Could KL-6 levels in COVID-19 help to predict lung disease?

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Abstract

Background: Coronavirus disease COVID-19 has become a public health emergency of international concern. Together with the quest for an effective treatment, the question of the post-infectious evolution of affected patients in healing process remains uncertain. Krebs von den Lungen 6 (KL-6) is a high molecular weight mucin-like glycoprotein produced by type II pneumocytes and bronchial epithelial cells. Its production is raised during epithelial lesions and cellular regeneration. In COVID-19 infection, KL-6 serum levels could therefore be of interest for diagnosis, prognosis and therapeutic response evaluation.

Materials and methods: Our study retrospectively compared KL-6 levels between a cohort of 83 COVID-19 infected patients and two other groups: healthy subjects (n = 70) on one hand, and a heterogenous group of patients suffering from interstitial lung diseases (n = 31; composed of 16 IPF, 4 sarcoidosis, 11 others) on the other hand. Demographic, clinical and laboratory indexes were collected. Our study aims to compare KL-6 levels between a COVID-19 population and healthy subjects or patients suffering from interstitial lung diseases (ILDs). Ultimately, we ought to determine whether KL-6 could be a marker of disease severity and bad prognosis.

Results: Our results showed that serum KL-6 levels in COVID-19 patients were increased compared to healthy subjects, but to a lesser extent than in patients suffering from ILD. Increased levels of KL-6 in COVID-19 patients were associated with a more severe lung disease.

Discussion and conclusion: Our results suggest that KL-6 could be a good biomarker to assess ILD severity in COVID-19 infection. Concerning the therapeutic response prediction, more studies are necessary.

Keywords: COVID-19, Interstitial lung disease, Lung infection, Biomarker, KL-6
Different studies highlight the importance of the quest for diagnostic or prognostic biomarkers in pulmonary fibrosing process [4–6]. Krebs von den Lungen 6 (KL-6) is a high molecular weight mucin-like glycoprotein produced by type II pneumocytes and bronchial epithelial cells. Its production is raised during epithelial lesions and cellular regeneration. In normal lungs, this glycoprotein is involved in fibroblast stimulation and apoptosis inhibition. In case of epithelial lesions, alveolo-capillary leak can occur and lead to an increase in serum KL-6 levels. Indeed, this modulation is not specific to COVID-19 infection and can be found in numerous other diseases associated with alveolar epithelial cell lesions (autoimmune diseases, radiation-associated pneumonia, drug-associated pneumonia, etc.). In COVID-19 infection, KL-6 serum levels could therefore be of interest for diagnosis, prognosis and therapeutic response evaluation.

Our study aims to compare KL-6 levels between a COVID-19 population and healthy subjects or patients suffering from interstitial lung diseases (ILDs). Ultimately, we ought to determine whether KL-6 could be a marker of disease severity and bad prognosis.

Materials and methods

Our study retrospectively compared KL-6 levels between a cohort of 83 infected patients (COVID-19 PCR positive patients hospitalized in Liège University Hospital between March 1st to April 20th 2020) and two other groups: healthy subjects (n = 70) on one hand, and a heterogenous group of patients suffering from ILD (n = 31; composed of 16 IPF, 4 sarcoidosis, 11 others) on the other hand.

Demographical (including age, sex, past medical history), clinical (including oxygen levels, Intensive Care Unit (ICU) indication) and admission laboratory indexes (including serum CRP, serum IL-6/KL-6, serum LDH, complete blood count, renal and liver functions) were collected. Chemistry analyses were run on the Abbott Alinity platform (Abbott Park, IL, USA) and KL-6 were measured with the Fujirebio Lumipulse 1200 instrument (Tokyo, Japan). High levels of KL-6 (45.6 UI/L) where defined as the value above the mean of the normal population + 2 SD (260.42 UI/L + (2 × 95.3)).

Results

Baseline characteristics and comparison between the three groups (Healthy Subjects, COVID-19 patients, ILD patients) are presented in Table 1.

Our results (Fig. 1) showed that KL-6 levels in COVID-19 patients were increased compared to healthy subjects, but to a lesser extent than in patients suffering from ILD (Fig. 1a). Of interest, increased levels of KL-6 in COVID-19 patients were associated with a more severe lung disease based on oxygen levels at admission to the ambient air [median SpO2 of 90% in high KL-6 level patients (n = 36) versus 94% in low KL-6 level patients (n = 47)]; p = 0.013; r = −0.271, Fig. 1b, c). However, high KL-6 were not linked to severe dyspnea (p = 0.585), or to ICU admission (p = 0.434). Similarly there was no association between high KL-6 levels and mortality (p > 0.05). Concerning laboratory values, despite an increase in CRP and fibrinogen levels in COVID-19 patients, there was no correlation between high KL6 levels and CRP (p = 0.482) or fibrinogen (p = 0.288). Confirmatory to previous results focusing on biological markers associated with severe COVID-19 infection, high KL-6 was correlated with high LDH.

Table 1 Baseline characteristics of the 3 groups, and comparison of their respective features

| Baseline characteristics | HS* (N = 70) | COVID19 (N = 83) | ILD (N = 31) | P values |
|--------------------------|-------------|-----------------|-------------|----------|
|                          | HS vs COVID19 | HS vs ILD | ILD vs COVID19 |
| Gender, M (%) | 35 (50%) | 52 (62.6%) | 23 (72%) | > 0.05 | < 0.05 | > 0.05 |
| Age | 58 (52–64) | 72 (58–82) | 69 (62–75) | < 0.001 | > 0.05 | < 0.01 |
| Leukocytes (/ml) | 6.21 (5.13–7.43) | 6.3 (4.68–8.61) | 8.77 (6.1–11.53) | > 0.05 | > 0.05 | < 0.01 |
| Neutrophils (/mm³) | 3.38 (2.81–4.22) | 4.65 (3.32–7.21) | 5.78 (4.31–8.19) | > 0.05 | < 0.001 | > 0.05 |
| Lymphocytes (/mm³) | 2.2 (1.71–2.49) | 0.92 (0.65–1.23) | 1.97 (0.87–2.2) | > 0.001 | < 0.001 | > 0.001 |
| CRP (mg/L) | 1.0 (0.5–2.4) | 6.3 (27–146) | 4.8 (2.1–9) | < 0.001 | < 0.001 | > 0.001 |
| Fibrinogen (g/L) | 2.88 (2.56–3.43) | 5.24 (4.03–6.23) | 3.43 (3.18–4.15) | > 0.001 | < 0.001 | < 0.001 |
| KL-6 (U/mL) | 254 (191–308) | 405 (277–592) | 897 (550–1885) | > 0.001 | < 0.001 | < 0.001 |

Data are expressed in median (IQR, inter quartile range)

Data are analyzed with Kruskall Wallis test and post Hoc: DunnTest and with Fisher’s test for the sex variable

* HS (healthy subjects): Complete blood count: N = 62; CRP: N = 52; Fibrinogen: N = 46
levels ($r = 0.31$, $p = 0.004$, Fig. 1c, f). Concerning platelet/lymphocyte ratio (PLR), we did not find a global correlation with KL-6, but noteworthy, high-KL-6 levels were associated to higher values of PLR ($p = 0.04$, Fig. 1d).

**Discussion**

KL-6 is known to be linked to alveolar damage [7]. Previous studies have demonstrated that COVID-19 infections were associated to potential lung fibrosing process induced by alveolar damage [8]. Therefore, using
biomarkers in order to predict lung evolution of severe COVID-19 infections could be of interest in order to identify patients with high risk of experiencing severe lung disease as well as significant parenchymal sequelae. Our study confirms that KL-6 level could be an indicator of COVID-19 infection severity. This was verified by the parallel impact on oxygen levels. Nevertheless, high KL-6 levels were not associated to more pronounced dyspnea, as this clinical feature was largely encountered in COVID-19 patients, regardless of their KL-6 levels. Similarly, there was no link between high KL-6 levels and ICU admission or death, for which we assume many other factors ought to be considered. Still, high KL-6 levels were interestingly correlated with other indicators of disease severity such as high LDH and PLR, as already mentioned in previous studies [9, 10].

Most recent studies focus on the current clinical-laboratory or CT features of COVID-19, but only a few are questioning the long-term impact of such infection. However, tissue inflammation and subsequent healing of the lungs can lead to pulmonary fibrosis. Our study confirms that KL-6—a recognized marker in lung fibrosing process—is increased in COVID-19 patients. This finding is in line with recent studies, describing the rise of other fibrosis biomarkers in this infection [8]. Therefore, the hypothesis of KL-6 as an indicator of lung disease (acute hypoxemia), and even of a possible evolution towards a fibrotic process in the course of a COVID 19 infection must be considered.

Conclusion
Taken together, these results suggest that KL-6 could be a good biomarker to assess ILD severity in COVID-19 infection. Concerning the therapeutic response and prognosis prediction, more studies are necessary.

Abbreviations
HS: Healthy subjects; ICU: Intensive care unit; ILD: Interstitial lung disease; KL-6: Krebs von den Lungen 6; LDH: Lactate dehydrogenase; PCR: Polymerase chain reaction; PLR: Platelet/lymphocyte ratio; SARS-COV 2: Severe acute respiratory syndrome-coronavirus.

Acknowledgements
The authors would like to highlight the work and dedication of the entire COVID-19 clinical investigation team at the University Hospital of Liège: Ancion A, Berg J, Bonhomme O, Bouquegneau A, Boye C, Bruls S, Darcis G, Delfragne J-G, Ghysen A, Gilbert A, Heinen V, Lambermont B, Malaise O, Martin M, Nguyen Dang D, Piazza J, Scezel D, Scezel J, Van Cauwenberge H, Von Frenckell C, Vroonen L.

Authors’ contributions
ANF conceptualization, data curation, investigation, writing, visualization, review, editing. LS resources, review. AL resources, review. MH data curation, formal analysis, visualization, review. BD review. FV review. BM review. MM review. RL review. EC conceptualization, methodology, investigation, resources, writing, review. JG conceptualization, methodology, data curation, investigation, writing, review. All authors read and approved the final manuscript.

Funding
There was no funding for this study. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 18 May 2020 Accepted: 29 October 2020

Published online: 24 November 2020

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