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Revisiting Chest X-ray potency as a gold standard candidate for early screening of clinical diagnosis for COVID-19 infection

Kohar Hari Santoso
Saiful Anwar Hospital, Jl. Jaksa Agung Suprapto No.2, Malang 65112, Indonesia

Mochamad Bachtiar Budianto
Department Oncology of Saiful Anwar Hospital, Jl. Jaksa Agung Suprapto No.2, Malag 65112, Indonesia.

Agung Setiawan
Saiful Anwar Hospital, Jl. Jaksa Agung Suprapto No.2, Malang 65112, Indonesia

Wiwit Nurwidyaningtyas
Depertement Molecular and Cellular Biology, Sekolah Tinggi Ilmu Kesehatan Kendedes, Jl. Raden Panji Suroso no.6 Malang, 65126, Indonesia.
Corresponding author email: wiwit.nurwidyaningtyas@gmail.com

***Abstract*---**Performing a chest X-ray in an anteroposterior (AP) play an importance role in suppporting the diagnosis COVID-19 infection related to alveolar injury. Positive PCR does not always mean that one person can transmit the COVID-19 infection to another person, because the virus cannot be transmitted when cell culture shows that the virus is not able to prouce in the cells. The aim of this study aims to analyze the potential of chest X-ray examination as a gold standard candidate for the early phase of COVID-19 diagnosis at Dr Saiful Anwar Hospital, Malang. Total 325 data on eligible patients who were treated in the COVID-19 intensive room were recapitulated and analyzed using a retrospective cohort design. The results of the PCR examination as the gold standard for the diagnosis of COVID-19 are projected on the chest X-ray AP feature. Logistic regression analysis was performed to describe the sensitivity of chest X-ray AP for COVID-19 diagnosis. The findings of this study indicate that pneumonia increased the risk of positive COVID-19 0.3 higher than patients who did not show pneumonia. Further studies are still needed to confirm circulating inflammatory markers that can be used as determinants of early-phase alveolar injury in clinical settings, so that a policy for supporting investigations with high accuracy can be formulated for establishing a clinical diagnosis of COVID-19 infection.

***Keywords*---**Penumonia, thorax rongent, Screening, early phase, COVID-19.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by mutations in the RNA virus Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2).[1,2] After being first discovered in Wuhan City, China in December 2019, this case rapidly spread throughout the world and the World Health Organization (WHO) declared it a pandemic case in March 2020.[1-4] Most people affected by COVID-19 may be asymptomatic, or even experience mild to moderate symptoms, and will recover without special treatment.[4,5] However, activation of innate and adaptive immunity in some people occurs continuously, causing an increase in pro-inflammatory cytokines that cause Acute respiratory distress syndrome (ARDS) and multiple-organ failure to occur rapidly, causing death, especially in the elderly age group or patients with co-morbid factors.[5,6]

Until May 2022, COVID-19 cases in Indonesia reached 6.05 million with 156,000 deaths and 5.9 million cases declared cured.[7] The main problem with COVID-19 infection is the disruption of the viral clearance system due to the production of protective vesicles with double membranes without PRR. which allows the virus to continue to multiply without activating the host's antiviral immune response.[5,6] The picture of lung consolidation with or without ground-glass opacities due to COVID-19 was validated by autopsy results confirming monocytes, macrophages, and multinucleated giant cells associated with diffuse alveolar injury. Although the results of the polymerase chain reaction (PCR) test were negative, the presence of vesicle bodies on pulmonary alveolar cells and macrophages remained for at least 2 weeks, thereby increasing the potential for viral clearance disruption.[6,8,9] The gold standard for the diagnosis of COVID-19 is still not fully reliable. As we know, clinical research studies and early detection, including the development of candidate diagnostic determinants for early screening for COVID-19 disease, are still developing and have not been agreed.[10,11]

The appearance of pulmonary infiltration on the AP chest X-ray confirmed in patients with COVID-19 infection due to alveolar injury.[12-14] Several reports regarding the sensitivity of chest X-ray examinations are still controversial. Our findings show that some patients with COVID-19 infection who had PCR negative, exhibited the appearance of pneumonia. The quality of service for patients with COVID-19 is a determinant of the success of health facilities, especially Referral Hospitals in handling the COVID-19 pandemic, begins with the accuracy of early diagnosis in order to increase the patient's survival rate. This study was designed to determine the sensitivity of chest X-rays in describing diffuse alveolar injury due to COVID-19 infection, so that hospital policies can be formulated, in order to improve the quality of reliable early diagnosis services.

Method

Study design and settings

This study only involved COVID-19 patients, both those who had and who had not been vaccinated against COVID-19 from November 2021 to February 2022. This study used a retrospective cohort design to address the sensitivity of AP Chest X-ray interpretation to PCR results.

Clinical outcome parameters

In this study, patient recovery and death were the two categories of clinical outcomes that were defined and measured. Recovery parameters were based on PCR test results of nasal/throat/airway aspirate swabs. Negative PCR findings were confirmed at least twice in a row in more than 24 hours. Parameter death was defined as death due to or related to COVID-19 infection during hospitalization. The length of stay in the hospital was recorded as a basic characteristic of the patient.

Data collection and Analysis

Data in the patient's medical record was collected using an observation list containing the patient's identity, medical history, type of treatment and clinical status and all data were completely anonymized. Prior to data collection, research approval letters from the hospital and ethical approval from the ethics committee were obtained. Because the study was retrospective, informed consent from the patient was not required and all data were confidential. The entire data collection process was discussed with hospital management and the ethics committee. Furthermore, the data that has been obtained is analyzed using STATA14 software for Mac. Data analysis was performed using Fisher's Exact, Chi-Squared, Independent T-Test, and Mann Whitney U analysis.

Results

Based on the characteristics of the participants, there was a significant difference between the age of the PCR-positive patients, which was lower than the age of the PCR-negative patients (p=0.007). There was no significant difference between systolic (p=0.810) and diastolic (p=0.439) and gender (p=0.177) based on PCR results (Table 1).

Table 1
Participant characteristic

Variable	PCR		*p*-value	OR	95%CI
	Positive n=112	Negative n=210			
Mean age (Years)	42.92±19.6	52.19±20.2	0.007*		
SBP (mmHg)	122.12±18.3	121.03±22.6	0.810		
DBP (mmHg)	75.82±10.4	73.69±14.0	0.439		
Gender, n(%)					
Male	44(39.29)	106(50.48)	0.177		

Female	68(60.71)	104(49.52)			
Presence of comorbid, n(%)					
Aorta Sklerosis	60(53.84)	68(32.5)			
Malignancy	9(7.69)	32(15)			
Fracture	-	5(2.5)			
TBC	9(7.69)	16(7.5)			
Lung odema	34(30.77)	89(42.5)			
Length of stay (days)	6.04±4.0	2.23±2.2	0.000*		
Chest X-ray, n(%)					
Pneumonia	48(42,86)	148(70.48)	0.001*	0.31	0.1512 -
Non - penumonia	64(57.14)	62(29.52)			0.6514
Luaran , n(%)					
Recovery	79(70.45)	133(63.25)	0.395		
Death	33(29.55)	77(36.75)			

Most of the respondents had comorbid aortic sclerosis and pulmonary oedema. Patients with positive PCR tend to have a longer length of stay compared to PCR negative patients (p = 0.000). Based on the results of the AP chest X-ray, it was found that 42.86% of patients with confirmed COVID-19 showed pneumonia and 57.14% of patients with confirmed COVID-19 did not show pneumonia. Of the total patients who did not have confirmed COVID-19, 70.48% of them also showed a chest X-ray of PA pneumonia. The results of the regression analysis showed that chest x-ray AP pneumonia was an indicator of COVID-19 sufferers and contributed an OR value of 0.3 (95% CI: 0.14-0.65) with a p value of 0.001. The number of recovered patients was higher in patients with positive PCR than in patients with negative PCR, although not statistically significant (p=395) (Table 1).

Discussion

The development of diagnostic tools to establish clinical diagnosis in the early phase of COVID-19 infection still needs to be improved and countinously evaluated in response to the pandemic situation.[15-17] The accuracy of the PCR test, which is currently believed to be the standard for diagnosing COVID-19 infection, also needs to be evaluated. Symptoms and signs of COVID-19 infection are used to determine whether the patient is in an infectious period that increases the risk of transmission or not.[5, 6,18] Concluding a positive PCR as a "case", does not necessarily determine a patient as a virus carrier and cannot determine whether the virus is active. It is possible that the population was infected long before the test and was not in a period of infection despite a positive PCR result.[19-21]

Based on this, it is important to develop a study to determine the gold standard for reliable diagnostic tests to be applied in the initial screening of cases. The results of this study indicate that the chest x-ray AP with the interpretation of pneumonia has an OR value of 0.31, this indicates that the chest X-ray results also cannot be a reliable diagnostic examination in the early screening phase. It is well known that COVID-19 infection leads to over-activation of immune responses

that induce tissue damage including alveolar injury which may lead to pathological chest X-ray AP in the late phase.[22-24] Based on this, it is likely that patients with elevated inflammatory cytokines in the early period of viral infection may not have demonstrated significant alveolar injury.[25-27]

An unusual feature on a computed tomography (CT) scan of the chest used as a diagnostic attribute for COVID-19, the clinical appearance can be bilateral and peripheral ground-glass opacities examined on chest CT scans of COVID-19 patients in the early stages of the disease, while the paving pattern is in the form of irregularly confirmed in the next phase of the disease.[28-29] In developing countries including Indonesia the cost of this examination is considered quite expensive so that the abnormal appearance due to lung infection is evaluated using a chest x-ray. However, the diagnostic performance of chest X-ray in the early stages of disease is very limited, as some pathological findings on chest computed tomography (CT) may not be detectable on X-ray.[30-32]

The findings of this study confirm the poor performance of the diagnostic chest X-ray if it is based on the conclusion that pneumonia is present or not. Based on this, it is still necessary to develop a more detailed study regarding the comparison of the pattern of alveolar damage due to COVID-19 infection in cases with mild, moderate and severe degrees, so that these differences can be identified as diagnostic target outcomes.

Conclusion

Chest X-ray AP examination with interpretation of pneumonia increased the risk of positive COVID-19 by 0.3 higher than patients who did not show pneumonia. Further studies are still needed to confirm circulating inflammatory markers that can be used as determinants of early-phase alveolar injury in a clinical setting, or to compare the appearance of alveolar damage due to COVID-19 infection with mild, moderate and severe degrees as the basis for determining policies related to diagnostic tests with high accuracy. better, for establishing a clinical diagnosis of COVID-19 infection.

Abbreviations

AP, antero posterior; ARDS, acute respiratory distress syndrome; DBP, Diastolic Blood Presure; PCR, polymerase chain reaction; WHO, World Health Organization; SARS-COV, Severe Acute Respiratory Syndrome Coronavirus; SPB, Systolic Blood Presure; TBC, Tuberculosis.

Ethics Approval and Consent to Participate

The research was approved by a local institutional ethics committee at the Saiful Anwar Hospital, Malang East Java, Indonesia with reference number: 070/08910/102.7/2022 which complies with the Declaration of Helsinki.

Competing Interest

The authors declare that they have no competing financial interest.

Authors' Contribution

MBB, KHS and AS developed the initial concept. MBB and WN significantly screened data and analysis. MBB and WN framework for the manuscript and oversaw the drafting of the manuscript. WN led the writing of the manuscript. All of the authors accepted last version of the article and signed the author's disclosure.

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References

1. Stawicki SP, Jeanmonod R, Miller AC, et al. The 2019-2020 Novel Coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2) Pandemic: A Joint American College of Academic International Medicine-World Academic Council of Emergency Medicine Multidisciplinary COVID-19 Working Group Consensus Paper. J Glob Infect Dis. 2020; 12 (2): 47-93. doi:10.4103/jgid.jgid_86_20
2. Dhama K, Khan S, Tiwari R, et al. Coronavirus Disease 2019-COVID-19. Clin Microbiol Rev. 2020; 33 (4): e00028-20. doi:10.1128/CMR.00028-20
3. Rahman S, Montero MTV, Rowe K, Kirton R, Kunik F Jr. Epidemiology, pathogenesis, clinical presentations, diagnosis and treatment of COVID-19: a review of current evidence. Expert Rev Clin Pharmacol. 2021; 14 (5): 601-621. doi:10.1080/17512433.2021.1902303
4. Long B, Carius BM, Chavez S, et al. Clinical update on COVID-19 for the emergency clinician: Presentation and evaluation. Am J Emerg Med. 2022; 54: 46-57. doi:10.1016/j.ajem.2022.01.028
5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020; 80 (6): 607-613. doi:10.1016/j.jinf.2020.03.037
6. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020; 39 (7): 2085-2094. doi:10.1007/s10067-020-05190-5
7. Data sebaran COVID-19 di Indonesia [Update 2022 May 12]. Available from: https://covid19.go.id/.
8. Filchakova O, Dossym D, Ilyas A, Kuanysheva T, Abdizhamil A, Bukasov R. Review of COVID-19 testing and diagnostic methods. Talanta. 2022; 244: 123409. doi:10.1016/j.talanta.2022.123409.
9. Dinnes J, Deeks JJ, Berhane S, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Rev. 2021; 3 (3): CD013705. doi:10.1002/14651858.CD013705.pub2
10. Safiabadi Tali SH, LeBlanc JJ, Sadiq Z, et al. Tools and Techniques for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)/COVID-19

Detection. Clin Microbiol Rev. 2021; 34 (3): e00228-20. Published 2021 May 12. doi:10.1128/CMR.00228-20
11. Majumder J, Minko T. Recent Developments on Therapeutic and Diagnostic Approaches for COVID-19. AAPS J. 2021; 23 (1): 14. doi:10.1208/s12248-020-00532-2.
12. Rousan LA, Elobeid E, Karrar M, Khader Y. Chest x-ray findings and temporal lung changes in patients with COVID-19 pneumonia. BMC Pulm Med. 2020; 20 (1): 245. doi:10.1186/s12890-020-01286-5
13. Ebrahimzadeh S, Islam N, Dawit H, et al. Thoracic imaging tests for the diagnosis of COVID-19. Cochrane Database Syst Rev. 2022; 5 (5): CD013639. doi:10.1002/14651858.CD013639.pub5
14. Osman AH, Aljahdali HM, Altarrazi SM, Ahmed A. SOM-LWL method for identification of COVID-19 on chest X-rays. PLoS One. 2021; 16 (2): e0247176. doi:10.1371/journal.pone.0247176
15. Mallah SI, Ghorab OK, Al-Salmi S, et al. COVID-19: breaking down a global health crisis. Ann Clin Microbiol Antimicrob. 2021; 20 (1): 35. doi:10.1186/s12941-021-00438-7.
16. Ortiz-Prado E, Simbaña-Rivera K, Gómez-Barreno L, et al. Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19), a comprehensive literature review. Diagn Microbiol Infect Dis. 2020; 98 (1): 115094. doi:10.1016/j.diagmicrobio.2020.115094.
17. Kevadiya BD, Machhi J, Herskovitz J, et al. Diagnostics for SARS-CoV-2 infections. Nat Mater. 2021; 20 (5): 593-605. doi:10.1038/s41563-020-00906-z.
18. A R, Wang H, Wang W, Tan W. Summary of the Detection Kits for SARS-CoV-2 Approved by the National Medical Products Administration of China and Their Application for Diagnosis of COVID-19. Virol Sin. 2020; 35 (6): 699-712. doi:10.1007/s12250-020-00331-1.
19. Rona G, Arifoglu M, Voyvoda N, Batirel A. Should CT be used for the diagnosis of RT-PCR-negative suspected COVID-19 patients?. Clin Respir J. 2021; 15 (5): 491-498. doi:10.1111/crj.13332.
20. Chong ZX, Liew WPP, Ong HK, et al. Current diagnostic approaches to detect two important betacoronaviruses: Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Pathol Res Pract. 2021;225:153565. doi:10.1016/j.prp.2021.153565.
21. Falzone L, Gattuso G, Tsatsakis A, Spandidos DA, Libra M. Current and innovative methods for the diagnosis of COVID-19 infection (Review). Int J Mol Med. 2021; 47 (6): 100. doi:10.3892/ijmm.2021.4933.
22. Han CH, Kim M, Kwak JT. Semi-supervised learning for an improved diagnosis of COVID-19 in CT images. PLoS One. 2021; 16 (4): e0249450. doi:10.1371/journal.pone.0249450.
23. Kong L, Cheng J. Classification and detection of COVID-19 X-Ray images based on DenseNet and VGG16 feature fusion. Biomed Signal Process Control. 2022; 77: 103772. doi:10.1016/j.bspc.2022.103772.
24. Sánchez-Oro R, Torres Nuez J, Martínez-Sanz G. Radiological findings for diagnosis of SARS-CoV-2 pneumonia (COVID-19). Med Clin (Engl Ed). 2020; 155 (1): 36-40. doi:10.1016/j.medcle.2020.03.004.

25. Peci A, Tran V, Guthrie JL, et al. Prevalence of Co-Infections with Respiratory Viruses in Individuals Investigated for SARS-CoV-2 in Ontario, Canada. Viruses. 2021; 13 (1): 130. doi:10.3390/v13010130.
26. Sharma A, Ahmad Farouk I, Lal SK. COVID-19: A Review on the Novel Coronavirus Disease Evolution, Transmission, Detection, Control and Prevention. Viruses. 2021; 13 (2): 202. doi:10.3390/v13020202.
27. Canovi S, Besutti G, Bonelli E, et al. The association between clinical laboratory data and chest CT findings explains disease severity in a large Italian cohort of COVID-19 patients. BMC Infect Dis. 2021; 21 (1): 157. doi:10.1186/s12879-021-05855-9.
28. Güneyli S, Atçeken Z, Doğan H, Altınmakas E, Atasoy KÇ. Radiological approach to COVID-19 pneumonia with an emphasis on chest CT. Diagn Interv Radiol. 2020; 26 (4): 323-332. doi:10.5152/dir.2020.20260
29. Chauhan N, Soni S, Jain U. Optimizing testing regimes for the detection of COVID-19 in children and older adults. Expert Rev Mol Diagn. 2021; 21 (10): 999-1016. doi:10.1080/14737159.2021.1962708.
30. Kundu R, Das R, Geem ZW, Han GT, Sarkar R. Pneumonia detection in chest X-ray images using an ensemble of deep learning models. PLoS One. 2021; 16 (9): 0256630. doi:10.1371/journal.pone.0256630
31. Agrawal T, Choudhary P. Segmentation and classification on chest radiography: a systematic survey [published online ahead of print, 2022 Jan 8]. Vis Comput. 2022; 1-39. doi:10.1007/s00371-021-02352-7
32. Laino ME, Ammirabile A, Posa A, et al. The Applications of Artificial Intelligence in Chest Imaging of COVID-19 Patients: A Literature Review. Diagnostics (Basel). 2021; 11 (8): 1317. doi:10.3390/diagnostics11081317