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Cross-sectional Study

Association of serum KL-6 levels on COVID-19 severity: A cross-sectional study design with purposive sampling

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ABSTRACT

Background: The main target of SARS-CoV2 is the alveolar type II (AT2) cells of the lung. SARS-CoV2 evades the innate immune system resulting in the release of proinflammatory cytokines (IL-1β, IL-6, TNF-α) which causes AT2 cell damage. Krebs von den Lungen (KL-6) is a specific biomarker of AT2 cell damage. KL-6 is produced in AT2 cells that are injured/regenerated.

Objective: Research that discusses the role of KL-6 in COVID-19 is still being debated and not much has been done in Indonesia.

Methods: This study was an analytical study with a prospective design on 75 COVID-19 patients who were treated. Subjects were divided into two large groups according to their degree of severity, 57 subjects with severe degrees and 18 subjects with non-severe degrees. The serum KL-6 levels were measured on days 0 and 6. Data were analyzed using paired *t*-test and independent *t*-test for data were normally distributed and Wilcoxon test and Mann Whitney test for data that were not normally distributed.

Result: In this study, the mean serum KL-6 for day 0 in the severe group was higher than the non-severe group with values of 45.70 U/mL and 44.85 U/mL. On day 6, the mean serum KL-6 in the severe group was lower than that in the non-severe group with values of 41.3 U/mL and 41.95 U/mL. Serum KL-6 in the severe group experienced an even greater decrease than the non-severe group.

Conclusion: There was no significant association between serum KL-6 values on 0 days in the severity of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). COVID-19 was first discovered in Wuhan China at the end of December 2019, three months later the virus spread to 200 countries in the world so that the World Health Organization (WHO) declared it a global pandemic [1]. In September 2020, the worldwide incidence of COVID-19 reached 31 million. The American continent is the country with the most cases in the world, followed by Southeast Asia, Europe, the Central Mediterranean, and Africa [2]. Indonesia recorded 271,000 COVID-19 cases and 10,000 deaths, which is the highest number in Southeast Asia. East Java is the second province with the highest number of cases after DKI Jakarta, which reached 42,000 with a death rate of 3000 people [3]. SARS-CoV2 shows mild-moderate manifestations and can develop into serious cases such as severe pneumonia to Acute Respiratory Distress Syndrome (ARDS) which is the main cause of death in COVID-19 [4].

SARS-CoV2 infects through a bond between the S protein and the host cell's angiotensin-converting enzyme 2 (ACE2) receptor. The upper respiratory tract is the first site of infection, but the main target of the virus is alveolar type II (AT2) cells. SARS-CoV2 can avoid or inhibit the innate immune system so that it easily reaches the lower respiratory tract and releases pro-inflammatory cytokines (IL-1β, IL-6, TNF-α). The release of proinflammatory cytokines causes damage to AT2 cells. Severe damage to AT2 cells causes cytokine storms and results in ARDS characterized by diffuse alveolar damage (DAD), hyperplasia of pneumocytes, and microvascular thrombosis [5]. Biomarker studies help understand the underlying mechanisms and pathophysiology of lung damage and thus improve therapeutic strategies and evaluation. One of the specific biomarkers of pulmonary alveolar cell damage that is currently being developed for research is von den lungen Krebs (KL-6)

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[6].

KL-6 is a mucin glycoprotein which is also referred to as MUC1. MUC1 is a single glycoprotein consisting of cytoplasm, transmembrane, and extracellular domains. MUC1 has a high molecular weight with large size of 200–500 nm. KL-6 is produced on the surface of AT2 epithelial cells. KL-6 is also produced in the epithelial cells of the bronchi, basal cells, and terminal bronchioles in lower numbers than AT2. KL-6 is increased in injured AT2 cells. The production of KL-6 can increase and decrease through the activity of the TNF-α converting enzyme (TACE). The expression of KL-6 protein correlated with changes in alveolar capillary permeability, indicating the association between increased KL-6 and barrier epithelial dysfunction in ARDS. KL-6 shows a correlation between bronchoalveolar lavage (BAL) and serum so that KL-6 produced in the lungs will be visible in the bloodstream [7].

Ruiz declared that the potential use of serum KL-6 in COVID-19 is a prognosis of disease activity and fibrosis [8]. Alessandro et al. said that serum KL-6 was higher in the severe group of COVID-19 compared to the non-severe group. The cut-off value of serum KL-6 in that study was 406 U/mL with a sensitivity of 89 % and a specificity of 83 % [9]. Awano, Xue, and Deng et al. said that KL-6 serum in COVID-19 patients was higher than in healthy patients. Serum KL-6 value of the severe group of COVID-19 was higher than the non-severe group. The study also stated that serum KL-6 undergoes dynamic changes with the patient's clinical condition so that it can be used as a biomarker of severity [10–12]. Other several studies have shown less significant results. Arnold et al. declared that serum KL-6 has a sensitivity of 86 % and a specificity of 45 % [13]. Kondo et al. said that serum KL-6 in ARDS patients was only increased in BAL compared to serum [14]. Based on the description above, we are interested in analyzing the association between serum KL-6 and the degree of severity of COVID-19.

2. Methods

Participants in this study were COVID-19 patients who met the inclusion and exclusion criteria. Participant inclusion criteria included patients diagnosed with COVID-19 and aged >18 years. Participants' exclusion criteria included patients who had unsuccessful blood draws by day 6 and patients diagnosed with lung, breast, and pancreatic cancer. Participants who were willing to take part in the research first received an explanation of the rights and obligations of the participants, in which they voluntarily filled out the informed consent form.

The design of this study was observational analytic with a prospective design that used consecutive sampling. This study reported the data based on the Strengthening the Reporting of Cohort Studies in Surgery (STROCSS) 2019 guideline [15]. The number of participants in this study was 75 participants were divided into two large groups namely severe (76 %) and non-severe (24 %). Severe groups consist of severe to critical categories. Non-severe groups consist of mild to moderate categories. Data collection was carried out at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia during the period May–October 2020. Data collection included participant characteristics, levels of KL-6, and the degree of severity of COVID-19.

The severity of COVID-19 in this study was assessed using WHO criteria at the time of the initial examination of the patient, which distinguished the severity of COVID-19 from being non-severe (mild-moderate category) and severe (severe-critical category). Mild: Symptomatic patient who meets the COVID-19 case definition without evidence of viral pneumonia or hypoxia. Moderate: clinical symptoms of pneumonia (fever, cough, dyspnoea, rapid breathing) but no signs of severe pneumonia, including SpO2 ≥90 % in room air or PaO2 ≥60 mmHg. (PaO2 measurements were obtained from patient medical records). Weight: obtained clinical symptoms of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one of respiratory rate >30 times/minute; severe respiratory distress or SpO2 <90 % or PaO2 ≤59 mmHg. (PaO2 measurements were obtained from patient medical records). Critically, in patients with ARDS, sepsis, and septic shock. Mild ARDS: 200 mmHg < PaO2/FiO2a ≤300 mmHg (with PEEP or CPAP ≥5 cmH2O). Moderate ARDS: 100 mmHg < PaO2/FiO2 ≤200 mmHg (with PEEP ≥5 cmH2O). ARDS weight: PaO2/FiO2 ≤100 mmHg (with PEEP ≥5 cmH2O).

KL-6 is a mucin glycoprotein that is expressed on alveolar type II (AT2) epithelial cells that are injured/regenerated. The increased height of KL-6 reflects the degree of severity of COVID-19. Serum KL-6 levels were measured using the Enzyme-linked immunosorbent assay (ELISA) method of the Bioassay technology laboratory E1980Hu brand in U/ml units. KL-6 was measured by blood serum taken on day 0, namely when the diagnosis was made and on day 6 after diagnosis.

The data are recorded in data collection sheets that have been arranged, processed, and analyzed descriptively using computer software or manually. The statistical analysis used to test the hypothesis is paired and independent *t*-test for normally distributed data, Wilcoxon test, and Mann Whitney test for data that are not normally distributed. The association between data from the results of statistical analysis is shown in tables, diagrams, and text.

3. Result

3.1. Participant characteristics

The mean age of the participants was 48.04 ± 11.66 years with an age range of 24–73 years. Most of the male participants were 46 participants (61.3 %) and the rest were female as many as 29 participants (38.7 %). Some of the participants experienced clinical symptoms as follows: fever as many as 51 participants (68.0 %), coughing as many as 63 participants (84.0 %), dyspnoea as many as 59 participants (78.6 %), diarrhea as many as 10 participants (13.0 %), anosmia as many as 5 participants (6.0 %)), 1 participant of muscle pain (2.0 %), 9 participants of nausea & vomiting (12.0 %), 9 participants of sore throat (12.0 %), 7 participants of colds (9.3 %), and 14 participants of weakness (18.6%). Most of them recovered after receiving treatment as many as 62 participants (82.7 %) and the rest died as many as 13 participants (17.3 %). Only 7 participants (9.3 %) had a history of smoking. Some of the participants also had comorbid diseases such as hypertension as many as 34 participants (45.3 %), diabetes mellitus as many as 24 participants (32.0 %), COPD as many as 1 participant (1.3 %), asthma as many as 3 participants (4.0 %), tuberculosis as many as 5 participants (6.7%), obesity as many as 8 participants (10.6 %), and heart disease as many as 8 participants (10.6 %).

The mean KL-6 level at curry 0 was 56.43 ± 31.20 U/mL with a median value of 45.1 (8.5–151.4) U/mL. The mean KL-6 level in the 6th curry was 52.61 ± 37.99 U/mL with a median value of 41.5 (4.6–163.7) U/mL. The results of the 75 participant examination showed several categories of the severity of COVID-19, as follows: 18 participants (24.0 %) moderate category, 35 participants (47.0 %) severe category, and 22 participants (29.0 %) critical categories. Details of participant characteristics can be seen in Table 1.

3.2. Changes in the value of KL-6 serum on day 0 and 6

The results showed that the KL-6 value on day 0 for the non-severe group was 44.85 (11.4–151.4) U/mL and the severe group was 45.70 (8.5–131.8) U/mL. The KL-6 value on day 6 for the non-severe group was 41.95 (4.6–157.4) U/mL and the severe group was 41.30 (4.6–163.7) U/mL. Serum KL-6 in the severe group experienced an even greater decrease than the non-severe group. Based on the data obtained, there was no significant association between serum KL-6 values and the severity of COVID-19 day 0 ($p = 0.895$; Table 2).

4. Discussion

Awano et al. declared that the mean serum KL-6 value of all participants on day 0 was 229 U/mL with a minimum value of 184 U/mL and a

Table 1
Characteristics of the participant based on the severity of COVID-19.

Characteristics	Non severe n = 18	Severe n = 57	p
Age	48.5 (24.0–78.0)	52.0 (25.0–73.0)	0.084
Gender			
Male	8 (44.4)	38 (66.7)	0.158
Female	10 (55.5)	19 (33.3)	
Clinical symptoms			
Fever	12 (66.7)	39 (68.4)	1.000
Cough	14 (77.7)	49 (85.9)	0.466
Crowded	7 (38.8)	52 (91.2)	<0.001*
Diarrhea	6 (33.3)	4 (7.0)	0.001
Anosmia	2 (1.1)	3 (5.2)	0.588
Muscle ache	0 (0.0)	1 (1.7)	1.000
Nauseous vomit	2 (11.1)	7 (12.2)	1.000
Sore throat	2 (11.1)	7 (12.2)	1.000
Cold	1 (5.0)	6 (10.5)	1.000
Weak body	5 (27.7)	9 (15.7)	0.303
Outcome			
Heal	18 (100.0)	44 (77.2)	–
Died	0 (0.0)	13 (22.8)	
Smoking history			
Smoker	1 (5.5)	6 (10.5)	1.000
Comorbid disease			
Hypertension	6 (33.3)	28 (49.1)	0.367
Diabetes mellitus	4 (22.2)	20 (35.0)	0.465
COPD	0 (0.0)	1 (1.7)	1.000
Asthma	0 (0.0)	3 (5.2)	1.000
Tuberculosis	0 (0.0)	5 (8.7)	0.329
Obesity	0 (0.0)	8 (14.0)	0.186
Heart disease	1 (5.5)	7 (12.2)	0.671
Laboratory Day 0			
Leukocytes	7050 (2870–14,110)	9720 (4530–25,150)	0.006*
Lymphocytes	18.8 (6.9–48.4)	10.3 (0.7–45.6)	0.001*
Neutrophils	68.7 (35.0–91.3)	80.2 (40.8–96.8)	0.007*
Procalcitonin	0.09 (0.01–0.47)	0.23 (0.01–7.04)	0.004*
CRP	1.4 (0.01–18.9)	6.2 (0.01–39.5)	0.011*
Ferritin	323.05 (24.1–1724.7)	1180 (38.5–6498.8)	0.001*
D-Dimer	980 (310–35,200)	1380 (190–35,200)	0.368
Laboratory Day 6			
Leukocytes	7110 (5080–13,160)	11,860 (3610–29,320)	<0.001*
Lymphocytes	23.45 (5.6–39.8)	9.5 (1.1–33.8)	<0.001*
Neutrophils	64.4 (35.0–88.4)	82.6 (46.4–99.2)	<0.001*
Procalcitonin	0.07 (0.01–0.47)	0.1 (0.01–14.71)	0.049*
CRP	0.55 (0.1–8.4)	3.1 (0.1–31.9)	0.006*
Ferritin	417.8 (34.3–2116)	983 (89.4–16,321)	0.009*
D-Dimer	920 (180–21,320)	2060 (190–35,200)	0.004*
Treatment			
Lopivia	5 (27.0)	24 (42.1)	–
Oseltamivir	2 (11.0)	6 (10.5)	
Avugan	1 (5.0)	1 (1.7)	
Remdisivir	1 (5.0)	1 (1.7)	
Hyloquin	9 (50.0)	19 (33.3)	
Actemra	0 (0.0)	2 (3.5)	
Crime scene	0 (0.0)	4 (7.0)	
Vitamin C	4 (22.2)	24 (32.0)	
Vitamin D	0 (0.0)	5 (8.7)	
Steroids	1 (5.0)	34 (59.6)	
Lovenox	10 (55.5)	26 (34.6)	
Heparin	3 (16.7)	32 (56.1)	
Arixtra	0 (0.0)	1 (1.7)	
NAC	15 (8.3)	35 (61.4)	
Isoprenosine	13 (72.2)	32 (56.1)	
Zinc	1 (5.0)	4 (7.0)	
Mechanical ventilation	0 (0.0)	13 (22.8)	
Non-mechanical ventilation	0 (0.0)	13 (22.8)	

Note: non severe consisting of mild and moderate covid-19 severity; severe consisting of the severity of Covid-19, severe and critical categories; *significant if $p < 0.05$.

Table 2
The serum KL-6 value is based on the degree of severity.

KL-6	Covid-19 severity		*p*
	non-severe	severe	
Day 0	44.85 (11.4–151.4)	45.70 (8.5–131.8)	0.895
Day 6	41.95 (4.6–157.4)	41.30 (4.6–163.7)	-
Delta	−3.2 (−66.4–39.5)	−3.1 (−109.9–111.8)	-

Note: non severe consisting of mild and moderate covid-19 severity; severe consisting of the severity of Covid-19, severe and critical categories.

maximum of 336 U/mL. On day 6, the mean score was 283 U/mL with a minimum value of 222 U/mL and a maximum value of 540 U/mL. When compared with previous studies, the mean serum KL-6 levels in this study showed lower values. The difference can be due to differences in methods and kits where previous studies used the Nanopia KL-6 reagent kit, Sexui medical. Co., Tokyo Japan antigen agglutination technique [10]. This study used Bioassay technology laboratory E1980Hu with *the* ELISA method. Racial and genetic differences also affect serum KL-6 values. Horimasu et al. said that the average serum KL-6 score was higher than in Japan due to Germany. The dominant participant in Germany containing the genotype A/A and Japan G/G [16].

Mason said that as many as 80 % of patients infected with COVID-19 experience non-severe symptoms, 14 % of which require hospital treatment. As many as 20 % of patients show severe symptoms, most of whom require treatment at the hospital and 5 % of this number are experiencing a critical phase so they require treatment in an intensive care unit (ICU) [17]. This study is different from the study conducted by Mason where there was a more severe group hospitalized. The explanation for this is because Dr. Soetomo General Academic Hospital, Surabaya is a referral center hospital for eastern Indonesia. Old age is more susceptible to infection and occurs with severe manifestations due to several reasons, namely a decrease in the system called immunosenescence. Cells also experience a decrease in a function called cellular senescence. Old age also occurs with systemic inflammation called inflammaging [18].

Gender did not show a significant difference in the degree of severity even though men were infected more. Cevix said that gender is related to the immune response. Men have higher congenital cytokines and chemokines than women. Women have stronger T cell activation than men. Increasing age in men leads to decreased T cell activation. This also suggests that older men are associated with a greater degree of disease severity and risk of death [19].

Shortness of breath and diarrhea are clinical symptoms that show a significant difference in severity. Shortness of breath is caused by damage to AT2 cells by viruses. The dysregulation of the immune system causes the virus to reach target cells directly. Diarrhea was more common in the severe-critical category. Diarrhea is associated with ARDS, use of mechanical ventilators, and care in the ICU but the link between diarrhea and severity is not fully understood and requires further clarification [20]. This study found no significant difference between smoking and severity and accordance to research conducted by Rosatto et al. [21].

In this study, the laboratory value showed a significant difference in the degree of severity. The laboratory for the non-severe degree group showed normal values. In the severe group, WBC showed normal/increased values and decreased lymphocytes, while neutrophils, CRP, procalcitonin, D dimer, and ferritin increased. Biomarkers such as WBC, neutrophil procalcitonin lymphocytes, CRP, D-dimer, ferritin showed significant differences with the WHO severity [22].

Dysregulation of the immune system causes the release of proinflammatory cytokines. The release of proinflammatory cytokines causes cell damage. Damaged cells release toxins that increase the release of pro-inflammatory cytokines, causing a cytokine storm. Cytokine storms cause neutrophil lymphocytes and macrophages to be released to the site of infection. Macrophages and IL-6 release ferritin, IL-6 also releases

CRP. Stress conditions cause an increase in the hormone cortisol, as a result, lymphocytes migrate to the peripheral circulatory system, then lymphocyte destruction and apoptosis occurs. Depression of T and B cells also causes low lymphocytes. Apart from being caused by damage to lung cells, the degree of severity is also caused by damage to other organs. D-dimers are released upon activation of coagulation and fibrinolysis [23].

This study assessed serum KL-6 is based on the degree of severity. On day 0, the median KL-6 value for the non-severe group was 44.85 U/mL, while the severe group was 45.70 U/mL. On day 6, the median serum KL-6 value for the non-severe grade group was 41.95 U/mL, while the severe group value was 41.30 U/mL. The KL-6 value in the severe group was higher on that two days examination. The higher the serum KL-6 value caused by the more severe/extensive AT2 cell damage. That damage or regeneration of AT2 is the main source of serum KL-6 [6].

This study assessed changes in the KL-6 serum on days 0 and 6 based on the severity. Serum KL-6 values in both groups decreased on day 6. The main decreased serum KL-6 in the non-severe group was 2.9 U/mL and in the severe group was 4.4 U/mL. The decrease was greater in the severe group. Xue et al. said that serum KL-6 value decreased on day 4 then increased sharply on day 8 and decreased again on day 16. On days 24 and 46 the serum KL-6 value increased again but not as much as on day 16. Serum KL-6 values were consistent with the clinical condition of the participant. Changes were found in the severe group, while the non-severe group tended to be stable [11]. Deng et al. said that serum KL-6 value has increased and reaches a peak for up to 1 month, then has a gradual decrease until the 6th month [12]. Awano et al. said that serum KL-6 experienced an increase on day 6 in the severe group, while the non-severe group tended to be stable [10]. Langer said that serum KL-6 can dynamically assess disease activity and pathophysiology [24]. This study and previously conducted serially showed dynamic changes in serum KL-6.

Awano et al. Deng et al., Xue et al. and Alessandro et al. said that serum KL-6 value in the severe group was higher than that in the non-severe group. Deng et al. Xue et al. and Alessandro et al. said that serum KL-6 normal patients have the same as the non-severe group [9–12]. This study and the previous study show different results. In this study, there was no significant association between serum KL-6 value on day 0 to the degree of severity. The serum KL-6 value in the severe group was not much different from the KL-6 value for the serum in the non-severe group This difference can be caused by several reasons. First is the number of samples, this study involved more subjects (75 samples) and more severity samples. In the previous study, the sample used was less in number and more in the non-severe.

Second, the cause of the degree severity is not only due to damage to AT2 cells. Apart from AT2 cells, endothelial cells are also the main targets of SARS CoV-2. SARS-CoV2 can infect endothelial cells directly [5]. Viral infection causes endothelial dysfunction. Endothelial dysfunction results in platelet adhesion, leukocyte aggregation, complement activation, and cytokine release leading to microvascular complications such as pulmonary embolism and deep vein thrombosis (DVT) [25]. There are also features of apoptosis, pyroptosis, and lymphocytic inflammation. These histopathologic features are associated with organ ischemia, tissue edema, and procoagulant status [5].

Limitation of the study, further research is needed on the role of serum KL-6 in COVID-19 with more average sample size. Further research is needed on the role of serum KL-6 in COVID-19 involving healthy controls. It is necessary to classify the severity of the subject on day 6.

SARS-CoV2 that enters the body destroys AT2 cells resulting in increased production of KL-6. KL-6 was mostly found in the pulmonary alveoli where the more severe the inflammation in the lungs, the higher the KL-6 level. This study is used to identify the severity of COVID-19 patients in the developing world with low resource settings to improve patient care management. In future research, it is expected that the data collection time for KL-6 can be $>$ 6 days, the participant group will be compared to several groups (normal, mild, and moderate severity), and the number of participants will be more and represent each age group.

5. Conclusion

Participants were mostly male (61.73 %). The mean age of the participants was 48 years. Most symptoms were cough (84 %), dyspnoea (78.6 %), and fever (68 %). As many as 9.3 % of the participants were smokers. The most common comorbidities were hypertension (45.3 %) and diabetes mellitus (32 %). The mortality rate was 17.3 % which occurred in the severe group. The mean value of KL-6 serum participants on day 0 was 56.43 $\pm$ 31.204 U/mL and day 6 of 52.61 $\pm$ 37.99 U/mL. Participants in the severe group were 76 %, while the non-severe group was 24 %. On day 6, there was a decrease in serum KL-6 values in both groups. There was no significant association between serum KL-6 on day 0 and severity.

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Author's contributor

All authors contributed toward data analysis, drafting, and revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Consent

Written informed consent was obtained from the patient.

Registration of Research Studies

- Name of the registry: Health Reseach Ethics Coommitee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.
- Unique Identifying number or registration ID: 1953/KEPK/IV/2020.
- Hyperlink to your specific registration (must be publicly accessible and will be checked):-.

Guarantor

Resti Yudhawati is the person in charge for the publication of our manuscript.

Ethical approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1953/KEPK/IV/2020).

Provenance and peer review

Not commissioned, externally peer-reviewed.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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