

Clinical subtyping for patients with acute exacerbations of interstitial lung diseases guided by serum KL-6 measurement

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Research Article

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Abstract

Introduction: Serum Krebs von den Lungen-6 (KL-6) measurement is widely used to assess disease activity or prognosis in patients with interstitial lung diseases (ILDs). However, the clinical differences between high and low serum KL-6 levels at the time of acute exacerbation (AE) of ILD are not well known.

Methods: Clinical parameters including age, sex, Charlson Comorbidity Index score (CCIS), blood biomarkers, high-resolution CT findings, and disease mortality were retrospectively compared between high and low KL-6 (cut-off value: 1000 U/mL) patients at the time of diagnosis of AE of ILDs.

Results: 38 high serum KL-6 and 57 low serum KL-6 patients were included. There was no significant difference in 6-month mortality between them ($P = 0.685$). Whereas serum lactate dehydrogenase was a significant predictor of 6-month mortality in the high serum KL-6 patients (odds ratio (OR), 1.006; 95% confidence interval (CI), 1.003-1.009; $P < 0.001$), CCIS (OR, 1.502; 95% CI, 1.242-1.838; $P < 0.001$) and sex (OR, 5.751; 95% CI, 1.121-105.163; $P = 0.033$) were significant predictors in low serum KL-6 patients. In addition, the incidences of congestive heart failure, symptomatic chronic pulmonary disease, cerebrovascular disease, and second metastatic solid tumours were significantly higher in non-survivors with low serum KL-6 than in other groups ($p < 0.05$).

Conclusions: The clinical features in patients with AEs of ILDs may differ depending on the serum KL-6 level, and clinicopathological examination according to this subtyping guided by the serum KL-6 level is essential.

Introduction

The prognosis of acute exacerbations (AEs) of interstitial lung diseases (ILDs) such as idiopathic interstitial pneumonias (IIPs), chronic hypersensitivity pneumonitis, and connective tissue disease-associated ILDs (CTD-ILDs) is generally poor (1,2). Furthermore, the pathological findings of patients with AEs of ILDs show not only diffuse alveolar damage (DAD), but also a variety of pathological conditions including organizing pneumonia (OP), diffuse alveolar haemorrhage (DAH), lung cancer, and bronchopneumonia (3). Despite pathological heterogeneity, it is very difficult to perform a lung biopsy during an AE due to severe respiratory failure. Therefore, it is necessary to plan the treatment strategies or attempt to accurately predict the disease prognosis using less invasive modalities such as symptoms, blood test results, and imaging findings in the clinical setting.

Krebs von den Lungen-6 (KL-6) is a high-molecular-weight mucin-like glycoprotein, also known as human mucin-1 (MUC1). It is expressed mainly on bronchiolar epithelial cells and type II pneumocytes in alveoli, particularly on proliferating and regenerating type II pneumocytes (4-6). An official American Thoracic Society/European Respiratory Society statement proposed that a serum KL-6 level above 1000 U/mL at the initial examination in patients with stable-state ILD is associated with a worse prognosis (7-9). In addition, a recent systematic review and meta-analysis reported that higher serum KL-6 levels were associated with an increased risk of AE of idiopathic pulmonary fibrosis (IPF) (10). On the other hand,

there are few reports of the clinical significance of the serum KL-6 level at the time of diagnosis of AEs, though we often see AEs of ILD patients with low KL-6 levels in the clinical setting (11,12).

In the present retrospective study, clinical parameters were compared between high and low serum KL-6 patients at the time of diagnosis of AEs of ILDs to attempt to classify their clinical features according to the serum KL-6 level.

Methods

Study location and patients

The retrospective cohort study involved patients seen between 2014 and 2018 at Yokohama City University Hospital and Yokohama City University Medical Center. The medical data of 95 patients with acute or subacute IIPs, including AEs of nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis (IPF), acute interstitial pneumonia, cryptogenic organizing pneumonia, drug-induced ILD, or AEs of CTD-ILDs treated with corticosteroid pulse therapy, were assessed. Patients who did not receive steroid pulse therapy or had sarcoidosis were excluded. Medical records at the time of diagnosis of AE were reviewed for data including age, sex, diagnosis of ILD, Charlson Comorbidity Index score (CCIS), blood parameters (partial pressure of oxygen in arterial blood/fraction of inspired oxygen (P/F ratio), KL-6 (normal < 500 U/mL), lactate dehydrogenase (LDH; normal, < 225 U/L), surfactant protein-D (SP-D; normal, < 110 ng/mL), high-resolution CT (HRCT) scores including ground-glass opacity (GGO) and honeycomb scores as assessed independently by two pulmonologists and two radiologists, and treatment regimens, including sivelestat Na hydrate, anticoagulation therapy before steroid pulse therapy, steroid use before steroid pulse therapy, and macrolides (13,14). Patients were classified as high serum KL-6 patients (≥ 1000 U/mL) and low serum KL-6 patients (< 1000 U/mL), and the extracted data were compared between the two groups.

Diagnosis of ILDs

Subtypes of IIP were confirmed from physical, serological, HRCT, and lung pathological findings, in accordance with the official statement for IIPs (7,15). Patients for whom lung biopsy could not be performed due to severe hypoxemia were diagnosed based on the HRCT classification (7,15). The CTD-ILD diagnosis was confirmed by physical, serological, and HRCT findings consistent with ILD, and lung biopsy was undertaken to exclude other pulmonary diseases. A diagnosis of drug-induced ILD was based on previously reported criteria (16). An AE of ILD was defined as: worsening of hypoxemia reflecting severely impaired gas exchange; worsening of dyspnoea; newly appeared alveolar infiltration on radiography; and absence of alternative aetiologies including pneumothorax, pulmonary embolism, infection, or heart failure (7,17-20).

Statistical analysis

Data were statistically analysed using JMP12 (SAS Institute Inc., Cary, NC, USA) and are shown as medians with 25th - 75th percentiles or numbers (%). Groups were compared using the Wilcoxon rank-sum test or Pearson's chi-squared test. Optimal parameter cut-off values were determined from receiver operator characteristic (ROC) curves. Survival curves were generated using the Kaplan-Meier method and compared using log-rank tests. Predictors of 6-month mortality were determined using multiple stepwise regression analysis. Values with $P < 0.05$ were considered significant.

Results

Patients' characteristics

Table 1 shows the clinical characteristics of the patients with AEs of ILDs; there were 38 (40%) patients with high serum KL-6 and 57 (60%) patients with low serum KL-6 levels. The diagnoses of the 95 patients who were all treated with corticosteroid pulse therapy were AE of idiopathic ILDs in 62 patients (65%) and AE of secondary ILDs in 33 patients (35%). There was no significant difference in the diagnoses between the high and low serum KL-6 groups. Other clinical parameters including age, sex, CCIS, symptom onset, blood biomarkers (P/F ratio and SP-D), ground-glass opacity scores calculated from HRCT, and treatment regimens except serum LDH and honeycomb score showed similar tendencies between these groups. High serum KL-6 patients with AEs of idiopathic or secondary ILDs and low serum KL-6 patients with AEs of idiopathic or secondary ILDs had similar 6-month mortality rates (Fig. 1).

Stepwise multiple logistic regression analysis

In both patients with high and low serum KL-6 levels, clinical parameters including age, sex, CCIS, diagnosis of ILDs, P/F ratio, serum LDH and SP-D, and the GGO and honeycomb scores were evaluated using stepwise multiple logistic regression analysis. Whereas serum LDH was a significant predictor of 6-month mortality in high serum KL-6 patients (OR, 1.006; 95% CI, 1.003-1.009; $P < 0.001$), CCIS (OR, 1.502; 95% CI, 1.242-1.838; $P < 0.001$) and sex (OR, 5.751; 95% CI, 1.121-105.163; $P = 0.033$) were significant predictors in low KL-6 patients (Table 2).

Relationship between 6-month mortality and serum LDH levels

In the patients with low serum KL-6 levels, the area under the ROC curve (AUC) was 0.541 in the evaluation of serum LDH as a predictor of 6-month mortality (Fig. 2A). The 57 patients were assigned to groups with either low LDH ($N = 11$) or high LDH ($N = 46$) levels based on the optimal cut-off (206 IU/mL). Log-rank tests showed that the Kaplan-Meier survival curves of these groups did not differ significantly ($P = 0.227$) (Fig. 2A). On the other hand, in the patients with high serum KL-6 levels, the AUC was 0.897 in the evaluation of serum LDH as a predictor of 6-month mortality (Fig. 2B). The optimal cut-off LDH level for estimating 6-month mortality was 381 IU/mL ($p < 0.001$). The 38 patients were assigned to groups with either low serum LDH ($N = 23$) or high serum LDH ($N = 15$) levels based on this cut-off. Log-rank tests showed that the Kaplan-Meier survival curves of these groups differed significantly ($P < 0.001$ (Fig. 2B)).

Relationship between 6-month mortality and CCIS

In the patients with low serum KL-6 levels, the AUC was 0.836 in the evaluation of CCIS as a predictor of 6-month mortality (Fig. 3A). The optimal cut-off CCIS value for predicting 6-month mortality was 4 points ($p < 0.001$). The 57 patients were assigned to groups with either low CCIS ($N = 41$) or high CCI ($N = 16$) levels based on this cut-off value. Log-rank tests showed that the Kaplan-Meier survival curves of these groups differed significantly ($P < 0.001$ (Fig. 3A)). On the other hand, in the patients with high serum KL-6 levels, the AUC was 0.663 in the evaluation of CCIS as a predictor of 6-month mortality (Fig. 3B). The 57 patients were assigned to groups with either low CCIS ($N = 27$) or high CCIS ($N = 11$) levels based on the same cut-off value. Log-rank tests showed that the Kaplan-Meier survival curves of these groups did not differ significantly ($P = 0.083$) (Fig. 3B).

Incidence of complications according to the serum KL-6 level and 6-month outcomes

Figure 4 shows a comparison of comorbidities in survivors with low serum KL-6 levels (A), non-survivors with low KL-6 levels (B), survivors with high serum KL-6 levels (C), and non-survivors with high serum KL-6 levels (D), respectively, from the left bar. The incidences of congestive heart failure (12%, 33%, 0%, 17%), symptomatic chronic pulmonary disease (29%, 73%, 46%, 50%), cerebrovascular disease (2%, 27%, 4%, 8%), and second metastatic solid tumours (2%, 33%, 4%, 17%) were the highest in non-survivors with low serum KL-6 levels (all $p < 0.05$). In this cohort, there was no difference in the rate of death from comorbidities between the high and low serum KL-6 groups (data not shown).

Discussion

Serum KL-6 measurement is thought to be useful for detecting the presence of ILDs, evaluating ILD activity, and predicting the prognosis in various types of ILDs (21). Several other clinical studies have proposed that serum KL-6 could predict the incidence of AEs, which are the most common cause of death in patients with ILD (9,10,22). On the other hand, there are few reports of the relationship between the serum KL-6 levels at the time of diagnosis of AE and these disease outcomes. Though it has been reported that serum LDH (cut-off value, 280 IU/L), KL-6 (cut-off value, 1000IU/L), P/F ratio (cut-off value, 100), and extent of abnormal HRCT findings were significant predictors of 3-month mortality in IPF patients with an AE, we often saw patients with a poor prognosis despite a normal KL-6 level at the time of AE diagnosis (11,12). Interestingly, in the present study, the ILD patients with high and low serum KL-6 levels had similar mortality, and it was shown that the prognostic factors were different between the two groups (high serum KL-6 group: serum LDH level; low serum KL-6 group: CCIS and sex).

A high KL-6 level was reported to be associated with the extent of lung fibrosis, which reflected regeneration of type II pneumocytes and/or enhancement of permeability following the destruction of the air-blood barrier in the affected lung (23-25). An increased serum LDH level, which is a non-specific biomarker, reflects lung inflammation and cellular damage in patients with ILD (26-28). The present study showed that high serum KL-6 patients tended to have a greater extent of fibrosis and higher serum LDH levels than the low serum KL-6 patients. In addition, in the high serum KL-6 group, patients with high

serum LDH levels were found to have higher GGO scores calculated from HRCT (13 points vs. 9 points ($p < 0.001$)) and lower P/F ratios (223 vs. 296 ($p = 0.004$)) than those with low serum LDH levels. From the above, patients with high serum KL-6 and LDH levels were considered to have more severe DAD with strong inflammation and increased permeability of the alveolar-capillary barrier.

Serum KL-6 has been reported to be a significant prognostic factor in AEs of ILDs, but the serum KL-6 levels at the time of AE diagnosis are wide ranging (11). In clinical practice, we also see patients whose serum KL-6 levels are not very high while meeting the diagnostic criteria for AE (12). In the present study, there proved to be no difference in 6-month mortality between the high and low serum KL-6 patients. There are several possible reasons for this. First, comorbidities significantly affect the clinical course of ILD (29). A retrospective cohort study of 272 patients with IPF suggested that there was a significant negative impact of arteriosclerosis, other cardiovascular diseases (mainly valvular heart disease, cardiac arrhythmias, dilated cardiomyopathy), lung cancer, and pulmonary and cancer comorbidities on survival (29). Another IPF study cohort that included 65 patients reported that baseline cardiovascular diseases were the predictors of an AE of IPF (30). In the present study, the comparison of comorbidities between survivors with low serum KL-6, non-survivors with low KL-6, survivors with high serum KL-6, and non-survivors with high serum KL-6 levels showed that the incidences of congestive heart failure, symptomatic chronic pulmonary disease, cerebrovascular disease, and second metastatic solid tumours were significantly higher in non-survivors with low serum KL-6 levels than in the other groups. Second, the pathological findings in patients with AE-IPF represent not only DAD, but also a variety of pathological conditions including OP, DAH, lung cancer, and bronchopneumonia (3). In fact, comparing two autopsy cases enrolled in the present study, though HO-1, which is an oxidative stress marker, was expressed to the same extent in lung cells in both the high KL-6 case and the low KL-6 case, in the former, DAD was the main component (Supplement Fig. S1 (case 1 (31))), and in the latter, DAH and pulmonary vascular microthrombosis were the main components (DAH findings were minor) (Supplement Fig. S1 (case 2 (12))). These results suggest that patients with low serum KL-6 levels do not have severe DAD, and that various comorbidities and histological types such as DAH and vascular thrombosis may have a strong impact on prognosis.

The present study has some limitations. First, the study was limited by the small number of patients and the absence of additional validation data sets. In order to generalize these findings, further validation studies are essential. Second, the clinical diagnoses of the enrolled patients were heterogenous, but there was no significant difference in the ILD diagnoses between the high and low serum KL-6 groups. Third, the low serum KL-6 group likely contained various pathological changes other than DAD, but pathological assessment was not performed after the onset of AE in all patients due to severe respiratory failure. Therefore, the credibility of this study will be increased by evaluating the relationship between clinical parameters such as blood examination and radiographic findings and prognosis in autopsy cases only.

Conclusions

The clinical features of patients with AEs of ILDs may differ depending on the serum KL-6 level, and clinicopathological examination according to this subtyping guided by the serum KL-6 level is essential.

List Of Abbreviations

AE, acute exacerbation

AUC, area under the ROC curve

CCIS, Charlson Comorbidity Index score

CI, confidence interval

CTD-ILD, connective tissue disease-associated ILD

DAD, diffuse alveolar damage

DAH, diffuse alveolar haemorrhage

GGO, ground-glass opacity

HRCT, high-resolution CT

HO-1, heme oxygenase-1

IIPs, idiopathic interstitial pneumonias

ILD, interstitial lung disease

IPF, idiopathic pulmonary fibrosis

KL-6, Krebs von den Lungen

LDH, lactate dehydrogenase

NEI, neutrophil elastase inhibitor

OP, organizing pneumonia

OR, odds ratio

P/F ratio, partial pressure of oxygen in arterial blood/fraction of inspired oxygen

PSL, prednisolone

ROC, receiver operating characteristic

SP-D, surfactant protein-D

Declarations

Funding

The authors declare that they are not funded by any funding body.

Conflicts of interests: None

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TY and HY were responsible for study conception, design, data analysis, and drafting manuscript; HY, TY, NR, AA and MK were responsible for acquisition of data; All authors were responsible for drafting and revision of the manuscript.

Ethics approval

The institutional review board at Yokohama City University Hospital approved this study (approval number B171100003).

Consent to participate

In this retrospective study, consent for participation was obtained by disclosing the clinical study with the description of the opt-out process (https://www.yokohama-cu.ac.jp/amedrc/ethics/ethical/fuzoku_optout.html). The severely ill condition or deep sedation of AE-ILD patients precluded us from obtaining informed consent from the patients themselves. Therefore, written informed consent was obtained from the patients' relatives or their legal guardians.

Consent for publication

Written consent for publication from the patients or their next of kin was obtained.

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Tables

Tables 1-2 are available in the Supplementary Files.

Figures

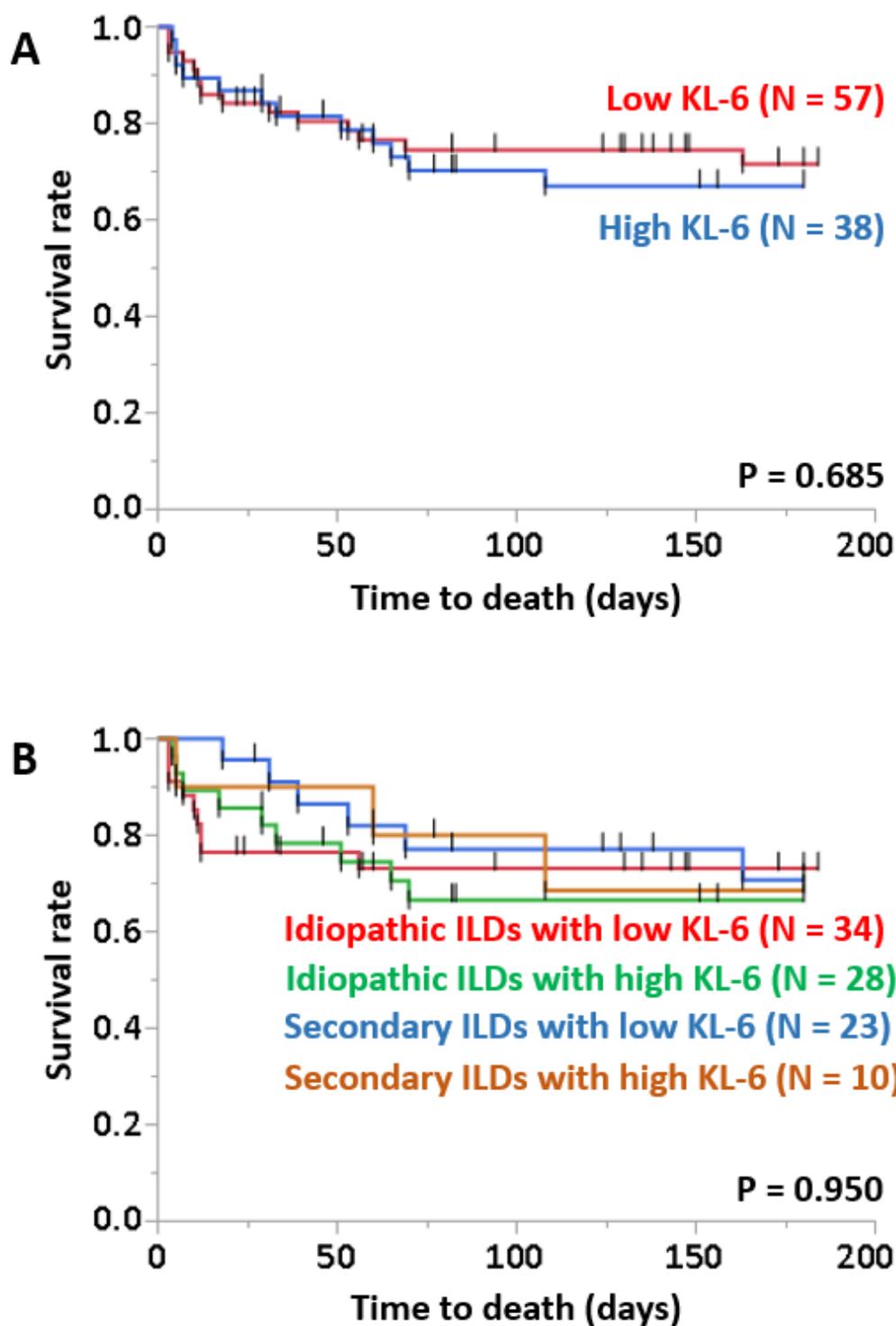
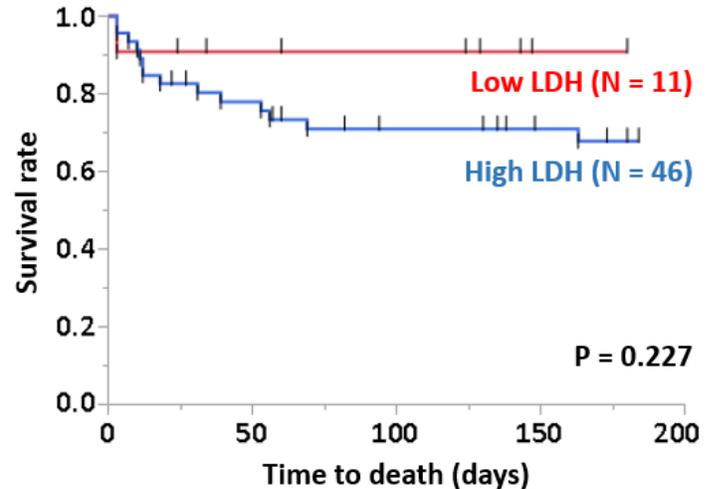
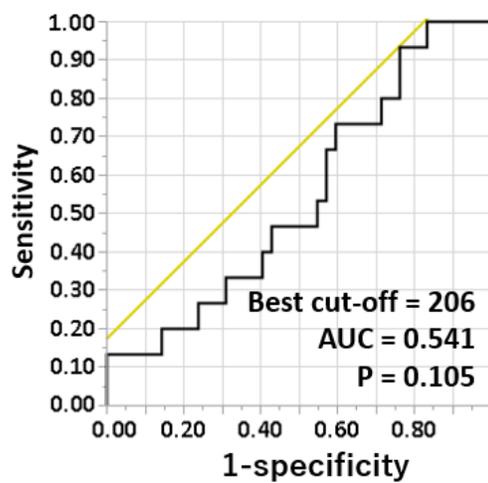


Figure 1

Comparison between high serum KL-6 and low serum KL-6 patients. The enrolled patients consist of 38 (40%) patients with high serum KL-6 (idiopathic: 28 patients, secondary: 10 patients) and 57 (60%) patients with low serum KL-6 (idiopathic: 34 patients, secondary: 23 patients) levels. There is no significant difference in the 6-month prognosis between the high and low serum KL-6 patients ($P = 0.685$ (Fig. 1A)). In addition, high serum KL-6 patients with AEs of idiopathic or secondary ILDs and low serum

KL-6 patients with AEs of idiopathic or secondary ILDs have similar 6-month outcomes ($P = 0.950$ (Fig. 1B)). Abbreviations: ILD, interstitial lung disease; KL-6, Krebs von den Lungen.

A. Low KL-6 group



B. High KL-6 group

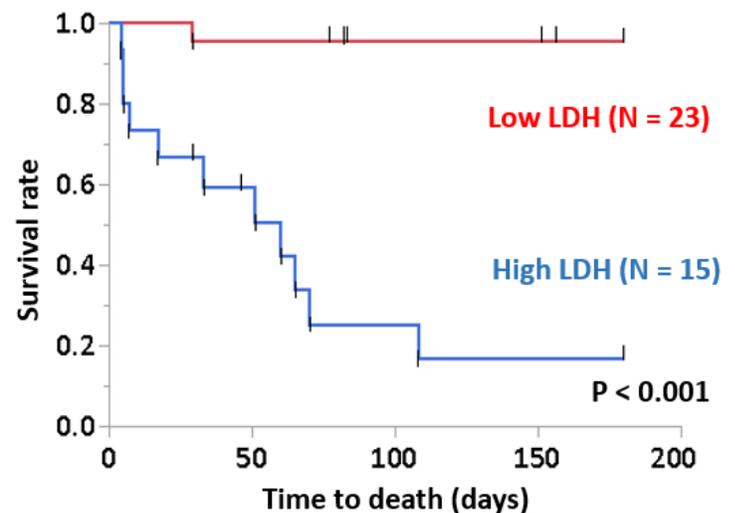
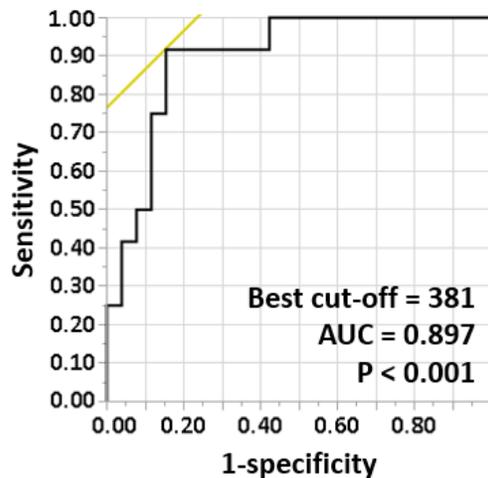
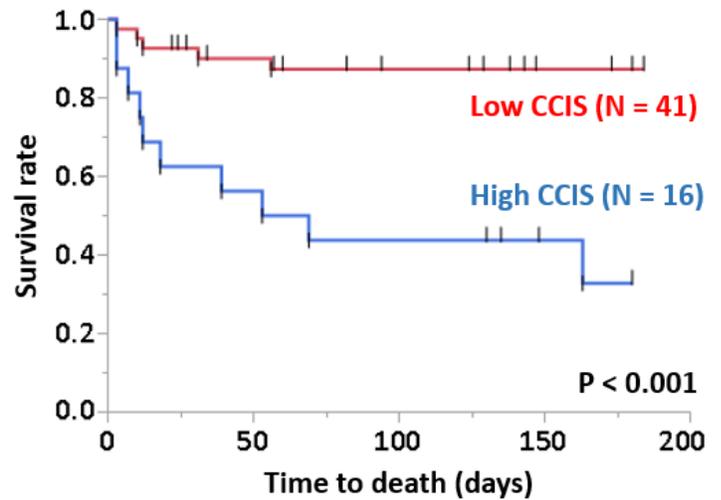
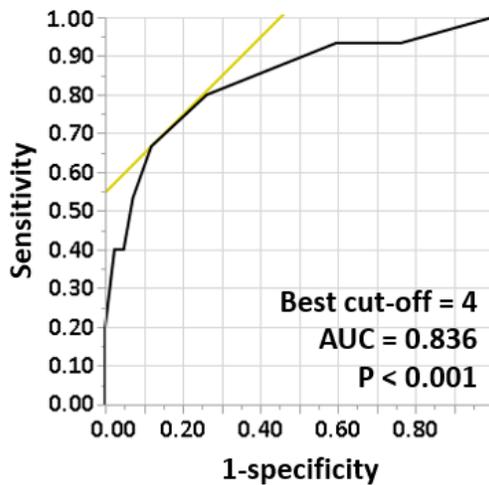


Figure 2

Relationship between 6-month mortality and serum LDH levels In patients with low serum KL-6 levels, the AUC is 0.541 in the evaluation of serum LDH as a predictor of 6-month mortality (A). Log-rank tests show that the Kaplan-Meier survival curves of these groups do not differ significantly ($P = 0.227$ (A)). On the other hand, in the patients with high serum KL-6 levels, the AUC value is 0.897 in the evaluation of serum LDH as a predictor of 6-month mortality (B). Log-rank tests show that the Kaplan-Meier survival curves of these groups differ significantly ($P < 0.001$ (B)). Abbreviations: AUC, AUC, area under the ROC curve; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen.

A. Low KL-6 group



B. High KL-6 group

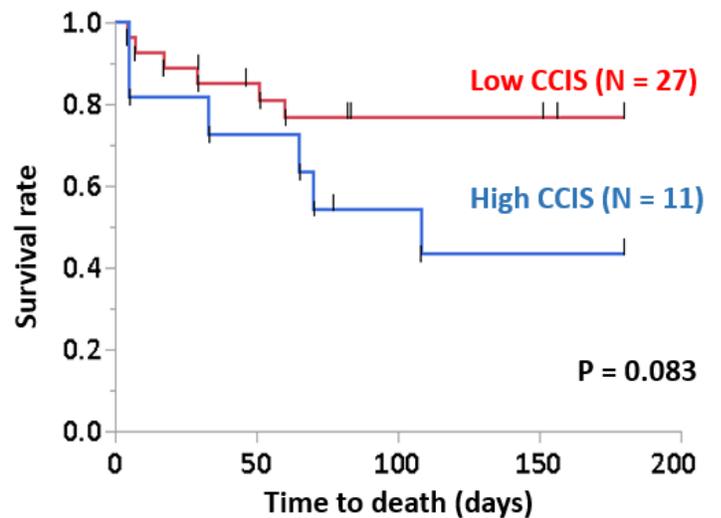
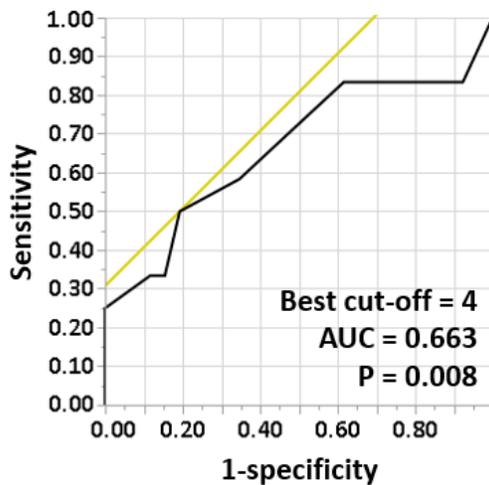


Figure 3

Relationship between 6-month mortality and CCIS In the patients with low serum KL-6 levels, the AUC is 0.836 in the evaluation of CCIS as a predictor of 6-month mortality (A). The optimal cut-off CCIS for estimating 6-month mortality is 4 points ($p < 0.001$). Log-rank tests show that the Kaplan-Meier survival curves of these groups differ significantly ($P < 0.001$ (A)). On the other hand, in the patients with high serum KL-6 levels, the AUC value is 0.663 in the evaluation of CCIS as a predictor of 6-month mortality (B). Log-rank tests show that the Kaplan-Meier survival curves of these groups do not differ significantly ($P = 0.083$ (B)). Abbreviations: AUC, area under the ROC curve; CCIS, Charlson Comorbidity Index score; KL-6, Krebs von den Lungen.

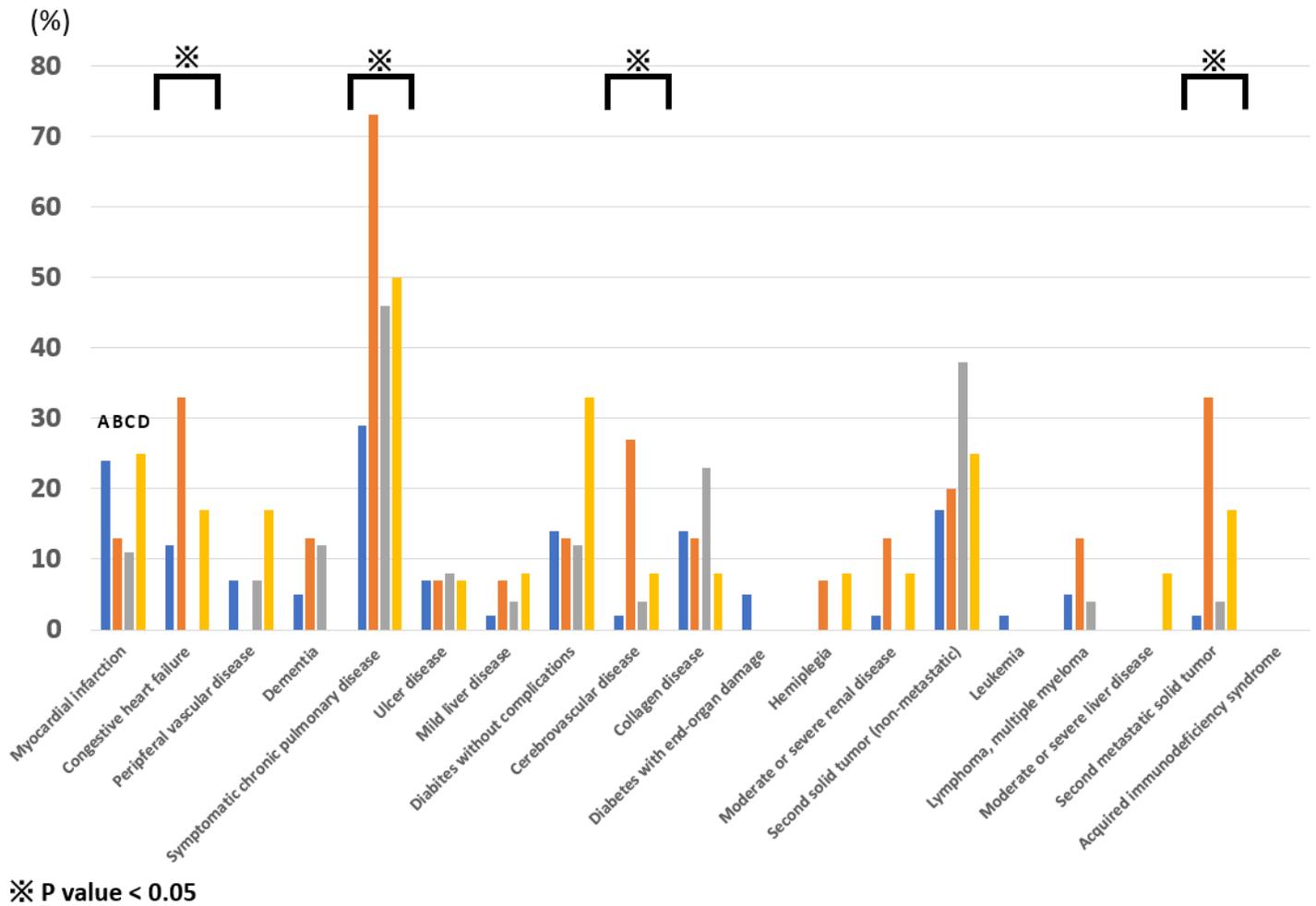


Figure 4

Incidence of complications according to serum KL-6 levels and 6-month outcomes From the left bar, there are four groups, including survivors with low serum KL-6 (A), non-survivors with low serum KL-6 (B), survivors with high serum KL-6 (C), and non-survivors with high serum KL-6 (D) levels. The incidences of congestive heart failure, symptomatic chronic pulmonary disease, cerebrovascular disease, and second metastatic solid tumour are significantly the highest in non-survivors with low serum KL-6 levels (all $p < 0.05$). Abbreviations: KL-6, Krebs von den Lungen

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.pptx](#)
- [Table2.pptx](#)
- [SupplementData20210418.docx](#)