



The Correlations Between Clinical Characteristics and Inflammation Markers with Chest X-rays in COVID-19 Patients at Ulin Hospital

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Abstract

Background: Chest x-ray is one of the parameters used to estimate the severity and prognosis of COVID-19. Arterial oxygen saturation (SaO₂), partial pressure of arterial oxygen (PaO₂), and respiratory index (PaO₂/FiO₂) can also predict the disease severity. Other parameters, like inflammation markers, have also been used as predictors for prognosis. Based on those considerations, this study aimed to examine their connection and find their correlation.

Methods: This was an analytic observational retrospective study. The samples were moderate-critical COVID-19 patients in Ulin General Hospital Banjarmasin from July to December 2021 who met the inclusion and exclusion criteria. Statistical tests were used to see the relationship between clinical characteristics and inflammation markers with chest X-rays using various scoring systems (Brixia, sRALE, and modified Soetomo score).

Results: The total number of subjects was 67. The data analysis found that the severity of the disease had a significant relationship with the severity of the chest x-ray ($P < 0.001$). The PF ratio also had a significant negative correlation ($P < 0.001$) with the severity of the chest x-ray. For inflammation markers, NLR, CRP, and LDH significantly correlated with a chest x-ray. The patient's outcome was also associated with a chest X-ray ($P < 0.015$).

Conclusion: There were significant correlations between clinical characteristics and inflammation markers on the chest X-ray severity, and sRALE was a better scoring system to assess chest X-ray severity than other scoring systems.

Keywords: COVID-19, chest X-ray, disease severity, inflammation markers, PF ratio

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INTRODUCTION

COVID-19 cases and deaths are still increasing every day. This situation requires a prediction system to identify the severity of COVID-19 and the risk of mortality.¹ Chest x-ray is one of the parameters used to estimate the severity and prognosis of COVID-19.² Arterial oxygen saturation (SaO₂), partial pressure of arterial oxygen (PaO₂), and respiratory index (PaO₂/FiO₂) can also predict the disease severity.¹

Other parameters, like inflammation markers, have also been used as predictors for prognosis.³ These variables complement each other. Based on those considerations, this study aimed to examine their connection and to find their correlation. Nevertheless, since chest X-rays have multiple scoring systems, we would like to compare them to

see which correlates best with a clinical condition.

METHODS

This retrospective observational analytic study was performed at Ulin General Hospital. There were 245 samples of COVID-19 patients from July 2021 until December 2021, with disease severity ranging from moderate to critical.

These patients were diagnosed by reverse transcriptase-polymerase chain reaction (RT-PCR) testing and treated in an isolation ward. Patients with incomplete medical record data, lung disease(s), comorbidity that can disrupt the respiratory and blood profiles, or severe immunocompromised conditions were excluded. After that, there were only 67 samples that could be collected and analyzed.

From those samples, we collected data about chest X-rays, disease severity, blood gas analysis, and inflammation markers (NLR, ALC, LDH, and CRP) that were tested less than 48 hours after patients were admitted to the hospital. The chest x-rays of the patients will be assessed by two radiologists using three scoring systems already well known in COVID-19 (Brixia, sRALE, and modified Soetomo scoring system). The Brixia scoring system divides chest X-rays into six regions. Each region is assessed for infiltrates (0=normal/no infiltrate; 1=infiltrates in interstitial; 2=infiltrates in interstitial and alveolar, with most in interstitial; and 3=infiltrates in interstitial and alveolar, with most in alveolar). The total scores are 18.

The sRALE (simplified Radiographic Assessment of Lung Edema) scoring system divides chest X-rays into two regions. Each region is assessed for the percentages of consolidations and infiltrates in the lung (0 = no consolidation; 1 = <25% of consolidations; 2 = 25 to 50% of consolidations; 3 = 50 to 75% of consolidations; and 4 = >75% of consolidations). The total scores are 8. The modified Soetomo scoring system divides chest X-rays into six regions. Each region is assessed for the percentages of infiltrates (0=no infiltrate; 1=infiltrates <50%; and 2=infiltrates >50%). The total scores are 12.

Furthermore, for the latter, we also collected the outcome of the samples (survive or non-survive). The data were analyzed using univariate and bivariate correlations based on the result of the normality test using Kolmogorov-Smirnov.

RESULTS

As we can see from Table 1, the majority of the samples were male (61.2%), aged <65 years old (74.6%), in critical condition (49.2%), had two comorbidities (29.8%) and survived (73.1%). Moreover, from the inflammation markers in Table 1, there were increased NLR (80.6%), decreased ALC (77.6%), increased CRP (100%), and increased LDH (97.0%). In blood gas analysis, it was observed that the PF Ratio ranged from >100 to 200 and had the highest frequency (35.8%).

Table 1. Demographic Characteristics and Inflammation Markers of Patients

Variables	N	%
Demographic Characteristics		
Gender		
Male	41	61.2
Female	26	38.8
Age (mean±SD)		
<65 years (49.83±11.218)	50	74.6
≥65 years (71.29±5.610)	17	25.4
Disease Severity		
Moderate	14	20.9
Severe	20	29.9
Critical	33	49.2
Comorbidities		
No comorbidity	11	16.4
1 Comorbidity	19	28.4
2 Comorbidities	20	29.8
≥3 Comorbidities	17	25.4
Outcome		
Survive	49	73.1
Non-survive	18	26.9
Inflammation Markers		
NLR (mean±SD)		
<3.13 (2.28±0.616)	13	19.4
≥3.13 (7.62±4.089)	54	80.6
ALC (mean±SD)		
>1500 (1772.56±263.570)	15	22.4
≤1500 (911.63±290.984)	52	77.6
CRP (mg/dl) (mean±SD)		
<6	0	0.0
≥6 (106.13±67.500)	67	100
LDH (U/L) (mean±SD)		
≤220 (186.5±27.577)	2	3.0
>220 (980.8±564.739)	65	97.0
PF Ratio (mean±SD)		
>300 (383.54±49.345)	16	23.9
>200–300 (240.39±29.613)	13	19.4
>100–200 (143.8±25.470)	24	35.8
≤100 (81.13±14.037)	14	20.9

Table 2. Correlation between disease severity and chest x-ray.

Variable	Total	Score	P
		Mean±SD	(r)
Disease Severity (Brixia)			
Moderate	14	4.29±2.301	<0.001* (0.475)
Severe	20	7.20±2.802	
Critical	33	8.55±3.241	
Disease Severity (sRALE)			
Moderate	14	2.64±0.929	<0.001* (0.466)
Severe	20	3.85±1.137	
Critical	33	4.36±1.141	
Disease Severity (Soetomo)			
Moderate	14	3.93±1.592	<0.001* (0.406)
Severe	20	5.85±1.927	
Critical	33	6.39±1.749	

Note: *Spearman's rho

Table 3. Correlation between blood gas analysis (PF ratio) and chest X-ray

PF Ratio	Total	Brixia Mean±SD	P (r)	sRALE Mean±SD	P (r)	Soetomo Mean±SD	P (r)
>300	16	5.31±3.301		2.94±1.181		4.56±2.190	
>200–300	13	5.92±2.813	<0.001*	3.38±1.121	<0.001*	4.92±1.801	<0.001*
>100–200	24	8.29±1.801	(-0.452)	4.08±0.929	(-0.538)	6.21±1.250	(-0.436)
≤100	14	8.93±3.452		4.93±1.141		6.93±2.129	

Note: *Spearman's rho

Table 4. Correlation between inflammation markers and chest X-ray

Variable	Total	Brixia Mean±SD	P (r)	sRALE Mean±SD	P (r)	Soetomo Mean±SD	P (r)
NLR							
<3.13	13	5.85±3.387	0.152	3.15±1.344	0.014*	4.92±2.253	0.122
≥3.13	54	7.59±3.259	(0.177)	4.02±1.205	(0.298)	5.91±1.896	(0.191)
ALC							
>1500	15	7.87±4.033	0.815	3.73±1.624	0.349	6.13±2.356	0.824
≤1500	52	7.07±3.124	(-0.029)	3.88±1.166	(-0.116)	5.59±1.881	(-0.028)
CRP (mg/dl)							
<6	0	-	0.004*	-	0.002*	-	0.002*
≥6	67	7.25±3.332	(0.346)	3.85±1.270	(0.374)	5.72±1.991	(0.371)
LDH (U/L)							
≤220	2	5.00±1.414	0.04*	4.00±0.000	0.049*	5.00±1.414	0.075
>220	65	7.32±3.354	(0.251)	3.85±1.289	(0.241)	5.74±1.289	(0.219)

Note: *Spearman's rho

In Table 2, we obtained that disease severity had a significant correlation with all chest x-ray scoring systems ($P<0.001$). The correlation coefficient (r) showed a good relationship, with the highest correlation belonging to the Brixia ($r=0.475$). From blood gas analysis, we also found that the PF ratio had a significant negative correlation with all chest x-ray scoring systems (Table 3). Nevertheless, in this case, sRALE had the highest correlation with the PF ratio ($r = -0.538$).

From Table 4, we can see significant correlations between some inflammation markers and chest X-rays. CRP and LDH significantly correlated with the severity of the chest x-ray. CRP correlated with all chest x-ray scoring systems, and sRALE had the highest correlation ($r=0.374$). Meanwhile, LDH had correlations with two scoring systems (Brixia and sRALE), with Brixia ($r=0.251$) having a slightly better correlation than sRALE ($r=0.241$). The NLR only correlated with sRALE. Meanwhile, ALC did not correlate with chest x-rays.

There was also a correlation between outcome and chest x-ray (based on Table 5), but only if we used the sRALE scoring system ($P<0.015$), while other scoring systems did not correlate at all.

Table 5. Correlation between outcome and chest X-ray

Variable	Total	Score Mean±SD	P
Outcome (Brixia)			
Survive	49	7.10±3.601	0.355
Non-survive	18	7.67±2.497	
Outcome (sRALE)			
Survive	49	3.65±1.316	0.015*
Non-survive	18	4.39±0.979	
Outcome (Soetomo)			
Survive	49	5.55±2.102	0.219
Non-survive	18	6.17±1.618	

Note: *Mann-Whitney U

DISCUSSION

In this study, we gathered 67 samples from patients. Most of them were male (61.2%). It has the same result as existing studies, such as Mukherjee et al and Abate et al.^{4,5} This might be caused by several things, such as higher and more active ACE2 expression in males than females. The expression of transmembrane protease serine 2 (TMPRSS2), which is affected by androgen receptors in males, also enhances the effect of the SARS-CoV-2 spike protein, so the virus can enter the body more easily. Another thing that makes males more susceptible to COVID-19 is that females have a better immune response (influenced by estrogen) and higher nitric oxide levels (NO).⁴

Another piece of data that we obtained from Table 1 was age. About 74.6% of subjects were under 65 years old. Karyono et al said that productive age patients are more affected by COVID-19 because, in that age range, patients are still actively working and dealing with many people in their daily activities, so they are more easily exposed to COVID-19.⁶ In terms of disease severity, this study found that 49.2% of the sample had critical conditions. Because the population for this study was taken from July 2021 to December 2021, the Delta variant of COVID-19 was dominantly hitting Indonesia during this period. This variant has more severe cases and a higher risk of being admitted to the intensive care unit than the previous variant.⁷⁻⁹

However, this study found that the number of living patients was greater than that of those who died. Various things can cause this. First, the administration of vaccines has already started. Second, many patients who died in this study population could not be used as research samples because they did not have complete medical records, so they were excluded.^{8,10}

Another exciting thing that we obtained was that the number of comorbidities did not determine the prevalence. Singh et al published the same thing.¹¹ However, in the study of Haryati et al, it was stated that the number of comorbidities affected the mortality in COVID-19 patients.³ Another study by Haryati et al also pointed out that the inflammation process caused changes in inflammatory marker values due to COVID-19 and released various types of inflammatory mediators during cytokine storms.¹²

In blood gas analysis, we observed a decrease in PF ratio with more samples, most of which were in the range >100 to 200. It has a similar result to a study by Tang et al, where COVID-19 decreased the PF ratio by an average of 198.5.¹³ The reason why there was a decreased PF ratio was due to intrapulmonary shunt that happened because of damaged alveoli from viral infections.¹⁴

Table 3 shows that the disease severity of COVID-19 correlates with chest x-ray severity, no matter which scoring is used to assess the severity of chest X-rays ($P<0.001$). However, Brixia had the

strongest correlation with $r=0.475$, followed by sRALE with $r=0.466$, and the modified Soetomo score with $r=0.406$. This result is the same as a study from Setiawati et al in Soetomo Hospital.¹⁵

Duc et al also did a similar study but stated that sRALE has the strongest correlation, not Brixia.¹⁶ Toussie et al studied the correlation between the number of infiltrates found in chest X-rays and the severity of the disease and also discovered a correlation.¹⁷ Chen et al said that when there were mild respiratory symptoms, they were usually followed by ground glass opacity (GGO) in a chest x-ray. Then, after the virus started to replicate faster, it would attack bronchioles and alveolar epithelia, causing leakage in the alveolar cavity. This will make conditions called "white lung" and their symptoms worse.¹⁸

For the blood gas analysis, there was a negative correlation between the PF ratio and chest x-ray ($P=0.001$), with sRALE having the highest correlation coefficient with $r = -0.538$. Baratella et al and Velissaris et al did similar studies, although they used different systems to assess the chest X-ray severity. They discovered a correlation between chest X-rays and PF ratio.^{19,20} This happened because there were infections in the epithelia of the lung parenchyma, and this condition disrupted gas exchanges.¹⁹

However, in some cases, the PF ratio did not correlate with chest X-rays because the hypoxemia condition was not only affected by the lung parenchymal but also by its vascularity.²¹ This theory is also supported by Kumar et al. They stated that sometimes the patient had respiratory failure type 1, but his chest X-rays still looked normal because the chest X-rays were unable to detect thromboembolism.²²

Inflammation markers also correlated with chest X-rays, although not all of them. CRP correlated with all chest X-ray scoring systems. LDH correlated with two scoring systems (sRALE & Brixia), while NLR correlated only with sRALE. However, ALC did not correlate at all with chest X-rays. Sensusiaty et al also observed the same thing with ALC.²³ However, Wagner et al said that ALC

could be used to measure the disease severity of COVID-19.²⁴ Fachri et al reported a correlation between comorbidities and chest X-rays with CRP.²⁵

Geetika et al also studied the correlation between chest X-rays (using Brixia and sRALE) and laboratory parameters such as CRP, ferritin, LDH, D-dimer, and leukocyte. In that study, there was a correlation between chest x-ray and laboratory parameters.²⁶ There is also another study that discovered a correlation between chest X-rays with CRP and LDH.²⁷ CRP and LDH are inflammatory markers that indicate inflammations and damage in cells. In this case, the CRP and LDH values indicate the amount of alveolar damage due to viral infection, which is reflected in the chest x-ray.^{28,29}

Zhang et al were the first team to find a correlation between NLR and lung lesions, however, they were using a CT scan.³⁰ Garg et al also had a similar result to our study, where they obtained a correlation between NLR, chest X-rays and outcome.³¹ A study from Kotok et al also reported a correlation between NLR and chest X-rays (using sRALE).³² NLR can affect the chest x-ray because, in COVID-19, neutrophils will increase and extravasate to the alveoli, leading to neutrophilic mucositis and thus creating infiltrates in the chest x-ray. In addition, lymphocyte cells will experience destruction due to infection, causing a decrease in the number of lymphocytes and increasing the NLR value.³³

This study found a correlation between patient outcomes and chest X-rays using sRALE scoring. Meanwhile, when using other scoring systems, there were no correlations. The correlation between patient outcomes and chest X-rays has been extensively studied. However, there are still a few studies that tried to compare various scorings. Borghesi et al discovered no correlation between the chest X-ray severity (using the Brixia score) and the outcome. Chest X-rays are only meaningful for the outcome if at least one other predictor factor is added as a variable.³⁴ This research was later refuted by Balbi et al, who reported a positive correlation (without considering comorbidities) between the Brixia score and the risk of death.³⁵

Yasin et al also found that the severity score (using sRALE) positively correlated with disease severity and death.³⁶ Kodikara et al also tried to examine the sRALE scoring system for risk of death. This study also attempted to make two modified scores from sRALE. The first score was a combination of the sRALE and RALE system assessments, while the second was a combination of the sRALE system and Brixia. The final results of this study indeed obtained a positive correlation between the severity of chest X-rays and mortality, and the second modified system (combined sRALE and Brixia) had the best correlation rate.³⁷

Kotok et al also reported that the group of patients with RALE scores with a median of 3 had more hospital admissions compared to those with a median of 2, and those with RALE scores with a median of 7 were more at risk for ICU admission.³⁸ However, some studies stated that there was no significant relationship between outcomes and chest X-rays because it relied on comorbidities.³⁹

LIMITATION

There are several limitations to this study. First, it was a single-center study with a relatively small sample. Second, since this study only focused on the total scores of the scoring systems, it lacked a correlation between the regions of chest X-rays and clinical conditions. And lastly, it was short of a correlation between the score and comorbidities.

CONCLUSION

There is a correlation between clinical characteristics (disease severity, blood gas analysis, and outcome) and inflammation markers (NLR, CRP, and LDH) with chest x-ray severity. In this study, we also found that sRALE is a better scoring system to measure chest x-ray severity than other scoring systems because it correlates the most with other variables. sRALE is shown to be a better scoring system because it is simple while still emphasizing the severity of lung conditions. The Brixia only measures the presence of the infiltrate but tends to ignore the size of it. The modified Soetomo score

tries to combine the scoring system of sRALE and Brixia, but it still lacks the simplicity of sRALE.

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CONFLICT OF INTEREST

None.

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