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# Serum Krebs von den Lungen (KL-6) level as a marker of exacerbation of interstitial lung diseases

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## Abstract

**Background:** Krebs von den Lungen (KL-6) is elevated in serum of interstitial lung disease (ILD) patients based on its leakage from the alveolar space into the blood; KL-6 is significantly higher in patients with acute exacerbation of ILDs (AE-ILD) compared with stable patients. This study aimed to determine the sensitivity and specificity of KL6 to detect AE-ILD.

**Results:** This is a prospective cross sectional observational study was carried out on 88 subjects at the Chest Department, Minia Cardiothoracic University Hospital, during the period from August 2018 to August 2019. This study was approved by the hospital research ethics board of Minia University and informed consent was obtained. History, examination, spirometry, ABGs, X-ray, HRCT, CBC, ESR, CRP, and KL6 levels were done to both stable and exacerbation groups of ILDs. The level of biomarkers is compared between both groups and control.
Statistical analysis done by using IBM SPSS statistical package version 20 ($\chi^2$ test and independent sample *t* test, ANOVA test, bivariate Pearson correlation analysis, and ROC curve analysis).
The study showed that there is a significant difference between stable and exacerbating groups regarding fever, signs of RHF, dyspnea scale, FVC, and PaO2.

**Conclusion:** KL-6 cutoff ≥ 187.5 U/ml could exhibit AE-ILDs with a sensitivity of 98% and a specificity of 97%. KL-6 is a more sensitive and specific marker to detect AE-ILD.

**Keywords:** Interstitial lung diseases (ILD), Exacerbation, Krebs von den Lungen (KL-6), Biomarkers

## Background

Acute exacerbation of interstitial lung diseases (AE-ILD) has considerable impact on morbidity, mortality, and quality of life. Pulmonary function testing (PFT) is used to monitor disease activity and predict its prognosis [1]. However, these examinations require specific medical facilities and may result in considerable discomfort to patients. Serum biomarkers offer several advantages over other methods, including being generally easy to perform, inexpensive, reproducible, and less invasive, Thus, the identification of serum biomarkers for interstitial lung diseases (ILDs) would greatly improve current diagnostic methods [2]. In patients with ILD, Krebs von den Lungen (KL-6) is strongly expressed on alveolar macrophages and the type II pneumocytes that are regenerated over the alveolar basement membrane after the death of type I pneumocytes during the first stage of fibrosing lung injury. The soluble form of KL-6 is evaluable in serum based on its leakage from the alveolar space into the blood due to an enhanced permeability or destruction of the air-blood barrier in the diseased lungs [3]. Serum KL-6 levels are elevated in several ILDs including idiopathic pulmonary fibrosis (IPF), hypersensitivity pneumonitis (HP), and connective tissue disease associated ILD (CTD-ILD) [4]. Baseline KL-6 is significantly higher in acute exacerbation of ILDs compared with stable disease [5]. Determination of the serum KL-6 in patients with AE-ILD has many advantages over conventional chest radiographs and high-resolution computed tomography (HRCT), and

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spirometry:KL-6 level is expressed as a quantitative value, can be measured repeatedly, and can be also measured in seriously ill patients, such as those under mechanical ventilation.

This study aimed to do the following:

1. Determine the sensitivity and specificity of KL6 to exhibit AE-ILD compared to other conventional laboratory markers
2. Correlate between level of KL-6 and both functional and laboratory parameters in patients with AE-ILD.

## Methods

### Study design

This is a prospective cross sectional observational study and was carried out on 88 subjects at the Chest Department, Minia Cardiothoracic University Hospital, during the period of 1 year from August 2018 to August 2019. This study was approved by hospital research ethics board of Minia University, and informed consent were obtained from either patients themselves or their relatives; sample size was according to time criteria.

Inclusion criteria are as follows:

1. Patients of AE-ILD are defined as a significant respiratory deterioration in the previous month and new typical radiologic findings on HRCT such as diffuse, bilateral ground-glass opacification, and the absence of other causes like fluid overload, left heart failure, or pulmonary embolism [6].
2. Patients of stable idiopathic pulmonary fibrosis (IPF) diagnosed as usual interstitial pneumonia (UIP) based on pattern of HRCT include the presence of bilateral, predominantly sub pleural, basal reticular abnormalities, or honeycombing and the absence of additional features incompatible with a diagnosis of IPF [7].
3. Patients of stable HP based on exposure to known causes of HP, abnormal PFT, and typical HRCT features of HP-like scattered ground-glass opacities, areas of mosaic appearance and air trapping, centrilobular nodules, and interlobular septal thickening [8].
4. Healthy control subjects of matched age, sex, and smoking index

Cases were classified into 3 groups:

1. *Group I*. Twenty-six patients with stable ILDs including the following:
   (a) Two patients with IPF
   (b) Twenty-four patients with Hypersensitivity pneumonitis
2. *Group II*. Forty-seven patients with AE-ILD including the following:
   (a) Eighteen patients with AE-IPF
   (b) Twenty-nine patients with AE of HP
3. *Group III*. Fifteen healthy control subjects

Exclusion criteria are as follows:

1. Pulmonary diseases other than ILDs (asthma, bronchiectasis, pneumonia, lung abscess, tuberculosis)
2. Pulmonary and extra pulmonary malignancies
3. Pulmonary embolism, fluid overload, and left sided heart failure
4. Cases of exacerbation due to pneumonia

All patients were subjected to the following:

1. History taking including age, sex, and smoking status
2. Physical examination including fever, clubbing, cyanosis, and signs of right-sided heart failure (RHF), i.e., congested neck veins, and lower limb edema.
3. Modified Medical Research Council (mMRC) dyspnea scale [9]
4. Spirometry was performed using a spirometer (ZAN 300, Oberthulba, Germany) as best of three consecutive readings within 100 ml [10].
5. Chest x-ray
6. High-resolution computed tomography (HRCT) chest
7. Arterial blood gasses (ABGs): partial pressure of $O_2$ ($PaO_2$), partial pressure of carbon dioxide ($PaCO_2$), and $O_2$ saturation ($SO_2$)
8. Laboratory investigations were done for both patient and control groups including the following:
   (a) Complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and renal and liver function tests
   (b) Serum human Krebs von den Lundgen-6 (KL6) using Bioassay Technology Laboratory KL-6 kit, Shanghai, China. This kit is an enzyme-linked immunosorbent assay (ELISA).

### Statistical analysis

Data were collected, revised, verified, coded, and then entered PC for statistical analysis done by using IBM SPSS statistical package version 20.

The following had been done:

1. Descriptive statistics
   (a) *For qualitative data*. Number (*N*) and percentage (%)
   (b) *For quantitative data*. Minimum, maximum, mean ($X\sim$), and standard deviation (SD)
2. Comparison of independent quantitative data among three groups by ANOVA and post hoc test.
3. Comparison of independent quantitative data among two groups by independent sample *t* test

**Table 1** Demographic data of all studied groups

| | Group I (stable), *N* = 26 | Group II (exacerbation), *N* = 47 | Group III (healthy control), *N* = 15 | *P* value | | |
|---|---|---|---|---|---|---|
| | | | | Group I and II | Group I and III | Group II and III |
| Age (years) | | | | | | |
| Mean ± SD | 51.03 ± 14.47 | 54.80 ± 15.06 | 41.73 ± 13.01 | 0.293 | 0.052 | 0.062 |
| Range | 23–89 | 21–85 | 27–66 | | | |
| Sex, *n* (%) | | | | | | |
| Males | 4 (15.4%) | 10 (21.3%) | 6 (40%) | 0.542 | 0.081 | 0.153 |
| Females | 22 (84.6%) | 37 (78.7%) | 9 (60%) | | | |
| Smoking | | | | | | |
| Yes | 2 (7.7%) | 2 (4.3%) | 0 (0%) | 0.860 | 0.114 | 0.089 |
| No | 22 (84.6%) | 39 (83%) | 15 (100%) | | | |
| Ex | 2 (7.7%) | 6 (12.8%) | 0 (0%) | | | |

*SD* standard deviation

4. Comparison of categorical data by Chi-squared test
   (a) Bivariate Pearson correlation analysis for association analysis
   (b) ROC curve analysis of different variables to assess diagnostic ability among cases and controls

For all tests, probability ($p$) was considered:

- Non-significant if ≥ 0.05
- Significant if < 0.05
- Highly significant if < 0.01
- Very highly significant if < 0.001

Grade of correlation or association is as follows:

- 0.00 to 0.24, weak or no association
- 0.25 to 0.49, fair association
- 0.50 to 0.74, moderate association
- 0.75+, strong association

## Results

In this study, mostly there was no statistical difference between group I (stable ILDs), group II (AE-ILDs), and healthy control as regards age, sex, and smoking status (Table 1).

The study showed that there was a significant difference between stable and exacerbation groups regarding fever, signs of RHF, and dyspnea scale (Table 2).

It was also found that patients with exacerbation had a statistically significant decrease in forced vital capacity (FVC), $PaO_2$, and $O_2$ saturation and a statistically significant increase in white blood cells count (WBCs) and KL6 in comparison with stable one (Tables 3 and 4).

**Table 2** Clinical characteristics of the diseased groups

| | Group I (stable), *N* = 26 | Group II (exacerbation), *N* = 47 | *p* value |
|---|---|---|---|
| Fever | | | |
| Yes | 1 (3.8%) | 17 (36.2%) | **0.002** |
| No | 25 (96.2%) | 30 (63.8%) | |
| Signs of RHF | | | |
| Lower limb edema | | | |
| Yes | 2 (7.7%) | 25 (53.2%) | **< 0.001** |
| No | 24 (92.3%) | 22 (46.8%) | |
| Congested veins | | | |
| Yes | 0 (0%) | 9 (19.1%) | **0.022** |
| No | 26 (100%) | 38 (80.9%) | |
| mMRC | | | |
| II | 9 (34.6%) | 4 (8.5%) | **0.004** |
| III | 16 (61.5%) | 30 (63.8%) | |
| IV | 1 (3.8%) | 13 (27.7%) | |

*RHF* right-sided heart failure, *mMRC* modified medical research council

**Table 3** Radiological findings of the diseased groups

| HRCT | Group I (stable), *N* = 26 | Group II (exacerbation), *N* = 47 | *p* value |
|---|---|---|---|
| Reticulation | 4 (15.4%) | 12 (25.5%) | 0.068 |
| Ground-glass | 21 (80.8%) | 17 (36.2%) | **< 0.001** |
| Honeycombing | 1 (3.8%) | 18 (38.3%) | **< 0.001** |

*HRCT* high-resolution computed tomography

We also discovered that the ground-glass and honeycombing appearance were more evident in exacerbation group ($p$ = 0.003) (Table 3).

There is significant increase in KL6 level in IPF versus both hypersensitivity and connective tissue (CT) disease $r$ ($p$ = 0.006 and 0.039), respectively (Fig. 5).

At a cut-off estimation of 187.5 U/mL, KL6 had an affectability of 98% and specificity of 97% to exhibit AE-ILD (Tables 5 and 6, Fig. 1).

The affectability and specificity of WBCs to exhibit AE-ILD were 60% and 70% with a cut-off estimation of 8.4 ($\times 10^3/\mu L$) (Table 6, Fig. 2), while the affectability and specificity of erythrocyte sedimentation rate (ESR) to exhibit AE-ILD were 54% and 56.7% with a cut-off estimation of 25.5 (Table 6, Fig. 3).

However, the affectability and specificity of C-reactive protein (CRP) to exhibit AE-ILD were 94% and 66.7% with a cut-off estimation of 3 (Table 6, Fig. 4).

In this work, there was a significant negative correlation between KL-6 level and both $PaO_2$ and FVC ($p$ = 0.0001, 0.0001; $r$ = − 0.0714, − 0.240, respectively) (Fig. 5).

## Discussion

Acute exacerbation is associated with higher morbidity and mortality in ILDs. Most of patients of AE-ILD are critically ill and some of them need intensive care and sometimes mechanical ventilation, so we are in need to find an easy, rapid, repeatable, and non-invasive method for diagnosis and follow-up. Serum KL-6 may be a useful biomarker in ILD [11, 12].

This study aimed to determine the sensitivity and specificity of KL6 to exhibit AE-ILD compared to other conventional laboratory markers, and to correlate between its serum level and clinical, functional, and laboratory parameters in those patients groups.

Our key findings were summarized in several points; clinical, functional, and radiological parameters of AE-ILD were taken as a primary outcome measures; patients with exacerbation were more feverish than stable patients; this accord to Olson et al.'s study which revealed that productive cough, fever, and flu-like symptoms are a clinical presentation of AE-ILD [13]. On the other hand, Kim et al. revealed that only one out of his 147 patients developed a mild fever [14].

This study also showed that there was a significant statistical difference between stable and exacerbating groups regarding lower limb edema and congested neck veins which is corresponding to a study by Hoeper et al., who informed that severe pulmonary hypertension (PH) with right heart failure (RHF), elevated jugular venous pressure, pulsatile, tender hepatomegaly, and peripheral edema can present with AE-ILD [15].

As regards dyspnea grade, this study revealed that patients with exacerbation had more dyspnea.

Collard et al. demonstrated that AE-ILD is usually accompanied by rapid deterioration of respiratory symptoms with increased dyspnea in the last month [6].

In another study by Leuschner and Behr, AE-ILD was characterized by rapid respiratory deterioration (marked increase in dyspnea and hypoxemia) and associated with new widespread alveolar abnormality [16].

We also found a significantly decrease in FVC in patients with AE-ILDs in comparison with the stable one. This match up with a study of Kondoh et al., which revealed that a decreased FVC is association with increased risk of AE-IPF [17]; also, a study of Collard et al. established that AE is more commonly observed in those with a low and/or recent decline in FVC, low DLCO, or those requiring supplemental oxygen [18].

Our study also reported a significant decrease in partial arterial oxygen pressure ($PaO_2$) and oxygen saturation among exacerbation group, which was compatible with a

**Table 4** Functional parameters of diseased groups

| | Group I (stable), *N* = 26 Mean ± SD, Range | Group II (exacerbation), *N* = 47 Mean ± SD, Range | *p* value |
|---|---|---|---|
| FEV1% | 72.42 ± 18.35, 44–115 | 63.19 ± 17.57, 20–97 | 0.038 |
| FVC% | 68.80 ± 17.67, 42–100 | 55.29 ± 13.52, 20–94 | **0.001** |
| $PaO_2$ mmHg | 77.88 ± 8.37, 63–89 | 48.82 ± 11.97, 29–95 | **< 0.001** |
| $O_2$ saturation% | 93.00 ± 7.19, 59–98 | 77.93 ± 11.10, 53–96 | **< 0.001** |

*FEV1* forced expiratory volume in first second, *FVC* forced vital capacity, *$PaO_2$* partial pressure of oxygen

**Table 5** Laboratory findings of studied groups

| | Group I (stable), *N* = 26 | Group II (exacerbation), *N* = 47 | Group III (healthy control), *N* = 15 | *P* value | | |
|---|---|---|---|---|---|---|
| | Mean ± SD, Range | Mean ± SD, Range | Mean ± SD, Range | Group I and II | Group I and III | Group II and III |
| WBCs (×$10^3$/μL) | 7.28 ± 2.08, 4–11 | 9.85 ± 2.68, 3.8–15 | 7.34 ± 1.88, 4.9–10.7 | **< 0.001** | 0.940 | **0.002** |
| ESR1 (mm/h) | 24.34 ± 26.20, 5–100 | 25.21 ± 23.11, 5–90 | 10.66 ± 8.63, 5–40 | 0.981 | **0.047** | **0.031** |
| ESR2 (mm/h) | 43.61 ± 37.81, 10–130 | 43.85 ± 32.07, 10–115 | 21.20 ± 17.28, 10–80 | 0.976 | **0.034** | **0.019** |
| CRP (mg/l) | 16.38 ± 44.14, 0–192 | 25.27 ± 25.20, 0–192 | 1.60 ± 3.56, 0–12 | 0.233 | 0.136 | **0.010** |
| KL6 (U/ml) | 137.38 ± 34.24, 95–284 | 301.89 ± 67.29, 140–532 | 48.40 ± 11.63, 27–53 | **< 0.001** | **< 0.001** | **< 0.001** |

*WBCs* white blood cells, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *KL-6* Krebs von den Lungen factor 6

study by Kondoh et al., who found that impaired baseline oxygenation is one of the risk factors for developing exacerbation [17].

The ground-glass and honeycombing appearance were evident in group II compared with group I ($p$ = 0.003). This agreed with a study by Collard et al. that showed that in most cases, AE-ILD manifests radiographically as new diffuse ground-glass opacification on chronic fibrotic changes consistent with fibrosing ILDs on HRCT [6].

Furthermore, serum level of biomarkers of AE-ILD (KL6, WBCs, ESR, and CRP) and their sensitivity and specificity to exhibit acute exacerbation were taken as a secondary outcome measures.

We found that WBCs were significantly higher in AE-ILD patient group (9.85 ± 2.68 × $10^3$/μL) than stable ILD patient group (7.62 ± 2.69 × $10^3$/μL); similarly, Ambrosini et al. also revealed increase in WBC count, C-reactive protein, and lactate dehydrogenase in AE-IPF, but these are non-specific and can be elevated in other entities such as acute interstitial pneumonitis (AIP) [19].

Akira et al. also revealed that there was a statistically significant difference between values of WBC, CRP, lactate dehydrogenase (LDH), and serum albumin before the exacerbation and those at the exacerbation. Forty-four patients presented an increase of WBC on the exacerbation. Elevated values of CRP and LDH were found in 55 and 43 cases, respectively [20].

Our work has shown that serum KL-6 level was elevated in patients with stable ILDs versus healthy control subjects.

Many other studies have supported that finding; Ohnishi et al. noted that higher levels of KL-6 are an important indicator for diagnosis of IPF [4].

Also, Zhu et al. have shown higher KL-6 levels in patients with idiopathic interstitial pneumonia than other types of parenchymal diseases [21].

Moreover, Qin et al.'s study also reported that KL-6 levels in ILD were significantly higher than pneumonia, other types of parenchymal diseases ($P$ < 0.000), and healthy controls ($P$ < 0.05) [22].

On comparing serum level of KL6 in stable versus exacerbation group, our study also revealed that there is elevation its level in AE-ILDs, This was also matched with a study by Ohshimo et al., which showed that the higher serum level of KL-6 at baseline in ILDS was a predictor for AE [23]. In the same hand, Okamoto et al. had reported an increase in serum KL-6 level during AE-HP [24].

It is well known from many previous studies that there was a variability in KL-6 cut-off estimation in both stable and exacerbation groups and among different types of ILDs. This was may be a consequence of racial variation, moreover, a variation in KL-6 kit type and the studied type of ILD.

Qin et al. found a cut-off estimation of KL6 312 U/ml, with affectability and specificity to diagnose ILD 84.7% and 85.3%, respectively [22].

Hamai et al. found higher range of KL6 (550–700 U/Ml) for differentiating IPF patients from control persons [12]. However, in a study by Okamoto et al., this marker in acute HP was 2710 U/ml and in chronic HP 1500 U/ml; these values were much higher than other studies [24].

Ohshimo et al. found that patients with AE had much more elevation in KL6 levels than stable IPF ($p$ < 0.0001), whereas serum chemokine c ligand 18 (CCL18) levels

**Table 6** ROC curve analysis of KL6, WBCs, ESR, and CRP between stable and exacerbation

| | AUC | *p* value | Sensitivity | Specificity | Positive predicted value (PPV) | Negative predicted value (NPV) | Confidence interval (CI 95%) | Cut-off point |
|---|---|---|---|---|---|---|---|---|
| KL6 | 0.977 | < 0.001 | 97.9% | 62% | 72.06 | 96.88 | 0.943–1 | 187.5 |
| WBC | 0.779 | < 0.001 | 70.2% | 69.2% | 69.31 | 69.7 | 0.674–0.883 | 8.55 |
| ESR | 0.504 | 0.124 | 53.2% | 67.7% | 62.35 | 59.13 | 0.362–0.646 | 25 |
| CRP | 0.825 | < 0.001 | 93.6% | 69.2% | 75 | 90.7 | 0.702–0.948 | 3 |

*WBCs* white blood cells, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *KL-6* Krebs von den Lungen factor 6

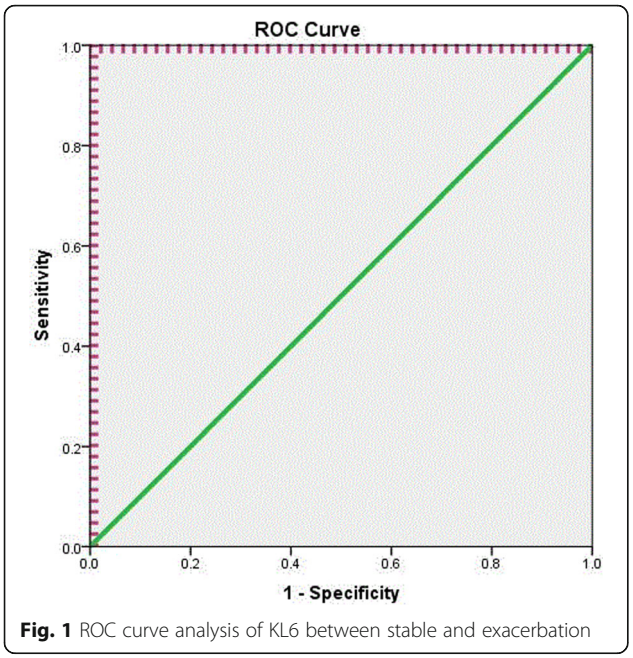


**Fig. 1** ROC curve analysis of KL6 between stable and exacerbation

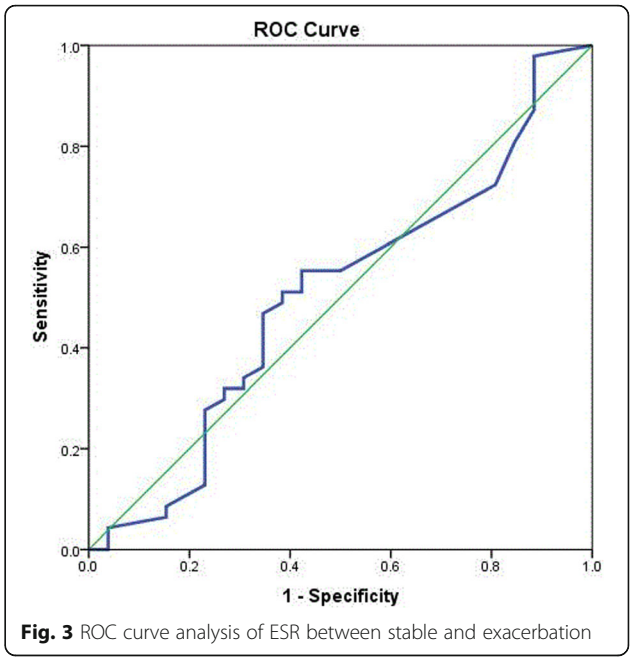


**Fig. 3** ROC curve analysis of ESR between stable and exacerbation

showed no difference between these groups ($p$ = 0.13). At a level of 1300 U/mL, the sensitivity and specificity of this marker to predict AE were 92% and 61% [23].

KL-6 values 500 U/mL was considered the common cutoff estimation in many studies [12].

Correspondingly, the current study revealed a serum KL-6 cut-off estimation of 187.5 U/mL in AE-ILDs with an affectability of 98% and specificity of 97%.

In this work, there is a significant negative correlation between KL-6 level and oxygen saturation, $PaO_2$, and FVC. This was consistent with a study by Qin et al. that reported a decrease in $O_2$ saturation and lung functions in patients with elevated KL-6 levels [22].

As a comparison between KL6 with other markers of AE-ILD as ESR, CRP, and WBCs, it was noticed in the current study that KL6 was a more sensitive and specific biomarker to detect AE-ILD than other markers.

Ambrosini et al. also revealed increase in white blood cell count, C-reactive protein, and lactate dehydrogenase in AE-IPF, but these are non-specific and can be

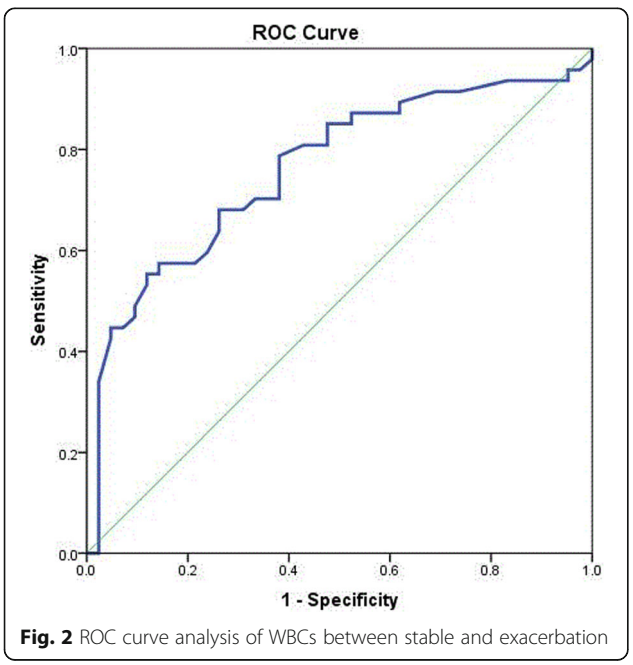


**Fig. 2** ROC curve analysis of WBCs between stable and exacerbation

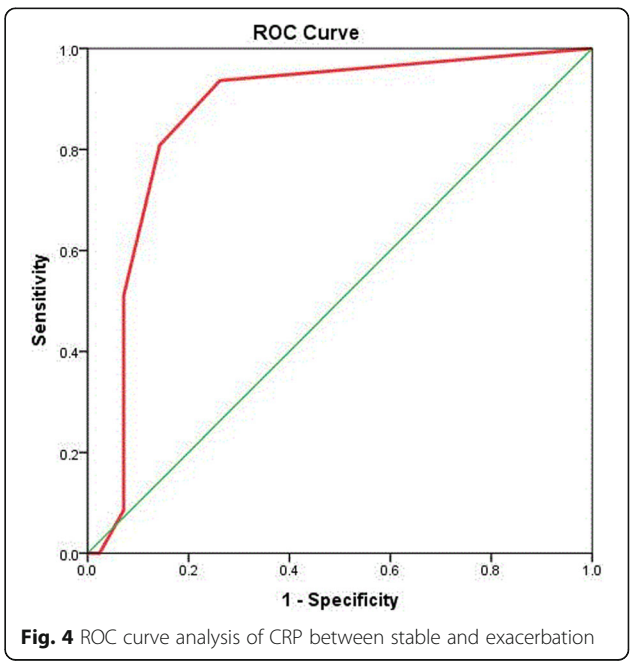


**Fig. 4** ROC curve analysis of CRP between stable and exacerbation

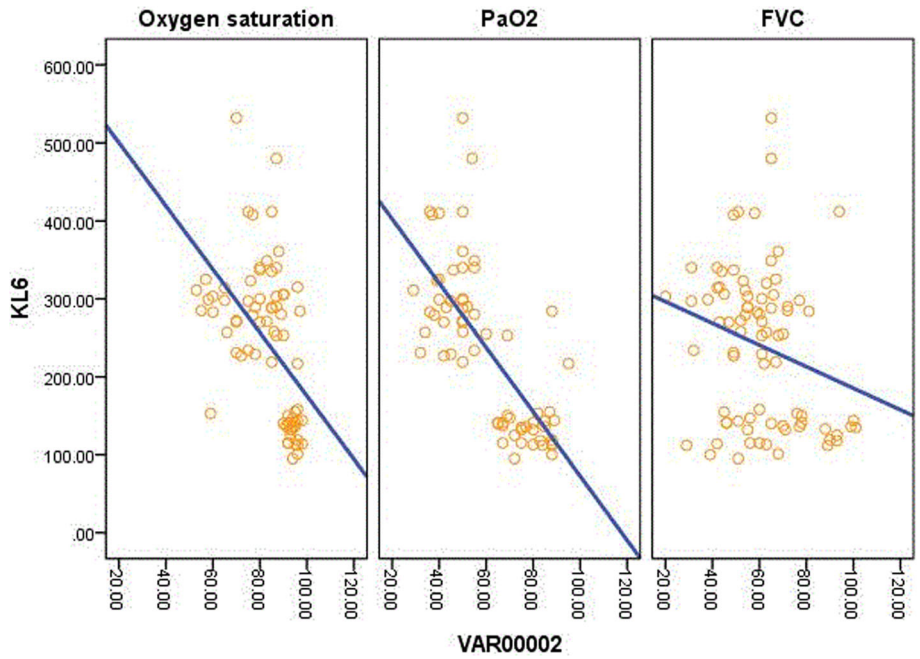


**Fig. 5** Correlation between KL6 and $O_2$ saturation, $PaO_2$, and FVC among all patients

elevated in other entities such as acute interstitial pneumonitis (AIP) [19].

Also in a study of Park et al., they found that patients with AE-ILD had increased WBC, ESR, and CRP levels but they did not study their specificity [25].

## Conclusion

KL-6 cutoff estimation ≥ 187.5 U/ml could exhibit AE-ILDs; there was a significant negative correlation between KL-6 levels and both $SO_2$ and FVC; moreover, KL-6 is a more sensitive and specific marker to detect AE-ILD compared to other markers like TLC, ESR, or CRP.

It is known that our study had a limited numbers of patients. Further prospective clinical studies of larger number of patients should be conducted to precisely determine the prognostic value of KL-6 in AE-ILD and to compare its specificity to other biomarkers of exacerbation.

### Abbreviations

KL-6: Krebs von den Lungen; ILD: Interstitial lung diseases; AE-ILD: Acute exacerbation of ILDs; PFT: Pulmonary function testing; IPF: Idiopathic pulmonary fibrosis; HP: Hypersensitivity pneumonitis; CTD-ILD: Connective tissue disease associated ILD; UIP: Usual interstitial pneumonia; mMRC: Modified Medical Research Council; FVC: Forced vital capacity; FEV1: Forced expiratory volume in first second; HRCT: High-resolution computed tomography; ABGs: Arterial blood gasses; CBC: Complete blood count; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; WBCs: White blood cells count; PH: Pulmonary hypertension; RHF: Right heart failure; $PaO_2$: Partial arterial oxygen pressure; AIP: Acute interstitial pneumonitis; CCL18: Serum chemokine c ligand 18

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### Authors' contributions

ZS conceived the publication design and prepared the manuscript. MHM revised the methods and results. EA performed the laboratory part of the research. MM collected the patients' data. All authors read and approved the final manuscript.

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### Availability of data and materials

Not applicable.

### Ethics approval and consent to participate

This study was approved by the hospital research ethics board of Minia University and informed consent were obtained from either patients themselves or their relatives.
Committee's reference number: not available

### Consent for publication

Not applicable.

### Competing interests

No competing interests.

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