

Relationship between RALE Score, Age, Gender, D-Dimer, Diabetes Mellitus and Hypertension with Mortality Rate of COVID-19 Patients in the Intensive Care Unit

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ABSTRACT

Introduction: The evaluation of changes in RALE scores on chest radiography and increased D-Dimer values of COVID-19 patients can be prognosticators of severity in the progressive phase and risk of ARDS. This study aims to determine the relationship between Rale scores and mortality of COVID-19 patients in the Intensive Care Unit (ICU) at RSUD Dr. Moewardi.

Methods: This research is an analytical observational study with a cross sectional approach was conducted on COVID-19 patients who had undergone a chest radiography and a D-Dimer examination at RSUD Dr. Moewardi in the period May 2021 to July 2021.

Results: This research included of 126 patients with 109 (87%) have died and 17 (13%) lived. Increased RALE and D-Dimer scores were associated with mortality of COVID-19 patients in the ICU while gender ($p=0.416$), age ($p=0.336$), diabetes mellitus (DM) ($p=0.852$), and hypertension ($p=0.464$) did not have a significant relationship with the outcome of COVID-19 patients admitted to the ICU with $p>0.05$. The RALE score has an OR = 7.566 (95% CI = 2.117-27.043) which means that the increase in the RALE score is 7.566 times greater for the death outcome than the RALE score which remains or decreases. The D-Dimer got an OR value of 3,679 (95% CI=1.169-11,576) which means that D-Dimer >2000 has a 3.655 times greater risk of death than D-Dimer <2000 in COVID-19 patients treated in the ICU.

Conclusion: There is a relationship between changes in RALE and D-Dimer scores with the mortality rate of COVID-19 patients in the ICU of RSUD Dr. Moewardi. Future research is expected to analyze other factors that have the potential to bias the results of the study such as changes in D-Dimer values, sociodemographic factors, clinical conditions and medical history in research subjects.

Keywords: chest radiography; d-dimer; ICU; RALE score

INTRODUCTION

Since the discovery of the first case of COVID-19 disease caused by a new variant of the betacoronavirus called severe acute respiratory syndrome-coronavirus-2 or abbreviated as SARS-CoV-2, the presence of this virus has continued to spread, until March

12, 2020, The World Health Organization (WHO) has declared COVID-19 a pandemic. Data on the spread of COVID-19, mortality and recovery rates continue to be reported regularly throughout the world. Reports of COVID-19 cases worldwide as of July 5 2021 reached 183,198,019 confirmed cases, and 3,971,687 people died due to COVID-19¹.

In Indonesia, according to the Ministry of Health (2021), the total number of Covid-19 case reached 2,313,829 people. This number was obtained after there were an addition of 29,745 cases in a day. Cases of recovered patients from Covid-19 increased by 14,416 people, bringing the total to date to 1,942,690 cases with a total of 309,999 active cases². In May to July 2021 at RSUD Dr. Moewardi, there were 3095 patients who were treated with a diagnosis of COVID-19 and as many as 405 patients who were treated in the ICU.

Identification and management of coagulopathy of COVID-19 patients at the time of hospital admission should be considered even if there are no severe symptoms because elevated levels of D-Dimer determine the severity of the disease³. Patients with comorbidities such as diabetes mellitus, hypertension and cardiovascular disease have an increase in ACE2 receptors. Elderly patients who have comorbidities have a greater risk factor for SARS-CoV-2 with worsening⁴.

Chest X-ray evaluation is a very important modality in the diagnosis of pneumonia and the evaluation of COVID-19 infection which varies in various countries. It has such low specificity and overall predictive value that it is not currently considered helpful for the diagnosis of COVID-19 infection by most clinicians. WHO guideline recommendations using Reverse Transcription - Polymerase Chain Reaction (RT-PCR) as the gold standard in diagnosing COVID-19.⁵ Although the WHO recommendation mentions not to use a chest X-ray as a COVID-19 diagnosis tool, several studies have explained that a chest X-ray can be associated with COVID-19 mortality rates. The purpose of this study was to determine whether changes in the RALE score on chest X-rays were associated with the mortality rate of COVID-19 patients treated in the intensive care unit (ICU) of RSUD Dr. Moewardi.

METHODS

This study is a retrospective analytic observational study by analyzing the data and medical records of patients in the period from May to July 2021 at the Radiology Department of Dr. Moewardi General Hospital Surakarta. The target population in this study were COVID-19 patients who were confirmed positive by PCR swab examination and treated in the ICU. The sampling technique in this study is non-probability sampling, namely consecutive sampling until met certain criteria until the number of research samples is reached. This research has been reviewed by the ethics committee of RSUD Dr. Moewardi Surakarta as evidenced by the existence of a certificate of ethical feasibility from the Health Research Ethics Committee of RSUD Dr. Moewardi Surakarta (KEPK) with the number 930/IX/HREC/2021.

All sample data will be analyzed to determine the characteristics of the research sample. The bivariate analysis in this study was to determine the relationship between RALE scores and risk variables (gender, age, D-Dimer, diabetes mellitus and hypertension) on the mortality outcome of COVID-19 patients admitted to the ICU. The demographic data was displayed in a cross table with the frequency value (%) then correlation analysis is performed with the Chi Square/Fischer Exact Test and followed by the odd ratio (OR) analysis to determine the level of risk. The relationship between RALE scores, age, gender, diabetes mellitus, and hypertension with the mortality rate of COVID-19 patients in the intensive care unit (ICU) of Dr. Moewardi Surakarta was evaluated by ordinal regression analysis. All data will be analyzed using Statistical Package for Social Science (SPSS) ver. 25. The value of α was determined is 0.05 with a 95% confidence interval for this study. The flow of the research is shown in Figure 1 and Figure 2

RESULTS

This study involved 126 COVID-19 patients in the ICU room at RSUD Dr. Moewardi. Demographic data (gender, age, diabetes mellitus, hypertension, RALE score, D-dimer and outcome) are presented with the value of the frequency distribution (%) (Table 1)

Based on Table 2, it is known that the gender of the patients was mostly male,

namely there were 71 patients (65.3%) with an age range > 50 years reaching 94 patients (74.6%). Diabetes mellitus with HbA1c > 6.5% reached 46 patients (32.5%), hypertension with systolic blood pressure >140 mmHg reached 41 patients (32.5%), D-dimer >2000 ng/ml was found in 95 patients (75.4%). The RALE score was mostly increased in 107 patients (84.9%) whereas it persisted and/or decreased in 19 patients (15.1%).

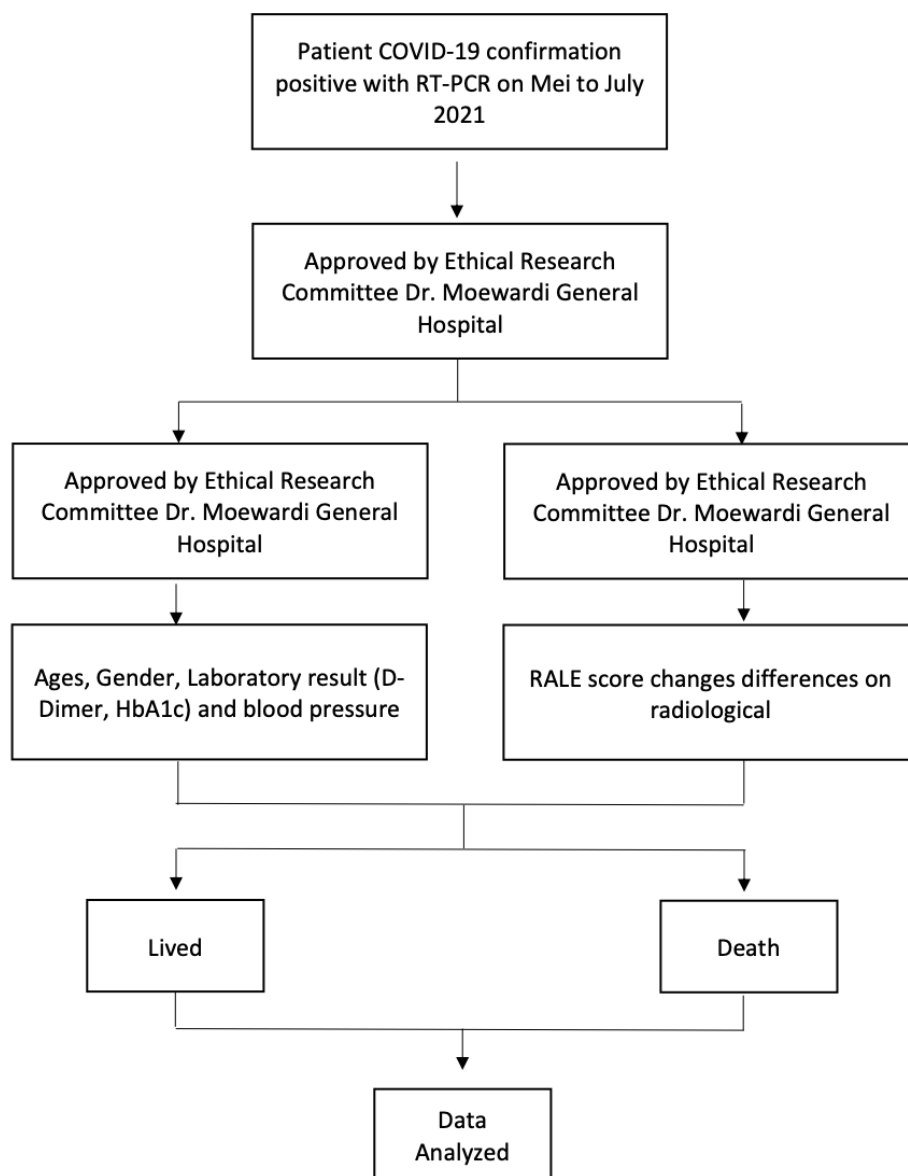
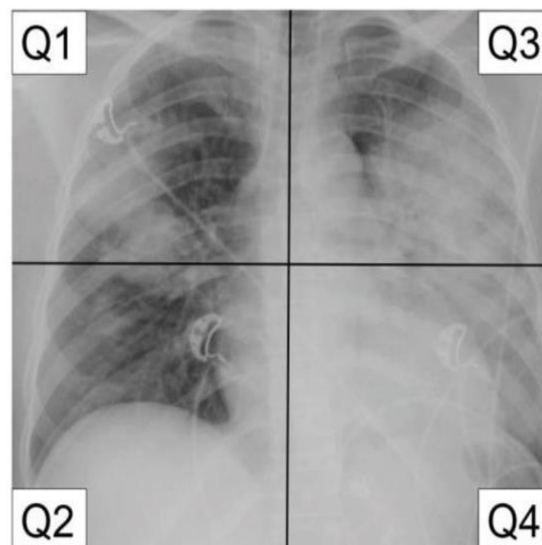
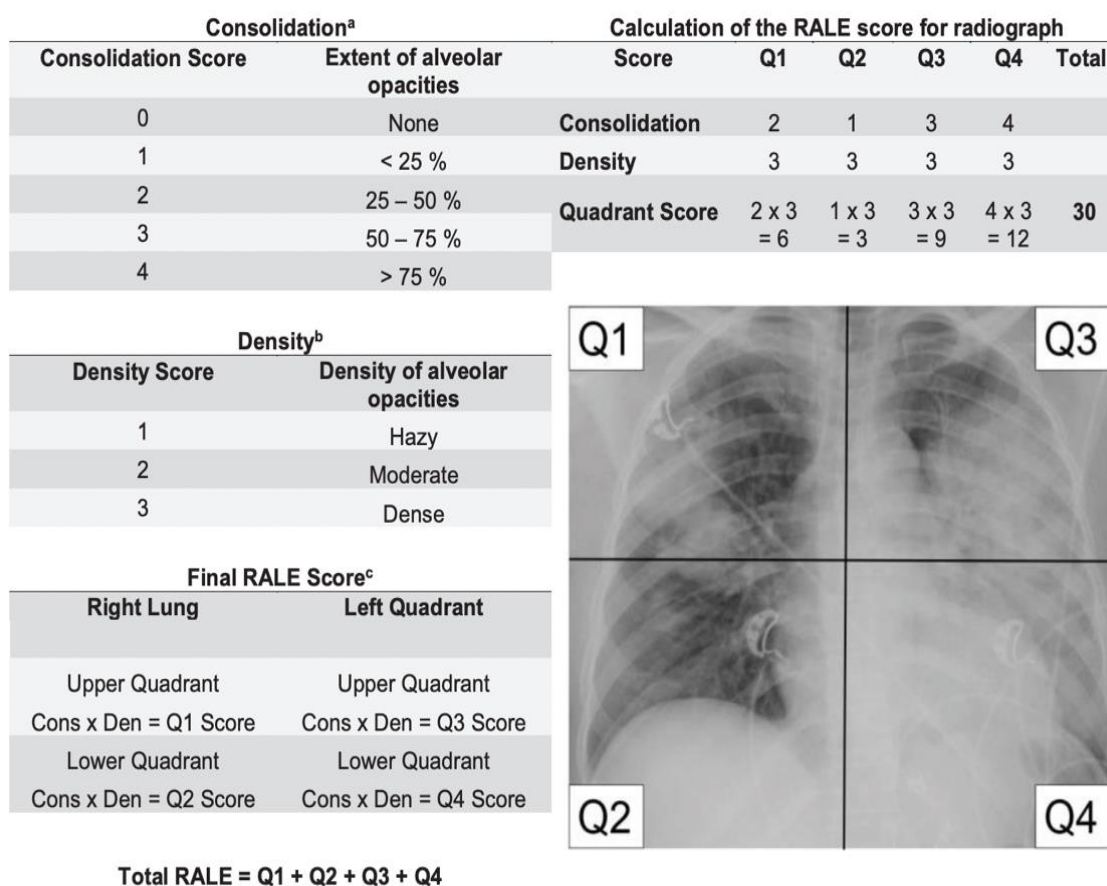


Figure 1. Research algorithm

Patients with death outcomes were 109 patients (86.5%) while 17 patients were alive (13.5%).

Based on Table 3 it is known that gender ($p = 0.416$), age ($p = 0.336$), DM ($p = 0.852$), and hypertension ($p = 0.464$) did not have a significant relationship with the outcome of COVID-19 patients admitted to the ICU with p value >0.05 . In the multivariate analysis, the RALE score got an OR = 7.566 (95% CI = 2.117-27.043) thus the RALE score increases 7.566 times with a greater risk of death than the RALE score remains and/or decreases. The results of the

statistical test got a value of $p=0.002$ ($p<0.05$), which reflect a significant relationship between the RALE score and the outcome of COVID-19 patients admitted to the ICU. In the study, D-Dimer got an OR 3,679 (95% CI = 1,169-11,576) which means that D-Dimer >2000 ng/ml has a 3.655 times greater risk of death than D-Dimer <2000 ng/ml. The results of the statistical test obtained a value of $p=0.024$ ($p<0.05$) so that it was significant between D-Dimer and the outcome of COVID-19 patients treated in the ICU.



^a Consolidation is scored for each quadrant
^b Density is scored for each quadrant having a consolidation > 0
^c If Quadrant consolidation Score is 0 than Quadrant score is 0

Figure 2. Rale Score Measurement

Table 1. Description of Covid-19 Patient Research Data in the Intensive Care Unit (ICU)

Variables	Frequency	%
Gender		
Female	55	43.7%
Male	71	56.3%
Ages		
<50 year old	32	25.4%
≥ 50 year old	94	74.6%
Diabetes Mellitus		
HbA1c < 6,5 %	80	63.5%
HbA1c ≥6,5 %	46	36.5%
Hypertension		
Systolic Blood Pressure < 140 mmHg	85	67.5%
Systolic Blood Pressure ≥140 mmHg	41	32.5%
D-dimer		
<2000	31	24.6%
≥2000	95	75.4%
Rale Score		
Still, decreased	19	15.1%
Increased	107	84.9%
Outcome		
Lived	17	13.5%
Died	109	86.5%

Table 2. Relationship between Rale Score and variables that are at risk/interference with the survival outcome of COVID-19 patients admitted to the ICU.

Variable	Lived (n=17)	Died (n=109)	OR (95%CI)	p value
Gender				
			Ref	0.761
Female	8 (47.1%)	47 (43.1%)	1.173 (0.421-3.268)	
Male	9 (52.9%)	62 (56.9%)		
Ages				
			Ref	0.765
<50-year-old	5 (29.4%)	27 (24.8%)	1.265 (0.409-3.918)	
>50-year-old	12 (70.6%)	82 (75.2%)		
DM				
			Ref	0.911
HbA1C <6.5%	11 (64.7%)	69 (63.3%)	1.063 (0.365-3.093)	
HbA1C >6.5%	6 (35.3%)	40 (36.7%)		
Hypertension				
			Ref	0.417
Systolic <140mmHg	10 (58.8%)	75 (68.8%)	0.648 (0.227-1.846)	
Systolic >140 mmHg	7 (41.2%)	34 (31.2%)		
D-Dimer				
			Ref	0.032*
<2000	8 (47.1%)	25 (21.1%)	3.324 (1.154-9.571)	
>2000	9 (52.9%)	86 (78.9%)		
RALE Score				
			Ref	0.004*
Still, decreased	7 (41.2%)	12 (11.0%)	5.658 (1.815-17.638)	
Increased	10 (58.8%)	97 (89.0%)		

Notes: ^a Chi square/ fhiser exact test ; ^b Mann whitney; * significance p≤0,05

Table 3 Analysis of risk factors related to outcomes in research

Variable	Wald	OR	p-value
Gender	0.661	1.637 (0.499 -5.367)	0,416
Ages	0.924	1.858 (0.525-6.571)	0.336
DM	0.035	1.121 (0.337-3.734)	0.852
Hypertension	0.537	0.630 (0.183-2.169)	0.464
RALE SCORE (increased)	9.696	7.566 (2.117-27.043)	0,002*
D-dimer (≥ 2000)	4.959	3.679 (1.169-11.576)	0.026*

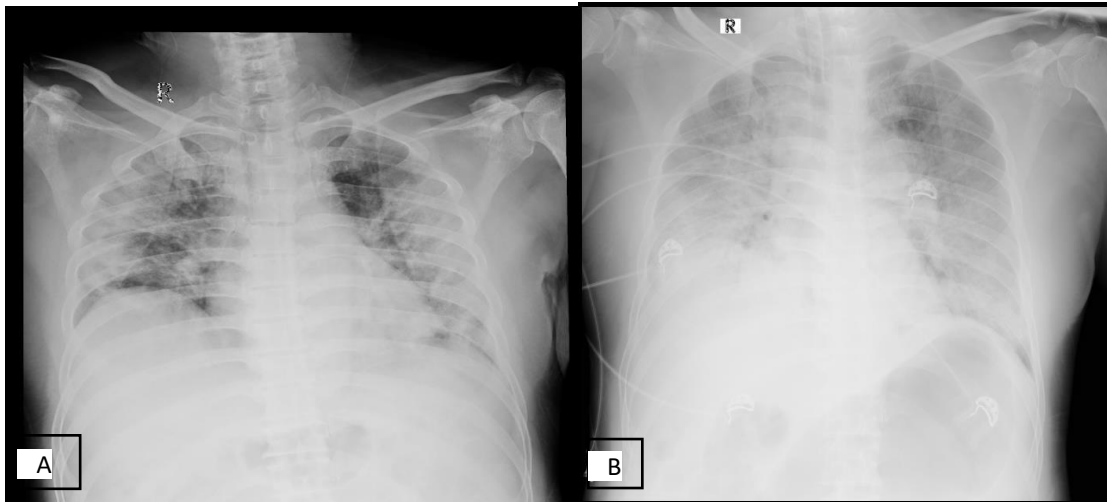


Figure 3. Chest X-ray in a 59-year-old male patient with diabetes mellitus and hypertension who is not living in the ICU. Picture A is a chest X-ray taken at the first ICU admission and picture B is a chest X-ray taken after 3 days of hospitalization in the ICU. In this patient, there was an increase in the consolidation and density of the chest X-ray on the 3-day treatment photo in the progressive phase.

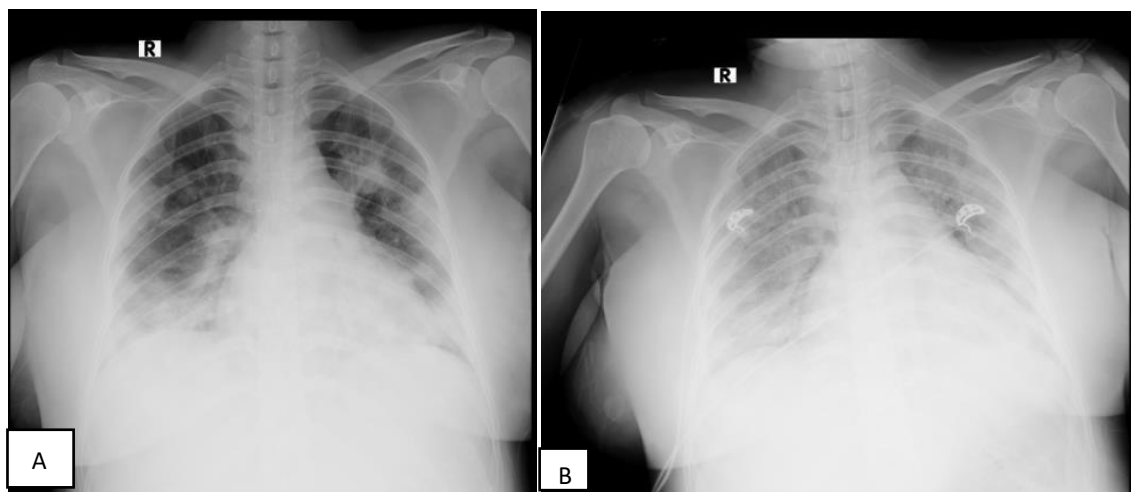


Figure 4. Chest X-ray in a 30-year-old female patient with no co-morbidities with diabetes mellitus and non-living hypertension in the ICU. Picture A is a chest X-ray taken at the first ICU admission and picture B is a chest X-ray taken after 3 days of hospitalization in the ICU. In this patient, there was an increase in the consolidation and density of the chest X-ray on the 3 days of treatment in the progressive phase.

DISCUSSION

The Radiographic Assessment of Lung Edema (RALE) score is one of the assessment scores for pulmonary edema by assessing the area and density of alveolar opacities on a simple chest X-ray developed by Warren et al in 2018. In a study conducted on patients with ARDS, the results showed that radiographic assessment The extent of pulmonary edema using the RALE score correlated well with a direct gravimetric assessment of pulmonary edema. In another study, increased RALE scores were independently associated with the severity of ARDS as well as response to conservative fluid management and clinical outcome. The RALE score can be used to stratify risk in ARDS patients and assess response to treatment clinically, or as an endpoint in clinical trials⁶. Zimatore et al in 2021 align with previous studies reported the RALE score provides a good diagnostic accuracy of interpretation of signs of pulmonary edema in ARDS patients undergoing ICU treatment with invasive ventilation. In our study, which consisted of 126 COVID-19 patients in the ICU, it was found that the proportion of patients who experienced living outcomes with persistent/decreasing RALE scores was 7 people (41.2%) while 10 people (58.8%) with increased RALE scores. The proportion of patients who experienced death with a persistent/decreasing RALE score was 12 (11.0%) while 97 people (89.0%) had an increased RALE score. This shows that in the living and death groups undergoing ICU care, a prognostic marker, RALE score increased more than the RALE score which remained/significantly decreased $p < 0.05$.

In the multivariate analysis, the OR for the RALE score on mortality outcomes in COVID-19 patients treated in the ICU reached 7.566 (95% CI = 2.117-27.043). This is in line with previous research by Sensusiati et al in 2020 which found that the RALE score can

predict mortality rates in COVID-19 patients in Surabaya hospitals. From this study, based on the ROC curve, Area Under the Curve (AUC) obtained a sensitivity of 96.7% and a specificity of 49.4%, to predict the mortality of COVID-19 patients in the hospital. Twice in the progressive phase there was an increase in the consolidated RALE score and density in both lung fields which was associated with the high number of patients with mortality in this study (Figure 3 and Figure 4).

Patients aged 50 years have a higher risk of death than COVID-19 patients < 50 years. Male patients aged more than 50 years with comorbidities have a significant association with an increased risk of death. In a study with linear regression, the ACE2 gene in the nasal epithelium was higher in older patients than in adults. Patients over 50 years of age have high ACE2 levels which can lead to decreased immunity, decreased organ function or accompanied by pre-existing comorbidities that can increase the risk of death⁹. From our research data, it was found that the number of COVID-19 patients undergoing treatment in the ICU was more at the age of >50 years, in the age group <50 years with a survival outcome of 5 people (29.4%) while those aged >50 years were 12 people (70.6%). In the group with death outcomes with age < 50 years as many as 27 people (24.8%) while age > 50 years as many as 82 people (75.2%). However, the proportion who experienced living and non-living outcomes was not significantly different by age with $p = 0.765$. In the multivariate test, the risk of death outcome based on age was found with OR=1.858 (0.525-6.571) with $p = 0.336$. This shows that statistically age is not significantly associated and becomes a risk factor for mortality in the care of COVID-19 patients in the ICU. Men and women differ in immune response, in SARS-CoV-2 women have a high immune response that protects against disease severity. There is an increase in CD4 T cells, Toll-like

receptor 7 (TLR7) which is useful for recognizing RNA viruses, an increase in interferon- α which is associated with lung tissue protection. Estradiol has an important role in hormone stimulation and increases antibody production and increases ACE2 which is a receptor that protects against ARDS. Testosterone is known to be immunosuppressed and decreases testosterone production associated with an increase in proinflammatory cytokines. In this study, it was found that the gender variable was the number of COVID-19 patients undergoing treatment in the ICU which was more male. In the outer group living with women as many as 8 people (47.1%) while men as many as 9 people (52.9%). In the death outcome group, 47 people (43.1%) were women and 62 men (56.9%). However, the proportion who experienced life and death outcomes was not significantly different by sex with $p=0.761$. In the multivariate test, the risk of death based on gender was obtained with $OR = 1.637$ (0.499 -5.367) with $p = 0.416$. This shows that gender is statistically not significantly related and is a risk factor for non-living outcomes in the care of COVID-19 patients in the ICU.

The International Society of Thrombosis and Hemostasis (ISTH) guidelines regarding the identification and management of coagulopathy in COVID-19 patients state that D-Dimer levels can vary by three to four times higher than the initial D-Dimer on admission to the hospital. In a study in China by Zhang *et al* in 2020 on 343 COVID-19 patients undergoing hospital treatment and grouped with D-Dimer levels >2000 ng/ml as many as 67 people and <2000 ng/ml as many as 276 people. It was found that patients with D-Dimer >2000 ng/ml had more deaths.³ So that in our study we used a cut-off value of D-Dimer of >2000 ng/ml. In the study, 8 people (47.1%) had 8 patients with D-Dimer >2000 ng/ml compared to 9 people (52.9%). The proportion of patients who experienced death with D-Dimer <2000

ng/ml was 23 people (21.1%) compared to D-Dimer >2000 ng/ml as many as 86 people (78.9%). This indicates that in the living and dying group who underwent ICU treatment, the D-Dimer value >2000 ng/ml was higher than the D-Dimer value <2000 ng/ml significantly $p<0.05$. The multivariate analysis showed results that were in line with previous studies where the $OR = 3,679$ (95% $CI = 1,169-11,576$) for D-Dimer, which means that D-Dimer >2000 ng/ml has a 3.655 times greater risk of death in patients COVID-19 admitted to the ICU. Therefore, the identification and management of coagulopathy in COVID-19 patients at the time of hospital admission should be considered even if there are no severe symptoms because elevated D-Dimer levels determine the severity of the disease.³ Research on D-dimer levels when COVID-19 patients enter the ICU is needed for the management of coagulopathy, assessing the risk and survival of COVID-19 patients.

Based on the Indonesian Endocrine Association, diabetes mellitus is where $HbA1c > 6.5\%$ ¹⁰. In our study, it was found that the number of COVID-19 patients undergoing treatment in the ICU was more with $HbA1c <6.5\%$. In the living group with $HbA1c <6.5\%$ there were 11 people (64.7%) while $HbA1c > 6.5\%$ were 6 people (35.3%). In the death outcome group with $HbA1c <6.5\%$ there were 69 people (63.3%) while $HbA1c > 6.5\%$ were 40 people (36.7%). However, the proportion who experienced the outcome of living and non-living patients did not differ significantly based on DM with $p=0.911$. In the multivariate test, the risk of death based on diabetes was obtained with $OR = 1.121$ (0.337-3.734) with $p = 0.852$. This shows that DM is statistically not significantly associated and is a risk factor for non-living outcomes in the care of COVID-19 patients in the ICU. DM patients with COVID-19 who are treated in the ICU can be influenced by the routine treatment history of these patients and can

also be influenced by the patient's blood glucose level before being infected with COVID-19. death in patients with uncontrolled glucose levels prior to COVID-19 infection¹¹.

In the European Society of Cardiology (ESC) Guidelines, hypertension is recognized in patients with a systolic blood pressure ≥ 140 mmHg¹². In our study the number of COVID-19 patients undergoing treatment in the ICU was more with systolic BP <140 mmHg as many as 10 people (58.8%) while systolic BP ≥ 140 mmHg as many as 7 people (41.2%). In the death outcome group with systolic BP <140 mmHg as many as 75 people (68.8%) while systolic BP ≥ 140 mmHg as many as 34 people (31.2%). However, the proportion who experienced survival and non-death was not significantly different based on hypertension with $p=0.417$. In the multivariate test, the risk of survival based on hypertension was obtained with OR = 0.630 (0.183-2.169) with $p = 0.464$. This shows that hypertension is statistically not significantly associated and becomes a risk factor for death outcome in the care of COVID-19 patients in the ICU. COVID-19 patients with hypertension can also be influenced by their medical history before being infected with COVID-19. Patients with controlled blood pressure and previously taking statin drugs before infection were associated with a reduced risk of death in severe COVID-19 patients¹³.

In our study we applied the use of RALE scoring systems at Dr. Moewardi General Hospital either in the diagnostic and in the prognostic approach with specific population included in this study were ICU patient. This study has several limitations. The retrospective design limits the inclusion of all potential confounders. The sample size of this study was relatively small. The lack of a non-COVID-19 control group in the study of the prognostic score, thus limiting evaluation of

sensitivity and specificity of CXR. Further study regarding its efficacy on a larger scale and possibly more heterogeneous cases and should be performed in the hope of its implementation on multiple healthcare centre with X-ray devices and without CT scans.

CONCLUSION

Based on the findings in this study, the conclusion that can be drawn is that there is a relationship between changes in the RALE and D-Dimer scores with the death outcome of COVID-19 patients in the ICU room of RSUD Dr. Moewardi Surakarta. However, there is no relationship between age, sex, diabetes mellitus, and hypertension with mortality outcomes in COVID 19 patients in the ICU room at RSUD Dr. Moewardi Surakarta. This study has several limitations including not analyzing other factors that have the potential to cause bias. Future research is expected to carry out further research by analyzing other factors that have the potential to bias the results of the study, such as changes in D-Dimer values, sociodemographic factors, clinical conditions and medication history in research subjects.

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