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THE CORRELATIONS BETWEEN CLINICAL CHARACTERISTICS AND INFLAMMATION MARKERS WITH CHEST X-RAYS IN COVID-19 PATIENTS AT ULIN GENERAL HOSPITAL BANJARMASIN

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Background: *Chest x-ray is one of the parameters 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 also have been used as predictors for prognosis. Based on those considerations, this study will examine their connection and find their correlation.*
Methods: *This is an analytic observational retrospective study design. The samples were moderate-critical COVID-19 patients in Ulin General Hospital Banjarmasin from July - 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-ray, using various scoring systems (Brixia, sRALE, and modified Soetomo score).*
Results: *Total subjects were 67 patients. The data analysis found that the severity of the disease had a significant relationship with the severity of the chest X-ray (sig. < 0.001). The PF ratio also had a significant negative correlation (sig. < 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 is also associated with a chest X-ray (sig. < 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, disease severity, inflammation markers, PF ratio, chest X-ray*

Introduction

COVID-19 cases and deaths from it are still increasing every day. This situation requires a necessity for a prediction system to identify the severity of COVID-19 and the risk of mortality from it.[1] Chest x-ray is one of the parameters 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 also have been used as predictors for prognosis.[3] These variables complement each other. Based on those considerations, this study will examine their connection and find their correlation.

Methods

This retrospective observational analytic study was performed at Ulin General Hospital. There were 245 samples from 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) test and treated in isolation rooms. Patients with incomplete medical record data, who have lung disease(s), comorbidity that can disrupt the respiratory and blood profile or with 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-ray, disease severity, blood gas analysis, and inflammation markers (NLR, ALC, LDH, & CRP) that were checked in less than 48 hours after patients were admitted to the hospital. Two radiologists will assess the chest x-ray with three scoring systems (Brixia, sRALE, and modified Soetomo scoring system). The Brixia scoring system divided chest X-rays into 6 regions. Each region will be asses for its infiltrates (0 = normal/no infiltrate, 1 = infiltrate 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. sRALE (simplified Radiographic Assessment of Lung Edema) scoring system divided chest X-rays into 2 regions. Each region will be asses for its percentages of consolidations/infiltrates in the lung (0 = no consolidation, 1 = <25% of consolidations, 2 = 25%-50% of consolidations, 3 = 50%-75% of consolidations, and 4 = > 75% of consolidations). The total scores are 8. The modified Soetomo scoring system divided chest X-rays into 6 regions. Each region will be asses for its percentages of infiltrates (0 = no infiltrate, 1 = infiltrates < 50% and 2 = infiltrates > 50%).

The total scores are 12. Furthermore, for the last one, we also collect the outcome of samples (survive or non-survive). The data will be analyzed using univariate and bivariate correlations based on the result from the normality test using Kolmogorov-Smirnov.

Result

Table 1. Demographic and Characteristic of Patients

Variable	Total	Presentation
Gender		
- Male	41	61,2%
- Female	26	38,8%
Age (Mean ± SD)		
- <65 y.o (49,83±11,218)	50	74,6%
- ≥ 65 y.o (71,29±5,610)	17	25,4%
Disease Severity		
- Moderate	14	20,9%
- Severe	20	29,9%
- Critical	33	49,2%
Comorbid		
- No Comorbid	11	16,4%
- 1 Comorbid	19	28,4%
- 2 Comorbidities	20	29,8%
- ≥3 Comorbidities	17	25,4%
Outcome		
- Survive	49	73,1%
- Non-survive	18	26,9%
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
- ≥6 (106,13±67,500)	67	100%
LDH (U/L) (Mean ± SD)		
- ≤220 (186,5±27,577)	2	3%
- >220 (980,8±564,739)	65	97%
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%

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%). And then, from the inflammation markers, there was increased NLR (80.6%), decreased ALC (77.6%), increased CRP (100%), and increased LDH (97%). In blood gas analysis, it was found that the PF Ratio ranged from >100 to 200 and had the most frequency (35.8%).

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

Variable	Total	Score Mean±SD	Sig. (r)
Disease Severity		Brixia	<0,001* (0,475)
- Moderate	14	4,29±2,301	
- Severe	20	7,20±2,802	
- Critical	33	8,55±3,241	
Disease Severity		sRALE	<0,001* (0,466)
- Moderate	14	2,64±0,929	
- Severe	20	3,85±1,137	
- Critical	33	4,36±1,141	
Disease Severity		Soetomo	<0,001* (0,406)
- Moderate	14	3,93±1,592	
- Severe	20	5,85±1,927	
- Critical	33	6,39±1,749	

*Spearman's rho

In table 2, we found that disease severity had a significant relationship with all chest x-ray scoring systems (sig. <0.001). From the correlation coefficient (r), it has a good relationship, with the highest correlation belonging to the Brixia (r = 0.475). And then, 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 has the highest correlation with the PF ratio (r = -0,538).

Table 3. Correlation between blood gas analysis (PF ratio) with chest x-ray

Variable	Total	Score Mean±SD	Sig. (r)
PF Ratio		Brixia	<0,001* (-0,452)
>300	16	5,31±3,301	
>200 – 300	13	5,92±2,813	
>100 – 200	24	8,29±1,801	
≤100	14	8,93±3,452	
PF Ratio		sRALE	<0,001* (-0,538)
>300	16	2,94±1,181	
>200 – 300	13	3,38±1,121	
>100 – 200	24	4,08±0,929	
≤100	14	4,93±1,141	
PF Ratio		Soetomo	<0,001* (-0,436)
>300	16	4,56±2,190	
>200 – 300	13	4,92±1,801	
>100 – 200	24	6,21±1,250	
≤100	14	6,93±2,129	

*Spearman's rho

From the Table 4, we can see significant correlations between some inflammation markers with a chest x-ray. CRP and LDH significantly correlate with the severity of the chest x-ray. CRP correlates with all chest x-ray scoring systems, and sRALE has the highest correlation (r = 0.374). Meanwhile, LDH has correlations with two scoring systems (Brixia and sRALE), with Brixia (r = 0,251) having a slightly better correlation than sRALE (r =0,241). For NLR, it only correlates with sRALE. Meanwhile, ALC does not correlate with a chest x-ray.

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

Variable		Total	Brixia Mean±SD	Brixia Sig. (r)	sRALE Mean±SD	sRALE Sig. (r)	Soetomo Mean±SD	Soetomo Sig. (r)
NLR				0,152 (0,177)		0,014* (0,298)		0,122 (0,191)
ALC	- <3,13	13	5,85±3,387		3,15±1,344		4,92±2,253	
	- ≥3,13	54	7,59±3,259	0,815 (-0,029)	4,02±1,205	0,349 (-0,116)	5,91±1,896	0,824 (-0,028)
CRP (mg/dl)	- >1500	15	7,87±4,033		3,73±1,624		6,13±2,356	
	- ≤1500	52	7,07±3,124	0,004* (0,346)	3,88±1,166	0,002* (0,374)	5,59±1,881	0,002* (0,377)
LDH (U/L)	- <6	0	-		-		-	
	- ≥6	67	7,25±3,332	0,04* (0,251)	3,85±1,270	0,049* (0,241)	5,72±1,991	0,075 (0,219)
Spearman's rho	- ≤220	2	5,00±1,414		4,00±0,000		5,00±1,414	
	- > 220	65	7,32±3,354		3,85±1,289		5,74±1,289	

There was also a correlation between outcome with chest x-ray (based on Table 5,), but only if we used the sRALE scoring system (Asymp. Sig. < 0,015), while other scoring systems did not correlate at all.

Table 5. Correlation between outcome with chest x-ray

Variable	Total	Score Mean±SD	Asymp. Sig.
Outcome		Brixia	0,355
- Survive	49	7,10±3,601	
- Non-survive	18	7,67±2,497	
Outcome		sRALE	**0,015***
- Survive	49	3,65±1,316	
- Non-survive	18	4,39±0,979	
Outcome		Soetomo	0,219
- Survive	49	5,55±2,102	
- Non-survive	18	6,17±1,618	

**Mann-Whitney U*

Discussion

In this study, we found 67 samples of patients. Most of them were male (61,2%). It has the same result as existing studies, such as Mukherjee et al. (2021) and Abate et al. (2020).[4,5] This could be caused by several things, such as higher and more active ACE2 expression in males than females. Then, 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).[5]

Another data that we found from the Table 1 was age. About 74,6% of it has an age < 65 years old. Karyono et al. (2020) 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] From disease severity, this study found 49.2% sample has critical conditions. Because the population for this study was taken from July 2021 to December 2021, the Delta variant of COVID-19 was hitting Indonesia during this period.[7,8] This variant has more severe cases and has a higher risk of being admitted to the intensive care unit than the previous variant.[9] However, this study found that the number of living patients was more than those who died. Various things can cause this. First, the administration of vaccines has already started.[8,10] Second, many patients who died from this study population could not be used as research samples because they did not have complete medical records, so they were excluded.

Another exciting thing that we found was that the number of comorbidities did not determine the prevalence. Sing et al. (2020)

found the same thing.[11] However, in the study of Haryati et al. (2021), it was stated that the number of comorbidities affected the mortality in COVID-19 patients.[3] Another study by Haryati et al. (2021) also found that the inflammation process causes changes in inflammatory marker values due to COVID-19, and it will release released various types of inflammatory mediators during cytokine storms.[12]

In blood gas analysis, we found a decrease in PF ratio has more samples, most of which are in the range >100-200. It has a similar result to Tang et al. (2020) study, where COVID-19 has decreased the PF ratio by an average was 198,5.[13] The reason why there was decreased PF ratio was due to intrapulmonary shunt happened because of damaged alveolar from viral infections.[14]

Table 2 shows that disease severity of COVID-19 correlates with chest x-ray severity, no matter which scoring is used to assess the severity of chest x-ray (sig. < 0,001). However, Brixia has the strongest correlation with r = 0,475, followed by sRALE with r =0,466. The last one was the modified Soetomo score with r = 0,406. It has a similar result to the study from Setiawati et al. (2021) in Soetomo Hospital.[15] Duc et al. (2022) also did a similar study but found that sRALE has the strongest correlation, not Brixia.[16] Toussie et al. (2020) study about the correlation between the number of infiltrates found in chest X-rays and the severity of the disease and also found a correlation.[17] Chen et al. (2020) said that when there are mild respiratory symptoms, it usually will be followed by ground glass opacity (GGO) in a chest x-ray. And then, after the virus starts replicating faster, it will attack bronchioles and alveolar epithelia, causing leakage in the alveolar cavity. It will make conditions called “white lung” and the symptoms worse.[18]

For the blood gas analysis, there was a negative correlation between the PF ratio and chest x-ray (Sig. 0,001), with sRALE having the highest correlation coefficient with r = - 0,538. Baratella et al. (2020) and Velissaris et al. (2021) did similar studies, although they used different systems to assess the chest x-ray severity. They found a correlation between a chest x-ray and the PF ratio.[19,20] This happened because there were infections in the epithelia of the lung parenchymal, and this condition disrupted gas exchanges.[19] But in some cases, the PF ratio does not correlate with a chest x-ray. Because the hypoxemia condition is not only affected by the lung parenchymal but also by its vascularity.[21] This theory is also supported by Kumar et al. (2021). They said that sometimes the patient has respiratory failure type 1 condition, but his chest x-ray still looks normal because chest x-ray cannot detect thromboembolism.[22]

Inflammation markers also correlate with chest X-rays, although not all of them. CRP correlates with all chest x-ray scoring systems. LDH correlates with two scoring systems (sRALE & Brixia), and NLR correlates only with sRALE. However, ALC does not correlate at all with a chest x-ray. Sensusiati et al. (2020) also found the same thing with ALC.[23] But Wagner et al. (2020) said ALC could be used to measure the disease severity of COVID-19.[24] And then for other inflammation markers, Fachri et al. (2022) found a correlation between comorbidities and chest x-ray with CRP.[25]

Geetika et al. (2022) also study the correlation between chest x-ray (using Brixia and sRALE) with laboratory parameters such as CRP, ferritin, LDH, D-dimer, and leucocyte. In that study, there was a correlation between a chest x-ray and laboratory parameters.[26] There is also another study that found a correlation between chest x-ray 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] For NLR, Zhang et al. (2020) were the first team to find the correlation between NLR and lung lesions. However, in this study, they were using CT-scan.[30] Garg et al. (2021) also had a similar result to our study, where they found a correlation between NLR with chest x-ray and outcome.[31] Study from Kotok et al. (2022) also reports a correlation between NLR and chest x-ray (using sRALE).[32] NLR can affect the chest X-ray because, in COVID-19, neutrophils will increase and extravasate to the alveolar, leading to neutrophilic mucositis, thus creating infiltrates in a chest x-ray. In addition, lymphocyte cells will experience destruction due to infection and cause a decrease in the number of lymphocytes 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 was no correlation. The correlation between patient outcomes and chest X-rays has been extensively studied. However, still few studies that tried to compare various scoring. Borghesi et al. (2020) found no correlation between the chest X-ray severity (using the Brixia score) and the outcome. Chest X-ray is 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. (2021), who found a positive

correlation (without considering comorbidities) between the Brixia score and the risk of death.[35] Yasin et al. (2020) also found that the severity score (using sRALE) positively correlated with disease severity and death.[36] Then Kodikara et al. (2021) also tried to examine the sRALE scoring system for risk of death. This study also tried 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 found 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] Then Kotok et al. (2021) also found that the group of patients with RALE scores with a median of 3 has more hospital admissions compared to a median of 2, and RALE with a median of 7 is more at risk for ICU admission.[38] However, there are studies that state that there is no significant relationship between outcomes and chest X-rays because it depends on comorbidities.[39]

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.

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