Original Article

Expression and significance of serum KL-6 in patients with acute respiratory distress syndrome

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Background: Acute respiratory distress syndrome (ARDS) is a common and serious complication that occurs in the ICU. the determination of early ARDS indicators, along with timely treatment, can potentially diminish medical costs and reduce ARDS-related mortality. In this report, we evaluated the clinical significance of circulating Krebs von den Lungen-6 (KL-6) content among patients with intra- and extrapulmonary ARDS to investigate the clinical significance of serum KL-6.

Methods: Patients who met the ARDS Berlin criteria and were hospitalized in the intensive care unit of the China-Japan Union Hospital of Jilin University between September 2021 and September 2022 were recruited for analysis. ARDS patients were divided into an intrapulmonary ARDS group (n=23) and an extrapulmonary ARDS group (n=27) based on their primary diagnosis. Baseline demographic data, including age and sex, and clinical data, including underlying diseases and mortality, of the two groups were collected and analyzed. Peripheral venous blood was collected on Day 0 (baseline), Day 1, Day 3, and Day 7. The kinetic levels of serum KL-6 were compared between patients who survived and those who died within one week of ARDS diagnosis. The prognosis, survival times, and status of patients within 28 days after diagnosis were evaluated.

Results: In the intrapulmonary ARDS group, patients who died had significantly higher serum KL-6 levels in the seven days following diagnosis than those who survived. In contrast, in the extrapulmonary group, the difference in KL-6 values between patients who survived and died was only significant on the first day after diagnosis. The peak levels of serum KL-6 in the death group were significantly higher than those in the survival group for both intra- and extrapulmonary ARDS (P=0.0253). The optimal cutoff value of the serum KL-6 level was 1,452.3 U/mL in intrapulmonary ARDS patients and 828.2 U/mL in extrapulmonary patients. Serum KL-6 levels higher than the cutoff levels were confirmed to be a significant prognostic predictor of poor survival within 28 days of diagnosis in patients with intra- and extrapulmonary ARDS.

Conclusions: The serum KL-6 level is potentially a good indicator for predicting the prognosis of patients with ARDS.

Keywords: Serum; Krebs von den Lungen-6 (KL-6); intrapulmonary acute respiratory distress syndrome (intrapulmonary ARDS); extrapulmonary ARDS

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Introduction

Acute respiratory distress syndrome (ARDS) is hypoxemic respiratory failure caused by non-cardiogenic pulmonary edema. It can be caused by intra- or extrapulmonary factors. Intrapulmonary ARDS typically occurs in the presence of diffuse pulmonary infections, aspiration, and pulmonary contusions. In contrast, extrapulmonary ARDS is caused by extrapulmonary sepsis, severe nonthoracic injuries, and hyperperfusion, which induce a systemic inflammatory response, which, in turn, accelerates ARDS formation (1). Although ARDS etiology varies, the pathogenesis is quite similar. ARDS pathogenesis involves acute damage to the alveolar-capillary membrane. In the case of intrapulmonary ARDS, alveolar epithelial cells are first involved, whereas in extrapulmonary ARDS, capillary vascular endothelial cells are first damaged (2).

ARDS is a common and serious complication that occurs in the ICU. One study in 2001–2002 in China reported that the largest contributing factors for ARDS were pneumonia (34.3%) and extrapulmonary sepsis (30.6%). Moreover, the annual ARDS prevalence in the ICU is 200 cases per 100,000 people, with in-hospital and 90-day mortality rates of 68.5% and 70.4%, respectively (3). A separate study reported that the average hospitalization cost increases every year, and the cost rises even further with enhanced disease severity and prolonged hospital stay (4). Hence, the determination of early ARDS indicators, along with timely treatment, can potentially diminish medical costs and reduce ARDS-related mortality.

Krebs von den Lungen-6 (KL-6) is a high molecular weight mucus glycoprotein. In normal lung tissues, this glycoprotein is mainly located in alveolar type II (AT-II) cells and is prominently expressed when AT-II is damaged or regenerated. As reported in a previous study (5), the serum levels of KL-6 elevate in patients with interstitial lung diseases (ILDs), which may be due to an elevation in KL-6 production by increasing permeability following the destruction of alveolar capillaries and results in regenerating of alveolar type II pneumocytes in the affected lung. Prior investigations revealed (5) that the serum KL-6 content is strongly associated with the alveolar-capillary permeability index, and it is speculated that enhanced KL-6 content in the circulation can potentially facilitate its leakage from the alveolar lumen.

Prior investigations involving circulating KL-6 content among ARDS patients (4,6) revealed markedly enhanced KL-6 content among deceased versus surviving patients. This suggests that the enhanced circulating KL-6 content among ARDS patients may potentially be associated with poor prognosis. However, these samples did not identify the causative factors for ARDS. In fact, there are no reports on the prognostic significance of circulating KL-6 content among patients with intra- and extrapulmonary ARDS. Moreover, no prior investigations have extensively reported on the dynamic alterations in circulating KL-6 content among patients with intra- and extrapulmonary ARDS.

In this report, we evaluated the clinical significance of circulating KL-6 content among patients with intra- and extrapulmonary ARDS. In short, we measured the circulating KL-6 levels among ARDS patients 1 week after diagnosis. Then, we assessed the correlation between circulating KL-6 levels and clinical outcomes in ARDS patients. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1787/rc).

Highlight box

Key findings

- The serum Krebs von den Lungen-6 (KL-6) level is potentially a good indicator for predicting the prognosis of patients with acute respiratory distress syndrome (ARDS).

What is known and what is new?

- Circulating KL-6 content among ARDS patients revealed markedly enhanced KL-6 content among deceased versus surviving patients.
- In this report, we evaluated the clinical significance of circulating KL-6 content among patients with intra- and extrapulmonary ARDS. In short, we measured the circulating KL-6 levels among ARDS patients 1 week after diagnosis. Then, we assessed the correlation between circulating KL-6 levels and clinical outcomes in ARDS patients.

What is the implication, and what should change now?

- KL-6 concentration can serve as a strong indicator of severely impaired alveolar type II (AT-II) cells and poor patient prognosis.

Methods

Study object

Patients who met the ARDS Berlin criteria and were hospitalized in the intensive care unit of the China-Japan Union Hospital of Jilin University between September 2021 and September 2022 were recruited for analysis. The following patients were eliminated from the analysis: (I) age <18 years; (II) pregnant women; those with malignant tumors, immune diseases, and hematologic diseases; (III)

those with prior emphysema, tuberculosis, occupational lung disease, or ILD; (IV) those with combined hepatic and renal insufficiency and acute coronary syndrome; and (V) those who withdrew or transferred halfway through the hospitalization. Fifty ARDS patients were finally enrolled, including 35 males and 15 females aged 64.9±15.4 years, and they were followed up until death or discharge. The discharged patients were classified as survivors. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Board of China-Japan Union Hospital of Jilin University (No. 20220609030), and informed consent was taken from all the patients.

Participants

(I) Data collection: clinical information, namely, sex, age, and primary etiology of the enrolled patients was collected. The peripheral venous blood was centrifuged and cold stored in the specimen bank at 0, 1, 3, and 7 days after ARDS diagnosis, the patient prognosis was monitored, and the time of death of deceased individuals was recorded.

(II) Case grouping: ARDS patients with intrapulmonary involvement, namely, those with pulmonary infection, aspiration pneumonia, and pulmonary contusion, were included in the intrapulmonary ARDS cohort (23 cases), and ARDS patients with extrapulmonary involvement, namely, nonpulmonary sepsis, severe pancreatitis, and nonthoracic injury, were categorized in the extrapulmonary ARDS cohort (27 cases).

(III) The ARDS patients were further divided into deceased (n=19) and surviving cohorts (n=31) based on their prognosis, among which 11 patients expired and 12 survived in the intrapulmonary ARDS cohort, and 8 patients died and 19 survived in the extrapulmonary ARDS cohort.

(IV) Assay method: the circulating KL-6 concentration of the enrolled patients was detected via the latex-enhanced immunoturbidimetric method with an EZ-400 semiautomatic specific protein analyzer, purchased in Nanjing, China. Based on the kit instructions, the reference circulating KL-6 content interval among normal healthy adults was ≤500 U/mL.

Statistical methods

MATLAB statistical software was used to analyze the data. Normally distributed measures are expressed as the mean (standard deviation). The linear trend test was employed for the assessment of the circulating KL-6 kinetic concentration between the deceased and surviving patients in each group within 1 week after ARDS diagnosis. A box-whisker plot was employed to show the peak circulating KL-6 concentration in each group of surviving and deceased ARDS patients. The Mann-Whitney *U* test was used to compare the difference in KL-6 levels between the intra- and extra-ARDS groups and the death/survival group. Receiver operating characteristic (ROC) curve analyses assessed the predictive performance of circulating KL-6 on the prognosis of intra- and extrapulmonary ARDS patients. Kaplan-Meier curves were employed to assess patient survival within 28 days of diagnosis. In the case of the Kaplan-Meier curve, the log-rank test was used to analyze the intergroup survival differences. $P<0.05$ was set as the significance threshold.

Results

Comparison of baseline information

No differences were observed in the age or sex of intra- versus extrapulmonary ARDS patients. The lung injury scores were higher among intrapulmonary ARDS patients than among extrapulmonary ARDS patients ($P<0.05$). Last, the initial oxygenation index, APACHE II score within 24 hours of diagnosis, underlying disease and morbidity, and time duration between intra- and extrapulmonary ARDS patients were not statistically significant ($P>0.05$) (*Table 1*).

Circulating KL-6 dynamic concentration among deceased and surviving patient populations with intra- and extrapulmonary ARDS

Circulating KL-6 kinetic concentration was monitored among deceased and surviving patients with intrapulmonary ARDS, and circulating KL-6 concentration was significantly elevated among the deceased versus surviving patients. We next compared the variables between the aforementioned cohorts at specific time points and observed marked differences on Day 0 ($P=0.0106$), Day 1 ($P=0.0317$), Day 3 ($P=0.0009$), and Day 7 ($P=0.0036$) (*Figure 1A*; Mann-Whitney *U* test). Once a peak trend was reached, over time, there was a decrease in circulating KL-6 concentration among the deceased patients (linear trend test, $P=0.0286$).

We observed no marked differences in the circulating

Table 1 Clinical profile assessment of patients with intra- and extrapulmonary ARDS

Characteristics	Intrapulmonary-ARDS (n=23)	Extrapulmonary-ARDS (n=27)	P value
Male	17 (73.91)	18 (66.67)	0.807
Age (years)	65.00±14.62	64.81±16.30	0.858
Death	11 (47.83)	8 (29.63)	0.303
Initial oxygenation index (mmHg)	130.95±26.50	141.39±41.70	0.255
The length of time (days)	11.64±4.27	16.75±8.48	0.102
Underlying diseases			
Hypertension	13 (56.52)	11 (40.74)	0.407
Diabetes	5 (21.74)	7 (25.93)	0.993
Coronary heart disease	6 (26.09)	6 (22.22)	>0.99
APACHE II score within 24 hours after diagnosis (scores)	23.74±6.04	22.29±4.88	0.652
Pulmonary injury score (scores)	2.99±0.48	2.19±0.51	<0.001

Data are presented as mean ± standard deviation or n (%). 1 mmHg =0.133 kPa. Use the Murry Lung Injury Scale to calculate lung injury score. APACHE II score, Acute Physiology and Chronic Health Evaluation Scoring System II. ARDS, acute respiratory distress syndrome.

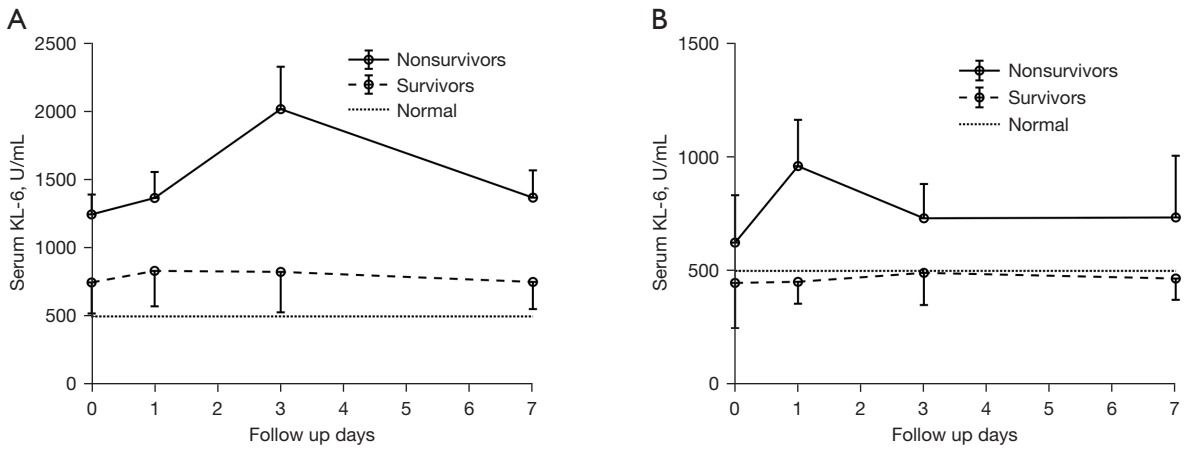

Figure 1 Comparison of serum KL-6 kinetic levels among the deceased and surviving intrapulmonary ARDS patients (A) and among the deceased and surviving extrapulmonary ARDS patients (B). Normal range of serum KL-6 levels: 0–500 U/mL. KL-6, Krebs von den Lungen-6; ARDS, acute respiratory distress syndrome.

KL-6 dynamic concentration among deceased versus surviving patients with extrapulmonary ARDS at any time point throughout the study, on Day 0 (P=0.3291), Day 1 (P=0.0061), Day 3 (P=0.1936), and Day 7 (P=0.7429) (*Figure 1B*).

To further elucidate the clinical value of circulating KL-6 concentration among intrapulmonary ARDS patients, we identified the peak circulating KL-6 concentration and computed its duration. We revealed that the circulating KL-6 concentration among deceased patients reached its peak on Day 3.0±1.5, at 1,985.8±649.1 U/mL. The peak was achieved on Day 2.4±2.4 among patients who survived, with 1,005.6±595.6 U/mL. The circulating KL-6 concentration was thus markedly elevated among deceased versus surviving patients, and differences compared between the survival and death groups at each time point and found to be statistically significant. (box-whisker plot *Figure 2A*; Mann-Whitney *U* test, P=0.0014).

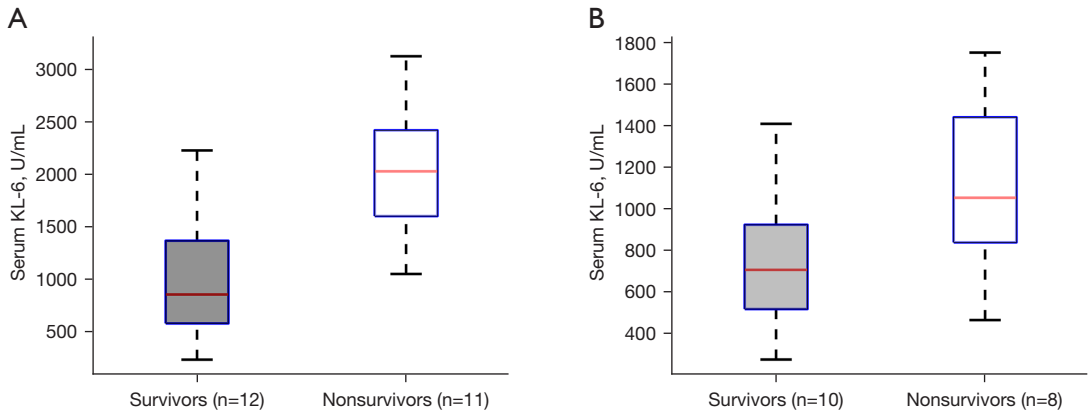

Figure 2 The peak circulating KL-6 concentration among the deceased and surviving intrapulmonary ARDS patients (A), and among the deceased and surviving extrapulmonary ARDS patients (B). KL-6, Krebs von den Lungen-6; ARDS, acute respiratory distress syndrome.

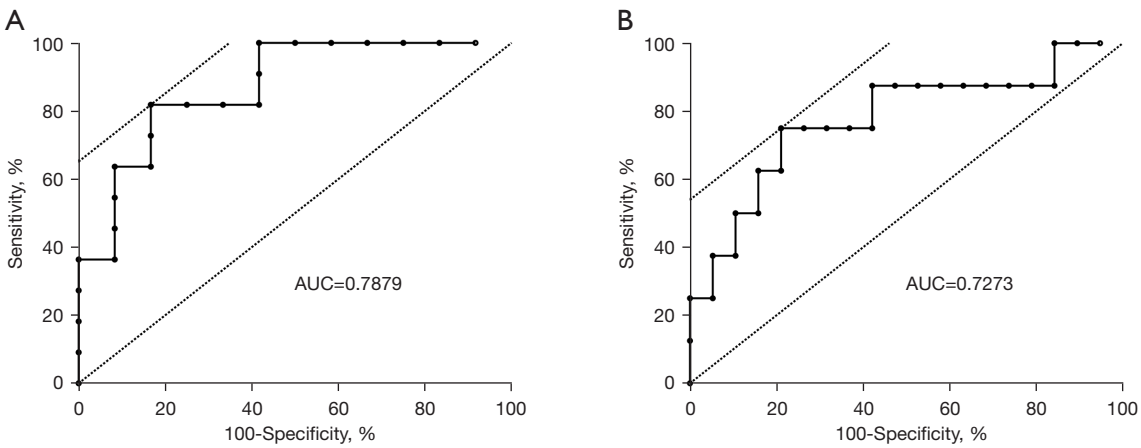

Figure 3 Determination of the optimal cutoff value of the circulating KL-6 concentration among intrapulmonary ARDS patients (A) and extrapulmonary ARDS patients (B) using ROC curve analysis. The highest circulating KL-6 concentration in an individual patient, whereby the vertical axis indicates the true positive rate (sensitivity), the horizontal axis presents the false-positive rate (100% – specificity), and the AUC represents the proportion of patients who died at the time of a positive test (elevated serum KL-6 level). KL-6, Krebs von den Lungen-6; ARDS, acute respiratory distress syndrome; ROC, receiver operating characteristic; AUC, area under the curve.

Among extrapulmonary ARDS patients, the circulating KL-6 concentration reached its peak on Day 3.5±3.0 among deceased patients and on Day 2.2±2.0 among surviving patients. The peak concentrations were 1,092.2±432.8 and 723.4±288.5 U/mL, respectively. Thus, there was a marked difference in the peak circulating KL-6 dynamic concentration between the deceased and surviving patients (P=0.0253; *Figure 2B*).

Prognostic significance of circulating KL-6 levels among deceased and surviving intra- and extrapulmonary ARDS patients

To determine the optimal cutoff value of circulating KL-6 concentration among intrapulmonary ARDS patients, we employed ROC curve analysis using the largest concentration of circulating serum KL-6 assay (*Figure 3A*).

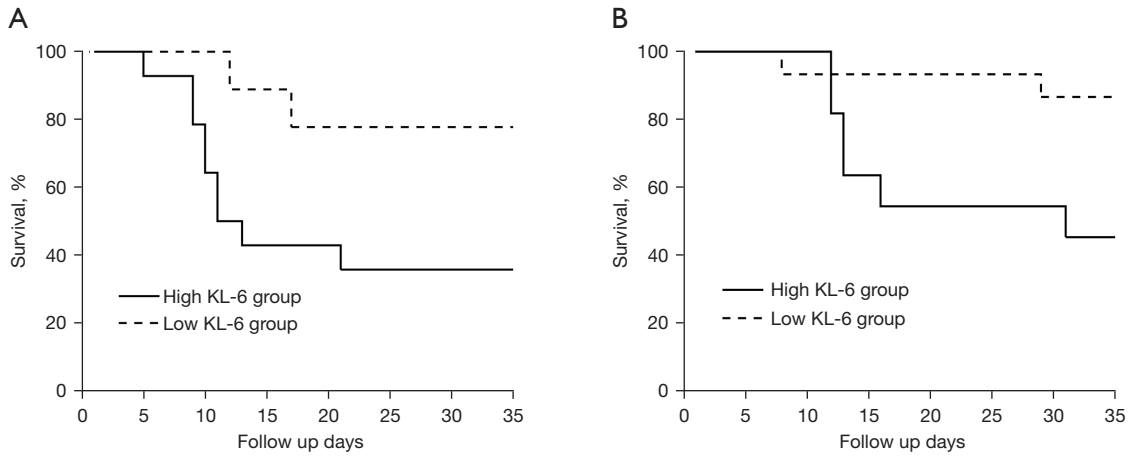

Figure 4 Circulating KL-6 concentration-based OS rates among intrapulmonary ARDS patients (A) and among extrapulmonary ARDS patients (B). The OS rates were drastically reduced among patients with elevated circulating KL-6 content compared to patients with reduced circulating KL-6 content in both intra- and extrapulmonary ARDS patients. KL-6, Krebs von den Lungen-6; OS, overall survival; ARDS, acute respiratory distress syndrome.

We revealed a circulating KL-6 content optimal cutoff value of 1,452.3 U/mL for estimating mortality risk, carrying a sensitivity and specificity of 81.82% and 83.33%, respectively, as well as a likelihood ratio of 4.91 and area under the curve (AUC) of 0.7879. Among the 23 intrapulmonary ARDS patients, 14 displayed circulating KL-6 levels above the threshold value, and 9 of those patients later expired. In contrast, only 2 out of 9 patients below the threshold value expired (Mann-Whitney *U* test, P=0.0014).

Based on our ROC curve analysis, the largest circulating KL-6 concentration among extrapulmonary ARDS patients revealed (*Figure 3B*) an optimal cutoff value of 828.2 U/mL for predicting associated mortality risk. The related sensitivity was 75.00%, and the specificity was 78.95%, with a likelihood ratio of 3.56 and an AUC of 0.7273. Among the 27 extrapulmonary ARDS patients, 11 exhibited circulating KL-6 concentration above the threshold value, and 6 of those patients later expired. In contrast, only 2 of the 16 patients below the cutoff value died (P=0.0004).

We employed cutoff-value-based Kaplan-Meier curve analysis to assess overall survival (OS) at days following diagnosis among intrapulmonary ARDS patients. We demonstrated that patients with circulating KL-6 concentration >1,452.3 U/mL experienced reduced OS compared to patients with circulating KL-6 concentration <1,452.3 U/mL (log-rank test, P=0.0006, *Figure 4A*).

The 28-day OS after diagnosis among extrapulmonary ARDS patients was assessed via cutoff value-based Kaplan-Meier curve analysis. We demonstrated that patients with circulating KL-6 concentration >828.2 U/mL experienced similar reduced OS rates as intrapulmonary ARDS patients compared to patients with reduced KL-6 concentration (P=0.0082, *Figure 4B*).

Discussion

Herein, circulating KL-6 concentration was assessed among intra- and extrapulmonary ARDS patients at various time points, as well as among patients who died and those who survived. We demonstrated that the circulating KL-6 concentration among expired intrapulmonary ARDS patients was markedly elevated compared to that among surviving patients during 0–7 days of the study. Meanwhile, among the extrapulmonary ARDS patients, the circulating KL-6 concentration of both the deceased and surviving patients were markedly different only on Day 1 and were not statistically significant at other time points. An assessment of the highest circulating KL-6 concentration from consecutive samples of each patient revealed that the circulating KL-6 concentration was markedly elevated among expired patients relative to the surviving intrapulmonary ARDS patients. Furthermore, we found that KL-6 concentration above the cutoff value was a strong indicator of poor OS in patients with both intra- and extrapulmonary ARDS up to 28 days after diagnosis.

Our analyses revealed that elevated circulating KL-6 concentration within 0–7 days of diagnosis among intrapulmonary ARDS patients was strongly linked to poor prognosis. Within 7 days of ARDS diagnosis, the circulating KL-6 concentration was markedly elevated among expired versus surviving patients. Early-stage intrapulmonary ARDS is typically dominated by damage to alveolar epithelial cells. KL-6 is ubiquitously expressed, and it obviously expressed when AT-II was damaged or regenerated. Hence, enhanced circulating KL-6 concentration may be closely related to the severity of damage to alveolar epithelial cells (5,7). Given this evidence, circulating KL-6 concentration may serve as a strong indicator of severely impaired AT-II and poor patient prognosis (8,9).

In the present study, we revealed that the circulating KL-6 concentration of expired intrapulmonary ARDS patients was markedly elevated compared to that of surviving patients within 1 week of diagnosis. However, circulating KL-6 concentration among expired patients reached its peak on Day 3.0±1.5, whereas among survivors, it was on Day 2.4±2.4. Therefore, at least one circulating KL-6 concentration evaluation within 7 days of ARDS diagnosis may be helpful in predicting prognosis. Over time, a decreasing trend in circulating KL-6 concentration was evident among expired patients; however, no reliable data were found to explain the gradual decrease in circulating KL-6 concentration among these patients. Prior investigations reported (10) that AT-II survival correlates with the severity of its damage. Even though AT-II has the potential to proliferate, once the damage becomes too severe, these cells are typically replaced by epithelial cells of bronchial origin. As a result, AT-II cells lose their regenerative and proliferative capacities, eventually resulting in fibrosis development and progression. Therefore, it is speculated that in the early stage of intrapulmonary ARDS diagnosis, AT-II may be damaged and regenerated, thus resulting in a rise in circulating KL-6 content. Moreover, with severely damaged AT-II, epithelial cell repair is also impaired, possibly bringing about cell death and an eventual reduction in circulating KL-6 content.

Herein, circulating KL-6 concentrations among surviving and deceased extrapulmonary ARDS patients were significantly different only on Day 1 after diagnosis. The early stage of extrapulmonary ARDS is typically dominated by capillary vascular endothelial cell damage. Meanwhile, the alveolar-capillary barrier is less damaged; therefore, large molecules such as KL-6 are not able to cross the barrier (2). KL-6 promotes fibroblast-based collagen secretion and accelerates wound healing, which, in turn, participates in the tissue fibrosis process (11), thereby leading to the unfavorable prognosis of KL-6 levels among extrapulmonary ARDS patients. This may be the reason why we observed no significant difference in circulating KL-6 concentration between the surviving and deceased patients.

Circulating assays of extrapulmonary ARDS patient serum KL-6 levels collected at any time point showed no significant differences between deceased and surviving patients. In fact, only on Day 1 was the circulating KL-6 concentration markedly distinct between the deceased and surviving patients. This was in contrast to previous large-scale reported results (5,9,12). When comparing circulating KL-6 concentration using the highest circulating assay value per patient, we demonstrated that circulating KL-6 concentration was markedly higher among expired patients relative to those of the surviving patients. Since the circulating KL-6 content reflects the extent of alveolar epithelial injury, it has certain predictive value for clinical regression among extrapulmonary ARDS patients. However, the present study concluded that the enhanced circulating KL-6 concentration among intrapulmonary ARDS patients was more valuable in predicting clinical prognosis.

Conclusions

This study provides a reference value for the efficacy of the serum KL-6 level for predicting prognosis in patients with intra- and extrapulmonary ARDS; however, there are several limitations. Specifically, the sample size was small, and the study duration was short. Further studies with larger patient populations over longer times are needed to verify the accuracy of our conclusions. Despite these limitations, this study has several strengths. First, this is the first study to consider the serum KL-6 level in relation to the origin of primary ARDS, thus providing insight into potentially different mechanisms underlying cell damage in ARDS. Second, given that the median survival time of ARDS patients is short, repeated measurements at four-time points (Days 0, 1, 3, and 7) during the early stage of disease progression provide an accurate portrayal of KL-6 kinetics. Third, given the ICU setting of this study, there was no loss to follow-up in our population, thus removing the chance of emigrant selection bias. Finally, the binary cutoff generated in the study was found to have high predictive value and thus has the potential for further external validation and application in clinical settings.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1787/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1787/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1787/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1787/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Ethics Committee of the China-Japan Union Hospital of Jilin University (No. 20220609030), and informed consent was taken from all the patients.

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