ORIGINAL ARTICLE

Korean J Intern Med 2025;40:321-329
https://doi.org/10.3904/kjim.2024.161

Initial and peak serum levels of Krebs von den Lungen-6 for predicting the prognosis of patients with COVID-19

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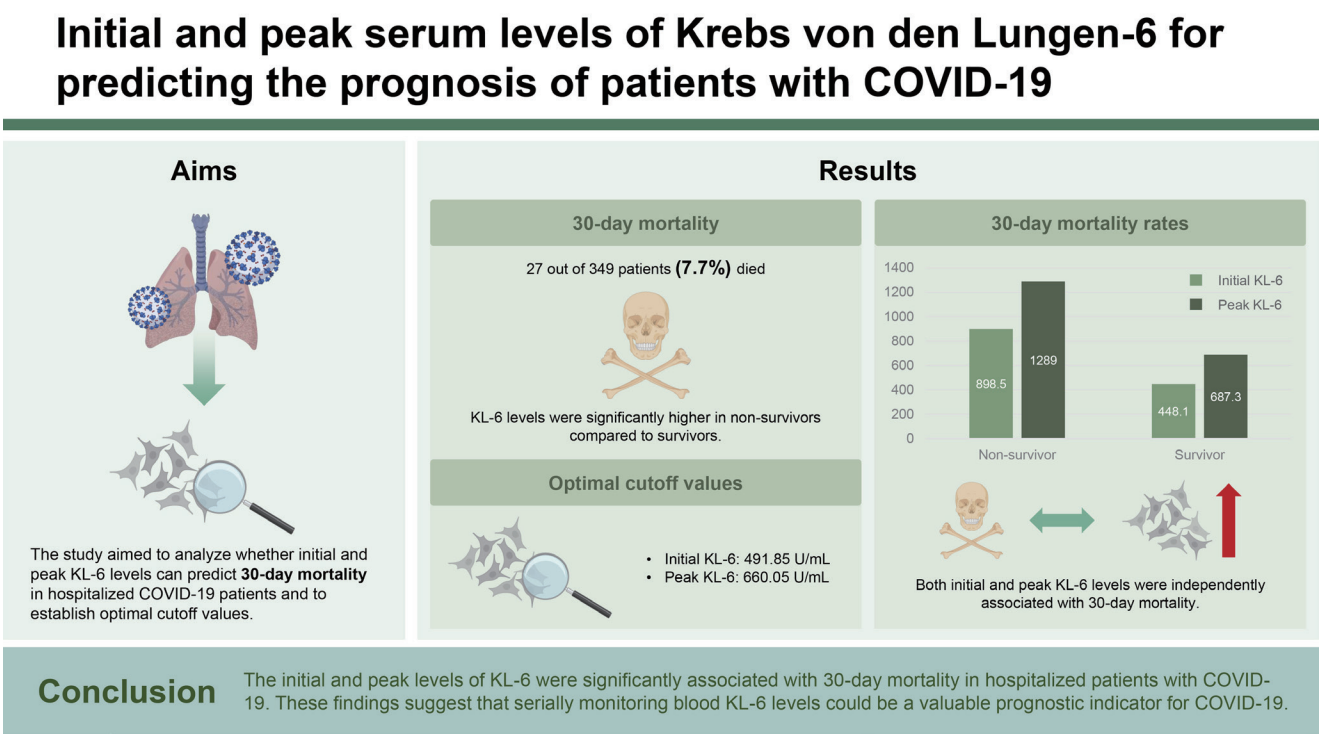

Background/Aims: Krebs von den Lungen-6 (KL-6) is associated with prognosis in patients with COVID-19. However, there is limited data on the correlation between the prognosis of COVID-19 and varying KL-6 levels at different time points. We investigated the optimal cutoff values of the initial and peak serum KL-6 levels to predict mortality and evaluated their correlation with mortality.

Methods: This retrospective cohort study collected data on serially collected serum KL-6 levels in patients hospitalized with COVID-19 between October 2020 and January 2022 at a single tertiary hospital in South Korea. The area under the receiver operating characteristic curve and Youden index were used to determine the cutoff points for the initial and peak KL-6 levels that best predicted 30-day mortality. The association between the initial and peak KL-6 values was assessed by univariate and multivariate logistic regression models.

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

Results: A total of 349 patients were included in this study. The mean initial and peak KL-6 levels were significantly higher in the non-survivor group than in the survivor group. The initial and peak KL-6 values that best predicted 30-day mortality were 491.85 U/mL and 660.05 U/mL, respectively. An initial KL-6 level greater than 491.85 U/mL and a peak KL-6 level greater than 660.05 U/mL were significantly associated with 30-day mortality.
Conclusions: The initial and peak levels of KL-6 were significantly associated with 30-day mortality in hospitalized patients with COVID-19. These findings suggest that serially monitoring blood KL-6 levels could be a valuable prognostic indicator for COVID-19.

Keywords: KL-6 antigen; COVID-19; Prognosis

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes permanent lung damage by destroying type II pneumocytes through a direct cytopathic effect [1]. Krebs von den Lungen-6 (KL-6) is a sialylated carbohydrate antigen and a high molecular weight glycoprotein prominently expressed on the surface of type II alveolar epithelial cells [2,3]. The levels of KL-6 can be elevated in patients with coronavirus disease 2019 (COVID-19) with poor prognosis, reflecting extensive damage to type II pneumocytes [4]. Elevated early serum KL-6 levels in patients with COVID-19 may be a significant indicator of progression to severe conditions, including pulmonary fibrosis and an increased risk of mortality [5-10]. However, there are few evaluations of the association between KL-6 levels measured at time points other than the initial level and clinical prognosis. This study aimed to evaluate the association between the clinical prognosis and the initial and peak KL-6 values in patients hospitalized with COVID-19.

METHODS

Study design

This retrospective cohort study included patients with COVID-19 treated at the Asan Medical Center, a 2,700-bed hospital in South Korea, from October 2020 to January 2022. Patients were diagnosed with COVID-19 through a positive polymerase chain reaction test conducted on nasopharyngeal swabs or sputum. Serum KL-6 levels were measured at least twice a week during hospitalization. Data on demographics, laboratory results, and clinical findings were collected by reviewing electronic medical records. For the measurement of serum KL-6, a sialylated carbohydrate antigen KL-6 kit (Nanopia® KL-6 Reagent; Sekisui Medical, Tokyo, Japan) was used. The initial KL-6 level was defined as the measurement taken at hospital admission for patients hospitalized for COVID-19, or at the time of diagnosis of COVID-19 for patients who were hospitalized for other reasons. The peak KL-6 level was defined as the highest KL-6 value among the serial measurements taken throughout the hospitalization period. The primary outcome of this study was the 30-day mortality among patients hospitalized with COVID-19, defined as death occurring within 30 days following either admission or the diagnosis of COVID-19, whichever occurred later. Based on monitoring results from the Korea Disease Control and Prevention Agency, the period of dominance for each COVID-19 variant was defined as the week when over 50% of the weekly variant tests were positive [11]. As a result, the periods were divided as follows: before the Delta variant became dominant (January 20, 2020–July 24, 2021), and Delta variant dominance (July 25, 2021–January 31, 2022). We defined patients diagnosed during the Delta variant dominance period as being infected with the Delta variant. Additionally, individuals who received at least one dose of any vaccine type were classified as vaccinated. We calculated the optimal cutoff values for the initial and peak KL-6 levels to predict the 30-day mortality and then assessed the association between KL-6 levels above these cutoff values and the 30-day mortality.

This study was approved by the Institutional Review Board of the Asan Medical Center, and informed consent was waived because of the retrospective nature of the study (IRB No 2022-0222).

Statistical analysis

Categorical variables were analyzed using a χ^2 or Fisher's

https://doi.org/10.3904/kjim.2024.161

Table 1. Baseline characteristic of patients with COVID-19

Variable	Non-survivor (n = 27)	Survivor (n = 322)	Total (n = 349)	*p* value
Age (yr)	74 (65.5–76.5)	62 (51–71)	63 (53–72)	< 0.001
Male	18 (66.7)	189 (58.7)	207 (59.3)	0.55
Comorbidity				
Diabetes mellitus	7 (25.9)	92 (28.6)	99 (28.4)	0.94
Hypertension	13 (48.1)	140 (43.5)	153 (43.8)	0.80
Cardiovascular disease	7 (25.9)	42 (13)	49 (14)	0.12
Chronic kidney disease	3 (11.1)	17 (5.3)	20 (5.7)	0.41
Chronic lung disease	2 (7.4)	11 (3.4)	13 (3.7)	0.60
Liver disease	0 (0)	21 (6.5)	21 (6)	0.34
Solid cancer	7 (25.9)	38 (11.8)	45 (12.9)	0.07
Hematologic malignancy	0 (0)	4 (1.2)	4 (1.1)	> 0.99
Rheumatology disease	0 (0)	7 (2.2)	7 (2)	0.95
Obesity	6 (22.2)	81 (25.2)	87 (24.9)	0.91
Initial laboratory findings				
WBC (/μL)	11,259 (6,350– 13,550)	6,900 (4,800–9,500)	7,000 (4,900–9,700)	0.008
Hb (g/dL)	12.3 (10.6–12.9)	12.9 (11.6–14.2)	12.9 (11.6–14.0)	0.04
Platelets (× 10^3/μL)	213 (129-295)	208 (154–265)	208 (153–266)	0.69
BUN (mg/dL)	25 (20.5–38.5)	17(12–24)	18 (12–25)	0.004
Creatinine (mg/dL)	0.9 (0.6–1.4)	0.8 (0.6–1.0)	0.8 (0.6–1.1)	0.92
AST (IU/L)	60 (40.5–76.0)	40 (27–61)	41 (28–64)	0.15
ALT (IU/L)	32 (24–53.5)	29 (18–49)	29 (18–49)	0.95
CRP (mg/dL)	10.0 (7.3 – 16.9)	6.7 (2.3–12.6)	7.1 (2.7–13.2)	0.01
Interval between admission and first sampling date (days)	4 (2.5–5.5)	3 (2–5)	3 (2–5)	0.16
Vaccination	7 (25.9)	94 (19.2)	101 (29.9)	0.70
Delta variant	14 (51.9)	204 (63.4)	218 (62.5)	0.43
COVID-19 severity				
Asymptomatic	0 (0.0)	15 (4.7)	15 (4.3)	0.001
Mild	1 (3.7)	28 (8.7)	29 (8.3)	
Moderate	1 (3.7)	19 (5.9)	20 (5.7)	
Severe	6 (22.2)	163 (50.6)	169 (48.4)	
Critical	19 (70.4)	97 (30.1)	116 (33.2)	
COVID-19 pneumonia[a)]	26 (96.3)	279 (86.6)	305 (87.4)	0.25
Treatment				
Remdesivir	22 (81.5)	244 (75.8)	266 (76.2)	0.67
Tocilizumab	9 (33.3)	110 (34.2)	119 (34.1)	> 0.99
Baricitinib	4 (14.8)	43 (13.4)	47 (13.5)	> 0.99
Glucocorticoid	24 (88.9)	262 (81.4)	286 (81.9)	0.47

Values are presented as median (interquartile range) or number (%).
WBC, white blood cell; Hb, hemoglobin; BUN, blood urea nitrogen; AST, aspartate transaminase; ALT, alanine transferase; CRP, C-reactive protein.
[a)]Presence of COVID-19 pneumonia at the time of admission.

exact test, and continuous variables were analyzed using a Student's t-test or Mann–Whitney's U test. The diagnostic accuracy of the initial and peak KL-6 levels in predicting the 30-day mortality was evaluated using receiver operating characteristic (ROC) curves. The area under the ROC curve (AUC), ranging from 0.5 (no discrimination) to 1.0 (perfect discrimination), quantified the discriminatory capacity of the KL-6 measurements. The optimal threshold for predicting 30-day mortality based on the KL-6 levels was determined using the cutoff point corresponding to the maximum Youden index, representing the point where the sum of the sensitivity and specificity is maximized. Univariate logistic regression was performed to examine the association between KL-6 levels and the 30-day mortality. This was followed by multivariable logistic regression with clinical variables with a *p* value less than 0.1 to adjust for potential confounders. A *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed using the R statistical software package (version 4.2.0; R Core team 2023; Vienna, Austria).

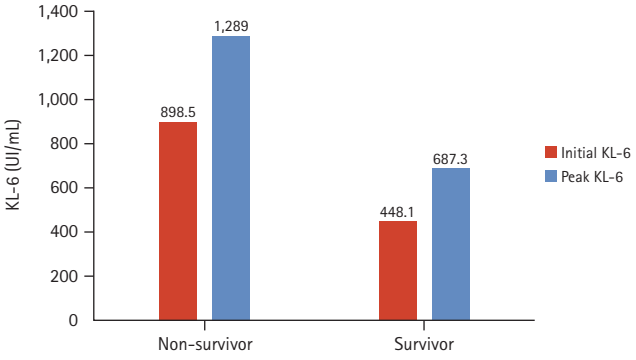

Figure 1. Initial and peak KL-6 levels in non-survivor vs. survivor groups. KL-6, Krebs von den Lungen-6.

RESULTS

A total of 349 patients were included in this study. Of the 349 patients, 27 (7.7%) died within 30 days. The baseline characteristics of the survivors and non-survivors are summarized in Table 1. The median age was 63 years, and 59.3% were male. The non-survivors were older compared to the survivors (median 74 vs. 62 yr, $p < 0.001$), but no significant differences were observed in terms of sex or prevalence of underlying conditions. White blood cell (WBC) counts (median 11,259 vs. 6,900/μL, $p = 0.008$), blood urea nitrogen (BUN) (median 25 vs. 17 mg/dL, $p = 0.004$), and C-reactive protein (CRP) (median 10.0 vs. 6.7 mg/dL, $p = 0.01$) levels were higher in the non-survival group. Among the patients in the study, 26 out of the 27 (96.3%) non-survivors and 279 out of the 322 (86.6%) survivors had COVID-19 pneumonia on their chest computed tomography scans at admission (Table 1).

KL-6 levels in patients with COVID-19

The initial KL-6 levels in the non-survivor group were significantly higher than those in the survivor group (mean 898.5 vs. 448.1 U/mL, $p = 0.006$). The peak KL-6 levels in the non-survivor group were also significantly higher than those in the survivor group (mean 1,289.0 vs. 687.3 U/mL, $p = 0.003$) (Fig. 1, Table 2). The median duration for serum KL-6 level to attain its peak after hospitalization was 11 days (interquartile range: 7–17 days) (Table 2). The trends in KL-6 levels over time for all patients, as well as for survivors and non-survivors, are presented in Figure 2. KL-6 levels were significantly higher in non-survivors compared to survivors in the days 0–5 and days 6–10 intervals. The initial and peak KL-6 levels were analyzed across various clinical and demographic variables, as shown in Supplementary Table 1. Patients aged over 60 years had higher peak KL-6 levels compared to those under 60 years (mean ± standard deviation, 802.9 ± 671.6 U/mL vs. 617.6 ± 622.1 U/mL, $p = 0.01$).

Table 2. Characteristics of continuously measured KL-6 levels

	Non-survivor	Survivor	Total	*p* value
Initial KL-6 level (U/mL)	898.5 ± 770.8	448.1 ± 440.0	482.9 ± 487.3	0.01
Peak KL-6 level (U/mL)	1,289.0 ± 941.7	687.3 ± 608.8	733.9 ± 658.8	0.003
Days to peak value	15 (9–24)	11 (6–17)	11 (7–17)	0.01

Values are presented as mean ± standard deviation or median (interquartile range).
KL-6, Krebs von den Lungen-6.

https://doi.org/10.3904/kjim.2024.161

Sex and other comorbidities, including diabetes mellitus, hypertension, cardiovascular diseases, chronic kidney diseases, and chronic lung diseases, did not show statistically significant differences in KL-6 levels. COVID-19 vaccination was associated with significantly lower initial and peak KL-6 levels, and patients receiving remdesivir therapy, those with pneumonia at admission, and those with severe COVID-19 infection had significantly higher initial and peak KL-6 levels (all $p < 0.05$). The KL-6 levels did not show significant differences regarding the presence of the Delta variant.

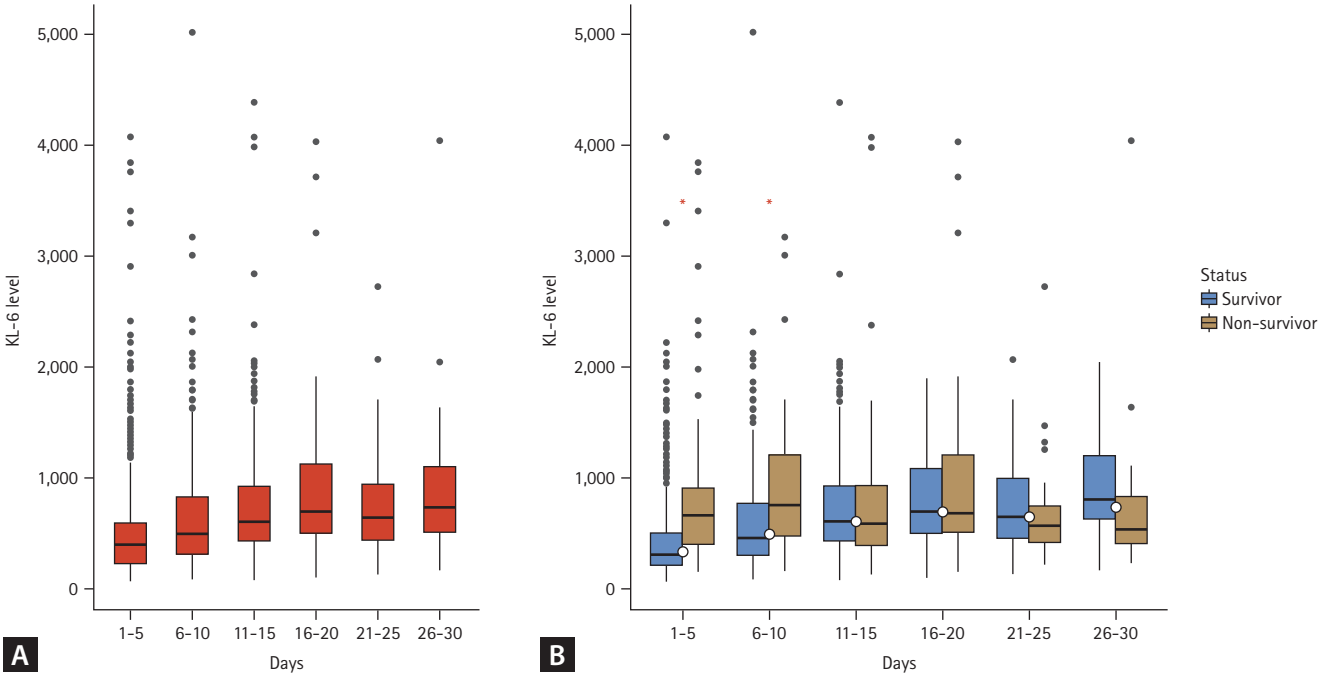

Figure 2. Trends in KL-6 levels over time. (A) KL-6 levels in all patients. (B) KL-6 levels in survivors and non-survivors over different time intervals. The red asterisks indicate statistically significant differences in KL-6 levels between survivors and non-survivors during days 0–5 and days 6–10. KL-6, Krebs von den Lungen-6.

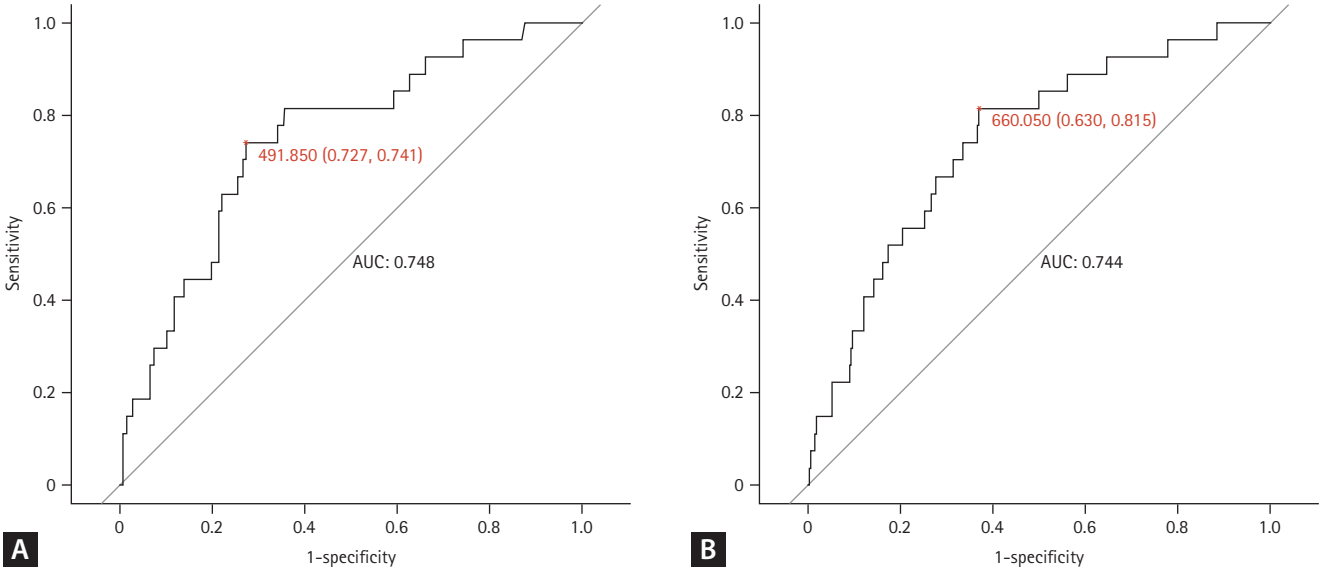

Figure 3. ROC curve for the initial and peak KL-6 levels for prediction of 30-day mortality. (A) Initial KL-6 value cutoff point. (B) Peak KL-6 value cutoff point. ROC, receiver operating characteristic; KL-6, Krebs von den Lungen-6; AUC, area under the ROC curve.

Predictive value of initial and peak KL-6 levels for 30-day mortality

An ROC curve analysis was conducted to determine the optimal initial and peak KL-6 cutoff values for predicting 30-day mortality. The analysis revealed that the initial and peak KL-6 values accurately identified patients at risk of 30-day mortality. The optimal initial KL-6 cutoff value to predict 30-day mortality was determined to be 491.85 U/mL, exhibiting a sensitivity of 72.7% and a specificity of 74.1% (AUC = 0.748). For the peak KL-6 value, the optimal cutoff value for predicting 30-day mortality was 660.05 U/mL, with a sensitivity of 63.0% and specificity of 81.5% (AUC = 0.744) (Fig. 3). In addition to KL-6, other biomarkers were examined to predict 30-day mortality, including WBC, hemoglobin, platelets, BUN, creatinine, aspartate aminotransferase, alanine aminotransferase, and CRP. Among these, the initial and peak KL-6 levels demonstrated the highest AUCs compared to those of the other biomarkers (Fig. 4).

When patients were categorized based on initial and peak KL-6 cutoff values, those in the high initial KL-6 group had a significantly higher 30-day mortality rate compared to those in the low KL-6 group (18.5% vs. 2.9%, $p < 0.001$), and the high peak KL-6 group had a significantly higher 30-day mortality rate compared to the low KL-6 group (15.6% vs. 2.4%, $p < 0.001$) (Supplementary Fig. 1). We further analyzed the 30-day mortality rates by stratifying patients into four groups based on their initial and peak KL-6 levels, as determined by the optimal cutoff values from the ROC analysis. Significant differences in the 30-day mortality rates were found among the four groups, as shown in Figure 5

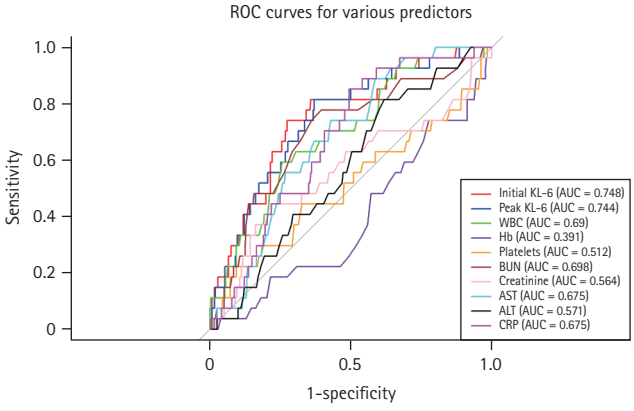

Figure 4. Comparison of ROC curves for predicting 30-day mortality using various biomarkers in patients with COVID-19. ROC, receiver operating characteristic; KL-6, Krebs von den Lungen-6; AUC, area under the ROC curve; WBC, white blood cell; Hb, hemoglobin; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CRP, C-reactive protein.

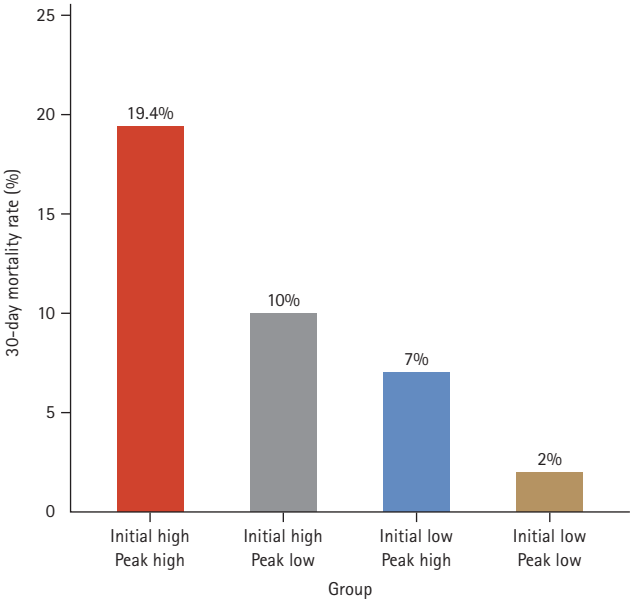

Figure 5. Thirty-day mortality rates stratified by initial and peak KL-6 levels. KL-6, Krebs von den Lungen-6.

Table 3. Logistic regression analysis to predict 30-day mortality in patients with COVID-19

	OR (95% CI)	*p* value
Elevated initial KL-6 level (≥ 491.85 U/mL)		
Univariate	7.60 (3.10–18.59)	< 0.001
Multivariate[a)]	4.54 (1.65–12.49)	0.003
Elevated peak KL-6 level (≥ 660.05 U/mL)		
Univariate	7.51 (2.77–20.34)	< 0.001
Multivariate[a)]	4.91 (1.47–16.40)	0.01

OR, odds ratio; CI, confidence interval; KL-6, Krebs von den Lungen-6.
[a)]Multivariate analyses were adjusted for age, cardiovascular disease, solid cancer, elevated C-reactive protein, and COVID-19 severity.

https://doi.org/10.3904/kjim.2024.161

($p < 0.001$ by chi-square test).

Associations of KL-6 levels with 30-day mortality

In the univariate logistic regression model, initial and peak KL-6 levels higher than the cutoff values (491.85 and 660.05 U/mL, respectively) were significantly associated with 30-day mortality (Table 3). Clinical variables significantly associated with 30-day mortality were age, solid cancer, elevated CRP levels, and critical COVID-19 infection (Supplementary Table 2). Cardiovascular disease was borderline significantly associated with 30-day mortality ($p = 0.07$). In the multivariate logistic regression model, elevated initial KL-6 (odds ratio [OR] 4.54, 95% confidence interval [CI] 1.65–12.49) and elevated peak KL-6 (OR 4.91, 95% CI 1.47–16.40) levels were significantly associated with 30-day mortality, independent of age, cardiovascular disease, solid cancer, elevated serum CRP level, and COVID-19 severity (Table 3, Supplementary Table 3). Additionally, in a sensitivity analysis that included multivariate logistic regression with COVID-19 vaccination, Delta variant infection, and remdesivir therapy, both initial and peak KL-6 levels were significantly associated with 30-day mortality (Supplementary Table 4).

DISCUSSION

In this retrospective cohort study, we found a significant correlation between KL-6 levels and 30-day mortality in patients with COVID-19. Particularly, elevated initial and peak KL-6 levels were markedly associated with an increased risk of death within 30 days, highlighting their predictive value. Given that KL-6 is prominently expressed on the surface of type II alveolar epithelial cells and is associated with poor prognosis in patients with COVID-19 owing to extensive lung damage, our results reinforce the predictive significance of initial KL-6 levels and highlight peak KL-6 levels as a notable predictor of patient outcomes. This dual assessment of KL-6 levels offers a nuanced understanding of COVID-19 disease progression and the potential for pulmonary fibrosis.

Given that elevated serum KL-6 levels are indicative of alveolar epithelial damage and the progression of pulmonary fibrosis, KL-6 has been used and validated as a potential biomarker for diagnosing and indicating the severity and progression of interstitial lung diseases, including idiopathic pulmonary fibrosis (IPF) [12-16]. The prognostic evaluation of patients with IPF can be enhanced by monitoring not only the baseline levels of KL-6 but also by observing its longitudinal changes over time [17]. Patients with COVID-19 experience a hyperinflammatory response owing to dysregulated host inflammatory processes leading to pulmonary fibrosis [18,19]. Up to 31% of patients with COVID-19 may develop COVID-19-induced acute respiratory distress syndrome, which has the potential to evolve into pulmonary fibrosis as part of the post-acute COVID-19 syndrome [20]. Therefore, KL-6 levels, reflective of the inflammatory process from COVID-19 and its progression toward pulmonary fibrosis, underscore the importance of regular monitoring as a critical biomarker for predicting disease progression and mortality in patients with COVID-19.

The relationship between KL-6 levels and the severity, mortality, and prognosis of COVID-19 has been established, highlighting a strong correlation between elevated KL-6 levels and disease severity [3,5-7,9,10,21-23]. These results align with our findings, emphasizing the significance of KL-6 as a valuable predictive tool for the early detection of severe COVID-19 cases. Maruyama et al. [6] sought to predict COVID-19 prognosis by determining the optimal cutoff values for initial and peak KL-6 levels, with the initial cutoff set at 412 U/mL (sensitivity 64.1%, specificity 70.4%) and the peak cutoff at 966 U/mL (sensitivity 81.6%, specificity 84.3%). The initial KL-6 cutoff value of 412 U/mL had lower prediction accuracy (AUC 0.69 vs. 0.75) than that described in the present study; however, the accuracy of the peak value (AUC: 0.89 vs. 0.74) was marginally higher. Maruyama et al. [6] measured KL-6 levels continuously to predict poor prognosis, defined as death or the requirement for an invasive mechanical ventilator for more than 28 days, whereas in our study we solely focused on mortality as the predictive outcome.

Similar to the findings of the present study, a prior study demonstrated a delayed peak among severely ill patients compared with patients with mild disease (21.8 vs. 15.3 days, $p = 0.015$) [24]. The present study revealed that non-survivors reached a peak KL-6 level later than survivors when tracking KL-6 levels continuously (15.0 vs. 11.0 days, $p = 0.009$). This suggests that solely evaluating early-phase KL-6 levels may lead to missing the peak value. In patients with poor prognosis, the duration to reach the peak KL-6 value was prolonged. Therefore, continuous monitoring of KL-6 levels throughout the disease course is important for accurately determining the peak value, thereby improving

prognosis prediction.

This study has several limitations. First, the retrospective design of the study and its reliance on a single-center hospitalized patient sample restrict its generalizability. The focus on high-risk patients with comorbidities further narrows the applicability of the study findings. Second, the initial KL-6 values were obtained at hospital admission, but because of varied hospitalization routes (hospital-acquired infection, transfer after clinical worsening from another hospital, or community-acquired infection), the dates of COVID-19 diagnosis and the initial KL-6 tests did not always align. Consequently, the initial KL-6 values may not accurately represent the levels at the time of confirmed diagnosis. Third, although the peak KL-6 values are valuable in predicting overall prognosis, there is a time lag in reaching the peak value, which may limit its practical use in early mortality prediction. However, as observed in Figure 5, differences in prognosis are evident when considering subsequent peak KL-6 levels, irrespective of the initial levels. This underscores the potential value of serial KL-6 level monitoring to accurately identify peak levels and predict patient outcomes. Additionally, estimating the half-life of KL-6, which could provide a better understanding of the kinetics of KL-6, was not feasible because of the limited data showing a clear decline in KL-6 levels during the observation period. Finally, excluding NIH severity at hospital admission as a confounder in the mortality analysis might limit the evidence supporting the use of KL-6 levels as independent predictors of mortality, irrespective of initial severity. However, this study employed the detection of COVID-19 pneumonia at hospital admission as an indirect method to evaluate the severity of the two groups, and the univariate analysis revealed that COVID-19 pneumonia did not significantly alter mortality predictions.

KEY MESSAGE

1. Elevated initial and peak KL-6 levels are strongly associated with 30-day mortality in hospitalized patients with COVID-19.
2. Continuous monitoring of KL-6 levels is essential, as both the initial and peak levels play a significant role in accurately predicting prognosis.

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Received : May 5, 2024
Revised : July 17, 2024
Accepted : August 19, 2024

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Conflicts of interest
The authors disclose no conflicts.

Funding
This work was supported by a grant from the National Research Foundation of Korea from the Ministry of Science and ICT, South Korea (grant number RS-2023-00219002).

Supplementary Table 1. Comparison of initial and peak KL-6 Levels across clinical and demographic variables

Variable	Initial KL-6			Peak KL-6		
	Yes	No	*p* value	Yes	No	*p* value
Age > 60 yr	520.3 ± 492.2	420.1 ± 474.3	0.06	802.9 ± 671.6	617.6 ± 622.1	0.01
Male	460.8 ± 493.5	498.1 ± 483.7	0.49	722.1 ± 702.4	741.9 ± 628.8	0.79
Diabetes mellitus	517.8 ± 669.9	469.1 ± 393.2	0.50	819.1 ± 860.4	700.1 ± 557.9	0.21
Hypertension	469.5 ± 404.7	493.5 ± 543.9	0.64	725.3 ± 600.6	740.6 ± 702.4	0.83
Cardiovascular diseases	528.7 ± 562.4	475.5 ± 474.6	0.53	792.7 ± 674.8	724.3 ± 656.8	0.51
Chronic kidney diseases	533.7 ± 421.3	479.9 ± 491.4	0.59	795.7 ± 606.1	730.1 ± 662.6	0.65
Chronic lung disease	584.8 ± 599.2	479.0 ± 483.1	0.54	797.5 ± 625.3	731.4 ± 660.9	0.72
Liver disease	442.3 ± 370.0	485.5 ± 494.2	0.62	748.2 ± 573.3	733.0 ± 664.7	0.91
Solid cancer	434.6 ± 474.7	490.1 ± 489.5	0.47	571.8 ± 584.8	757.9 ± 666.6	0.06
Hematologic malignancy	334.8 ± 234.6	484.7 ± 489.4	0.29	1,189.5 ± 1,623.5	728.6 ± 643.2	0.61
Rheumatology disease	333.2 ± 174.3	486.0 ± 491.3	0.06	699.0 ± 481.0	734.6 ± 662.5	0.85
Obesity	528.3 ± 573.7	467.9 ± 455.3	0.37	817.4 ± 678.2	706.1 ± 651.2	0.18
Delta variant	443.6 ± 323.6	506.6 ± 562.7	0.19	724.4 ± 598.2	739.5 ± 694.0	0.83
Covid-19 vaccination	363.4 ± 295.3	531.6 ± 539.5	< 0.001	537.3 ± 396.4	813.9 ± 725.1	< 0.001
Remdesivir therapy	520.5 ± 523.2	362.7 ± 322.7	0.001	790.4 ± 650.7	552.6 ± 655.9	0.004
Pneumonia at admission	533.5 ± 514.4	234.6 ± 175.2	< 0.001	818.6 ± 682.7	317.4 ± 263.4	< 0.001
Severe COVID-19[a)]	532.7 ± 504.5	261.2 ± 321.2	< 0.001	822.8 ± 674.5	337.9 ± 389.9	< 0.001

Values are presented as mean ± standard deviation.

KL-6, Krebs von den Lungen-6.

[a)]Represents the severe and critical patient groups based on the NIH COVID-19 severity grade

Supplementary Table 2. Univariate logistic regression analysis for 30-day mortality in COVID-19 patients

Variable	Univariate analysis	
	OR (95% CI)	*p* value
Age	1.07 (0.01–1.11)	< 0.001
Sex	1.40 (0.18–3.37)	0.42
Diabetes mellitus	0.87 (0.13–2.05)	0.77
Hypertension	1.20 (0.12–2.66)	0.64
Cardiovascular disease	2.33 (0.11–5.63)	0.07
Chronic kidney disease	2.24 (0.12–7.28)	0.22
Chronic lung disease	2.26 (0.12–9.04)	0.31
Liver disease	0.33(0.13–infinite)	0.99
Solid cancer	2.62 (0.11–6.35)	0.04
Hematologic malignancy	7.52 (0.12–3.68)	0.99
Obesity	0.85 (0.13–2.06)	0.74
Elevated CRP (≥ 7.5 mg/dL)	2.79 (0.09–6.94)	0.02
COVID-19 pneumonia	2.69 (0.11–17.00)	0.19
COVID-19 severity		
Asymptomatic to moderate	Reference	
Severe	1.14 (0.22–5.81)	0.87
Critical	6.07 (1.37–26.98)	0.02
Delta variant	0.62 (0.28–1.37)	0.24
Covid-19 vaccination	0.85 (0.35–2.08)	0.72
Remdesivir therapy	1.41 (0.52–3.84)	0.51
Elevated initial KL-6 level (≥ 491.85 U/mL)	7.60 (3.10–18.59)	< 0.001
Elevated peak KL-6 level (≥ 660.05 U/mL)	7.51 (2.77–20.34)	< 0.001

OR, odds ratio; CI, confidence interval; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6.

https://doi.org/10.3904/kjim.2024.161

Supplementary Table 3. Results of the multivariate logistic analysis

Characteristic	Initial KL-6 level (≥ 491.85 U/mL)		Peak KL-6 level (≥ 660.05 U/mL)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Elevated KL-6	4.54 (1.65–12.49)	0.003	4.91 (1.47–16.40)	0.01
Age	1.06 (1.01–1.10)	0.01	1.06 (1.02–1.10)	0.01
Cardiovascular diseases	1.42 (0.47–4.27)	0.54	1.79 (0.60–5.35)	0.30
Solid cancer	7.08 (2.07–24.22)	0.002	7.19 (2.13–24.25)	0.002
COVID-19 severity				
Asymptomatic to moderate	Reference		Reference	
Severe	1.26 (0.20–8.03)	0.80	1.03 (0.16–6.59)	0.97
Critical	4.41 (0.70–27.66)	0.11	3.13 (0.48–20.42)	0.23
Elevated CRP (≥ 7.5 mg/dL)	2.58 (0.98–6.77)	0.055	2.66 (1.01–7.01)	0.048

KL-6, Krebs von den Lungen-6; OR, odds ratio; CI, confidence interval; CRP, C-reactive protein

Supplementary Table 4. Results of the sensitivity analysis with variables including remdesivir therapy, vaccination status, and infection with Delta variant

Variable	Initial OR (95% CI)	*p* value	Peak OR (95% CI)	*p* value
Elevated initial KL-6 level	5.42 (1.84–15.92)	0.002	-	-
Elevated peak KL-6 level	-	-	5.42 (1.58–18.59)	0.01
Age	1.05 (1.01–1.10)	0.02	1.06 (1.01–1.10)	0.01
Cardiovascular diseases	1.59 (0.53–4.77)	0.41	1.97 (0.66–5.86)	0.22
Solid cancer	8.42 (2.33–30.41)	0.001	8.42 (2.39–29.67)	< 0.001
COVID-19 severity				
Asymptomatic to moderate				
Severe	0.81 (0.10–6.67)	0.85	0.74 (0.10–5.71)	0.77
Critical	2.80 (0.35–22.62)	0.34	2.17 (0.29–16.47)	0.45
Remdesivir therapy	1.73 (0.47–6.34)	0.41	1.53 (0.42–5.52)	0.52
COVID-19 vaccination	1.54 (0.47–5.06)	0.47	1.24 (0.39–3.97)	0.71
Delta variant	0.42 (0.15–1.22)	0.11	0.44 (0.15–1.28)	0.13
Elevated CRP (≥ 7.5 mg/dL)	3.14 (1.13–8.72)	0.03	3.26 (1.16–9.17)	0.03

OR, odds ratio; CI, confidence interval; KL-6, Krebs von den Lungen-6; CRP, C-reactive protein.

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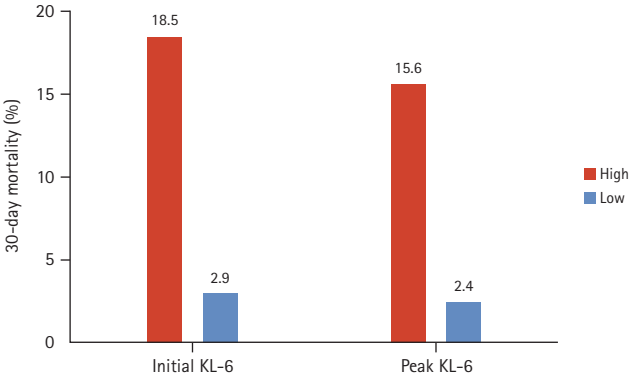

Supplementary Figure 1. Difference in 30-day mortality based on optimal cut-off levels of initial and peak KL-6. KL-6, Krebs von den Lungen-6.