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The relationship between neutrophil-lymphocyte ratio and quick sequential organ failure assessment on Covid-19 patients' mortality

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Abstract

***Introduction*: Coronavirus disease 19 (Covid-19) transmission could lead to varied symptoms, from mild, moderate, severe, and critical symptoms that require intensive care. The transmission can be predicted by the neutrophil-lymphocyte ratio (NLR) and the quick Sequential Organ Failure Assessment (qSOFA) value when the patient is admitted to the emergency department (ED) to anticipate the high mortality rate.**

***Methods*: This study was an observational analytic study with a retrospective cohort study to analyze the medical records of Covid-19 patients from July to December 2020 at the North Maluku Referral Hospital. NLR and qSOFA were calculated on admission to the ED.**

***Results*: The total of Covid-19 patients was 268 (245 were alive and 23 died). There was an increase in NLR in patients who died with a cut-off value of 12.42, a sensitivity of 82.6%, and a specificity of 89% (area under the receiver operating characteristic [ROC] curve [AUC] 0.894; p<0.001). There was also an increase in qSOFA with a cut-off of 2, sensitivity 73.9%, and specificity 85.3% (AUC 0.861; p<0.001). The mortality of patients with qSOFA ≥2 was 32.1%.**

***Conclusion*: There was a significant relation between NLR and qSOFA with mortality that happened in Covid-19 patients.**

Key words: Covid-19, mortality, NLR, qSOFA.

Introduction

In December 2019, coronavirus disease was spread in Wuhan, Hubei, China. It was known as coronavirus disease 19 (Covid-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). On March 11th, 2020, WHO confirmed Covid-19 as a global pandemic with many cases worldwide. On February 23th, 2021, total cases of Covid-19 in Indonesia were as much as 1,298,608, with recovered cases as much as 1,104,990, and total death of 35,014. (1)

North Maluku is one of the three other provinces in Indonesia that has the least health laboratory of the Ministry of Health. (2) In 2020 during the pandemic, the polymerase chain reaction (PCR) examinations cannot be performed in North Maluku Province, so the sample cases must be sent to other laboratories. The result came out after 24 hours. The total cases in North Maluku Province until the end of December 2020 were 3,878 confirmed cases, recovered cases were 3,111, and 110 deaths.

Among the confirmed cases, as many as 657 patients were hospitalized. (3) The disease transmission was rapid with varied kinds of symptoms. About 40% of cases were mild illnesses (cough, fever), 40% were moderate illnesses (bilateral pneumonia), 15% with severe symptoms, and the rest 5% were critical or severe illnesses with organ failure that needed the Intensive Care Unit

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(ICU) for the treatment. (4)
The mechanism of the severe symptom emersion in Covid-19 patients is still unclear. The weakened immune system was suspected of worsening the condition after the infection of SARS-CoV-2, giving more severe infection and even death. (5) Infection is initiated by an inflammatory reaction from the body. A severe inflammatory only reacts to a weak adaptive immune response, followed by an imbalanced immune response. Therefore, circulating biomarkers can represent inflammatory and immune status as potential predictors in the prognosis of Covid-19 patients. (6) As an inflammatory reaction indicator, the severe Covid-19 patients demonstrated a decrease in lymphocyte cells, an increase in neutrophils, and an increasing in neutrophil to lymphocyte ratio, known as the neutrophil-lymphocyte ratio (NLR). (7)
Another study on 131 patients of Covid-19 demonstrated a relationship between the increased NLR and mortality, in which the NLR threshold value of ≥3.3 was closely related to increased mortality. (8)
In 2001, the first study on NLR in Slovakia stated that NLR was considered a simple and quick parameter to determine the systemic inflammation and stress in severe illness patients in the ICU with normal values of 0.78-3.53. Increased NLR occurs in the first 24 hours at ICU due to the significant increase of neutrophils and a decrease in lymphocytes. The total white blood cell population change as the response of the immune system to surgical stress and systemic inflammation or sepsis. (9)
Sepsis is a life-threatening organ dysfunction caused by a disorder immune response to infection. These infections can be caused by bacteria, fungi, or, in Covid-19, caused by the SARS-CoV-2. (10) Organ dysfunction in sepsis was determined by the Sequential Organ Failure Assessment (SOFA) score. (11) Sepsis is mainly caused by bacterial infection, but pneumonia cases in Wuhan were caused by the virus (Covid-19), which was isolated from respiratory aspirates and already infected the lungs. (12) SARS-CoV-2 can cause sepsis due to the infection. Sepsis can be predicted by periodically evaluating the SOFA scores in the severe illness of Covid-19 patients in the ICU. It can estimate the potential organ failure and risk of death. (13)
The Third International Consensus for Sepsis has developed a simple clinical score to identify faster the patients who have the risk for sepsis, namely quick SOFA (qSOFA). The qSOFA score can be practically used in the emergency room (ER) or ward. The qSOFA criteria consist of respiratory rate ≥22/min, mental changes or impaired consciousness, and systolic blood pressure ≤100 mmHg. (11) qSOFA is a fast, simple, and reliable diagnostic way to determine patients at risk of infection in the emergency room. (14)
An observational cohort study of 760 patients compared the SOFA and qSOFA scores, which resulted in the prediction of patients' mortality in patients with severe sepsis and septic shock were more effective using the qSOFA rather than SOFA scores. (15)
Another study with 879 patients with suspected infection treated in the emergency department found that qSOFA predicted mortality in the hospitals (with the area under the receiver operating characteristic curve [AUC] 0.80) better than SIRS (AUC 0.65) and severe sepsis (AUC 0.65). (16)
NLR measurements are required to measure risk stratification, assess prognosis, and warn the early signs of severe Covid-19 symptoms. NLR measurement is a simple and easy blood test in daily clinical practice, cost-effective, and a helpful assessment and consideration for treating patients. (6) The qSOFA has been confirmed to be used as a simple clinical score to predict mortality in septic patients due to Covid-19 in both the emergency department and ICU. (16)

Materials and method

This study was analytic observational with a retrospective cohort study conducted on the medical record data of the Covid-19 patients. Those patients were treated at several Covid-19 referral hospitals in North Maluku Province from July to December 2020. The study was conducted for five months from January to May 2021, at several Covid-19 referral hospitals in North Maluku Province. They were:

1. Regional General Hospital Chasan Bosoirie Ternate, Ternate City
2. Regional General Hospital Jailolo, West Halmahera Region
3. Regional General Hospital Tidore, Tidore Island
4. Regional General Hospital Tobelo, North Halmahera Region
5. Regional General Hospital Labuha, South Halmahera Region

Sampling method

Sampling was conducted consecutively, and all the patients were eligible for the inclusion and exclusion terms as being the sample at the referral hospitals from July to December 2020. The inclusion criteria were age ≥18 years and <65 years, confirmed positive for Covid-19 PCR swab, treated in Covid-19 referral hospitals, and had routine hema-

tology laboratory data and complete resume of a medical record. Whereas the exclusion criteria were pregnant women and immunocompromised patients.

Tools and materials

Tools and materials used in this study included medical records of the Covid-19 patients, blood pressure (noninvasive blood pressure), awareness assessment sheet (Glasgow coma scale [GCS]/alert, verbally responsive, painfully responsive, or unresponsive scale [AVPU]), respiration, blood sample for a complete blood test, and data collection sheet.

Data collection

The medical records obtained in this study will be entered in a fundamental data collection sheet that contained identity, age, sex, and comorbidities. The NLR and qSOFA scores were measured based on laboratory test results and a resume of the patient when still in the emergency room. The final data collection was the last condition of the patients when discharged from the hospital (alive or deceased).

Data analysis

Data was collected through the Special Sheet of Collector and was analyzed using the SPSS version 22. The relation between NLR and qSOFA scores was tested using the Mann-Whitney U-test. Cut-off determination was analyzed using the receiver operating characteristic (ROC) curve with $p<0.05$.

Study protocol ethics

Informed consent from the patients was collected through the referral hospitals and the approval from the Biomedical Study Ethics Commission Faculty of Medicine Airlangga University was given under number 99/EC/KEPK/FKUA/2021.

Results

Study characteristics

Of 268 subjects (patients), there were 149 males and 119 females. Their age ranged from 19 to 63 years old. The lowest systolic blood pressure was 80 mmHg and the highest was 200 mmHg. The respiration rate was 18-60 per minute. A nasal cannula was set at 2-3 liters/minute for the lowest oxygen fraction and the highest one with a non-rebreathing mask set at 8-10 liters/minute (**Table 1**).

Among 268 subjects, 245 (91.4%) were alive and the rest 23 (8.6%) died. The group division method followed the surveillance of the Centers for Disease Control and Prevention, which divide the group into three age groups: 1) >18-29 years (37 patients, 13.8%), 2) 30-49 years (105 patients, 39.2%), and 3) 50-64 years (126 patients, 47%). Twenty-three patients who died were all aged ≥30 years: 9 patients (3.4%) aged 30-49 years and 14 patients (5.2%) aged 50-64 years (**Table 2**).

Identification of the NLR, qSOFA scores, and mortality of Covid-19 patients at the North Maluku Referral Hospitals

The lowest NLR obtained from the emergency room at the time the patients arrived was 0.98, meanwhile, the highest one was 32.79 (the average was 8.17). The qSOFA evaluation, which consisted of systolic blood pressure, breathing, and mental state, indicated that 50 patients (18.7%) had a systolic blood pressure drop ≤100 mmHg, 173 patients (64.6%) had increased respiration ≥22 per minute, and 22 patients (8.2%) had a mental state disorder (**Table 3**).

Analysis of the relation between the NLR and mortality in Covid-19 patients

Patients who died had an increased NLR with a median value of 15.72, while patients who were alive had an NLR value with a median value of 6.46 (**Table 4**).

Since the subjects were not normally distributed, the Mann-Whitney test was applied. The result demonstrated a significant value of the NLR between the deceased and living patients ($p<0.05$), or had a significant relationship between the NLR and mortality.

Analysis of the relationship between qSOFA scores and mortality in Covid-19 patients

The study demonstrated that the dead patient (23 people) had an increased qSOFA score with a maximum score of 3, which means that all three qSOFA parameters met the condition. Of 23 dead patients, 17 patients had a qSOFA score ≥2, and the rest 6 patients had a qSOFA score <2 (**Table 5**).

The Mann-Whitney test resulted in there was a significant qSOFA score between the dead and living patients ($p<0.05$), or a significant qSOFA score with the mortality.

The cut-off value of NLR in predicting mortality of Covid-19 patients

The NLR ROC value in predicting mortality obtained an AUC value of 0.894 ($p<0.001$) and a cut-off value of 12.42 (**Table 6**).

Cut-off value in predicting mortality of the Covid-19 patients

The ROC curve of qSOFA score in predicting

mortality obtained an AUC value of 0.861 ($p<0.001$) and a cut-off value of ≥1.5. The cut-off value was rounded to 2 because it was impossible to have a 0.5 score (**Table 7**).

Discussion

Characteristics of study subjects

This study had an observational analytical study with a retrospective cohort study analyzing medical record data from July to December 2020 at five Covid-19 referral hospitals in North Maluku Province. From the 268 subjects (149 men [55.6%] and 119 women [44.4%]) (**Table 2**), this study revealed that men were more vulnerable to getting infected with Covid-19 than women. Men also likely get more serious symptoms that required being taken to the hospital. The high prevalence of Covid-19 in men was possibly related to smoking habits, alcohol consumption, and most men doing outdoor activities (work) more often than women which allows the disease. (17)

Innate immunity is related to sex chromosomes that differentiate the response to inflammation and susceptibility to disease between males and females. For example, X chromosomes encode several genes that regulate the immune system. It demonstrated the low levels of the incoming virus in the female body. Toll-like receptor 7 (TLR7) is a cell surface receptor that is likely more abundant in women than men. This receptor can increase the immune response even in Covid-19. In contrast, angiotensin-converting enzyme 2 (ACE2) receptors are more concentrated in men, making them more vulnerable to SARS-CoV-2 infection. Smoking habits worsen the condition because it suppresses the body's immune response to viruses (an antiviral mechanism) and disturb the role of cytokines in innate immunity in the respiratory tract mucosa, making it easier for viral replication and disease to worsen. (18)

Table 2 presents a total of 23 patients who died and all of them were ≥30 years (9 patients [39%] were in the group of 30-49 years and 14 patients [61%] were in the group of 50-64 years). According to the Centers for Disease Control and Prevention (CDC), the mortality rate of Covid-19 patients is doubled in a group of 30-49 years and quadrupled in the group of 50-64 years. The mortality rate increased to 4-10 times in a group of 30-49 years and 30 times in a group of 50-64 years. (17,19)

Having comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, chronic heart disease, chronic obstructive pulmonary disease, cerebrovascular disease, and chronic liver disease can worsen the outcome impact of Covid-19. The complications that occurred are shock, acute kidney injury (AKI), and acute respiratory distress syndrome (ARDS). (18) Chronic pulmonary disease will block the airflow and possibly increase the risk of respiratory complications such as ARDS. On the other hand, hypoxaemic conditions in Covid-19 patients can injure the cardiac myocytes and trigger apoptosis, so patients with coronary heart disease potentially fall into a severe condition that leads to higher mortality. Prolonged hypertension also can damage the vascular structures, so it is vulnerable to get serious infections. Diabetes mellitus also weaken the immune system by triggering the dysfunction of pro-inflammatory cytokines. (18)

The comorbidities found in the subjects of this study were diabetes mellitus, hypertension, chronic kidney disease (CKD), bronchitis, and pulmonary tuberculosis (**Table 2**). Meanwhile, the complications that occurred after the Covid-19 infection were pneumonia, ARDS, sepsis, and AKI. Moreover, there was a patient that had comorbidities at the same time. Patients with comorbid hypertension, diabetes mellitus, and CKD were treated pharmacologically by the internist and could be well controlled. Therefore, as much as possible minimized the confounding factors. **Table 2** shows that 11 patients died due to complications of pulmonary (pneumonia, bronchopneumonia, ARDS, sepsis), four patients due to kidney problems (CKD and AKI), five patients due to hypertension, and three patients due to diabetes mellitus. This study did not specifically analyze the predisposing comorbidities but demonstrated that pulmonary infection was the main reason which caused the Covid-19 patients to die at referral hospitals in North Maluku.

Oxygenation parameters were obtained from the assessment of peripheral oxygen saturation (SpO2) divided by the fraction of inspired oxygen (FiO2). Another previous study reported that the arterial oxygen pressure (PaO2) and the FiO2 ratio of 300 was equal to the SpO2/FiO2 ratio of 315, and the PaO2/FiO2 ratio of 200 was equal to the SpO2/FiO2 ratio of 235. (20) According to this ratio, from the total of 268 patients, 21 patients had a SpO2/FiO2 ratio of ≤235 (moderate to severe symptoms), and 247 patients had a SpO2/FiO2 ratio of >235 (mild to moderate symptoms). Of 21 patients that met the criteria of moderate to severe ARDS with a SpO2/FiO2 ratio of ≤235, four patients were alive, and the rest 17 patients died (**Table 2**).

A retrospective observational study in Japan on Covid-19 patients divided the group into 2 groups based on SpO2/FiO2 ratio ≤235 (moderate-severe symptoms) and SpO2/FiO2 ratio >235 (normal-mild symptoms). The SpO2/FiO2 ratio examination

when patients were admitted to the ER can help clinicians to identify severe Covid-19 symptoms and can determine early treatment interventions. (21)
Another study in Korea on 59 patients with Covid-19 pneumonia even got a cut-off value of SpO2/FiO2 >179 for living patients (100% survival rate, p<0.001), while SpO2/FiO2 ≤179 obtained 5 patients (31.3%) alive and 11 patients (68.8%) died. If uses a cut-off value of SpO2/FiO2 315, regression analysis will show a significant effect on mortality. (22)
However, the SpO2/FiO2 ratio parameter has several weaknesses that the measurement accuracy is influenced by tissue hypoperfusion conditions, hemoglobin levels, severe anemia, and the use of vasopressors. (23)

Relationship between the NLR and mortality of Covid-19 patients

Infection is always indicated by an inflammation in the beginning, so as Covid-19. The more intense the inflammatory process the more adaptive the immune response will weaken as well as the imbalance of the immune response. It will be detected in the biomarkers examined in the blood of Covid-19 patients. In February 2020, a study in China compared several hematological parameters, namely NLR, lymphocyte monocyte ratio (LMR), platelet lymphocyte ratio (PLR), and C-reactive protein in 93 Covid-19 patients, and found that NLR was an independent factor to predict the worsening Covid-19 patients with a cut-off value of ≥3.3, specificity 63.6%, and sensitivity 88%. (24)
Another study that compared the hematological predictors of mortality in hospitalized Covid-19 patients demonstrated that from 225 patients, 21.4% had neutrophilia and 52.7% had lymphopenia. Therefore, an increase in NLR was significantly associated with mortality (p<0.001) and critical care in the ICU. (25) It supports the theory that neutrophil is the first cell to respond to inflammation and also innate immunity, while lymphocyte plays a role in adaptive immunity. (26)
This study was conducted on 268 patients treated at 5 Covid-19 referral hospitals in North Maluku Province from July to December 2020. The finding was similar to several previous studies in various countries. There was a significant increase in the NLR value of Covid-19 patients, which a higher value of NLR in Covid-19 obtained from patients who died than those who lived. NLR value in dead patients had a median value of 15.72, while patients who lived had a median of 6.46. The results of the NLR ROC in predicting mortality obtained an AUC value of 0.894 (p<0.001) with a cut-off value of ≥12.42.
Many studies consist of the systematic review of meta-analysis that focused on NLR predictive value on severity and mortality of the Covid-19 patients. There were 13 studies involving 1579 patients which determined the predictive value in NLR and demonstrated that NLR had 78% specificity (95% CI 0.73-0.83) and a sensitivity of 78% (95% CI 0.70-0.84) to the severity of Covid-19. Other 10 studies involving 2967 patients to determine the predictive value of NLR on mortality in Covid-19 patients demonstrated that the specificity was 83% (95% CI 0.74-0.89), sensitivity 83% (95% CI 0.75-0.89), and the cut-off value of NLR≥6.5. (27)
This study had a significant difference in the NLR cut-off value compared to previous studies. Yang AP et al. (2020) and Wang X. et al. (2020) had the same NLR cut-off values of ≥3.3, meanwhile, Li X. et al. (2020) found the cut-off value of NLR ≥6.5; while in our study the cut-off value was ≥12.42. In Yang AP's study (2020), the authors excluded the subjects (patients) who had chronic obstructive pulmonary disease, while Wang X. (2020) specialized in subjects aged 56-71 years with various comorbidities. These specific criteria of sample causing the study of Li X. (2020) had a high cut-off value due to including all subjects from various age groups with various comorbidities and resulted much higher than Yang AP and Wang X.
The individual immune response is varied. The high increase in NLR in this study was most likely due to hyperinflammation where neutrophils increased in response to the SARS-CoV-2 antigen. The neutrophil activity persisted in the circulation for a long period, while lymphocytes had a significant downward due to excessive activation against viral infections as good defense cells in the blood as well as in the lymph node tissue. (23) According to the statistical results obtained, there was a relationship between NLR and mortality of Covid-19 patients with a cut-off value of ≥12.42, a sensitivity of 82.6%, and a specificity of 89% with a positive predictive value of 41.3% (**Table 8**).
A study in Banda Aceh, Indonesia, about NLR and the severity of Covid-19 in patients who had just been hospitalized demonstrated that the NLR value in severe cases was 4.63-8.50; while the patient who died had an NLR value of 7-15.17. Patients with high NLR had severe clinical visible Covid-19 symptoms such as cough, breathing difficulty, fever, pneumonia, and low oxygen saturation (<93%), so the subjects needed respiratory support in the ICU. (28) The previous study reports are similar to this study in those patients with high NLR demonstrated symptoms of pneumonia followed by complications of sepsis and used ventilators in the ICU.

This is not impossible that the patients had a "cytokine storm" or a bacterial infection along with a viral infection.

Relationship between the qSOFA and mortality in Coivd-19 patients

qSOFA score has been used to predict mortality in septic patients and septic shock in the emergency room. It used a more simple parameter in measuring the value, such as respiration, systolic blood pressure, and mental state, compared to the SOFA score which needs the laboratory assessment to also take more time. Study in developed countries along with the limited facility and time, the qSOFA score is effective to predict mortality in septic patients at tertiary hospitals.

A study about the qSOFA utilization on 236 septic patients in Korea obtained qSOFA scores of ≥2 at the beginning of the treatment in the ER. This value is very useful in predicting the disease severity. The medical tools used for 72 hours in early treatment could predict the mortality in 28 days for patients with bacteremia. (29) The analysis of qSOFA score in pneumonia patients has been performed often in various studies. Many studies compared the efficacy and accuracy of qSOFA and SOFA scores. It also demonstrated that the qSOFA score can be used to evaluate pneumonia severity. The severity analysis is also even recommended to simultaneously combine both scores and get the qSOFA cut-off value of ≥2 as the mortality prognostic factor in 30 days. (30)

From those various study reports, whether qSOFA could be applied in the analysis of Covid-19 patients is still unclear. Javed et al. discussed the qSOFA correlation to Covid-19 patient severity at a tertiary hospital in Lahore and assessed the outcome. (31) The analysis was about the probability of patient mortality when they were hospitalized. The result demonstrated that there were a significant correlation between the qSOFA when hospitalized and the severity, which 60% of patients who died in the hospital having a qSOFA value of ≥2, and patients with qSOFA=3 had the outcome of 100% died.

The report above is similar to this retrospective study. It found that qSOFA could be used and demonstrated a significant relationship between qSOFA scores and mortality in Covid-19 patients ($p<0.05$), with the cut-off value of qSOFA ≥2 (17 [73.9%] of 23 patients who died had a qSOFA score ≥2).

This study demonstrated that qSOFA ≥2 had a 32.1% patient mortality compared to the study of Freud et al., (32) which found a 24% mortality with qSOFA >2. Sociocultural differences and limited medical facilities can affect patient mortality. So, in this case, qSOFA provides a simple and fast solution in providing an assessment of septic patients. (33)

Liu S. et al. (2020) in China reported that SOFA and qSOFA could predict the mortality of Covid-19 patients in hospitals. As many as 140 critical illnesses of Covid-19 patients were calculated in the SOFA and qSOFA scores when first entered the ER. The result demonstrated that SOFA was more effective on sensitive markers than qSOFA. qSOFA can be used because it is simple, rapid, and has acceptable accuracy even though it is inferior compared to SOFA. qSOFA can be used in the ER if SOFA parameters are not worked out. A multicenter retrospective cohort study observed the severity scores in Covid-19 with pneumonia patients by comparing PSI, CURB-65, qSOFA, and MuLBSTA assessed at hospital admission and predicted the outcome whether they died during the treatment, when enlisted to the ICU, or when used a ventilator. The previous study involved 10,238 subjects and found that qSOFA had the most specific score (specificity 95.7%), simple to perform, but only 26.2% sensitivity. (34)

According to the statistical results, our study confirmed a relationship between the qSOFA and mortality of Covid-19 patients with a cut-off value of ≥2, a sensitivity of 73.9%, and a specificity of 85.3%, with a positive predictive value of 32.1%.

Conclusion

This study confirms that the NLR and qSOFA could be used as a rapid and simple parameter for early identification and mortality prediction of Covid-19 patients in the ER at a region or referral hospital, which has a minimum laboratory facility. This study revealed that the cut-off value for NLR and qSOFA were ≥12.42 and ≥2, respectively.

Table 1. Characteristics of the study subject

	n	Median (min-max)
Age (years)	268	48 (19-63)
Body weight (kg)	268	62.5 (45-85)
Systolic blood pressure	268	120 (80-200)
Diastolic blood pressure	268	79.5 (35-120)
SpO2	268	96 (31-100)
FiO2	268	24.5 (21-80)
SpO2/FiO2 ratio	268	353.57 (81.25-476.19)
RR	268	22 (18-60)

Legend: SpO2=peripheral oxygen saturation; FiO2=fraction of inspired oxygen; RR=respiratory rate.

Table 2. Sex, age group, and outputs

No	Characteristic	n (%)	Dead, n (%)
1	Sex		
	- Male	149 (55.6)	11 (4.1)
	- Female	119 (44.4)	12 (4.5)
2	Age		
	- >18-29 years	37 (13.8)	0
	- 30-49 years	105 (39.2)	9 (3.4)
	- 50-64 years	126 (47)	14 (5.2)
3	Outcome		
	- Alive	245 (91.4)	
	- Dead	23 (8.6)	23 (8.6)
4	Comorbidities		
	- Diabetes mellitus	29 (10.8)	3 (1.1)
	- Hypertension	19 (7.1)	5 (1.8)
	- Pulmonary tuberculosis	10 (3.7)	2 (0.7)
	- Chronic obstructive pulmonary disease	8 (3.0)	0
	- Chronic kidney disease	10 (3.7)	4 (1.5)
	- Congestive heart failure	9 (3.4)	1 (0.3)
5	Complications		
	- Pneumonia/bronchopneumonia	88 (32.8)	4 (1.5)
	- Sepsis	5 (1.8)	4 (1.5)
	- Acute respiratory distress syndrome	5 (1.8)	3 (1.1)
	- Acute kidney injury/chronic kidney disease	15 (5.6)	4 (1.5)
6	SpO2/FiO2 rasio		
	- ≥235	247 (92.2)	6 (2.2)
	- <235	21 (7.8)	17 (6.3)

Legend: SpO2=peripheral oxygen saturation; FiO2=fraction of inspired oxygen.

Table 3. NLR, qSOFA score, and mortality of Covid-19 patients at the North Maluku Referral Hospitals

Study variables	n	Average±SD	Median (min-max)
NLR	268	8.17±5.932	7.15 (0.98-32.79)
Systolic ≤100 mmHg, n (%) - Yes - No	 50 (18.7%) 218 (81.3%)		
RR ≥22/min, n (%) - Yes - No	 173 (64.6%) 95 (35.4%)		
Mental state, n (%) - Disturbed - Not disturbed	 22 (8.2%) 246 (91.8%)		
qSOFA score, n (%) - 0 - 1 - 2 - 3	 88 (32.8%) 127 (47.4%) 40 (14.9%) 13 (4.9%)	0.92±0.817	1 (0-3)
Mortality, n (%) - Dead - Alive	 23 (8.6%) 245 (91.4%)		

Legend: NLR=neutrophil-lymphocyte ratio; qSOFA=quick Sequential Organ Failure Assessment; Covid-19=coronavirus disease 19; RR=respiratory rate; SD=standard deviation.

Table 4. The differences between the NLR in patients who died and alive

Patient life	n	Median (min-max)	p
- Dead - Alive	23 245	15.72 (4.17-32.79) 6.46 (0.98-30.44)	<0.001

Legend: NLR=neutrophil-lymphocyte ratio.

Table 5. The differences between the qSOFA scores in patients who died and alive

Patient life	n	Median (min-max)	p
- Dead - Alive	23 245	3 (0-3) 1 (0-3)	<0.001

Legend: qSOFA=quick Sequential Organ Failure Assessment.

Table 6. NLR cut-off value in predicting mortality in the Covid-19 patients

NLR	Mortality	
	Dead, n (%)	Alive, n (%)
≥12.42	19 (41.3%)	27 (58.7%)
<12.42	4 (1.8%)	218 (98.2%)

Legend: NLR=neutrophil-lymphocyte ratio; Covid-19=coronavirus disease 19.

Table 7. qSOFA score cut-off value in predicting mortality

qSOFA score	Mortality	
	Dead, n (%)	Alive, n (%)
≥2	17 (32.1%)	36 (67.9%)
<2	6 (2.8%)	209 (97.2%)

Legend: qSOFA=quick Sequential Organ Failure Assessment.

Table 8. Sensitivity, specificity, PPV, NPV, and variable accuracy of the NLR and qSOFA

Variable	Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR	≥12.42	82.6%	89%	41.3%	98.2%	88.4%
qSOFA	≥2	73.9%	85.3%	32%	97.2%	84.3%

Legend: PPV=positive predictive value; NPV=negative predictive value; NLR=neutrophil-lymphocyte ratio; qSOFA=quick Sequential Organ Failure Assessment.

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