

## Original article

# Risk factors for potential persistent lung abnormality on chest radiographs in post COVID-19 patients

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### Abstract:

**Background:** Most COVID-19 pneumonia survivors develop abnormal chest radiographs (CXR) that progress to interstitial lung disease. This study aimed to identify potential risk factors for persistent CXR abnormalities in post COVID-19 patients. **Methods:** The study included hospitalized COVID-19 pneumonia patients at Phramongkutklo Hospital between July 2021 and June 2022. At 12 weeks after discharge, CXR were evaluated based on the extent of abnormal infiltration, using a scoring system. The primary objective was to determine risk factors during COVID-19 infection associated with persistent CXR abnormalities at 12 weeks. **Results:** Among 120 patients (56% male; mean age 58 years), 76 (63%) exhibited persistently abnormal CXR at 12 weeks after discharge. The group with persistent CXR abnormalities had significantly higher mean age (62 vs. 52 years,  $p < 0.001$ ), longer hospital stays (21 vs. 14 days,  $p < 0.001$ ), higher rates of hypertension (61.8 vs. 27.3%,  $p < 0.001$ ), dyslipidemia (44.7 vs. 27.4%,  $p = 0.04$ ), use of oxygen support (85.5 vs. 45.5%,  $p < 0.001$ ), and use of HFNC or NIV (44.7 vs. 15.9%,  $p < 0.001$ ) compared to the group with complete resolution. Laboratory revealed significantly elevated levels of serum LDH ( $p < 0.001$ ), CRP ( $p = 0.002$ ), and peak CRP ( $p = 0.001$ ) in the group with persistent CXR abnormalities. Multivariable analysis identified a longer hospital stay ( $> 14$  days), hypertension, use of oxygen therapy (HFNC, NIV, or ETT), and serum LDH levels  $> 250$  U/L as significant factors associated with CXR abnormality. **Conclusion:** A longer hospital stays  $> 14$  days, hypertension, use of oxygen therapy, and serum LDH  $> 250$  U/L were identified as risk factors for persistent CXR abnormality from COVID-19 at 12 weeks.

**Keywords:** ● Coronavirus disease 2019 ● Post COVID-19 ● Chest radiograph  
● Interstitial lung disease

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## นิพนธ์ต้นฉบับ

# ปัจจัยเสี่ยงของความผิดปกติที่ยังหลงเหลืออยู่บนภาพถ่ายรังสีทรวงอก ในผู้ป่วยหลังการติดเชื้อโควิด 19

พัฒนพล อร่ามอารีรักษ์<sup>1</sup> และ สุภวัฒน์ ปวราจารย์<sup>2</sup>

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### บทคัดย่อ

**บทนำ** ผู้ที่หายจากปอดอักเสบโควิด 19 สามารถพบภาพถ่ายรังสีเอกซเรย์ทรวงอกผิดปกติ และสามารถกลายเป็นโรคปอดอินเตอร์สติเชียลได้ วัตถุประสงค์เพื่อหาปัจจัยเสี่ยงของความผิดปกติที่ยังหลงเหลืออยู่บนภาพถ่ายรังสีทรวงอกในผู้ป่วยหลังการติดเชื้อโควิด 19 เมื่อครบ 12 สัปดาห์ **วิธีการศึกษา** รวบรวมผู้ป่วยปอดอักเสบโควิด 19 ที่เข้ารับการรักษาในโรงพยาบาลพระมงกุฎเกล้า ตั้งแต่เดือนกรกฎาคม พ.ศ. 2564 ถึงมิถุนายน พ.ศ. 2565 โดยที่ 12 สัปดาห์หลังจากจำหน่ายจะประเมินภาพถ่ายรังสีเอกซเรย์ทรวงอกโดยใช้ระบบคะแนนเพื่อประเมินระดับความผิดปกติ **ผลการวิจัย** ผู้ป่วย 120 ราย มีผู้ที่ยังหลงเหลือความผิดปกติบนภาพถ่ายรังสีทรวงอก 76 ราย (ร้อยละ 63) โดยกลุ่มที่มีความผิดปกติที่ยังหลงเหลือบนภาพถ่ายรังสีทรวงอกจะมีอายุเฉลี่ย (62 vs. 52 ปี,  $p < 0.001$ ) ระยะเวลานอนโรงพยาบาล (21 vs. 14 วัน,  $p < 0.001$ ) โรคความดันโลหิตสูง (ร้อยละ 61.8 vs. 27.3,  $p < 0.001$ ) โรคไขมันในเลือดสูง (ร้อยละ 44.7 vs. 27.4,  $p = 0.04$ ) ได้การบำบัดด้วยออกซิเจน (ร้อยละ 85.5 vs. 45.5,  $p < 0.001$ ) และการรักษาด้วย HFNC หรือ NIV (ร้อยละ 44.7 vs. 15.9,  $p < 0.001$ ) สูงกว่ากลุ่มที่ภาพถ่ายรังสีเอกซเรย์ทรวงอกหายเป็นปกติ และพบว่าระดับซีรัม LDH ( $p < 0.001$ ) CRP ( $p = 0.002$ ) และค่าสูงสุดของ CRP ( $p = 0.001$ ) เพิ่มขึ้นอย่างมีนัยสำคัญในกลุ่มที่มีความผิดปกติที่ยังหลงเหลือบนภาพถ่ายรังสีทรวงอก การวิเคราะห์หลายตัวแปรพบว่า ระยะเวลานอนโรงพยาบาล  $> 14$  วัน โรคความดันโลหิตสูง การรักษาด้วยออกซิเจน (HFNC, NIV, หรือ ETT) และระดับซีรัม LDH  $> 250$  U/L เป็นปัจจัยที่สำคัญ **สรุป** ระยะเวลานอนโรงพยาบาล  $> 14$  วัน โรคความดันโลหิตสูง การรักษาด้วยออกซิเจน และระดับซีรัม LDH  $> 250$  U/L เป็นปัจจัยเสี่ยงของความผิดปกติที่ยังหลงเหลืออยู่บนภาพถ่ายรังสีทรวงอกในผู้ป่วยหลังการติดเชื้อโควิด 19 ที่ 12 สัปดาห์

**คำสำคัญ:** ● โควิด 19 ● ภาพถ่ายรังสีเอกซเรย์ทรวงอก ● โรคปอดอินเตอร์สติเชียล

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## Introduction

Patients who have recovered from COVID-19 infection often exhibit interstitial lung disease (ILD) with persistent reticular opacities and ground-glass opacities on chest radiographs (CXR) beyond 4 weeks of follow-up<sup>1</sup>. High-resolution computed tomography (HRCT) scans can clearly reveal a range of characteristics, from ground-glass opacities (GGO) to pulmonary fibrosis (PF)<sup>2</sup>. Notably, two studies have reported significant rates of persistent abnormalities on chest computed tomography (CT) scans among COVID-19 survivors, with rates of 42.3%<sup>3</sup> and 70%<sup>4</sup> at 3 months after discharge.

In general, chest CT scans offer clearer visualization of lung abnormalities compared to chest X-rays. The severity score obtained from chest CT scans demonstrates effective predictive capability for post-COVID-19 fibrosis, featuring a sensitivity of 86.1% and a specificity of 78%.<sup>5</sup> However, there are limitations, particularly in settings with a high prevalence of COVID-19 cases where performing CT scans may not be feasible in all hospitals. On the other hand, chest X-rays are more accessible, quicker to perform, and can effectively monitor post-infectious complications. The sensitivity of portable chest X-rays is inferior to that of CT scans, with rates of 69% compared to 97-98%.<sup>6</sup> However, in certain publications, they are reported to be equivalent.<sup>7</sup> Furthermore, scoring systems such as the Radiographic Assessment of Lung Edema (RALE) score<sup>8</sup> can provide insights into disease severity based on chest X-ray abnormalities, which are associated with inflammation in COVID-19 patients.<sup>6,9,10</sup>

This study aims to determine factors that influence the persistence of abnormalities on chest radiographs at 12 weeks after recovering from COVID-19 infection. The findings of this study may guide healthcare providers in managing care of post-COVID-19 patients, including the need for ongoing monitoring, follow-up imaging, or specialized interventions.

## Materials and methods

### Study design

A retrospective cohort study was conducted on patients with a history of hospitalization due to COVID-19 infection who were followed up at the respiratory clinic of Phramongkutklao Hospital from July 2021 to June 2022. Ethical approval was obtained by the Institutional Review Board, Royal Thai Army Medical Department (No. R029h/66\_Exp)

### Patients

Patients who were over 20 years of age and had a history of hospitalization due to COVID-19 infection were eligible for enrollment in the study. As part of the criteria, these patients were required to undergo a CXR at least 12 weeks after their COVID-19 infection during the follow-up period. However, individuals with a pre-existing interstitial lung disease (ILD), bronchiectasis, tuberculosis, or chronic lung disease with baseline CXR abnormalities, as well as those with recurrent COVID-19 infection, were excluded from participation.

## Data collection

Baseline characteristic data including age, sex, height, weight, smoking history, and underlying diseases were collected. Treatment data during COVID-19 admission, such as length of hospital stay, medications (including antivirals, corticosteroids, anti-inflammatory drugs, and antibiotics), oxygen therapy, and baseline laboratory test, were also recorded for the study. At the 12-weeks after discharge from hospital, the chest X-rays were reviewed and graded for radiographic severity score.

## The radiographic severity score

The radiological severity score was defined as a scoring system based on the proportion of abnormalities observed in each lung that have been proposed in previous study.<sup>6</sup> The scoring categories were as follows: 0 (no abnormality), 1 (abnormality  $\leq$  25%), 2 (abnormality 25-50%), 3 (abnormality 51-75%), and 4 (abnormality  $\geq$  75%). The scores from both lungs were combined to obtain a total score ranging from 0 to 8 points. Based on the radiological severity scores, the patients were categorized into two groups: the persistent CXR abnormality group (scores ranging from 1 to 8) and the complete resolution group (score of 0).

## Outcome

The main objective of the study was to identify risk factors during COVID-19 infection that are associated with persistent abnormalities on chest radiography (CXR) at 12 weeks. In addition, the secondary objectives involved determining the incidence of persistent CXR abnormalities resulting from COVID-19 and developing a clinical predictive score for persistent chest radiographs abnormality in post COVID-19 patients.

## Statistical analysis

Based on previous studies, the incidence of complete chest radiographic resolution in community-acquired pneumonia at 12 weeks was found to be 89.7%,<sup>11</sup> while the incidence of lung fibrosis in post COVID-19 infection was reported as 42.3%.<sup>3</sup> To detect a significant difference between these rates, a sample size of 76 participants was calculated with a power of 90%. Descriptive statistics, such as frequencies, means (SD), or medians [interquartile range (IQR)], were used depending on the distribution of the data. Categorical variables were compared using the chi-square test or Fisher's Exact test as appropriate, while continuous variables were compared using the Mann-Whitney U test between two groups. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant. Logistic regression analysis was done to identify risk factors of persistent CXR abnormality. Variables identified with a  $p$ -value of  $< 0.05$  in univariate analysis were selected for inclusion in a combined multivariate analysis. Statistical analysis was performed with STATA version 14.

## Model development

Our model development approach involved complete-case analysis. We included all relevant clinical parameters in a multivariable logistic regression model to identify significant predictors of persistent CXR abnormality. To decide which predictors to keep, we used backward elimination based on two criteria: statistical significance indicated by the  $p$ -value of each predictor and the overall predictive performance of the model measured by the area under the receiver operating characteristic curve (AuROC).

## Score derivation and validation

Scores were assigned to each predictor in the final model based on their logit coefficients. During score transformation, the denominator was set as the lowest coefficient among all predictors, and the other coefficients were used as numerators. After dividing the coefficients, the products were rounded to whole numbers. Subsequently, scores were calculated for each patient in the development cohort. The scores were further divided into three risk groups: low, moderate, and high probability of having persistent CXR abnormality, using an appropriate cut-off point.

## Results

A total of 120 patients were included in the study, of whom 68 (56%) patients were male, with a mean age of 58 years. After 12 weeks of hospital discharge, 76 patients (63%) were found to have persistently abnormal chest radiographs. The group of persistent CXR abnormality patients exhibited several notable differences compared to the group that achieved complete resolution. Specifically, the persistent CXR abnormality group had a significantly higher mean age (62 vs. 52 years,  $p < 0.001$ ), longer length of stay (21 vs. 14 days,  $p < 0.001$ ), a higher prevalence of hypertension (61.8 vs. 27.3%,  $p < 0.001$ ), dyslipidemia (44.7% vs. 27.4%,  $p = 0.04$ ), greater use of oxygen support (85.5 vs. 45.5%,  $p < 0.001$ ), and a higher rate of using high flow nasal cannula (HFNC) or noninvasive ventilation (NIV) (44.7 vs. 15.9%,  $p < 0.001$ ). These findings are summarized in Table 1.

Baseline laboratory data showed significantly higher serum lactate dehydrogenase (LDH) (312 vs. 227.5 U/L,  $p < 0.001$ ), c-reactive protein (CRP) (39.8 vs. 13 mg/L,  $p = 0.002$ ), and peak CRP (96 vs. 36.1 mg/L,  $p = 0.001$ ) in persistent CXR abnormality group compared to complete resolution group (Table 2).

The risk of persistent CXR abnormality was examined using logistic regression in the univariable analysis. Age over 60 years [odds ratio 3.11 (95%CI: 1.41-6.85),  $p = 0.01$ ], hospital stay longer than 14 days [odds ratio 5.12 (95%CI: 2.23-11.45),  $p < 0.001$ ], underlying hypertension [odds ratio 4.32 (95%CI: 1.02-9.70),  $p < 0.001$ ], the use of oxygen support [odds ratio 7.09 (95%CI: 2.96-16.96),  $p < 0.001$ ], and the use of HFNC or NIV [odds ratio 4.28 (95%CI: 1.70-10.80),  $p = 0.002$ ] were identified as significant risk factors (Table 3). Additionally, the multivariable analysis was adjusted

**Table 1** Baseline characteristics

Variables	Complete resolution (N=44)	Persistent CXR abnormality (N=76)	p-value
Age (year), mean $\pm$ SD	51.9 $\pm$ 16.1	62.2 $\pm$ 12.6	< 0.001*
Male N, (%)	24 (54.6%)	44 (57.9%)	0.43
LOS (days), median (IQR)	14 (10-17)	21 (15-32)	< 0.001*
BMI (kg/m <sup>2</sup> ), median (IQR)	26.6 (23.8-30.2)	25.2 (22.2-28.6)	0.16
Hypertension (N, %)	12 (27.3%)	47 (61.8%)	< 0.001*
Dyslipidemia (N, %)	12 (27.4)	34 (44.7%)	0.04*
Diabetes mellitus (N, %)	11 (25%)	28 (36.8%)	0.13
CKD over stage 3 (N, %)	3 (6.8%)	7 (9.2%)	0.47
Smoking status (N, %)	8 (18.1%)	8 (10.5%)	0.18
Oxygen support (N, %)	20 (45.5%)	65 (85.5%)	< 0.001*
Cannula (N, %)	11 (25%)	21 (27.6%)	0.46
HFNC or NIV (N, %)	7 (15.9%)	34 (44.7%)	0.001*
ET intubation (N, %)	2 (4.6%)	10 (13.2%)	0.11

\*p-value < 0.05 shown statistically significant

CXR, chest X-ray; LOS, length of stay; BMI, body mass index; CKD, chronic kidney disease; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; ET, Endotracheal tube

**Table 2** Baseline laboratory data during COVID-19 infection

Variables	Complete resolution (N=44)	Persistent CXR abnormality (N =76)	p-value
White blood cell count (/ $\mu$ L)	6,150 (4,800-8,600)	6,050 (4,700-7,350)	0.72
Lymphocyte count (/ $\mu$ L)	1,280 (892-1,831)	1,096 (820-1,498)	0.20
Neutrophil count (/ $\mu$ L)	3,743 (2,755-6,217)	4,144 (3,119-5,811)	0.39
Platelet count (/ $\mu$ L)	212,500 (166,000-245,500)	193,500 (157,000-256,000)	0.97
Serum LDH (U/L)	227.5 (187.5-282.5)	312 (239-448)	< 0.001*
Baseline CRP (mg/L)	13.0 (5.3 – 40.0)	39.8 (14.2-98.0)	0.002*
Peak CRP (mg/L)	36.1 (9.7-89.2)	96.0 (42.2-138.1)	0.001*

Data shown as median with interquartile range.

\*p-value < 0.05 shown statistically significant

LDH, lactate dehydrogenase; CRP, c-reactive protein;  $\mu$ L, microliter; U/L, unit per liter; mg/L, milligram per liter.

for baseline age, sex, comorbidity, length of stay, BMI, and oxygen support. Hospital stay longer than 14 days (OR 2.92, 95%CI: 1.06-8.03), underlying hypertension (OR 3.59, 95%CI: 1.11-11.58), and the use of oxygen support (HFNC or NIV or ET intubation) (OR 3.29, 95%CI: 1.11-9.79) were determined to be independent and significant risk factors for persistent CXR abnormality (Table 4).

**Table 3** Univariable analysis for risk of persistent CXR abnormality

Variables	Odds ratio	95% confidence interval	p-value
Age > 60	3.11	1.41-6.85	0.01*
Male gender	1.15	0.54-2.42	0.72
Length of stay > 14 day	5.12	2.23-11.45	< 0.001*
BMI	0.96	0.89-1.03	0.29
Hypertension	4.32	1.92-9.70	< 0.001*
Dyslipidemia	2.16	0.97-4.82	0.06
Oxygen support	7.09	2.96-16.96	< 0.001*
HFNC or NIV	4.28	1.70-10.80	0.002*

\*p-value < 0.05 shown statistically significant

BMI, body mass index; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation

**Table 4** Multivariable analysis for risk of persistent CXR abnormality

Variables	Odds ratio	95% confidence interval	p-value
Age > 60	1.26	0.45-3.54	0.67
Male	1.20	0.49-2.91	0.69
Length of stay > 14 day	2.92	1.06-8.03	0.04*
BMI	0.93	0.85-1.03	0.16
Hypertension	3.59	1.11-11.58	0.03*
Dyslipidemia	0.76	0.25-2.29	0.62
Oxygen support (HFNC or NIV or ETT)	3.29	1.11-9.79	0.03*

(Adjusted by baseline age, sex, comorbidity, LOS, BMI, oxygen support)

\*p-value < 0.05 shown statistically significant

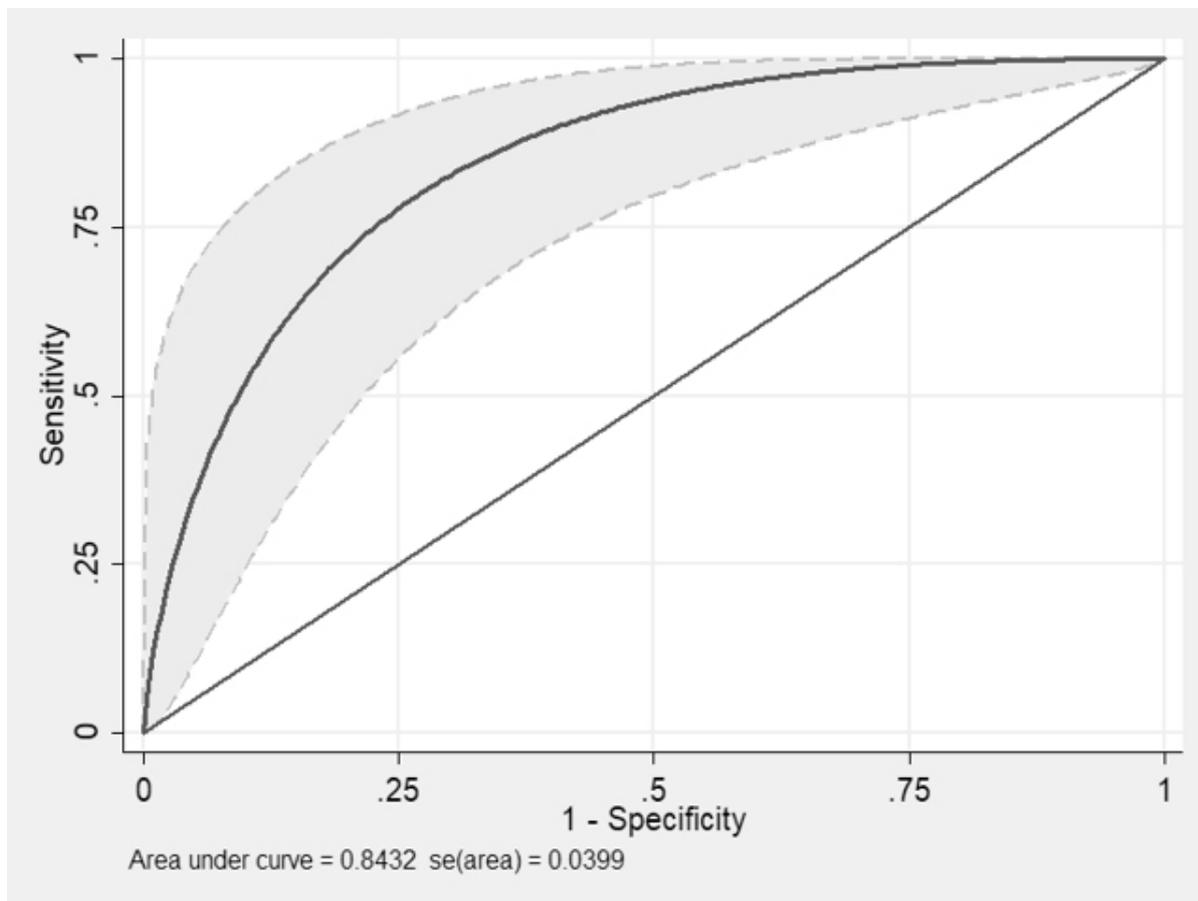
BMI, body mass index; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation

A predictive score was developed using a reduced multivariable logistic model to derive a scoring system that incorporates significant risk factors and laboratory data, such as serum LDH (with a cut-off level >250 U/L). The resulting scoring system yielded a total score of 10 (Table 5). Our findings indicate that utilization of this predictive score significantly enhances the accuracy of predicting persistent CXR abnormality at 12 weeks in post COVID-19 patients. This improvement is demonstrated by an area under the receiver operating characteristic curve (AuROC) of 0.84, as depicted in Figure 1.

Each potential predictor in the multivariable model was assigned a specific score based on its logistic regression coefficient. The scoring scheme resulted in a total score ranging from 0 to 10. To make the scores more clinically applicable, they were further divided into three risk sub-categories. The low-risk group had scores ranging from 0 to 2, the moderate-risk group had scores ranging from 3 to 8, and the high-risk group had scores ranging from 9 to 10. For each

**Table 5** Risk score deviation using multivariable logistic regression coefficients

Variables	Odds ratio (95%CI)	p-value	coefficient	Score
Hypertension	4.36 (1.62-11.74)	0.004	1.471679	3
Length of stay > 14 day	3.82 (1.28-11.41)	0.016	1.340345	3
Oxygen support (HFNC or NIV or ETT)	1.70 (0.54-5.40)	0.368	0.530444	1
Serum LDH > 250 U/L	4.93 (1.81-13.46)	0.002	1.596040	3
<b>Total score</b>				<b>10</b>

**Figure 1** The receiver operating characteristic curve (ROC) of developing score for predicted persistent CXR abnormality

risk group, the positive predictive values (PPV) were calculated. The low-risk group had a positive predictive value of 11.11 (95%CI: 1.38-34.71), the moderate-risk group had a positive predictive value of 69.01 (95%CI: 56.92-79.46), and the high-risk group had a positive predictive value of 90.91 (95%CI: 70.84-98.88). (Table 6)

**Table 6** Distribution of complete resolution vs persistent CXR abnormality across different level of risk categories (low risk, moderate risk, and high risk)

Risk categories	Score	Complete resolution (N = 40)	Persistent CXR abnormality (N = 71)	PPV	95% confidence interval
Low	0-2	16 (88.9%)	2 (11.1%)	11.11	1.38-34.71
Moderate	3-8	22 (31%)	49 (69%)	69.01	56.92-79.46
High	9-10	2 (9.1%)	20 (90.9%)	90.91	70.84-98.88

PPV, positive predictive value

### Discussion

In this study, risk factors for potentially persistent chest radiographs abnormalities were identified as length of hospital stay longer than 14 days, underlying hypertension, and the use of oxygen support (HFNC or NIV or ET intubation). These factors were consistent with a previous study by Li, et al.<sup>12</sup> However, the study by Wallis, et al.<sup>10</sup> identified different predicted factors for persistent CXR abnormality at 12 weeks in patients with post-COVID-19 pneumonia, including longer length of stay, higher level of serum LDH, obesity, and smoking status.

We observed that 63% of patients had persistent CXR abnormalities at 12 weeks after COVID-19 infection, which is higher than the incidence reported in a previous study by Mandal, et al., where the incidence of persistent CXR abnormality in post-COVID-19 infection was 38%.<sup>13</sup>

Currently, there is no research explaining a mechanism by which these risk factors contribute to the development of persistent CXR abnormalities. It is assumed that these risk factors are also associated with an increased likelihood of severe COVID-19 pneumonia,<sup>10,14</sup> which can potentially lead to persistent abnormalities in CXR. Further studies are needed to investigate this mechanism.

This study also developed a clinical predictive score that may help assess the likelihood of patients having persistent CXR abnormality, particularly in the high-risk group (score 9-10), which may be prone to developing interstitial abnormalities in the future. However, further studies are needed to validate this model.

The potential benefits of this study lie in identifying persistent lung abnormalities, aiding in the tailoring of treatment strategies for individuals with post-COVID-19 complications. For instance, if certain radiographic patterns are consistently observed, clinicians may develop targeted therapies or rehabilitation programs to address specific issues. Furthermore, the understanding the long-term consequences of COVID-19 may provide public health strategies including preventive measures and vaccination campaigns. This understanding can also contribute to assessing the overall burden of the disease on healthcare systems.

There are limitations in this study, including retrospective data, a lack of information on the COVID-19 vaccination status of patients and the potential for interpretation bias in chest radiographs. Moreover, the study was conducted during the Delta variant of COVID-19 pandemic in Thailand, which may have different effects compared to other variants. Additionally, chest radiographs abnormality may spontaneous recovery over time, a long-term follow-up study may necessary.

### Conclusion

The risk factors for persistent chest radiography abnormality caused by COVID-19 at 12 weeks include the length of hospital stay longer than 14 days, underlying hypertension, the use of oxygen therapy (including HFNC, NIV, ET intubation), and serum LDH levels above 250 U/L. To predict this outcome, a clinical predictive score may be helpful, although further studies are necessary to validate its effectiveness across different variants of SARS-CoV-2.

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