings of chest radiography and chest computed tomography. Patients with COVID-19 admitted to our hospital were categorized as having mild, moderate, or severe illness according to their respiratory status, as follows: 1) patients who did not receive supplemental oxygen were considered to have mild illness; 2) patients who received supplemental oxygen ( $\leq$ 4 L/min) to maintain 92% saturation of percutaneous oxygen (SpO<sub>2</sub>) were defined as having moderate illness; and 3) patients who presented with <92% SpO<sub>2</sub> while receiving supplemental oxygen (4 L/min) were considered to have severe illness. Severe illness was defined according to a previous study because of the small number of events involving intubation and death [17]. When patients with COVID-19 became critical and required mechanical ventilation or extracorporeal membrane oxygenation (ECMO), they were transferred to other hospitals to receive these treatments. The Ethics Committee of the Kanagawa Cardiovascular and Respiratory Center approved the study protocol (approval no. KCRC-20-0053; February 24, 2021), and the requirement for obtaining patient consent was waived as this was a retrospective study and high anonymity was ensured.

### 2.2. Measurements

Information on the following patient characteristics and examination data was obtained on admission or when the physicians determined the necessity: age, sex, vital signs, body mass index, smoking history, comorbidities such as ILD, serum KL-6 levels, disease severity, use of high-flow nasal cannula or noninvasive positive-pressure ventilation, and outcome. When patients were transferred to other hospitals to receive treatment with mechanical ventilation or ECMO, we contacted the hospitals to collect information on the use of mechanical ventilation or ECMO and the patients' outcomes. The SpO<sub>2</sub>/fraction of inspiratory oxygen (FiO<sub>2</sub>) ratio was used to assess the patients' oxygenation status. Some patients did not receive oxygen therapy and no patient received mechanical ventilation at our hospital.

We examined the serum KL-6 levels that were measured on admission and at other time points (when needed as determined by the physicians). Moreover, we assessed the maximal KL-6 levels during treatment and calculated the differences between the peak levels and the levels on admission ( $\Delta$ KL-6). Serum KL-6 levels were measured using the Nanopia KL-6 Reagent kit (Sekisui Medical Co., Ltd., Tokyo, Japan).

### 2.3. Statistical analysis

All analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan). To compare the data of the severe and nonsevere groups, Fisher's exact test was performed for categorical variables and the Mann–Whitney *U* test was used for continuous variables.

Pearson's product-moment correlation coefficients were used to assess the correlation between serum KL-6 levels and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio.

To determine the optimal cutoff level that can discriminate survivors from nonsurvivors, receiver operating characteristic (ROC) curve analyses were performed. The Kaplan–Meier method was used to estimate the survival function. The log-rank test was performed to assess the difference between survivors and nonsurvivors. Statistical significance was set at  $p < 0.05$ .

### 3. Results

#### 3.1. Patient characteristics

Among the 356 patients, 296 were classified into the non-severe illness group (patients with mild to moderate illness) and 60 were classified into the severe illness group. The median age of the patients was 69 years, and 218 (61.2%) patients were men. In addition, 52% of the patients had a smoking history, without a difference between the severe and non-severe illness groups. Patients in the severe illness group were older than those in the nonsevere illness group (age, 74 vs. 67 years;  $p < 0.001$ ). The proportion of patients with preexisting ILD was higher in the severe illness group than in the non-severe illness group (16.7% vs. 3.4%,  $p < 0.001$ ). Forty-two patients were transferred to other hospitals to receive intensive care, such as mechanical ventilation and ECMO. The median hospital stay duration was 14 days (range, 10–21 days). Six patients died despite treatment with anti-inflammatory and/or antiviral drugs, mechanical ventilation, and ECMO. ARDS occurred in these patients, and all of them died of acute respiratory failure.

#### 3.2. Correlation between serum KL-6 levels and disease severity or prognosis in patients with COVID-19

The serum KL-6 levels were higher in the severe illness group than in the nonsevere illness group on admission (Table 1). In the nonsevere illness group, the KL-6 levels did not increase after admission. However, the KL-6 levels increased in the severe illness group after admission, and significant

differences in the KL-6 level elevation after admission were observed between the nonsevere and severe illness groups. The KL-6 levels on admission in nonsurvivors did not differ from those in survivors. In survivors, the KL-6 levels did not increase after admission. However, the KL-6 levels increased after admission in nonsurvivors, and significant differences in the KL-6 level elevation after admission were observed between nonsurvivors and survivors.

We analyzed the correlations between KL-6 levels and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio on admission and between the maximal KL-6 levels and the lowest SpO<sub>2</sub>/FiO<sub>2</sub> ratio using Pearson's correlation coefficients (Fig. 1a and b). The median time from onset to the date when the maximal KL-6 level was recorded was 19 days (range, 10–38 days). Negative correlations were found between KL-6 levels and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio on admission ( $r = -0.478$ ,  $p < 0.001$ ) and between the maximal KL-6 levels and the lowest SpO<sub>2</sub>/FiO<sub>2</sub> ratio ( $r = -0.438$ ,  $p < 0.001$ ). The correlation between KL-6 levels and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio was more obvious on admission.

We evaluated the changes in KL-6 levels (Fig. 2a and b). Although the serum KL-6 levels in the severe illness group were higher than those in the nonsevere illness group, the levels tended to change in the same way. In particular, in nonsurvivors, the KL-6 levels measured at the third time point (37 days [range, 20–61 days] from disease onset) were higher than those measured on admission and at the second time point (16 days [range, 10–32 days] from disease onset).

To determine the optimal cutoff level that could discriminate the severe illness group from the nonsevere illness group, ROC curve analysis was performed. For evaluating disease severity, the optimal cutoff value of the maximal KL-6 level was 495 U/mL, with a sensitivity of 58.3%, a specificity of 86.1%, and an area under the curve (AUC) of 0.77 (Fig. 3a). In addition, ROC curve analysis was also performed to determine the optimal cutoff level that could discriminate survivors from nonsurvivors. For predicting the risk of mortality, the optimal cutoff value of the maximal KL-6 level was 684 U/mL, with a sensitivity of 83.3%, a specificity of 90.5%, and an AUC of 0.89 (Fig. 3b).

We compared the survival rate between patients with COVID-19 with serum KL-6 levels  $\geq 684$  U/mL and those with serum KL-6 levels  $< 684$  U/mL using the Kaplan–Meier method (Fig. 4). The survival rate of patients with COVID-19 with KL-6

**Table 1 – Serum KL-6 levels on admission and maximal KL-6 levels during the hospital stay in the nonsevere and severe illness groups and the survivor and nonsurvivor groups of patients with COVID-19.**

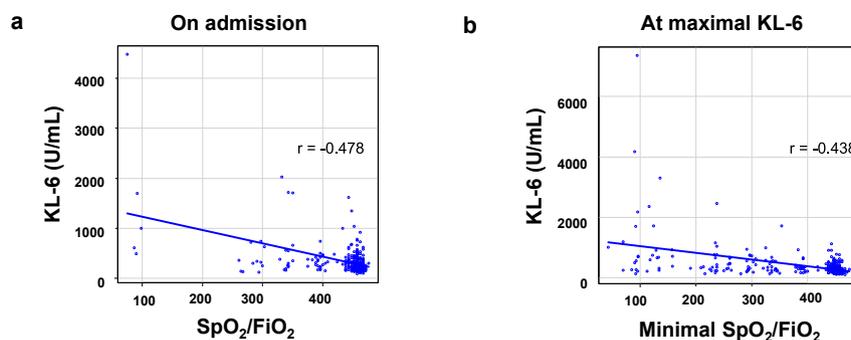
	Nonsevere illness group (n = 296)	Severe illness group (n = 60)	p Value
KL-6 on admission	255 (191–339)	320 (235–564)	<0.001
KL-6 max <sup>a</sup>	267 (203–364)	549 (310–939)	<0.001
$\Delta$ KL-6 <sup>b</sup>	37 (0–88)	339 (118–488)	<0.001
	Survivor group (n = 350)	Nonsurvivor group (n = 6)	p Value
KL-6 on admission	259 (193–359)	313 (288–666)	0.083
KL-6 max <sup>a</sup>	283 (207–417)	1006 (764–1142)	0.001
$\Delta$ KL-6 <sup>b</sup>	64 (5–180)	818 (607–1565)	0.002

Data are presented as median (interquartile range).

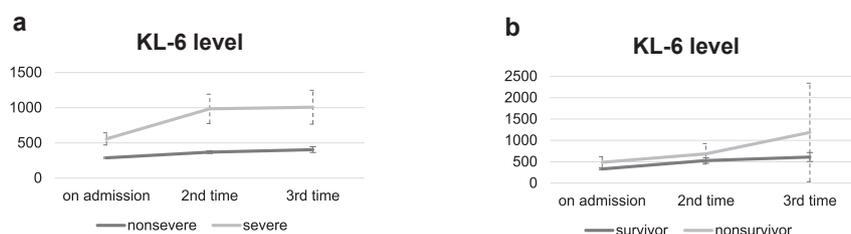
KL-6, Krebs von den Lungen-6; COVID-19, coronavirus disease 2019.

<sup>a</sup> KL-6 max: maximal KL-6 levels after admission.

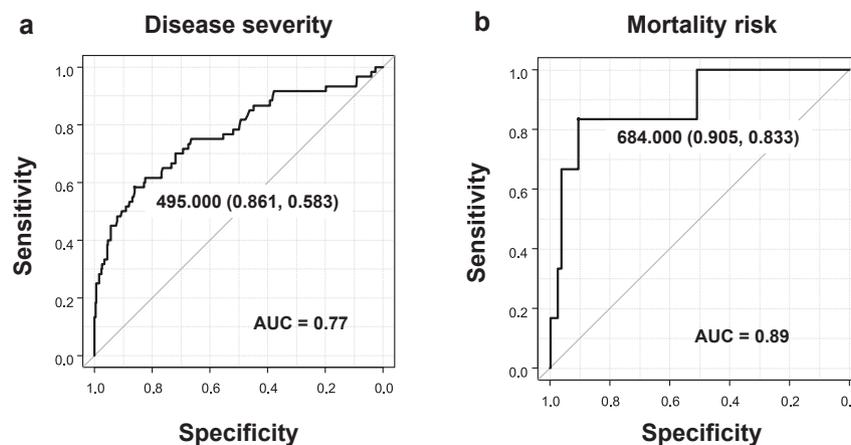
<sup>b</sup>  $\Delta$ KL-6: difference in KL-6 levels between the values on admission and the maximal values.



**Fig. 1** – Correlation between KL-6 levels and  $\text{SpO}_2/\text{FiO}_2$  ratio (a) on admission and (b) when the lowest  $\text{SpO}_2/\text{FiO}_2$  ratio was observed, using Pearson's correlation coefficients. KL-6, Krebs von den Lungen-6;  $\text{SpO}_2$ , saturation of percutaneous oxygen;  $\text{FiO}_2$ , fraction of inspired oxygen.



**Fig. 2** – Changes in mean KL-6 levels. The error bars indicate standard error. (a) Serum KL-6 levels tended to change in the same way between the severe and nonsevere illness groups. (b) In nonsurvivors, the KL-6 levels measured at the third time point were higher than those measured on admission and at the second time point. KL-6, Krebs von den Lungen-6.



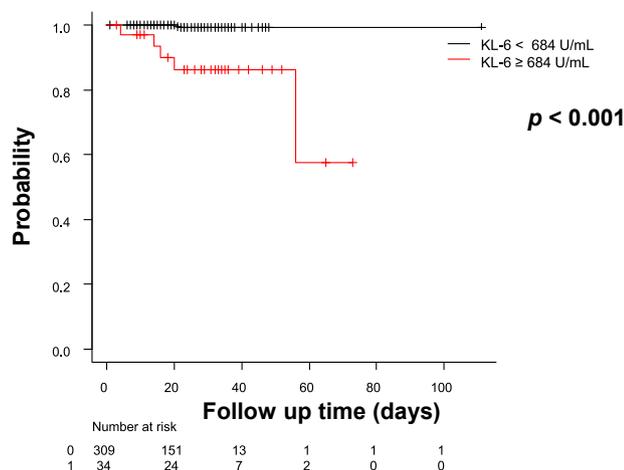
**Fig. 3** – Receiver operating characteristic curves for predicting (a) disease severity and (b) mortality risk. For evaluating disease severity, the optimal cutoff value of the maximal KL-6 level was set at 495 U/mL. For predicting the risk of mortality, the optimal cutoff value of the maximal KL-6 level was set at 684 U/mL. KL-6, Krebs von den Lungen-6; AUC, area under the curve.

levels  $\geq 684$  U/mL was significantly lower than those with KL-6 levels  $< 684$  U/mL ( $p < 0.001$ ).

#### 4. Discussion

In this study, negative correlations were observed between KL-6 levels and the  $\text{SpO}_2/\text{FiO}_2$  ratio on admission and between the maximal KL-6 levels and the lowest  $\text{SpO}_2/\text{FiO}_2$  ratio. The

KL-6 levels on admission and the maximal KL-6 levels were higher in the severe illness group than in the nonsevere illness group. The maximal KL-6 levels in nonsurvivors were higher than those in survivors. The optimal cutoff value of the maximal KL-6 level for discriminating survivors from nonsurvivors was 684 U/mL, with high sensitivity and specificity. Thus, these findings show that serum KL-6 levels are associated with disease severity and oxygenation and predict prognosis in patients with COVID-19.



**Fig. 4 – Comparison of survival between patients with COVID-19 with KL-6 levels  $\geq 684$  U/mL (red line) and those with KL-6 levels  $< 684$  U/mL (black line), using the Kaplan–Meier method. COVID-19, coronavirus disease 2019; KL-6, Krebs von den Lungen-6. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)**

Although KL-6 has been reported to be useful for evaluating the severity of COVID-19 [15,16], to our knowledge, no study has demonstrated the correlation between serum KL-6 levels and mortality in patients with COVID-19. Our findings may be clinically useful because they show that data from noninvasive blood tests could enable the prediction of severe disease and mortality in patients with COVID-19, which could help in the selection of therapeutic agents such as corticosteroids and antiviral drugs. Although treatments should be selected on the basis of not only serum KL-6 levels but also computed tomography findings or respiratory condition, intensive treatment using such drugs may be necessary when elevated serum KL-6 levels are detected.

KL-6 is a mucin-like high-molecular-weight glycoprotein expressed in type II pneumocytes and respiratory bronchiolar epithelial cells [7]. It has been shown to be strongly expressed by atypical and regenerated type II pneumocytes in tissue sections obtained from patients with ILDs [18,19]. In addition, it is strongly expressed in areas of destruction in pulmonary structures, in loose stroma, and in epithelial cells of lymph vessels [20]. Although KL-6 production by regenerated type II pneumocytes may be associated with KL-6 level elevation in patients with ILDs, both the destruction of the alveolar–capillary barrier and the enhancement of alveolar–capillary barrier permeability play important roles in the elevation of serum KL-6 levels [21].

Elevated serum KL-6 levels have been observed in patients with various types of ILDs and ARDS [9,10]. Among patients with ARDS, the serum KL-6 levels in nonsurvivors were higher than those in survivors and positively correlated with the oxygenation index and negatively correlated with arterial oxygen tension [22]. In this study, serum KL-6 levels were negatively correlated with the  $\text{SpO}_2/\text{FiO}_2$  ratio. These findings suggest that serum KL-6 levels are correlated with the severity

of COVID-19. In fact, diffuse alveolar damage and severe endothelial damage have been reported in patients with COVID-19 [6,23]. Although the precise mechanisms of KL-6 production induced by SARS-CoV-2 infection are uncertain, the high serum KL-6 levels in patients with COVID-19 in the severe illness group and the nonsurvivor group may be associated with severe lung damage, subsequently resulting in hypoxia.

In addition, the optimal cutoff value of the maximal serum KL-6 level for evaluating disease severity was 495 U/mL in this study. A previous smaller study suggested 371 U/mL as the optimal cutoff value of the maximal serum KL-6 level for evaluating disease severity [15]. The findings of the present study on the correlation between the maximal serum KL-6 levels and the severity of COVID-19 are consistent with those reported in the previous study.

In addition, we demonstrated that 684 U/mL as the optimal cutoff value of the maximal serum KL-6 level had high sensitivity and specificity in discriminating survivors from nonsurvivors. Additionally, we showed that a maximal KL-6 level of  $>684$  U/mL predicted worse prognosis, using the Kaplan–Meier method. Several studies have reported that serum KL-6 levels are correlated with the prognosis of patients with pulmonary diseases other than COVID-19. Patients with IPF with KL-6 levels  $<1000$  U/mL showed a more favorable prognosis than those with KL-6 levels  $\geq 1000$  U/mL [13]. Patients with ARDS with serum KL-6 levels  $>530$  U/mL showed lower survival rates [14]. The findings of these studies support our findings because the development of ARDS caused by COVID-19 is a risk factor for death in patients with COVID-19. Moreover, a recent study reported that patients with ILD are at an increased risk of death from COVID-19 [24].

This study had several limitations. First, this was a single-center retrospective study and the number of enrolled patients was relatively small. As our hospital is assigned to treat patients with mild to severe illness, patients with critical conditions were not admitted. This may have influenced the small number of deaths in our hospital (six patients, 1.7%). Second, we used various drugs, including mainly methylprednisolone, favipiravir, remdesivir, tocilizumab, and azithromycin, in treating patients with COVID-19. In addition, eight patients had already been receiving treatment for COVID-19 before admission to our hospital, including four patients using corticosteroids. Therefore, the outcomes may differ according to the types of drugs used to treat patients. Third, some patients had ILDs before the onset of COVID-19. High serum KL-6 levels have been reported in patients with ILD [25]. However, although no statistical significance was observed, the serum KL-6 levels in nonsurvivors without ILD were higher than those in survivors. In addition, the serum KL-6 levels in the severe illness group without ILD were higher than those in the nonsevere illness group without ILD. Thus, we believe that ILD had no significant influence on serum KL-6 levels in both groups in this study.

In summary, this study suggests that serum KL-6 levels are negatively associated with the  $\text{SpO}_2/\text{FiO}_2$  ratio on admission, and patients with KL-6 levels  $\geq 684$  U/mL are likely to have a significantly poorer outcome than those with KL-6 levels  $<684$  U/mL.

## 5. Conclusions

A negative correlation was observed between KL-6 levels and the SpO<sub>2</sub>/FiO<sub>2</sub> ratio on admission and between the maximal KL-6 levels and the lowest SpO<sub>2</sub>/FiO<sub>2</sub> ratio. The survival of patients with COVID-19 with KL-6 levels ≥684 U/mL was significantly poorer than those with KL-6 levels <684 U/mL.

## Conflict of Interest

The authors declare no conflicts of interest

## Acknowledgments

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