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Original Article

Association between chest X-ray score and clinical outcome in COVID-19 patients: A study on modified radiographic assessment of lung edema score (mRALE) in Indonesia

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Abstract

Radiological examinations such as chest X-rays (CXR) play a crucial role in the early diagnosis and determining disease severity in coronavirus disease 2019 (COVID-19). Various CXR scoring systems have been developed to quantitively assess lung abnormalities in COVID-19 patients, including CXR modified radiographic assessment of lung edema (mRALE). The aim of this study was to determine the relationship between mRALE scores and clinical outcome (mortality), as well as to identify the correlation between mRALE score and the severity of hypoxia (PaO2/FiO2 ratio). A retrospective cohort study was conducted among hospitalized COVID-19 patients at Dr. Soetomo General Academic Hospital Surabaya, Indonesia, from February to April 2022. All CXR data at initial admission were scored using the mRALE scoring system, and the clinical outcomes at the end of hospitalization were recorded. Of the total 178 COVID-19 patients, 62.9% survived after completing the treatment. Patients within non-survived had significantly higher quick sequential organ failure assessment (qSOFA) score (p<0.001), lower PaO2/FiO2 ratio (p=0.004), and higher blood urea nitrogen (p<0.001), serum creatinine (p<0.008) and serum glutamic oxaloacetic transaminase (p=0.001) levels. There was a significant relationship between mRALE score and clinical outcome (survived vs deceased) (p=0.024; contingency coefficient of 0.184); and mRALE score of ≥2.5 served as a risk factor for mortality among COVID-19 patients (relative risk of 1.624). There was a significant negative correlation between the mRALE score and PaO_2/FiO_2 ratio based on the Spearman correlation test (r=-0.346; p<0.001). The findings highlight that the initial mRALE score may serve as an independent predictor of mortality among hospitalized COVID-19 patients as well as proves its potential prognostic role in the management of COVID-19.

Keywords: Clinical outcome, CXR scoring system, mRALE score, severity, hypoxia

Introduction

Since its first outbreak in Wuhan in March 2019, coronavirus disease 2019 (COVID-19) has presented with a wide range of symptoms and various clinical manifestations, with shortness of breath and hypoxia among the important hallmarks. In severe conditions, acute respiratory

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distress syndrome (ARDS) has been recognized as the main clinical manifestation, leading to life-threatening and fatal multi-organ failure [1]. Nevertheless, early detection of hypoxemia in COVID-19 patients is challenging due to a phenomenon known as 'silent hypoxemia' or 'happy hypoxia'. Despite a significant decline in oxygen level, patients with happy hypoxia may not have typical complaints of shortness of breath until in an advanced clinical stage of pneumonia. Therefore, timely identification of COVID-19, particularly in patients with 'silent hypoxia' is critical to prevent the progression of pneumonia to more severe conditions, including ARDS [2].

Radiological assessments play a crucial role in identifying and evaluating the severity of the disease, enabling the anticipation of clinical outcomes for COVID-19 patients [3]. A computed tomography (CT) scan has been recognized as the most effective modality for early disease detection and severity assessment due to its high sensitivity [2,4-6]. However, routine use of CT scan becomes increasingly challenging due to constraints of resources and difficulty of sterilization procedures, placing an excessive burden on the radiology unit [7]. Therefore, the American College of Radiology recommends chest X-ray (CXR) examination as it is a cost-effective, practical, and widely available diagnostic method that can be easily carried out in various clinical settings, including bedside assessment for patients in intensive care unit (ICU) [4,5,8]. It has been evidenced to effectively detect COVID-19-associated pneumonia and other pulmonary abnormalities in COVID-19 patients [8].

To objectively assess COVID-19 pulmonary manifestations using CXR, experts have proposed a CXR scoring system to quantitatively evaluate the severity and monitor the progression of the disease. This scoring system has been proven useful for the assessment of lung abnormalities, serving as a prognostic indicator for intubation and mortality among hospitalized COVID-19 patients [7,9]. Previous studies have reported an inverse correlation between the CXR score and oxygen saturation, suggesting that lung abnormalities evaluated through the CXR score may serve as an indirect indicator of compromised oxygenation [8,10]. High CXR scores have been independently linked to decreased pressure of arterial oxygen to fractional inspired oxygen concentration ratio (PaO_2/FiO_2) or more advanced stage of hypoxia, as well as increased mortality [11].

One of the CXR scoring systems applied to COVID-19 patients is the modified radiographic assessment of lung edema (mRALE), a modified and simplified version of the RALE scoring system initially developed for patients with acute respiratory distress syndrome (ARDS) [7,9,11,12]. Its application for COVID-19 patients is considered pertinent since CXR findings often indicate multifocal alveolar opacity and many hospitalized patients develop ARDS during the course of the disease [12]. However, in Indonesia, the use of the mRALE score to assess the severity of lung abnormalities in COVID-19 patients has been little practiced, and studies verifying the validity of this score, as well as exploring its correlation with clinical outcomes in COVID-19 patients, are still limited. Therefore, the aim of this study was to identify the association between mRALE score and clinical outcome in hospitalized COVID-19 patients in Indonesia. In addition, the correlation between mRALE score and the severity of hypoxia was assessed.

Methods

Study design, setting and sample

A retrospective cohort study was conducted among hospitalized COVID-19 patients treated at the Internal Medicine Isolation Ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from February to April 2022. Using a consecutive sampling technique, patients of ≥18 years of age with RT-PCR-confirmed COVID-19 and had CXR examination on hospital admission during the period of February 1 to April 30, 2022, were included in the study. Patients whose CXR images showed massive pleural effusion, atelectasis, pulmonary edema, or a history of prior lung disease or infection (e.g., pulmonary tuberculosis or chronic obstructive pulmonary disease), which might potentially reduce the accuracy of CXR score assessment and patients who were discharged from the hospital on request were excluded from the study.

Study variables

The main outcome (dependent variable) of the study was the clinical outcome of the COVID-19 patients; defined as a patient's ultimate condition following the completion of treatment and divided into survived or dead. In addition, the secondary outcome, the level of hypoxia, was also assessed. The severity of hypoxia was measured based on the PaO2/FiO2 ratio. It was categorized as mild (PaO2/FiO2 ratio of 300–201 mmHg), moderate (200–101 mmHg), and severe following previous studies (≤100 mmHg) [13,14]. The main independent variable of the study was patients' CXR findings upon admission. CXR data was quantified using the mRALE severity score.

In addition, other plausible confounding variables such as demographic characteristics (age and gender) and clinical profiles (quick sequential organ failure assessment (qSOFA) score, comorbidities and laboratory findings) at patients' initial admission were also assessed and analyzed. The scoring system of qSOFA is an assessment to identify patients with suspected infection who are at higher risk of mortality. The score ranges from 0–3, assigned one point to each of the following criteria: low systolic blood pressure (≤100 mmHg), high respiratory rate (≥22 x/min), altered mental status (Glasgow coma scale of <15) [15,16]. A score ≥2 indicates more severe. Laboratory tests included hemoglobin, leukocytes, platelets, blood urea nitrogen (BUN), serum creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and random blood glucose (RBG).

mRALE scoring

mRALE score was assessed by assigning a score (ranging from 0–4) to each lung (right and left) based on the percentage of lung involvement or the presence of consolidation, ground glass opacity, or haziness. The scoring details are as follows: 0 if no lung involvement, 1 if <25% involvement, 2 if 25–50% involvement, 3 if >50–75% involvement, and 4 if >75% involvement. The score obtained for each lung was then multiplied by an overall density score (1=hazy, 2=moderate, 3=dense). The term moderate density was a description of the density between hazy opacity and dense consolidation. In cases where different parts of the lungs have varying densities, a score was assigned based on the dominant density. The sum of scores from both lungs yields the mRALE score, ranging from 0 to 24. Notably, other CXR findings such as pleural effusion were not included in the scoring system calculation [12].

Statistical analysis

Data on demographic and clinical characteristics were presented as percentage (%), median (interquartile ranges), and mean ± standard deviation (SD) as appropriate. Mann-Whitney analysis was performed to compare the patients' characteristics between the survived and deceased group. A Chi-squared test was used to determine the relationship between the levels of patients' baseline mRALE score and the main clinical outcome variable (mortality). A receiver operating characteristic (ROC) test was subsequently conducted to identify the cut-off value for mRALE score, categorizing it into low and high mRALE score.

In addition, the Spearman correlation test was used to identify the correlation between mRALE scores and the severity of hypoxia. A $p<0.05$ was considered statistically significant. All data analyses were performed using SPSS software version 25 (IBM, New York, USA).

Results

Baseline characteristics of the patients

A total of 178 patients were included in the study and the characteristics and clinical profiles are presented in **Table 1**. Out of total patients, 51.1% were females, the median age was 53 years and the vast majority of the patients (87.1%) had at least one comorbidity. The most common comorbidity among the patients was chronic kidney disease (CKD) (40.4%), followed by hypertension (33.1%), diabetes (27.0%), malignancy (16.8%), cardiovascular diseases (CVD) (11.2%), human immunodeficiency virus (HIV) infection (7.9%), and autoimmune disease (3.4%). In terms of the outcomes, 62.9% of the patients survived and less than half (45.2%) received antiviral therapy. The result of CXR mRALE severity score assessment ranged from 0–24 with a median of 2.5.

Table 1. Characteristic of patients' demographic and clinical characteristics (n=178)

Variables	Frequency (Percentage)
Gender	
Male	87 (48.9)
Female	91 (51.1)
Age (year), median (range)	53 (19–86)
Comorbidities	
Diabetes mellitus	48 (27.0)
Hypertension	59 (33.1)
Chronic kidney disease (CKD)	72 (40.4)
Cardiovascular diseases (CVD)	20 (11.2)
Malignancy	29 (16.83)
Human immunodeficiency virus (HIV)	14 (7.9)
Autoimmune disease	6 (3.4)
mRALE score, median (range)	2.5 (0–24)
Antiviral therapy	81 (45.2%)
Outcome	
Survived	112 (62.9)
Dead	66 (37.1)

Comparisons of demographic and clinical characteristics between survived and death groups

A comparative analysis of the patients' characteristics between the two outcome groups (**Table 2**). The age (p=0.013), CKD event (p=0.014), qSOFA score (p<0.001), PaO2/FiO2 ratio value (p<0.001), BUN (p<0.001), serum creatinine (p<0.008), and SGOT (p<0.001) were significantly different between the recovered and deceased patients. The patients within the non-survival group had older age (median age: 56 vs 50 years), higher qSOFA score (median: 2 vs 0), lower PaO_2/FiO_2 ratio (median: 343.5 vs 390.0 mmHg), higher BUN (median: 45.5 vs 15 mg/dL) and higher SGOT levels (53.5 vs 34.5 u/L) compared to survived group (**Table 2**). The mean of mRALE scores was not significantly different between outcome groups (median of survived vs died: 2 vs 3; p=0.062) (**Table 2**).

Table 2. Comparison of patients' demographic and clinical characteristics between outcome groups (n=178)

Variables	Group		p-value
	Survived	Dead	
Gender, n (%)			
Male	55 (63.2)	32 (36.8)	0.936
Female	57 (62.6)	34 (37.4)	0.936
Age (year), median (range)	50 (19–86)	56 (20–82)	0.013*
Comorbidities, n (%)			
Diabetes mellitus	29 (60.4)	19 (39.6)	0.806
Hypertension	32 (54.2)	27 (45.8)	0.127
Chronic kidney disease (CKD)	37 (51.4)	35 (48.6)	0.014*
Cardiovascular diseases (CVD)	9 (45)	11 (55)	0.130
Malignancy	15 (51.7)	14 (48.3)	0.248
Human immunodeficiency virus (HIV)	10 (71.4)	4 (28.6)	0.690
Autoimmune disease	5 (83.3)	1 (16.7)	0.415
qSOFA score, median (range)	0 (0–3)	2 (0–3)	<0.001**
Blood analysis, median (range)			
PaO2/FiO2 ratio (mmHg)	390.0 (135–814)	343.5 (80–714)	0.004*
Hemoglobin (g/dL), mean±SD	9.8±3.26	9.5±2.6	0.429
Platelets (10^3/µL)	269.5 (1–927)	225.5 (18–98)	0.240
BUN (mg/dL)	15 (4–187)	45.5 (6–220)	<0.001**
Serum creatinine (mg/dL)	1.08 (0.13–22.8)	2.09 (0.19–24.9)	0.008*
SGOT (unit/L)	34.5 (9–539)	53.5 (5–1029)	0.001*
SGPT (unit/L)	29 (5–427)	28.5 (8–392)	0.307
RBG (mg/dL)	108 (44–536)	123 (45–579)	0.131
mRALE score, median (range)	2 (0–24)	3 (0–24)	0.062

*Statistically significant at p=0.05
**Statistically significant at p=0.001

Association between mRALE score and clinical outcome

Based on this mRALE data, a ROC test was conducted and obtained mRALE cut-off value associated with mortality. Our data indicated that mRALE cut-off 2.5 was associated with mortality, leading to the establishment of two mRALE score categories: low (<2.5) and high (≥2.5).

The association between mRALE scores (divided into low and high) and clinical outcomes is presented in **Table 3**. The Chi-squared analysis revealed a statistically significant weak association between mRALE score and clinical outcomes (p=0.024; contingency coefficient, C=0.184), and mRALE score of ≥2.5 was associated with a higher risk of mortality among COVID-19 patients, with a relative risk (RR) of 1.624.

Table 3. Association between mRALE score and clinical outcome in COVID-19 patients

mRALE score	Outcome		p-value	Contingency coefficient
	Survived	Dead		
Low mRALE score (<2.5)	61 (68.5%)	28 (31.5%)	0.024*	0.184
High mRALE score (≥2.5)	38 (42.7%)	51 (57.3%)		
RR (95% CI)	0.743 (0.579–0.953)	1.624 (1.090–2.420)		

*Statistically significant at p=0.05

Correlation between mRALE scores and hypoxia severity

The correlation between the patients' mRALE scores and the severity of hypoxia based on PaO_2/FiO_2 ratio is presented in **Figure 1**. The Spearman correlation test suggested a significant negative correlation between the mRALE scores and PaO_2/FiO_2 ratio (r=-0.346; p<0.001), indicating that the lower the mRALE score the higher the PaO_2/FiO_2 ratio, of COVID-19 patients.

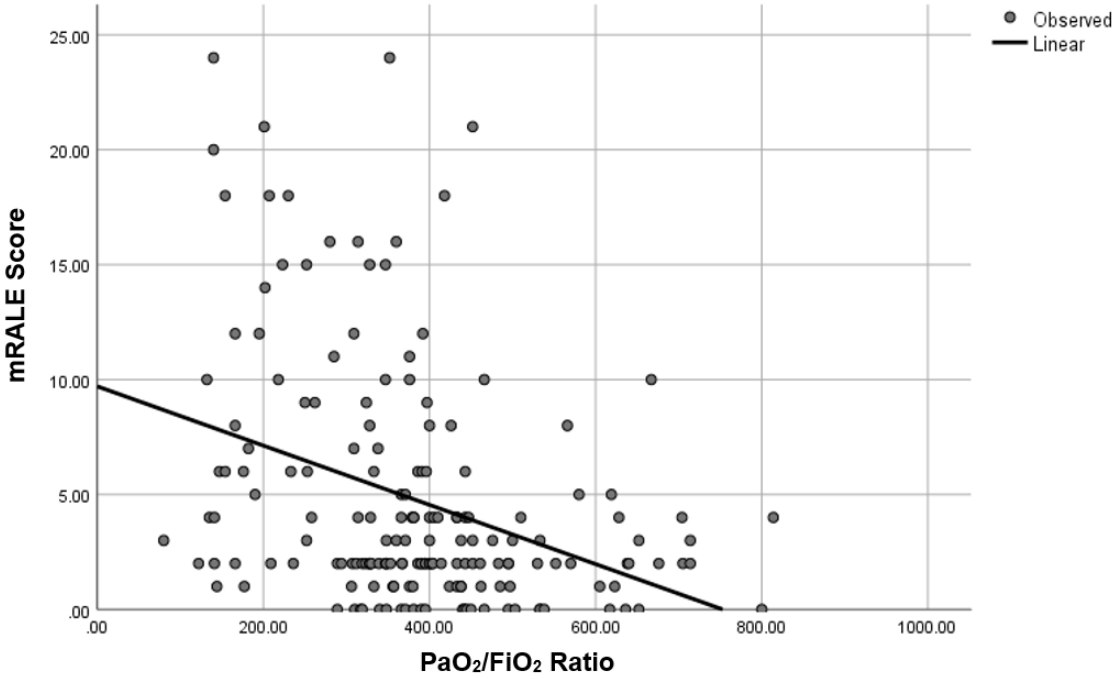

Figure 1. Correlation between mRALE score and the severity of hypoxia based on PaO_2/FiO_2 ratio in COVID-19 patients.

Discussion

In emergency settings, CXR has been evidently useful for the diagnostic purposes of COVID-19 cases [8]. It plays a crucial role in determining the severity of pneumonia and monitoring the rapid progression of lung abnormalities in COVID-19 patients [4,8], in which the extent of pulmonary opacity on CXR has been correlated with disease outcomes [17]. A CXR scoring system, such as mRALE, has recently been developed to quantitatively assess the severity of COVID-19 and helps identify high-risk patients, enabling timely initiation of therapy to prevent unfavorable outcomes [7-9,11,12,18]. In the present study, the association between mRALE score

and the clinical outcome among COVID-19 patients, as well as determine the correlation between mRALE score and the severity of hypoxia were assessed. The patients' characteristics between the two outcome groups were also compared to identify possible risk factors that might contribute to mortality among COVID-19 patients.

Our data suggested that the patients who died were significantly older than those who recovered (**Table 2**). This aligns with previous studies, reporting that younger patients had a higher likelihood of surviving COVID-19 [19-21]. Older age has consistently emerged as a robust independent predictor of mortality among COVID-19 patients [22-24]. Having diminished immune responses, such as reduced immunological function of B and T cells, along with overproduction of type 2 cytokines, as well as vulnerability to various comorbidities, have put the elderly at a higher risk for unfavorable outcomes [22-25]. Corresponding to earlier investigations [26-28], patients in the non-survival group also had significantly higher qSOFA score, lower PaO_2/FiO_2 ratio, and higher BUN and SGOT levels compared to those in the survival group (**Table 2**). These conditions, respectively indicative of sepsis, severe hypoxia, and impaired kidney and liver function, have been linked to poor COVID-19 outcomes and serve as valuable predictors of COVID-19-associated mortality [26-30].

Our Chi-squared analysis revealed a significant relationship between mRALE score and clinical outcome of COVID-19 ($p<0.05$), in which the higher the mRALE score, the more likely the patients die of COVID-19. This suggests that initial mRALE score may serve as an independent predictor of mortality in hospitalized COVID-19 patients, and mRALE score of ≥2.5 was associated with mortality among COVID-19 patients. These findings confirmed the results of previous investigations, justifying that initial CXR score, such as CXR severity score (CXR-SS) and Brixia CXR score, at patients' arrival served as a significant independent predictor of COVID-19-related mortality, and often appeared to be higher in deceased compared to survived patients [9,27,31-34].

The Spearman correlation suggested a significant negative correlation between mRALE score and PaO_2/FiO_2 ratio (r=-0.346; $p<0.001$), in which the higher the mRALE score, the lower PaO_2/FiO_2 ratio. PaO2/FiO2 ratio is a marker of hypoxia, and has been considered a useful predictor for both mortality and mechanical ventilator requirement among COVID-19 patients [6,27]. This finding was consistent with those of previous studies, suggesting that CXR score was negatively associated with PaO_2/FiO_2 ratio [35,36], and elevated baseline CXR score was independently correlated with lower PaO_2/FiO_2 ratio, indicative of poor oxygenation and diminished survival rates [8,10,11]. In COVID-19 patients, the quantitative assessment of lung opacity using the CXR score at the onset of therapy exhibits a highly significant clinical association with oxygenation and patient outcome, which serves as a reliable indicator of respiratory function. The finding from this present study, thereby, offers further evidence for considering PaO_2/FiO_2 ratio as a critical parameter in assessing disease severity in COVID-19 patients with severe respiratory symptoms.

This study had some limitations that should be discussed. Certain data that might be associated with patients' clinical outcomes, such as history of smoking and COVID-19 vaccination, as well as the body mass index were not completely documented and therefore were unable to be analyzed. Furthermore, this study was conducted at only one tertiary referral hospital in East Java; therefore, the sample enrolled might not represent the overall characteristics of patients in a wider area. Consequently, a multicentered investigation involving a larger sample size is important to further confirm the present results.

Conclusion

Our data suggested that the patients who died during hospitalization were significantly older and had lower baseline PaO_2/FiO_2 ratio, higher qSOFA score, as well as higher BUN and SGOT levels. The Chi-squared analysis revealed a significant relationship between mRALE score and clinical outcome, suggesting that a high mRALE score was associated with mortality among COVID-19 patients. This finding suggested that the initial mRALE score may serve as an independent predictor of mortality among hospitalized COVID-19 patients and highlights its potential prognostic role in the management of COVID-19.

Ethics approval

Ethical approval was obtained from the Ethical Committee of Dr Soetomo Academic General Hospital, Surabaya, Indonesia (0550/KEPK/XII/2022). The patients provided their signed informed consent prior to the study.

Competing interests

The authors declare that there is no conflict of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

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