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Short Communication

Relationship between interleukin-6 (IL-6) levels and chest X-ray severity scoring in COVID-19 patients

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Abstract

The severity of coronavirus disease 2019 (COVID-19) may be measured by interleukin-6 (IL-6) and chest X-rays. Brixia score of the chest radiographs is usually used to monitor COVID-19 patients' lung problems. The aim of this study was to demonstrate the relationship between IL-6 levels and chest radiographs (Brixia score) that represent COVID-19 severity. A retrospective cohort study was conducted among COVID-19 patients who had a chest X-ray and examination of IL-6 levels at H. Adam Malik General Hospital, Medan, Indonesia. A multinomial logistic regression analysis was conducted to evaluate the association between IL-6 levels and the severity of the chest radiograph. A total of 76 COVID-19 patients were included in the study and 39.5% of them were 60–69 years old, with more than half were female (52.6%). A total of 17.1%, 48.7%, and 34.2% had IL-6 level of <7 pg/mL, 7–50 pg/mL and >50 pg/mL, respectively. There were 39.5%, 36.8% and 23.7% of the patients had mild, moderate and severe chest X-rays based on Brixia score, respectively. Statistics analysis revealed that moderate (OR: 1.77; 95% CI: 1.05–3.32) and severe (OR: 1.33; 95% CI: 1.03–3.35) lung conditions in the chest X-rays were significantly associated with IL-6 levels of 7–50 pg/mL. IL-6 more than 50 pg/mL was associated with severe chest X-ray condition (OR: 1.97; 95% CI: 1.15–3.34). In conclusion, high IL-6 levels significantly reflected COVID-19 severity through chest X-rays in COVID-19 patients.

Keywords: COVID-19, interleukin-6, thoracic image, severity, scoring system

Introduction

Since its outbreak in Wuhan, coronavirus disease 2019 (COVID-19) has presented a heterogeneous clinical manifestation, with 5–20% progressing to severe and requiring intensive care due to multiple organ damages [1]. This phenomenon highlights the need to identify the characteristics of patients who should be prioritized for potential progression to severe outcomes through the prevention of hyperinflammation. The challenge that arises is how the role of the clinical laboratory may contribute effectively and efficiently to assist in managing COVID-19 patients [2]. Practical markers may help screen, manage, and prevent serious complications [2].

COVID-19 is diagnosed through a screening process that involves inquiring about recent contacts and travel history within the past two weeks [3]. Additionally, more precise screening

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methods, such as molecular testing, serology, and viral culture, should be performed. Real-time polymerase chain reaction (RT-PCR) is a molecular technique used for diagnostic purposes. Utilizing radiographic modalities in the management of COVID-19 is unavoidable. The effect of COVID-19, especially on the airway, is visualized optimally using radiological examinations [4]. The continuous improvement in the availability of different modalities and equipment specifications has greatly enhanced the importance of radiological examinations in diagnosing diseases, assessing the severity, and determining the complications. Radiological examinations also help rule out the diagnosis of other diseases whose symptoms are similar to COVID-19, in addition to assessing the patient's comorbidities [5].

Supporting diagnostic modalities with high sensitivity and specificity values are needed to assess COVID-19 quickly. Radiological examination for COVID-19 holds a critical function to confirm the diagnosis, assess the progressivity and severity of COVID-19, and determine other diseases with similar symptoms [6]. One of the radiological examinations is a chest X-ray. The chest radiograph has lower sensitivity than computerized tomography (CT) scans, but it is the first-line screening examination due to its ease of use and wide availability [7]. The Brixia score is applied to the chest radiographs to monitor lung abnormalities in COVID-19 patients [8]. The Brixia score is used for the regular assessment of chest examinations in individuals with COVID-19. It exhibits a robust correlation with the severity of COVID-19 and its outcomes, which provides a valuable assistance for clinical decision-making, particularly during the peak of the epidemic, when individuals with moderate to severe symptoms become evident [9].

In conjunction with the aforementioned background and the absence of studies regarding the importance of IL-6 in COVID-19 prognosis, the aim of this study is to further understand the relationship between IL-6 and the severity of COVID-19 reflected through the chest X-rays scoring at H. Adam Malik General Hospital, Medan, Indonesia.

Methods

Study design and setting

A retrospective cohort design was used to conduct this study by retrieving the secondary data. The data was obtained from the medical records, which included chest X-ray and IL-6 results from the confirmed COVID-19 patients at H. Adam Malik General Hospital, Medan, Indonesia. IL-6 levels were grouped into <7 pg/mL, 7–50 pg/mL, and >50 pg/mL. The patient's chest X-rays were assessed based on the Brixia score, which indicates the severity based on the total score: mild (0–6), moderate (6–12), and severe (12–18).

Study participants

The study population consisted of confirmed COVID-19 patients hospitalized at H. Adam Malik General Hospital, Medan, Indonesia, from 1 January to 31 December 2021. The patients who were 20–80 years old with the history of chest X-ray and IL-6 level examination were included. The inclusion criteria: (1) COVID-19 patients were confirmed using RT-PCR from nasal/nasopharyngeal swabs; (2) IL-6 was examined on days 7–14 following COVID-19 confirmation; and (3) chest radiography was performed on days 7–14 following COVID-19 confirmation. The exclusion criteria: (1) unidentified age, gender, and IL-6 results; (2) previous history of diseases that increased IL-6 other than COVID-19, such as rheumatoid arthritis, ankylosing spondylitis, psoriasis and Crohn's disease; and (3) patients with disturbances on chest radiograph, such as pulmonary oedema and pleural effusion.

Study variables

The independent variable in this study was the level of IL-6 in COVID-19 patients, while the dependent variable was the morphological picture of the thoracic X-ray examination, measured using the Brixia score.

The Brixia score, developed by Borghesi and Maroldi [10], was created as a semi-quantitative assessment of lung severity and progression in COVID-19 patients. The score determination was divided into two steps [10]. First, chest X-ray taken posteroanterior or anteroposteriorly were divided into six zones: (1) upper zone (A and D), above the inferior wall of the aortic arch; (2)

middle zone (B and E), below the upper zone and above the inferior wall of the right inferior pulmonary vein (hilum structure); and (3) lower zone (C and F), below the inferior wall of the right inferior pulmonary vein (lung base). The imaginary separator line between the upper and middle zones was called Line A. Line A is at the same level as the lower boundary of the aortic arch. Line B, the imaginary line between the middle and lower zones, was at the same level as the lower boundary of the right inferior pulmonary vein [10,11]. In the second step, each zone was scored based on the lung abnormalities: (1) 0, absence of lung anomalies; (2) 1, infiltrates in the interstitial area; (3) 2, infiltrates in the interstitial and alveolar areas, with the interstitial area being more prominent; and (4) 3, infiltrates in the interstitial and alveolar areas, with the alveolar area being more prominent. The chest radiograph score represents the total score obtained by evaluating the six lung zones. Additional radiographic characteristics, such as pleural effusion or pulmonary vascular dilatation, are not accounted for in the scoring system, but are documented in the chest X-ray report [10,11].

Statistical analysis

The data was presented in a frequency distribution table, which provided the patients characteristics. A multinomial logistic regression analysis was conducted to evaluate the association between IL-6 levels and the severity of chest radiograph. The statistical results were considered significant if the *p*-value was less than 0.05. The data was analyzed statistically analysis using the SPSS Statistics version 21 (IBM, New York, USA).

Results

Characteristics of confirmed COVID-19 patients

A total of 76 COVID-19 patients included in this study and their characteristics are presented in **Table 1**. Most aged 60–69 years (39.5%), followed by 50–59 (31.6%), >70 (14.5%), and <50 (14.5%). More than half of the study subjects were female (52.6%). IL-6 levels were grouped into three with percentage of each group as follows: 7–50 pg/mL (48.7%), >50 pg/mL (34.2%), and <7 pg/mL (17.1%). The chest X-ray assessment revealed mild in 39.5% patients, moderate (36.8%), and severe condition (23.7%) based on the Brixia score.

Table 1. Characteristics of confirmed COVID-19 patients based on demographic profiles, IL–6 levels, and chest radiography (n=76)

Patient characteristics	Total	Percentage
Age		
<50 years	11	14.5%
50–59 years	24	31.6%
60–69 years	30	39.5%
>70 years	11	14.5%
Gender		
Man	36	47.4%
Woman	40	52.6%
Interleukin-6 level		
<7 pg/mL	13	17.1%
7–50 pg/mL	37	48.7%
> 50 pg/mL	26	34.2%
Chest radiograph (Brixia score)		
Mild	30	39.5%
Moderate	28	36.8%
Severe	18	23.7%

Relationship between IL-6 levels and severity of chest radiograph

Thirty-seven patients had IL-6 levels of 7–50 pg/mL; 53.3% of them had mild severity of chest radiograph, followed by moderate at 50.0% and severe at 38.9. Patients who had IL-6 levels >50 pg/mL were 26 people, consisting of 55.6% with severe chest radiograph, followed by moderate (28.6%) and mild (26.7%).

A multinomial logistic regression analysis was conducted to evaluate the association between IL-6 levels and the severity of chest radiograph. The statistical analysis revealed that patients with IL-6 levels ranging from 7–50 pg/ml had a higher chance to have moderate (odds ratio (OR) 1.77,

95% confidence interval (CI) 1.05–3.32) and severe chest radiographs based on Brixia score (OR: 1.33; 95% CI: 1.03–3.35) compared to those with IL-6 <7 pg/mL. In addition, compared to patients that had IL-6 <7 pg/mL, those with IL-6 more than 50 pg/ml had a higher chance of having severe Brixia score (OR: 1.97; 95% CI: 1.15–3.34) (**Table 2**).

Table 2. Associations between IL-6 levels and severity of chest radiographs based on Brixia score

Interleukin-6 level	Severity of the chest radiographs based on Brixia score					
	Mild		Moderate		Severe	
	OR	*p*-value	OR	*p*-value	OR	*p*-value
<7 pg/mL	Ref	Ref	Ref	Ref	Ref	Ref
7–50 pg/mL	0.38 (0.28–3.78)	0.001	1.77 (1.05–3.32)	0.001	1.33 (1.03–3.35)	0.001
> 50 pg/mL	0.13 (0.13–1.34)	0.003	0.13 (0.13–1.34)	0.003	1.97 (1.15–3.34)	0.003

Discussion

Radiological examination plays a vital role in finding and managing COVID-19 patients. Clinically, COVID-19 presents as pneumonia and therefore the dominant imaging findings are atypical pneumonia [12]. Chest radiograph has lower sensitivity compared to CT scan, but they may be used as a first method due to its wide availability and ease of use [13]. A chest radiograph is often examined during the initial stage of the disease. The lung abnormalities are mostly visualized during 10–12 days after disease onset [14]. In the early stage of the disease, there is a slight opacity of faint consolidation in the lower lobe of the lungs [15]. In the late stage, acute respiratory distress syndrome occurs with various findings, such as pan-lobar patterns, multiple consolidations, and lung structure disorders, which require endotracheal support [16]. A chest radiograph is insensitive for early lung abnormalities, but it may help to monitor lung abnormalities in critical COVID-19 patients in intensive care units [17].

The characteristics of patients in this study showed that 39.50% of COVID-19 patients had an increase in IL-6 in the age group 60–69 years and 14.50% of the age group <50 years. The results of this study are in line with a previous study, which found that most COVID-19 patients with increased IL-6 were aged >60 years (73%) [18], and another study in which most age groups were >60 years (65.39%) [19]. A study also found that most patients aged 45–64 years (42.5%), followed by ≥65 years (38.32%), and <45 years (19.52%) [18-20].

Age has been associated with the severity of the COVID-19 illness [21]. The ageing process leads to notable alterations in the immune response and the development of chronic inflammatory diseases. There is variation in individual features due to the fact that the ageing of the immune system differs among individuals [21]. An important indicator of an ageing immune system is a decrease in the quantity of lymphocytes associated with the shrinking of the thymus, suppressed hematopoiesis, and insufficient peripheral regulation. Other components related to ageing are mild, sterile, and systemic inflammatory process, which initiates an impaired signaling between cells as an integrative sign of ageing [21]. The present study found that the majority of patients were elderly. These results indicate that the elderly have a greater risk of experiencing COVID-19, which may be caused by people with advanced age having risks in the form of long-term health problems, including a greater chance of acquiring COVID-19. As a person ages, the immune system tends to weaken, which causes older people to have difficulty fighting infections. The elderly should also be concerned about less elastic lung tissue and organ damage due to more intense inflammation [10,22].

Infected elderly individuals with SARS-CoV-2 sometimes have excessive activation of the immune system and blood clotting in small blood vessels, resulting in a cytokine storm. The underlying reason behind the increased vulnerability of the elderly to cytokine storms remains uncertain [23]. One potential mechanism involves heightened activation of the nucleotide-binding domain and leucine-rich repeat protein-3 (NLRP3), which is a part of the inflammasome in immune cells and alveolar macrophages in the lung. The increased activity of NLRP3 activation, resulting from prolonged stimulation, leads to the development of pulmonary fibrosis [24]. The activity of NLRP3 is often regulated by Sirtuin-2, a protein associated with longevity that declines as one ages. The decrease in Sirtuin-2 is worsened by SARS-CoV-2 infection and

may enhance the overactivity of NLRP3, leading to the initiation of cytokine storms in older individuals [24]. One potential explanation for the heightened vulnerability to COVID-19 infection among older individuals may be the reduction in T cells that occurs as a result of ageing [24].

This study showed that most COVID-19 patients were women, comprising 52.6%, and men accounting for 47.4%. The findings of this study align with multiple studies that reported the highest proportion of patients was female, including an investigation in Surabaya (51.4%) [25] and a study in China (52%) [26]. According to a study, ACE2 expression, the receptor for SARS-CoV-2 to bind to host cells, showed a significant rise of up to 100% in several body parts, including the adrenal glands, adipose tissue, esophagus, and heart in Asian women [27]. ACE2 expression also elevates in the lung, blood vessels, colon, and adrenal glands [27].

A study in India using the Brixia score found that most patients were mild (39.5%), followed by moderate (36.8%) and severe (23.7%) [28]. The study revealed that chest radiographs and patients' comorbidities were significantly associated with the severity of COVID-19 [28]. The present study showed that chest X-ray examination is essential in managing COVID-19 patients. Chest X-rays may be used as the first modality in the management of COVID-19 to determine the severity and monitor the development of COVID-19 over time [20,21].

An association between IL-6 levels and the severity of chest radiography was found in this study, in which those who had IL-6 levels of >50 pg/mL had a 1.97 times higher risk of severe lung condition. Elevated levels of IL-6 substantially enhance the likelihood of severe clinical presentation of COVID-19 through chest X-ray [29,30].

Very few studies correlate the severity of COVID-19 based on chest radiographs with IL-6 levels, whereas COVID-19 severity is often assessed with a CT scan. Yilmaz *et al.* study in Turkey found that severe lung conditions from a CT scan were associated with high IL-6 levels (p=0.018) [31]. In one study, out of 76 patients with elevated IL-6, 29 had severe lung damage, and 47 had non-severe lung damage [32]. Another study found a significant association was observed between the levels of IL-6 and the severity of COVID-19 (p<0.0001, RR 3.94, OR 5.75) [33].

The limitations of CT scans and radiologists in Indonesia make chest radiographs an essential examination in diagnosing and determining the severity of COVID-19 [34-36]. Applying the Brixia score to the chest X-rays is vital in predicting mortality because it is a simple supporting examination and is available in almost all hospitals [34-36]. Therefore, this scoring system could be used in the clinical setting, in particular in low-resource settings.

Conclusion

The majority of individuals hospitalized COVID-19 patients in this study were 60–69 years old, with a higher prevalence among females. Elevated level of IL-6 is significantly associated with an increased likelihood of severe lung conditions in the chest X-rays of patients with COVID-19. An immediate chest radiograph may be an initial reference when providing therapy to COVID-19 patients.

Ethics approval

This study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia (22/UN5.2.1.1.2.2.17/SPB/2022).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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