ORIGINAL ARTICLE

The Relationship of Chest X-Ray in COVID-19 Patients and Disease Severity in Arifin Achmad General Hospital Riau

Aulia Rahman[1]*, Sri Melati Munir[1], Indra Yovi[1], Andreas Makmur[2]

[1]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Riau/Arifin Achmad General Hospital, Riau, Indonesia.

[2]Department of Radiology, Faculty of Medicine, University of Riau/Arifin Achmad General Hospital, Riau, Indonesia.

ARTICLE INFO

Article history:
Received 12 May 2021
Received in revised form 26 September 2021
Accepted 28 September 2021
Available online 30 September 2021

Keywords:
COVID-19,
Chest X-Ray,
Comorbidities,
Severity,
Infection disease.

ABSTRACT

Introduction: Coronavirus Disease 2019 (COVID-19) pandemic is caused by SARS-CoV-2 which spreads rapidly throughout the world and causes clinical manifestations in various organs, especially in the lungs. Clinical symptoms arise from asymptomatic, mild, moderate, severe, and critical symptoms in patients with or without the comorbid disease. Chest X-ray examination is one of the modalities in the diagnostic of COVID-19 which is cheap and easy to do.

Methods: This study was performed by analyzing medical record data of confirmed COVID-19 patients from March to December 2020. This study aimed to examine the relationship between chest X-ray and the degree of disease severity.

Results: The results showed that from the examined 542 total samples, the highest number was found in the age group of 40-49 years old (23.6%), women (53%), mild degree of COVID-19 (67.9%), normal chest X-ray (54.6%), predominance on the lower zone of the lung, peripheral and bilateral on abnormal chest X-ray, no comorbid (56.3%), hypertensive in comorbid disease (26.6%). There was a significant relationship between chest X-ray and comorbidity towards COVID-19 severity ($p = 0.000$).

Conclusion: Chest X-ray can determine disease severity, therefore it can be used as the first modality for triage and treatment evaluation in COVID-19 patients.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection and was first reported in Wuhan, China at the end of December 2019. World Health Organization (WHO) declared COVID-19 as a pandemic on 11 March 2020.[1,2] The manifestations of COVID-19 are similar to SARS-CoV and MERS-CoV which affect lung organs and also have a wide impact on other organs, such as cardiovascular, gastrointestinal tract, liver, kidneys, eyes, and skin. The most common clinical manifestations are cough, shortness of breath, fever, and sore throat. The clinical course of the patient could be without clinical symptoms, then worsen to a critical condition and become ARDS, respiratory failure, and death.[3–5] Imaging plays an important role in the diagnosis and management of COVID-19. Chest X-ray is considered to be the first-line imaging modality for the initial triage of suspected COVID-19 cases. Although chest X-ray is considered insensitive for detecting pulmonary involvement in early-stage disease, they can be useful diagnostic tools for monitoring rapid progress in critically ill patients who are admitted to the intensive care unit (ICU). Chest X-ray can reflect disease severity, thus it is useful for monitoring the changes in chest X-ray during treatment.[6–9]

*Corresponding author: dr_auliarahman@yahoo.com

Jurnal Respirasi, p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v7-I.3.2021.114-121

METHODS

This was an analytical study with a cross-sectional design. This study aimed to examine the correlation between chest X-ray and COVID-19 severity using secondary data, namely medical records of inpatients of PINERE Room Arifin Achmad General Hospital Riau. This study was conducted in March 2021 by taking medical record data from March to December 2020. The sample was taken by total sampling. The inclusion criteria were medical record data from adult COVID-19 patients aged ≥18 years old who were treated in PINERE Room Arifin Achmad General Hospital Riau and had complete data with criteria degree severity: mild illness if patients with symptoms without evidence of viral pneumonia or hypoxia; moderate illness if clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) but no signs of severe pneumonia including SpO2 > 93% with room air; severe illness if clinical signs of pneumonia plus one of respiratory rate > 30 breaths/minute, severe respiratory distress, or SpO2 < 93% in room air; and critical illness if patients with Acute Respiratory Distress Syndrome (ARDS), sepsis and septic shock.[10] Incomplete medical record, chest X-rays not worth reading, history of pulmonary tuberculosis, bronchiectasis, lung cancers and tumor metastases in the lungs, pleural effusions, pneumothorax, and hydropneumothorax were excluded from the sample.

Chest X-rays are assessed with the Brixia Score method. The lungs are divided into six zones on frontal chest projection: upper zones (right and left), middle zones (right and left) and lower zones (right and left) which are assessed based on the lung abnormalities detected with a score of 0 if no lung abnormalities, a score of 1 with interstitial infiltrates, a score of 2 with interstitial and alveolar infiltrates (interstitial predominance) and a score of 3 with interstitial and alveolar infiltrates (alveolar predominance). The scores of the six lung zones are then added to obtain an overall CXR score ranging from 0 to 18. In this study, we divide the research subjects into 4 groups: normal chest X-ray (score of 0), mild pneumonia (1-6), moderate degree (7-12), and severe degree (13-18).[7]

The data obtained were analyzed with a statistical package for social science (SPSS) software 2.4 version. The relationship between chest X-ray and COVID-19 severity was analyzed using the Chi-Square test. The results with p values < 0.05 were considered to be statistically significant. This study had been approved ethically by the Medical Research Ethics Unit Faculty of Medicine, the University of Riau with the number B/013/UN19.5.1.1.8/UEPKK/2021.

RESULTS

The number of research subjects included was 542 patients. The age range was 18 - 91 years old and the median was 43 years old. Group of 40-49 years old (128, 23.6%) and female (287, 53%) were the largest numbers. The characteristics of the subjects are presented in Figure 1 and Figure 2.

Disease severity was determined by the pulmonologist when the COVID-19 patient was hospitalized early and was recorded in the medical record. In this study, the highest number was found in the mild COVID-19 group (368, 67.9%). The second was the moderate degree group (114, 21.03%) and the third was the severe degree group (43, 7.93%). COVID-19 group with a critical severity had the lowest number among other groups (17, 3.14%) as shown in Figure 3.

Chest X-ray of the research subjects was assessed by a radiologist using the Brixia Score method taken from chest X-ray of COVID-19 patient in early hospitalization. This study divided the research subjects into 4 groups: normal chest X-ray (score of 0), mild pneumonia (1-6), moderate degree (7-12), and severe degree (13-18). Normal chest X-ray image was found (296, 54.6%) more than those which were abnormal (246, 45.4%). The group of subjects with mild pneumonia degree (160, 29.5%) had the largest number among the group of research subjects with chest X-ray abnormalities, followed by moderate (71, 13.1%) and severe group (15, 2.8%). Abnormal chest X-ray feature of COVID-19 patients in this study was mostly bilateral pneumonia in (204, 37.6%), peripheral (177, 32.7%), and lower zone of the lung (220, 40.6%) as seen in Table 1.

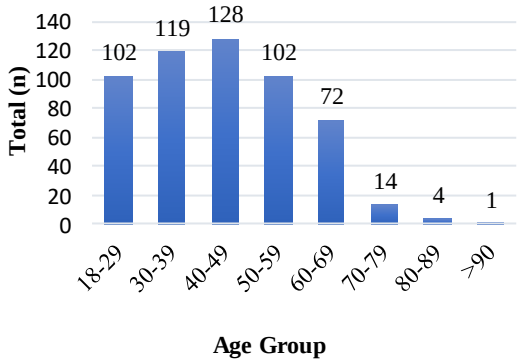

Figure 1. Characteristics of the research subjects based on age

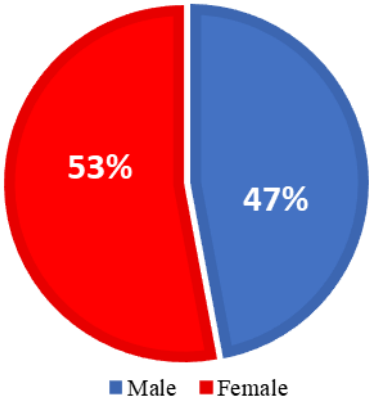

Figure 2. Characteristic of the research subjects based on gender

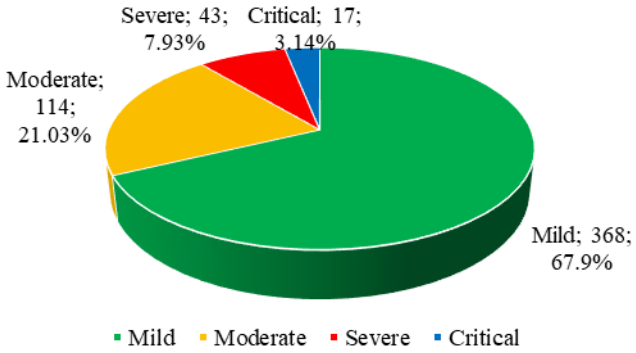

Figure 3. Disease severity of the research subjects

Table 1. Chest X-ray results of the research subjects

Chest X-ray	n	%
Pneumonia severity (N=542)		
Normal (score 0)	296	54.6
Pneumonia	246	45.4
Mild (score 1-6)	160	29.5
Moderate (score 7-12)	71	13.1
Severe (score 13-18)	15	2.8
Laterality (N=246)		
Right Unilateral	24	4.4
Left Unilateral	18	3.3
Bilateral	204	37.6
Distribution (N=246)		
Peripheral	177	32.7
Central	3	0.6
Diffuse	66	12.2
Zonal Predominance (N=246)		
Upper	14	2.6
Middle	12	2.2
Lower	220	40.6

Table 2. The relationship between pneumonia severity on chest X-ray and COVID-19 severity

Chest X-ray	Severity of disease		*p-Value*	PR 95% CI
	Mild - Moderate n (%)	Severe - Critical n (%)		
Pneumonia Severity				
0 - 6 (Normal – Mild Pneumonia)	436 (95.6)	20 (4.4)	**0.000***	18.957 (10.230-35.126)
7 - 18 (Moderate-Severe Pneumonia)	46 (53.5)	40 (46.5)		
Laterality				
Unilateral	42 (17.07)	0	**0.000***	
Bilateral	154 (62.60)	50 (20.33)		
Distribution				
Peripheral	162 (65.85)	15 (6.010)		
Central	2 (0.81)	1 (0.41)	**0.000****	
Difuse	32 (13.01)	34 (13.82)		
Zonal Predominance				
Upper	11 (4.47)	3 (1.22)		
Middle	8 (3.25)	4 (1.63)	0.251**	
Lower	177 (71.95)	43 (17.48)		

** Chi-Square Test*
***Mann-Whitney U test*

Chest X-ray results were grouped into normal-mild pneumonia and moderate-severe pneumonia groups. Furthermore, bivariate analysis was performed with COVID-19 severity which was grouped into mild-moderate and severe-critical groups. The bivariate analysis used Chi-Square statistical test, which statistically gave a significant value if p <0.05. The result found that there was a significant relationship between the severity of pneumonia on chest X-ray and COVID-19 severity (PR 18.957; 95% CI 10.230-35.126; p = 0.000) from the total of 542 research subjects analyzed as shown in Table 2. The statistical analysis results of 246 research subjects who had chest X-ray abnormalities showed a relationship between pneumonia laterality and disease severity (p = 0.000). Significant results were also obtained between the distribution of pneumonia to disease severity (p = 0.000). There was no significant relationship between pneumonia zone and disease severity (p = 0.251).

Table 3. Comorbidities of the research subjects

Comorbidity	n	%
No	305	56.3
Yes	237	43.7
Hypertension	144	26.6
Diabetes mellitus	76	14
Kidney failure	32	5.9
Cardiovascular disease	26	4.8
Malignancy	24	4.4
Hepatobiliary disease	10	1.8
Cerebrovascular disease	9	1.7
Asthma	7	1.3
COPD	5	0.9
Gastrointestinal disease	3	0.6
HIV-AIDS	3	0.6
Hyperthyroidism	2	0.4
Autoimmune disease	1	0.2

Table 4. The relationship between comorbidity and COVID-19 severity

Comorbidity	n (%)	Severity Disease		*P Value*	PR 95%CI
		Mild-Moderate	Severe-Critical		
No	305 (56.27)	297 (54.79)	8 (1.48)	**0.000***	10.435 (4.848-22.462)
Yes	237 (43.72)	185 (34.13)	52 (9.59)		
Hypertension	144 (26.6)	114	30	**0.000***	3.228 (1.866-5.584)
Diabetes mellitus	76 (14)	52	24	**0.000***	5.513 (3.052-9.957)
Kidney failure	32 (5.9)	18	14	**0.000****	7.845 (3.664-16.798)
Cardiovascular disease	26 (4.8)	18	8	**0.004****	3.966 (1.644-9.569)
Malignancy	24 (4.4)	21	3	0.741	
Hepatobiler disease	10 (1.8)	6	4	**0.017****	5.667 (1.552-20.691)
Cerebrovascular disease	9 (1.7)	6	3	0.067	
Asthma	7 (1.3)	6	1	0.562	
COPD	5 (0.9)	3	2	0.097	
Gastrointestinal dsiease	3 (0.6)	3	0	1.000	
HIV-AIDS	3 (0.6)	2	1	0.297	
Hyperthyroidism	2 (0.4)	2	0	1.000	
Autoimmune disease	1 (0.2)	1	0	1.000	

**Chi-Square Test*
***Fisher Exact Test*

Comorbidities were concluded by the pulmonologist or other specialists in Arifin Achmad General Hospital Riau based on anamnesis, physical examination, laboratory examination, or other supporting examinations. Most of the research subjects did not have comorbidities (305, 56.3%) but they were not much different from the group that had comorbidities (237, 43.7%). The most common comorbidities found were hypertension (144, 26.6%), diabetes mellitus (76, 14%), kidney failure (32, 5.9%), cardiovascular disease (26, 4.8%), and malignancy (24, 4.4%) as seen in Table 3.

Based on the results of statistical analysis of the research subjects, it was found that there was a significant relationship between comorbidities and COVID-19 severity (PR 10.435; 95% CI 4.848-22.462; p = 0.000). Comorbidities which had a significant relationship to COVID-19 severity in this study include hypertension (PR 3.228; 95% CI 1.866-5.584; p=0.000), diabetes mellitus (PR 5.513; 95% CI 3.052-9.957; p = 0.000), kidney failure (PR 7.845; 95% CI 3.664-16.798; p = 0.000), cardiovascular disease (PR 3.966; 95% CI 1.644-9.569; p = 0.004), and hepatobilier disease (PR 5.667; 95% CI 1.552-20.691; p = 0.017).

DISCUSSION

The characteristics of the research subjects found that the 40-49 years old age group had the largest number (128, 23.6%). The results of this study are not much different from the study conducted by Huang, *et al*., which found that the 25-49 years old group (49%) was the most group infected with COVID-19.[3] Guan, *et al*. also had the 15-49 years old age group (55.1%) as most group infected with COVID-19.[10] Data from Indonesian COVID-19 Task Force stated that the 31-45 years old age group had the highest number (29.3%).[11] However, Chen, *et al*. found that 50-59 years old age group was slightly more infected (30%).[4] Zhang, *et al.* also found that the slightly older group was more infected, namely the 50-69 years old age group (49.3%).[12] Borghesi, *et al.* found the 70-79 years old age group (26.8%).[13] The difference in the number of infections in each age group was probably influenced by the ratio of age groups and different levels of mobility in each region. Tay argued that older people and people with comorbidities have a greater likelihood of impaired immune response leading to abnormalities and failure to eradicate pathogens. This condition is caused by aging lung tissue, which causes changes in dendritic cell maturation and migration to lymphoid organs, which then disrupts T-cell activation. The contradictory results were found in children who tended to have no severe disease despite experiencing high viral titers.[14]

Female was found (53%) more than male (47%) in this study. Data from the Indonesian COVID-19 Task Force also found females (51.1%) were more infected than males (48.9%).[11] Shang, *et al*. obtained similar results in which females (52.6%) were more infected compared to males (47.4%).[15] Yue, *et al.* also obtained the same results (55.8%).[16] However, Zhang, *et al*. found different results, with the male group was more infected (50.7%) compared to the female group (49.3%).[12] Hu, *et al*. also found that male were slightly higher than female (51.4%).[17] There was no significant gender difference as the number of COVID-19 cases continued to increase. It is important to note that COVID-19 figures show a difference in mortality rates between male and female. This difference is due to Angiotensin-Converting Enzyme 2 (ACE2) which is located on the X chromosome. Different immunoregulatory functions of sex hormones estrogen and testosterone, physiological factors, and different lifestyles are also thought to play a role.[14,18,19]

This study found the mild group (67.95%) was the largest group. The results of this study are similar to the Chinese Center for Disease Control (CDC) report with 80.9% mild or moderate cases, 13.8% severe cases, and 4.7% critical cases of 44,672 cases ofCOVID-19 outbreak.[20] Yue, *et al.* also found the mild group was the largest (75.6%), but this group was combined with the moderate group.[16] Lian, *et al.* found a much higher number (90.08%) for the mild degree group.[21]

It can be seen that 296 chest radiographs were found normal (54.6%) in this study. This was similar to the results of a study conducted by Weinstock, *et al*., which found 371 patients (58.3%) had normal images. The subjects with mild symptoms had the largest number of subjects with images of chest X-ray abnormalities (160, 29.5%). This result is not much different from the results of a study conducted by Weinstock, *et al*., which found 195 patients (30.7%) had mild symptoms.[22]

Pneumonia on chest X-ray of COVID-19 patients in this study was mostly bilateral (204, 37.6%), at the peripheral (177, 32.7%), and dominance in the lower lung zone (220, 40.6%). This result is not much different from the results of a study conducted by Weinstock, *et al.* which also found that the most were bilateral (133, 20.9%), at peripheral (225, 35.4%) and dominance in the lower lung zone (215, 33,8%).[22] Kaleemi, *et al*. also obtained similar results of chest X-ray COVID-19 patients with bilateral, peripheral, and dominant distribution in the lower lobe.[23]

This study found a significant relationship between chest X-rays in COVID-19 patients and disease severity based on Chi-Square test results (PR 10.605; 95% CI 6.531-17.220; p = 0.000). Guan, *et al*. stated that patients with severe disease had a higher incidence of pneumonia than patients with mild disease.[10] According to Toussie, *et al*., the severity of opacity in the initial chest X-ray was associated with the need for hospitalization and intubation. Patients with at least two lung zone opacities were more likely to require hospitalization and those with opacity in at least three lung zones were more likely to require intubation.[24] A study conducted by Borghesi, *et al*. concluded that chest X-ray severity scores were associated with mortality.[25] Wong, *et al.* reported that findings on chest X-ray changed over time and reached their peak at 10-12 days from the onset of symptoms. Patients who are in the "early stages" of disease are characterized by the presence of ground-glass density, which may be very difficult to detect on chest X-ray.[26]

Blain, *et al*. obtained more pictures of bilateral pneumonia than unilateral (69%), but in this study, he did not associate whether there was a relationship with the disease severity. This study also found that the lower lung field area was more dominant than other areas, but he also did not mention whether there was any relationship with the degree of disease severity.[27] Wong, *et al*. mentioned in their study that pneumonia abnormalities on chest X-rays were more bilateral (50%). Peripheral abnormalities were more compared to other areas (41%). The lower zone was found more than other zones (50%). Wong's study also did not mention whether there was a relationship between the image of chest X-ray pneumonia in bilateral lungs, distributed in the periphery, and lower lung field zones to the degree of COVID-19 severity.[26] Cozzi, *et al.* also found the same thing that there were more pictures of chest X-ray abnormalities in the group which affected bilateral (69.2%) compared to unilateral ones. Pneumonia abnormalities were more distributed in the periphery (57.7%) compared to central or diffuse areas. This study also found dominance in the lower lung (58.5%) compared to the upper or middle zone. This study did not explain whether there was a significant relationship between laterality, distribution, and zone domination of chest X-ray abnormalities on the degree of disease severity.[28]

The result of this study showed that the numbers of the non-comorbidities patient (305, 56.3%) were larger than the patients who had comorbidities. The five most common comorbidities in this study were hypertension (144, 26.6%), diabetes mellitus (76, 14%), kidney failure (32, 5.9%), cardiovascular disease (26, 4.8%), and malignancy (24, 4.4%). The results of this study are similar to the results of a study conducted by Li, *et al*., who got hypertension (35, 47.3%) in the first order of comorbidities found in COVID-19 patients, followed by diabetes (14, 18.9%) and coronary heart disease (6, 8.1%).[29] Zhang, *et al*. also found similar results with hypertension in the first place as much as 42 people (30%), followed by diabetes mellitus as much as 17 people (12.1%), liver disease as many as 8 people (5.7%), and coronary heart disease as many as 7 people (5%).[12]

Hypertension has been identified as the chronic disease that most COVID-19 patients suffer from. ACE2 receptor which mediates SARS-CoV-2 invasion via the glycoprotein spikes binding pathway - widely expressed in the lungs and heart. The balance between ACE1 and ACE2 is very important to control levels of Angiotensin II. The binding of SARS-CoV-2 with ACE2 causes excessive release of angiotensin II through the renin-angiotensin system (RAS), resulting in increased cardiac load, cardiomyocyte hypertrophy, and high blood pressure.[30,31] Diabetics are more susceptible to infection because their immune system is compromised. Immune dysfunction in diabetics can be affected by hyperglycemia, altered cytokine production, impaired T cell-mediated immune response, inhibition of neutrophil chemotaxis, ineffective microbial clearance, and phagocytic cell dysfunction. Another hypothesis suggests that ACE2 may play an important role in COVID-19 severity infection in diabetic individuals because the virus uses ACE2 to attack the host pneumocytes and it is also expressed in pancreatic tissue. In addition, diabetics have been shown to have elevated levels of proinflammatory cytokines, especially IL-1, IL-6, and TNF-α as well as other markers, such as C-reactive protein, D-dimer, and fibrinogen. This in turn can prolong the cytokine storm and cause severe illness in diabetics with COVID-19 infection. The role of markers in COVID-19 is to induce diabetes.[31–33]

This study also examined whether there was a relationship between COVID-19 severity and comorbidities in the research subjects. After combining mild to moderate degree in a group and severe to critical in a group for Chi-Square statistical tests, the results of the statistical test showed that there was a significant relationship between the degree of disease severity and comorbidities (PR 2.258; 95% CI 1.943-2.625; p = 0.000). This study also obtained the results of several comorbidities that had a significant relationship with the degree of disease severity, including hypertension (PR 3.228; 95% CI 1.943-2.625; p = 0.000), diabetes mellitus (OR 5.513), kidney failure (OR 7.845), cardiovascular disease (OR 3.966), and hepatobiliary disease (OR 5.667).

This study is similar to the study of Surendra, *et al*. in Jakarta which obtained significant results on comorbidities, such as hypertension (p-value <0.0001), diabetes (p-value <0.0001), cardiovascular disease (p-value <0.0001), failure kidney (p-value <0.0001), and liver disease (p-value <0.032). The difference is in the study, Surendra, *et al* studied the relation of comorbidities and the outcome of treatment (returning home with recovery or death).[34] Hu, *et al.*'s study in Wuhan found only diabetes (p-value <0.001) and cardiovascular disease (p-value <0.001) which were related to the degree of disease severity.[17]

According to Zhang, *et al.*, patients with severe COVID-19 were associated with a higher frequency of comorbidities. His research found that patients with comorbidities showed a higher severity than those without comorbidities.[12] Wang, *et al*. found in their

study that COVID-19 patients treated in the ICU were older and had a higher number of comorbidities more than patients who were treated in a regular ward. This suggests that age and comorbidities may be risk factors for poor outcomes. Comorbidities such as hypertension, diabetes, and coronary heart disease can affect COVID-19 severity.[35] This, according to Chen, *et al*., is related to an imbalance of ACE2 and cytokine storms caused by disorders of Glucolipid metabolism (GLMD).[36]

CONCLUSION

The proportion of 40-49 year age group was the most common and women are more found than men in this study. The severity of COVID-19 is highest in the mild grade group and the number decreases with increasing severity. The normal group in the CXR assessed with the Brixia Score method found more than the abnormal CXR images. The higher the degree of pneumonia, the lower the proportion found. The majority of CXRs found were bilateral, peripheral, and predominantly in the lower lung fields. Research subjects who do not have comorbidities are found more than those who have comorbidities. The five most common comorbidities are hypertension, diabetes mellitus, kidney failure, cardiovascular disease, and hepatobiliary disease. There is a significant relationship between CXR images and the severity of COVID-19 also between comorbidities and the severity of COVID-19. The CXR can determine the severity of the disease so that it can be used as the first modality for triage COVID-19 patients.

Acknowledgement

The authors gratefully acknowledge the Director of Arifin Achmad General Hospital, Department of Pulmonology and Respiratory Medicine, Department of Radiology, staff of Medical Record, staff of PINERE ward for their great support in this study.

REFERENCES

1. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K, *et al*. Pneumonia of Unknown Aetiology in Wuhan, China: Potential for International Spread Via Commercial Air Travel. *J Travel Med*. 2020;27(2):1-3.
2. World Health Organization. Pneumonia of Unknown Cause – China. https://www.who.int/csr/don/05-january-2020-pneumonia-of-unkown-cause-china/en/. Diakses 13 Desember 2020.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
4. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. *Lancet*. 2020;395(10223):507-13.
5. Rodriguez-MoralesAJ,Cardona-OspinaJA,Gutiérrez-OcampoE,Villamizar-Pena R, Holguin-Rivera Y, Escallera-Antezana JP, *et al*. Clinical, Laboratory and Imaging Features of COVID-19: A Systematic Review and Meta-Analysis. *Travel Med Infect Dis*. 2020;(3)34.
6. Tsakok M, Shaw R, Murchison A, Ather S, Xie C, Watson R, *et al*. Diagnostic Accuracy of Initial Chest Radiograph Compared to SARS-CoV-2 PCR in Patients with Suspected COVID-19. *BJR|Open*. 2020;2(1):20200034.
7. Borghesi A, Maroldi R. COVID-19 Outbreak in Italy : Experimental Chest X-Ray Scoring System for Quantifying and Monitoring Disease Progression. *Radiol Med*. 2020;125(5):509-13.
8. Manna S, Wruble J, Maron SZ, *et al*. COVID-19: A Multimodality Review of Radiologic Techniques, Clinical Utility, and Imaging Features. *Radiol Cardiothorac Imaging*. 2020;2(3):e200210.
9. Zu ZY, Jiang Mdi, Xu PP, Chen W, Ni QQ, Lu GM, *et al*.Coronavirus Disease 2019 (COVID-19): A Perspective from China. *Radiology*. 2020;296(2):E15-E25.
10. Burhan E, Dwi Susanto A, Isbaniah F, Aman Nasution A, Ginanjar E, Pitoyo CW, et al. Pedoman Tatalaksana COVID-19 Edisi 3 Tim Editor Perhimpunan Dokter Paru Indonesia (PDPI) Perhimpunan Dokter Spesialis Kardiovaskular Indonesia (PERKI) Perhimpunan Dokter Spesialis Penyakit Dalam Indonesia (PAPDI) Perhimpunan Dokter Anestesiologi Dan Terapi; 2020.6-7
11. Guan W, Ni Z, Hu Y, W Liang, C Ou, J He, *et al*. Clinical Characteristics of Coronavirus Disease 2019 in China. 2020. N Engl J Med. 2020;382:1708-20.
12. COVID-19 STP. Peta Sebaran. Satgas Penanganan COVID-19 [Internet]. 2021 [cited 2021 April 03]. Available form: https://covid19.go.id/peta-sebaran
13. Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, *et al*. Clinical Characteristics of 140 Patients Infected with SARS-Cov-2 in Wuhan, China. *Allergy Eur J Allergy Clin Immunol*. 2020;75(7):1730-1741.
14. Borghesi A, Zigliani A, Masciullo R, Golemi S, Maculotti P, Farina D, *et al*. Radiographic Severity Index in COVID-19 Pneumonia: Relationship to Age and Sex in 783 Italian Patients. *Radiol Medica*. 2020;125(5):461-464.
15. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The Trinity of COVID-19: Immunity, Inflammation and Intervention. *Nat Rev Immunol*. 2020;20(6):363-374.

16. Shang J, Wang Q, Zhang H, Wang X, Wan J, Yan Y, *et al*. The Relationship between Diabetes Mellitus and COVID-19 Prognosis: A Retrospective Cohort Study in Wuhan, China. *Am J Med*. 2021;134(1):e6-e14.
17. Yue H, Bai X, Wang J, Yu Q, Liu W, Pu J, *et al*. Clinical Characteristics of Coronavirus Disease 2019 in Gansu Province, China. *Ann Palliat Med*. 2020;9(4):1404-1412.
18. Hu L, Chen S, Fu Y, Gao Z, Long H, Ren HW, *et al*. Risk Factors Associated with Clinical Outcomes in 323 Coronavirus Disease 2019 (COVID-19) Hospitalized Patients in Wuhan, China. *Clin Infect Dis*. 2020;71(16):2089-98.
19. Yuki K,Fujiogi M, Koutsogiannaki S.COVID-19 Pathophysiology: A Review. *Clin Immunol*. 2020;215:108427.
20. Giri M, Puri A, Wang T, Guo S. Comparison of Clinical Manifestations, Pre-Existing Comorbidities, Complications and Treatment Modalities in Severe and Non-Severe COVID-19 Patients: A Systemic Review and Meta-Analysis. *Sci Prog*. 2021;104(1):1-24.
21. Surveillances V. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):145-151.
22. Lian JS, Cai H, Hao SR, Jin X, Zhang XL, Zheng L, *et al*. Comparison of Epidemiological and Clinical Characteristics of COVID-19 Patients with and without Wuhan Exposure. *J Zhejiang Univ Sci B*. 2020;21(5):369-377.
23. Weinstock MB, Echenique A, Russel JW, Leib A, Miller JA, Cohen DJ, *et al*. Chest X-Ray Findings in 636 Ambulatory Patients with COVID-19 Presenting to an Urgent Care Center: A Normal Chest X-Ray is No Guarantee Contrast Reaction View Project Pancreatic IRE View Project. *J Urgent Care Med*. 2020;14(7):13-18.
24. Kaleemi R, Hilal K, Arshad A, Martins RS, Nankani A, Haq TU, *et al*. The Association of Chest Radiographic Findings and Severity Scoring with Clinical Outcomes in Patients with COVID-19 Presenting to the Emergency Department of a Tertiary Care Hospital in Pakistan. *PLoS One*. 2021;16:1-11.
25. Toussie D, Voutsinas N, Finkelstein M, Cedillo MA, Manna S, Maron SZ, *et al*. Clinical and Chest Radiography Features Determine Patient Outcomes in Young and Middle-Aged Adults with COVID-19. *Radiology*. 2020;297(1):E197-E206.
26. Borghesi A, Zigliani A, Golemi S, Carapella N, Maculotti P, Farina D, *et al*. Chest X-Ray Severity Index as a Predictor of In-Hospital Mortality in Coronavirus Disease 2019: A Study of 302 Patients From Italy. *Int J Infect Dis*. 2020;96:291-293.
27. Wong HYF, Lam HYS, Fong AHT, Leung ST, Chin TWY, Lo CSY, *et al*. Frequency and Distribution of Chest Radiographic Findings in Patients Positive for COVID-19. *Radiology*. 2020;296(2):E72-E78.
28. Blain M, Kassin MT, Varble N, Wang X, Xu Z, Xu D, *et al*. Determination of Disease Severity in COVID-19 Patients Using Deep Learning in Chest X-Ray Images. *Diagnostic Interv Radiol*. 2021;27(1):20-27.
29. Cozzi D, Albanesi M, Cavigli E, *et al*. Chest X-Ray in New Coronavirus Disease 2019 (COVID-19) Infection: Findings and Correlation with Clinical Outcome. *Radiol Medica*. 2020;125(8):730-7.
30. Li J, Xu G, Yu H, Peng X, Luo Y, Cao C. Clinical Characteristics and Outcomes of 74 Patients with Severe or Critical COVID-19. *Am J Med Sci*. 2020;360(3):229-35.
31. Xia F, Zhang M, Cui B, An W, Chen M, Yang P, *et al*. COVID - 19 Patients with Hypertension are at Potential Risk of Worsened Organ Injury. *Sci Rep*. 2021:1-10.
32. Roy S, Mazumder T, Banik S. The Association of Cardiovascular Diseases and Diabetes Mellitus with COVID-19 (SARS-CoV-2) and Their Possible Mechanisms. *SN Compr Clin Med*. 2020;2(8):1077-82.
33. Gupta R, Ghosh A, Singh AK, Misra A. Clinical Considerations for Patients with Diabetes in Times of COVID-19 Epidemic. *Diabetes Metab Syndr Clin Res Rev*. 2020;14(3):211-12.
34. Angelidi AM, Belanger MJ, Mantzoros CS. Commentary: COVID-19 and Diabetes Mellitus: What We Know, How Our Patients should be Treated Now, and What Should Happen Next. *Metabolism*. 2020;107:154245.
35. Surendra H, Elyazar IRF, Djaafara BA, Ekawati LL, Saraswati K, Adrian V, *et al*. Clinical Characteristics and Mortality Associated with COVID-19 in Jakarta, Indonesia: A Hospital-Based Retrospective Cohort Study. Lancet Reg Health West Pac. 2021 Apr;9:100108.
36. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al*. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-9.
37. Chen Y, Gong X, Wang L, Guo J. Effects of Hypertension, Diabetes and Coronary Heart Disease on COVID-19 Diseases Severity: A Systematic Review and Meta-Analysis. *medRxiv*. 2020.03.25.20043133.