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Serum Krebs Von Den Lungen-6 (KL-6) as a useful biomarker for evaluation of COVID-19 disease severity

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Abstract
Aim: The study aimed to investigate the role of KL-6 in severe and non-severe COVID-19 patients.
Methods: In our study, 160 patients with COVID-19 were enrolled after being confirmed by RT-PCR. Estimation of KL-6, C-reactive protein (CRP) and lactate dehydrogenase (LDH) were performed, with comparing their levels in severe and non-severe cases. Study of the relationship between KL-6 and inflammatory marker was carried out by using the Spearman correlations.
Results: The results showed an increase in CRP, LDH & Kl-6 levels in the sera of COVID-19 patients, and highly significant increases were observed in their levels in severe patients than in non-severe cases (p= 0.001, p= 0.000 & p= 0.000), respectively. Spearman's correlation showed significant correlation between KL-6 & inflammation.
Conclusion: It can be concluded that KL-6 seems to be a useful biomarker in the prognosis of COVID-19.

Keywords: COVID-19, lung injuries, Kl-6

Introduction

COVID-19 is an enveloped RNA beta-coronavirus that causes a rapidly progressive disease, and is also termed as (Severe Acute Respiratory Syndrome Coronavirus 2 or SARS Co V2), a member of Corona viride family, and the first outbreak of the infection occurred in the city of Wuhan in China, 2019 [1, 2]. The World Health Organization (WHO) classified the disease to mild, moderate, severe & critical in accordance with the clinical symptom severity including; oxygen saturation levels (SpO_2) and radiological findings [3, 4, 5].

The frequently observed COVID-19 symptoms include sore throats, fevers, dry coughs, malaise as well as shortness of breaths, and they range from mild to severe manifestation, e.g. pnmonia to the acute respiratory distresses syndromes (ARDSs), which is the major death cause in COVID-19 due to diffuse damage to the alveolar cells [6, 7, 8]. One specific indicator of lung alveolar cell damage currently used in studies and researches is Von Den Lungen Kreb or (KL-6) [9, 10]. KL-6 is mucin glycoproteins with a highly molecular weight also referred to as Humans Trans membrane Mucin-1(MUC-1) which is expressed strongly on diverse epithelial cell type surfaces, particularly type-2 pneumocyte, respiratory bronchiolar epithelial cell and bronchial gland serus cell [11, 12]. KL-6/MUC1 is released into the surrounding tissues and subsequently enters the bloodstream when the alveolar epithelium and alveolar-capillary membrane are destroyed, leading to increased levels of KL-6/MUC1 [13, 14]. Many recent studies indicated that the serum concentrations of (KL-6) is raised in severe pulmonary involvement patient and was shown to be correlated with Covid-19 severity in various respiratory diseases especially in acute respiratory distress syndrome, interstitial lung disease (ILD), hypersensitivity pneumonitis and idiopathic palmonary fibroses (IPF) [15, 16], which could be applied as new biomarkers for assessment of the severity of COVID-19 and prediction of lung injury prognosis [17, 18]. Hence, our present study aims at determining KL-6 roles as a marker for pulmonary disease progressions and detecting COVID-19 prognostic values and severity.

Materials and Methods

In the present study, 160 COVID-19 patients were enrolled from March to July 2022. Positive results from the RT PCR (Reverse Transcriptase Polymerase Chain Reactions) testing supported COVID-19 diagnosis. In accordance with the results of a chest CT scanning, peripheral oxygen saturation, and respiratory rate, the disease was equally divided into severe and non-severe group). In severe cases, there were clinical signs of pneumonia with one of the following criteria established by WHO interim guidance for defining severe disease [19]: (1) Respiratory rates >30 breath/minute, (2) Oxygen saturations <90% in room air and (3) Partial oxygen pressures in arterial blood ≤300. Patients with non-severe illness showed oxygen saturation levels below 94% with radiographic and clinical signs of lower respiratory tract infection [20]. Blood samples were drawn to measure levels of S. KL-6 using ELISA Kits (Eagle Biosciences, USA), while the inflammatory markers: C-reactive proteins (CRP), Lactate dehydrogenases (LDH) have been estimated using commercial kits produced by Abbott Laboratories (Abbott, Architect, USA).

Statistical analysis

SPSS 18 was used for statistical analysis, and the results were expressed as (Mean± SD). For comparing between severe and non-severe groups, the independent t-test was used. The Spearman correlation was applied to find out the relation between the markers in the study.

Results

In our current study, 160 COVID-19 patients were involved, and equally categorized into 2 group (severe & non-severe). The average age of COVID-19 patient was 65 yrs regarding age, a no significant variation was demonstrated between the study group. Table (1) showed the laboratory results for COVID-19 patient.

Table 1: Distribution of clinical & demographic characteristic in COVID-19 patient

Parameters	Mean ± SD
No. of patients (N)	160
Age (years)	60.248±14.944
CRP mg/dl	7.025±5.661
LDH U/L	396.781±257.357
KL-6 U/ml	750.600±197.852

KL-6= Kreb-Von-Den-Lungen-6. CRP= C-reactive protein. LDH= Lactate dehydrogenase.

Significant variations in mean values of CRP, LDH & KL-6 between severe and non-severe group are reported in table-2. There was highly significantly increase in S. KL-6, CRP and concentrations & in patients with severe COVID-19 than in non-severe group (p<0.05).

Table 2: Distribution of biochemical characteristics in severe & non-severe patient

Parameters	Non-severe patient (n= 80)	Severe patient (n= 80)	P-values
Age (yrs.)	50.28±13.094	70.84±8.159	NS
CRP mg/dl	2.94±2.497	11.111±4.987	0.000
LDH U/L	246.13±63.385	547.435±290.099	0.000
KL-6 U/ml	255.826±179.253	1245.38±2706.098	0.001

Spearman's correlation exhibited a strong significant relationship between KL-6 concentration and inflammatory markers in both groups as demonstrated in table (3).

Table 3: Correlations between KL-6 & laboratory parameters among COVID-19 groups

Parameter	Inflammatory markers	Correlation	P value
KL-6 U/mL Non- sever group	CRP mg/dl	0.064	0.000
	LDH U/L	0.165	
KL-6 U/mL Sever group	CRP mg/dl	0.76	0.000
	LDH U/L	0.040	

Discussion

The current study revealed that severely infected Covid19 cases were older than non-severely infected COVID-19 cases. In accordance with our results, [21-24] reported that age has fundamental roles in COVID-19 mortality and severity due to deterioration of the immune system, which is considered as a immense producer of pro-inflammatory cytokine (Cytokine storms) that leads to cell damage. Additionally, elderly people with heart disease, hypertension and lung illness have higher rates of COVID-19 mortality because these conditions are linked to highly angiotensin converting enzyme2 or (ACE2) production, this enzymes utilized by COVID-19 viruses to adhere to the cell and produce inflammation [25]. Recent investigations revealed that individuals with severe COVID-19 have elevated inflammatory marker level related to endothelial dysfunctions, cytokine storm syndrome (CSS) & coagulopathies [26-29].

The C-reactive proteins are highly sensitive biomarkers of tissue destruction, inflammations and disease course [30]. Recent studies have shown that high CRP production plays as an indicator of lung lesion and coronavirus severity through excessive cytokine and tissue destruction [31, 32].

Nearly all types of human cells contain the intracellular enzyme lactate dehydrogenase (LDH), which is also found in large quantities in kidneys, lungs, muscles, cardiac and hepatic cells. Because large amounts of LDH are released into the circulation, LDH is considered an inflammatory indicator of tissue damage. Several evidence-based studies indicate highly significant increased LDH levels in severely infected patient with COVID-19 than in non-severely infected. Furthermore, high blood LDH has a relationship with COVID-19 severity & predicts higher death [33-36].

Statistical analysis found a significant elevation in CRP & LDH concentrations (p<0.05) in severely infected patients with COVID-19 than in non-severely infected patients. These findings agreed with [37-41], who revealed a connection between poor COVID-19 outcomes and laboratory biomarkers of disease activity.

Serum indicators serve as clinical evaluation tools to predict the level of inflammation and disease progress [42]. More recently, antigen of KL-6 was recognized as specific indicator in lung injuries and alveolar epithelial proliferations [43]. It is the mucin like glycoprotein expressed in membranes surfaces of alveolar type-II pneumocyte (AEC-II) with bronchiolar epitheliaum cell [44]. Increased levels of KL-6 reflect more extensive injury to the alveolar epithelium and type II pneumocyte regeneration [45].

According to our study, patients with severe infection showed a highly significant increased S. KL-6 levels than those in non-severe patients. These findings were in line with previous studies which reported that there was a highly significant S. KL-6 levels in severe COVID-19 than those with moderate infections or healthy groups [9, 46-51]. We also found positive correlations between KL-6 & inflammatory markers (CRP and LDH) in agreement with [48, 52, 53]. As a result, to determine COVID-19 severity & forecast outcome in lung injuries in patients with COVID-19, the KL-6 could be a helpful biomarker.

In conclusion, this study confirmed an increased levels of S. KL-6 in severely infected COVID-19 patient. It may contribute to diagnosing the severity for lung injury.

Conclusion

It can be concluded that KL-6 seems to be a useful biomarker in the prognosis of COVID-19.

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