Diagnostic Model of COVID-19 Infection Based on the Combination of Clinical Symptoms, Chest Radiography and Laboratory Test

Herikurniawan,[1] Cleopas Martin Rumende,[1] Siti Setiati,[2] July Kumalawati[3], Belinda Thania Deslanthy[1]

[1]Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2]Clinical Epidemiology Unit, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.
[3]Department of Clinical Pathology, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Herikurniawan, MD. Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: herikurniawan.md@gmail.com.

ABSTRACT

Background*: COVID-19 is an infection caused by SARS-COV 2.For screening the patient, Rapid antigen for COVID-19 is used with a high diagnostic value. However, there are still some cases of false-negative even with clinical symptoms suggesting COVID-19.Undetected COVID-19 patients certainly will increase transmission. A simple and practical diagnostic model, using determining factors, is required to guide physicians through a quicker decision making process, especially when deciding the need for the isolation rooms for patients with COVID-like symptoms.* ***Methods****: This study is a cross-sectional study. The study was conducted at CiptoMangunkusumo Hospital, Jakarta.History of contact with COVID-19, clinical symptoms, laboratory examination, and chest radiograph data were taken from medical records. Bivariate and multivariate analyses were conducted to assess the effect sizes of patient factors on the diagnostic results.ROCcurve and Hosmer-Lemeshow calibration was used to make the scoring.* ***Results****: There were 187 patients with the majority of subjects in the age group < 60 years old. The selected variables in this scoring systemwere contact history,fever/history of fever, dyspnea with respiratory rate >20 breaths/minute, leucocyte ≤ 10.000 cells/mLand typical chest radiography. The area under the curve for this model was 0,777 (CI95% (0,706-0,847), P<0,001). The probability was 82% with a cut-off point ≥ 4.* ***Conclusion****: Determinant models based on the combination of contact history, presence or history of fever, dyspnea, leucocyte count ≤ 10.000 cells/mL and typical chest radiography provides good accuracy to aid physicians in managing isolation room needs for patients with suspected COVID-19.*

Keywords**:** *COVID-19, SARS-CoV 2 diagnostic model, scoring.*

INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is a challenging health problem in the world, with rapid disease progression. Up until April 19th, 2022, there had been over 500 million global cases of COVID-19, with Indonesia being one of many countries with a high case rate. As of April 19th, 2022, Indonesia had recorded more than four million confirmed cases, with 155.937deaths.[1]

The approach of history taking, contact history, and ancillary tests are used to diagnose COVID-19. The clinical symptoms may be varied and atypical. Fever is the most common symptom. The other symptoms are respiratory symptoms (cough, dyspnea, rhinorrhea, and sore throat), systemic viral infection symptoms (malaise, myalgia, headache), and gastrointestinal symptoms (nausea, vomit, diarrhoea, abdominal pain). From some studies the ancillary tests for COVID-19 are haematology, laboratory test, and chest radiography. The haematology test in COVID-19 typically shows leucopenia, leucocytosis, lymphocytopenia, and increased neutrophil to lymphocyte ratio (NLR). In chest radiography, a lesion such as infiltrate/opacity/consolidation with bilateral peripheral distribution and a lower lobe predominance would typically be seen.[3,4]

The diagnostic gold standard for COVID-19 is *real-time polymerase chain reaction* (RT-PCR). For screening the patient, rapid antigens are usually used. However, there are cases in which the COVID-19 infection is not detected by rapid antigen testing. The longwait times required for PCR results and the lower sensitivity of rapid antigen testing leads to an increased transmission risk. If the patient is clinically suspicious for COVID-19, but screening results are negative, isolation should be carried out while waiting for the PCR results. For this reason, a clinical guide is required to determine whether a patient needs an isolation room. This study aimed to build a diagnostic model by using simple, widely available and used parameters. The final scoring system could add diagnostic value and guide physicians through a better decision making process, especially for patients with COVID-19 like syndromes.

METHODS

This study was a cross-sectional study. Secondary data was used with consecutive sampling methods. The inclusion criteria were COVID-19 suspected patients, aged ≥18 years old, and treated at Cipto Mangunkusumo Hospital, Jakarta, from March to June 2020. The exclusion criteria were patients who had incomplete laboratory tests and chest radiography, suffered from an autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis), chronic kidney disease stage V, or severe hepatic disease. Sample sizes required for this study were calculated using the rule of thumb formula. Variables analyzed in this study were contact history, fever, respiratory symptoms, systemic viral infection symptoms, gastrointestinal symptoms, typical abnormalities of chest radiography, leucocyte (≤ 10.000 *cells/μL*), lymphocyte (≤ 1.500 *cells/μL*), NLR (≥ 5,8), C-reactive protein (CRP ≥ 5 mg/L). Samples were collected and analyzed by different independent investigators to prevent any potential bias.

The definition of contact history was people with a history of physical contact or in the same room (radius <1m) with confirmed cases of COVID-19 without using standard personal protective equipment (PPE) within 2 days before onset until 14 days after onset. The definition of fever was body temperature ≥ 37.5^{0}C at the first coming in admission or history of fever within 14 days before admission. The respiratory symptoms include cough and/or dyspnea with frequency > 20 breaths/minute, and/or sore throat and/or *rhinorrhea*. Systemic viral infection symptoms include headache and/or myalgia and/or malaise. Gastrointestinal symptoms include nausea and/or vomiting, and/or diarrhoea, and/or abdominal pain. The definition of a typical abnormality of chest radiography was an abnormality in chest radiography including infiltrates or opacities or consolidation with bilateral and peripheral distribution, predominant in the lower lobes. Data was analysed using Statistical Product and Service Solution (SPSS) version 23.0 with univariate, bivariate, and multivariate analyses. Variables with $p < 0.25$ from bivariate analysis were included in the multivariate analysis. We used a logistic regression technique to determine each variable's contribution to COVID-19 diagnosis. The scoring system was made by using coefficient (B) and standard error. The scoring system has also been tested with the *receiver operating characteristics* (ROC) curve and calibrated using the *Hosmer-Lemeshow test.*

Ethics Approval and Consent to Participate

The data were taken from medical records, thus we did not need informed consent from

the participants. This study was approved by the Institutional Review board at University of Indonesia, reference number: KET-576/UK2.F1/ETIK/PPM.00.02/2020.

RESULTS

This study was conducted from March until June 2020. We included 196 patients, of which 9 patients were excluded (4 systemic lupus erythematosus patients, 2 hepatic cirrhosis patients, and 3 stadium V chronic kidney disease patients). Hence, one hundred eighty-seven patients were analyzed. The majority of patients were older than 60 years old (65.2%) and male (53,4%) as seen from **Table 1**.

Hypertension (18.7%) and diabetes mellitus (18.7%) are the most common comorbid diseases (**Table 1**). There are 70 COVID-19-confirmed cases. Confirmed cases are defined as cases with at least one positive RT-PCR result, whereas negative cases are defined as cases with at least two negative RT-PCR results as seen in **Table 1**.

Table 1. Demographical and clinical characteristics of subjects (n=187).

Variables	No. of sample (%)
Age	
< 60 years old	122 (65.2)
≥ 60 years old	65 (31)
Gender	
Male	100 (53.5)
Female	87 (46.5)
Contact History	
in positive patient	22 (12)
in negative patient	165 (88)
Swab Result	
Positive	70 (37.4)
Negative	117 (62.6)
Comorbidity	
Diabetes Mellitus	35 (18.7)
Hipertension	35 (18.7)
Malignancy	24 (12.8)
CAD	13 (7)
Tuberculosis	11 (5.9)
Chronic Kidney Disease	12 (6.4)
Stroke	7 (3.7)
Heart Failure	3 (1.6)
COPD	2 (1.1)
Asthma Bronchial	2 (1.1)
Leucocyte, cells /uL	
≤ 10.000	97 (51.9)
> 10.000	90 (48.1)
Lymphocyte, cells /uL	
< 1500	137 (73.3)
≥ 1500	50 (26.7)
NLR[a]	
< 5,8	97 (51.9)
≥ 5,8	90 (48.1)
CRP[b] **(mg/L)**	
< 5	31 (16.6)
≥ 5	156 (83.4)

[a]NLR: neutrophil to lymphocyte ratio;[b]CRP: C-reactive protein

All of the included subject had at least one symptoms. Fever and history of fever are reported in 65.2% patients. The most common respiratory symptom is cough (72.2%) and the most common gastrointestinal symptom was nausea (23.5%) as seen in **Table 1**.

Leucocyte ≤ 10,000 cells/uL is found in 51.9% of cases, Lymphocyte ≤ 1500 cells/μL in 73.3% of cases, NLR ≥ 5.8 in 51.9% of cases and CRP ≥ 5 mg/L in 83.4% of cases. Typical abnormality of chest radiograph is shown in 20.9% of patients as seen in **Table 1**. The variables from bivariate analysis with $p < 0.25$ were then included in the multivariate analysis. After multivariate analysis,some of the variables with $p > 0.05$ were excluded from scoring.

Results from the multivariate analyses show that the contact history, presence of dyspnea, leucocyte count ≤ 10,000 cells/uL, typical chest radiography are statistically significant predictors, as seen on **Table 2-3**. Although fever history is not statistically significant in the multivariate analysis, it is a clinically important factor that should not be disregarded when interpreting the results of the scoring system.

In the multivariate analysis, we created a score for each variable. Contact history with a confirmed COVID-19 patients is worth 3 points, fever/history of fever, 1 point, dyspnea with respiratory rate 20 breaths/minute, 2 points, leucocyte ≤ 10,000 cells/uL 2 points and typical chest radiography 2 points. The total score is 10 points as seen from **Table 4**.

From the ROC curve analysis, the area under the curve is 0.77 with a cut-off point of 4 (**Figure 1A**). This diagnostic value for a scoring system with a cut-off point of 4 has good specificity (88.03%) as seen from **Figure 1**.

DISCUSSION

The cumulation of clinical symptoms and workup results can be utilized to predict the diagnosis of COVID-19. Scoring systems provide a simple assessment tool that can supplement

Table 2. Analysis of clinical symptoms for the diagnosis of COVID-19.

Variables	COVID-19 N (%)	Non-COVID-19 N (%)	P Bivariate	PMultivariate	OR (CI 95%)
Contact History					
Yes	18 (81,8)	4 (18.2)	**<0.001**	**<0.001**	8.673 (2.573-29.231)
No	52 (31.5)	113 (68.5)			
Fever/History Fever					
Yes	49 (40,2)	73 (59.8)	0.185	0.192	1.658 (0.776-3.539)
No	21 (32.3)	44 (67.7)			
Cough					
Yes	53 (39.2)	82 (60.8)	0.255		
No	17 (24.3)	35 (29.9)			
Dyspnea					
Yes	16 (47.0)	18 (53.0)	**0.139**	0.024	2.708 (1.141-6.503)
No	54 (35.5)	99 (64.5)			
Sore Throat					
Yes	16 (45.7)	19 (54.3)	**0.176**	0.671	0.820 (0.328-2.048)
No	54 (35.5)	98 (64.5)			
Rhinorrhea					
Yes	6 (30.0)	14 (70.0)	0.320		
No	64 (38.3)	103 (61.7)			
Nausea					
Yes	14 (31.8)	30 (68.2)	**0.243**	0.387	0.679 (0.283-1.631)
No	56 (39.1)	87 (60.9)			
Vomiting					
Yes	12 (63.1)	19 (36.9)	0.512		
No	58 (37.1)	98 (62.9)			
Diarrhoea					2.742
Yes	11 (55.0)	9 (45.0)	**0.072**	0.085	(0.871-8.632)
No	59 (35.3)	108 (64.5)			
Abdominal Pain	7 (31.8)	15 (68.2)	**0.371**		
Yes	63 (38.1)	102 (61.9)			
No					
Myalgia					
Yes	3 (20.0)	12 (80.0)	**0.118**	0.093	0.242 (0.046-1.268)
No	67 (38.9)	105 (61.1)			
Headache					
Yes	7 (31.8)	15 (68.2)	**0.371**		
No	63 (38.1)	102 (61.9)			
Malaise					
Yes	24 (36.3)	42 (63.4)	**0.476**		
No	46 (38.0)	75 (62.0)			

Table 3. Analysis of ancillary tests for diagnosis of COVID-19.

Variables	COVID-19 N (%)	NON COVID-19 N (%)	P Bivariate	P Multivariate	OR (CI 95%)
Chest Radiography					
Typical	21 (53.8)	18 (46.2)	0.015	0.003	3.487 (1.515-8.026)
Atypical	49 (33.1)	99 (66.9)			
Leucocyte (≤ 10.000)					
Yes	50 (51.5)	47 (48.5)	< 0.001	0.024	2.381 (1.120-5.063)
No	20 (22.2)	70 (77.8)			
Lymphocyte(≤1.500)					
Yes	49 (35.7)	88 (64.3)	0.270		
No	21 (42)	29 (58)			
NLR(≥5,8)					
Yes	24 (24.7)	73 (75.3)	<0.001	0.071	0.504 (0.234-1.061)
No	46 (51.1)	44 (48.9)			
CRP(≥5)					
Yes	54 (34.6)	102 (65.4)	**0.058**	0.656	0.803 (0.307-2.104)
No	16 (51.6)	15 (48.4)			

Table 4. C-COVID score (clinical COVID score).

Variables	Assesment	Score
Contact History with COVID-19	Yes	3
Fever ≥ 37,5 / Fever History	Yes	1
Dyspnea (RR > 20breaths/minute)	Yes	2
Leucocyte (≤ 10.000 /uL)	Yes	2
Typical Chest Radiography (Infiltrat/Opacity/Consolidation with bilateral, peripheral, and lower zone predominant)	Yes	2
Total		10
Score ≥ 4 (at least 1 clinical symptoms included) Suspect COVID 19: (Probability 82%), PPV 74% NPV 77%		

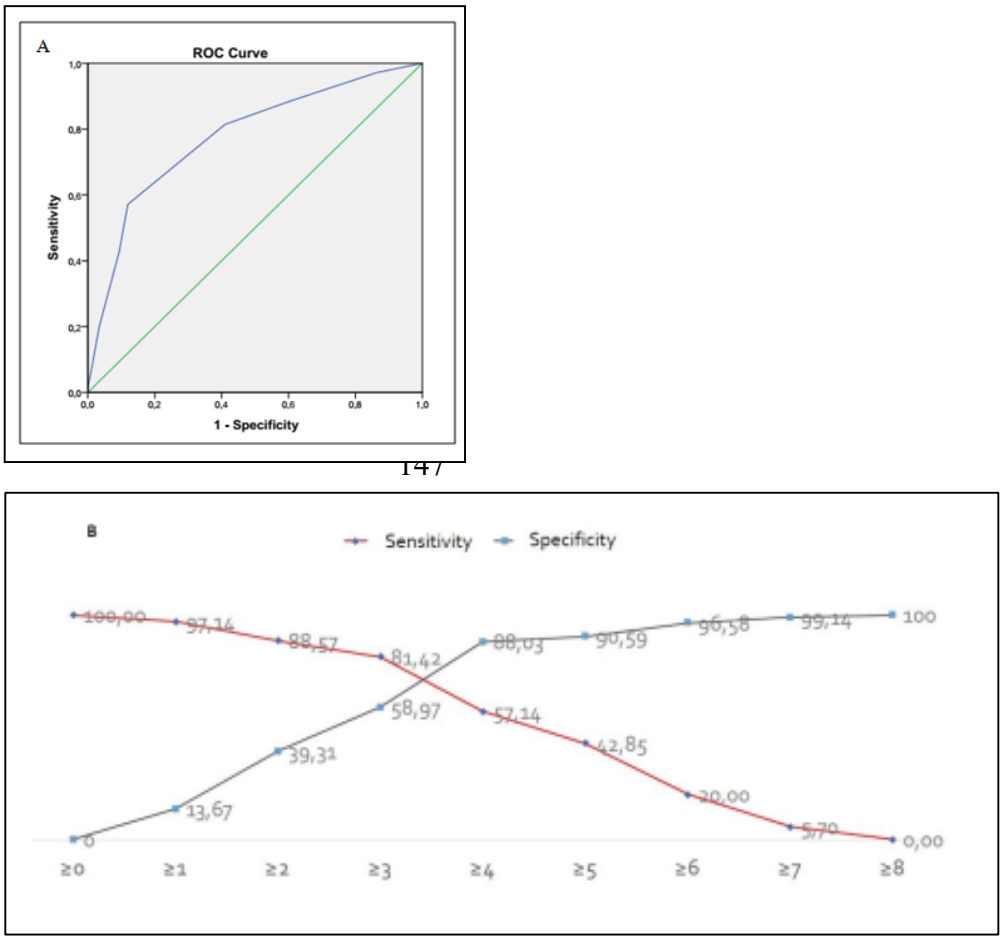

Figure 1. A. ROC curve of the scoring system. B. Cut-off curve between senstivity and specificity of the scoring system.

clinician judgment. This study was aimed to create a diagnostic scoring system for COVID-19 based on common clinical symptoms, simple laboratory tests and diagnostic imaging which are available in most primary healthcare centers. Our scoring system consisted of 5 variables: contact history with COVID-19 patients, presence or history of fever, dyspnea with respiratory rate > 20 breaths/minute, leucocyte count ≤ 10.000 cells/uL and typical chest radiography.

In this study, the information can be easily obtained from history taking. Contact history was one important determining factor in this study. Multivariate analysis showed that contact history

was statistically significant with OR 8.673 (CI 95% 2.573-29.231, p < 0.001). Droplets from coughing, sneezing, or talking may occur within < 1 meter distance. This theory is reinforced by a study from Chu et al., who showed that physical distancing over 1 meter has a better protective effect than < 1 m (OR 0.18).[8] SARS-CoV-2 will stay in fomites (contaminated object or environment): for 2 hours in plastic and stainless steel, 4 hours in copper, and 24 hours in carton.[9] A study by Van Doramalen et al. reported that SARS-CoV-2 would live in aerosol nebulizer at least for 3 hours; and to 16 hours long in another study. Therefore, airborne transmission may occur. The growing evidence that supports droplets as well as airborne particles as the transmission mechanism of SARS-CoV-2 emphasises that contact history in suspected patients is imperative.

Dyspnea are not as frequent as fever or cough. This may happen because dyspnea appears after 3 days of onset. Although the frequency of dyspnea is not very frequent, but dyspnea is the most common symptom which bring patients to the hospital. Dyspnea was statistically significant in this study with OR 2.708 (CI 95% (1.141-6.503), p= 0.024). Song et all also reported that dyspnea was significant for diagnosis with COVID-19.[5] In this study, we combine subjective symptoms of dyspnea and objective assessment of tachypnea (>20 breaths/minutes), so it will be more specific for helping diagnosis COVID-19.

Fever is the most common symptom in COVID-19. But in this study, fever was not statistically significant. It is hypothesized that there was potential bias in collected data. Because we conducted the data from medical record, which is we did not know whether the temperature at that time was influenced by the previous use of antipyretic drug or not. The result of this study contradict with a meta-analysis by Cao et al. reported that fever occurred in 87.3% of patients. The meta-analysis study from Islam MA (2021) showed that the prevalence of fever in COVID-19 patient was high (79.43%), especially in severe and critical illness patient (91.69%). Therefore, fever is an important clinical presentation of COVID-19. We decided to include this symptom in our scoring to reduce the risk of missed diagnosis.

Several studies have emphasized evaluation of abnormal leucocyte in COVID-19 patients, with both leucopenia and leucocytosis. Leucocyte£ 10.000 cells/ml was one of the variables which was statistically significant with OR 2.381 (CI 95% (1.120-5.063), p=0.024). Leucocyte have well-known role in immunity response to infection. Change in leucocyte indicate a systemic inflammatory condition caused by the patient's immune system. Normal leucocyte or lower (leucopenia) usually happens in the initial stage of infection. Sun et al. reported that confirmed COVID-19 patients had lower leucocyte than non-COVID-19 patients (p < 0.001).[12-14] But during observation with severe condition have higher leukocyte level (leukocytosis) than those with mild-moderate condition. Therefore, leukocyte count may assist in assessing the probability of patient having more severe disease. Additionally, differential count components in COVID-19 patients show lower eosinophil and lymphocyte levels and higher levels of neutrophils and monocytes compared to healthy people.[15] Peng et al. found that NLR showed significant positive correlations with PSI, CURB-65 and MuLBSTA. Increased neutrophil-to-lymphocyte ratios (NLR) may serve as a predictor for severity of disease. It explained, that our patient had mild moderate symptoms, which was the reason the increased NLR was not significant in this study.[5]Besides that,lymphopenia (absolute lymphocytecount(ALC) < 1500 cells/mL) was not statistically significant. This finding agreed with Mardani et al. and Song et al. also reported no significant relation between lymphocyte and diagnosis COVID-19. In the initial stage of SARS-CoV-2 infection, the lymphocyte may be normal. As severity increases, the lymphocyte would decrease, so it actually makes lymphocytes an excellent indicator of the severity of COVID-19, but not for diagnosis COVID-19. A systematic review by Huang et al. reported that COVID-19 patients had three times the risk for adverse outcomes if they had had leucocytes < 1.100 cells /mL.[16]

CRP ≥ 5 mg/dL was statistically significant in this study. This result is similar to Ferrari et al. Some studies have indeed reported increased

CRP in COVID-19 patients. However, this protein is not an adequate diagnostic marker because of its low specificity for COVID-19. A study by Wang et al. showed an increase in CRP following a lung lesion in COVID-19. Therefore, CRP is more effective as an indicator for prognosis rather than for diagnosis of COVID-19.[17,18]

Typical abnormalities in chest radiography occurred in 20.9% of the subjects. As many as 53.8% from those groups were confirmed cases of COVID-19. The results from multivariate analysis showed a statistically significant association with OR 3.487 (CI95% (1.515-8.026), p= 0,003), as supported by Wong et al. who described a typical abnormality of COVID-19 as multifocal consolidation or opacity with bilateral distribution in the peripheral and lower lobe of the lungs.[4,19] Cozy et al. described opacities or reticular nodular consolidation with bilateral peripheral distribution and lower zone predominance as a typical radiograph lesions in COVID-19. This lesion is caused by activation of ACE-2 receptors, which are expressed more in pneumocytes located distally. This provides evidence that SARS-CoV2 tends to infect the distal areas.[20,11]Study from Smith DL et al. showed that the typical chest X ray of COVID-19 (patchy or confluent, GGO or consolidation in the peripheral area and mid to lower lung zone distribution) had high specificity (96.6%) so that the typical chest x ray is good for guiding the diagnosis.[21]

Scoring systems are proposed as diagnostic tools to help clinicians manage suspected patients. It includes history of contact, clinical symptoms and simple laboratory tests and imaging. This scoring system is simple, cost-effective and accessible workup, include: contact history with COVID-19 patients (3 points), fever/history of fever (1 point), dyspnea with respiratory rate > 20 breaths/ minute (2 points), leucocyte ≤ 10,000 cells/uL (2 points) and typical chest radiography (2 points). The total score is 10 points. ROC analysis revealed AUC = 0.77 for score cut-off ≥ 4 suggested that patients of suspected COVID-19. Hence, we recommend using a cut-off point ≥ 4 for the score and as importantly, taking into account the clinical symptoms. This scoring system has been tested and will be able to establish a suspected COVID-19 diagnosis with a specificity of 88.03%. Calibration tests for this scoring system, using the Hosmer and Lemeshow Test, resulted in a p-value of 0.590, indicating good validation.

This scoring may be used for clinical practice. Patients with a score ≥ 4 can be recommended to be treated in isolation while waiting for the PCR results. By using this scoring, the physician can decide the needs for isolation room for patient and will reduce the risk of transmitting COVID-19 infection. In addition, patients with negative antigens, but with a 4 score or more than 4, must also remain vigilant considering that antigen is not the gold standard so that COVID-19 cannot be excluded.

On the other hand, this study has potential biases and limitations in the form of sample size and limited sample collection time. The sample size was quite small because the data in this study was only collected from one center (Cipto Mangunkusumo Hospital), as one of the COVID-19 referral centers in Jakarta. Therefore, wider range of populations from multiple center is still needed. Careful interpretation and implementation in other centers, involving patients with more variable demographical characteristics, is warranted to evaluate the reliability and validity of this scoring system, in the assessment of suspected COVID-19 cases. This study is a one-center study, which adds to its limitations. In addition, the study used secondary data and was conducted at the beginning of the COVID-19 pandemic in Indonesia, and so the study conditions may differ from current conditions.

Further research can be carried out in multiple centers and with a larger sample size, to ensure that the results of previous studies can be externally validated in different populations.

CONCLUSION

This diagnostic model, taking into consideration contact history, fever/history of fever, dyspnea with respiratory rate > 20 breaths/ minute, leucocyte ≤ 10,000 cells/μL and typical chest radiography, provides diagnostic value with a good specificity to help direct decision making in patients with suspected COVID-19.

Patients with a score ≥ 4 can be recommended to be treated in isolation while waiting for the PCR results.

ABBREVIATION

COVID-19:Coronavirus Disease 2019; SARS-CoV-2:Severe Acute Respiratory Syndrome-Coronavirus-2; WHO:World Health Organization; NLR: Neutrophil to lymphocyte ratio; RT-PCR:Reverse transcription polymerase chain reaction; PPE : Personal protective equipment; ROC:Receiver operating characteristics; SPSS: Statistical Product and Service Solution; OR:Odds ratio; CI:Confidence interval; CRP:C-reactive protein; PPV : Positive predictive value; NPV:Negative predictive value; LR:Likelihood ratio; ACE-2 : Angiotensin converting enzyme-2; ALC:Absolute lymphocyte count.

CONFLICT OF INTEREST

The authors declare no competing interests.

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