ISSN: 1607-8322, e-ISSN: 2220-5799 **Anaesthesia, Pain & Intensive Care**

Vol 26(5); October 2022 DOI: 10.35975/apic.v26i5.2032

ORIGINAL RESEARCH **INTENSIVE CARE**

Clinical relevance of IL-6 and lactate levels within 24 hours of ICU admission of COVID–19 patients in predicting mortality rate

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Abstract

Background & objective: Patients with COVID-19 have Acute Respiratory Distress Syndrome (ARDS) which progresses to lung edema and disorders of the liver, kidneys and heart associated with cytokine storms, which are the body's immune response to SARS-CoV-2. SARS-CoV-2 patients showed clinical neutrophilia, increased D-Dimer and increased IL-6. In addition, increased lactate dehydrogenase and increased aminotransferase are often found. This study aimed to analyze the clinical relevance of increased IL-6 and lactate in the first 24 hours of ICU-admission of COVID-19 patients in predicting mortality rate.

Methodology: This study was a retrospective cohort design. The study was conducted in the Intensive Care Unit (ICU) of Dr. Moewardi Surakarta Hospital. The study was conducted by tracing the medical records of COVID-19 patients treated in the ICU of Dr. Moewardi Surakarta Hospital during the period of March 1, 2020 to March 31, 2021 that met the admission criteria. The patient's mortality assessment is seen as the patient's condition for a maximum of 30 days after discharge from the hospital.

Results: Variables that meet the regression model are the lactate levels (OR = 3,143; P = 0.064) as well as the IL-6 levels (OR = 25.41; p<0.001). AUC score of 86.9% with significance of < 0.001. IL-6 levels and lactate levels in the study can be used as predictors of mortality rates with 95.7% sensitivity and 60% specificity. Lactate levels in COVID-19 cases in severe cases can be related to lung damage and tissue damage. Lactate levels have also been recognized as a marker of poor prognosis in patients with COVID-19. IL-6 as a predictor of mortality risk has been recognized and the administration of IL-6 inhibitors in COVID-19 patients may lower the risk of mortality.

Conclusion: Raised IL-6 and lactate levels in this study can be a predictor of the mortality rate of COVID-19 patients within 24 hours of ICU-admission.

Key words: IL-6; Lactate; ICU; COVID-19; SARS-CoV-2

Citation: Nugroho A, Hapsari PP, Santoso SB, Permana SA, Sitompul H. Clinical relevance of IL-6 and lactate within 24 hours of ICU-admission of COVID 19 patient in predicting mortality rate. Anaesth. pain intensive care 2022;26(5):689−694.

DOI: 10.35975/apic.v26i5.2032

1. Introduction

WHO declared the COVID 2019 outbreak a global pandemic on March 11, 2020. As of March 21, 2020 there were 234,074 confirmed cases, with 9,840 deaths in 177 countries.[1] Clinical symptoms of SARS-CoV-2 are very widespread, ranging from asymptomatic, mild upper airway infection, fever, dry cough, shortness of breath, up to severe pneumonia with respiratory failure even death.[2] These symptoms resemble those of other coronaviruses, severe acute respiratory syndrome (SARS) and middle east respiratory syndrome (MERS). Patients with COVID-19 have Acute Respiratory Distress Syndrome (ARDS) which progresses to lung edema and disorders of the liver, kidneys and heart associated with cytokine storms, which are the body's immune response to SARS-Cov-2.[3,4] SARS-CoV-2 patients showed clinical neutrophilia, increased D-Dimer and increased IL-6. In laboratory examinations of COVID-19 patients obtained nonspecific results, but an increase in lactate dehydrogenase and increase in aminotransferase are often found.[5,6]

IL-6 is a cytokine with pleiotropic activity that participates in defense against acute environmental stress, such as infection and tissue injury, by activating acute phase reactions, immune responses, and hematopoiesis. IL-6 is released not only by immune-mediated cells, but also vascular endothelial cells (VE), mesenchymal cells, fibroblasts and many other cells in response to various stimuli including receptor ligands such as Toll (TLR) and proinflammatory cytokines such as IL-1 or TNF-α.[7–9]

Lactic acid or lactate is the product of metabolic processes. Lactate is produced daily as much as approximately 1400 mmol/L. From glucose all tissues can produce lactic acid and pyruvate acid. Hyperlactatemia is the body's physiological response to a state of heavy activity but increased lactate levels at rest is a serious problem found in patients. Assessment of lactate levels is performed in patients with shock who experience hemodynamic disorders, sepsis, postoperative, brain injury, asthma, liver failure, poisoning, and acute lung injury. Thus, the increase in mortality rate is determined by high lactate levels at the initial examination. Hyperlactatemia associated with a decrease in blood pH will lead to a state of lactic acidosis.[8–11]

The state of metabolic acidosis with lactate levels ≥5 mmol/L and arterial pH of 2 mmol/L is called lactic acidosis. Lactic acidosis usually has a high mortality rate in critical patients, at concentrations > 8 mmol/L predicting death. Mortality reports reached 83% in patients with lactate levels > 10 mmol/L. Prognosis depended on the basic disease, lactic acidosis as an indicator of the severity of the shock state, and its response to therapy.[8,10,11]

Based from literature above, this study aimed to analyze the clinical relevance of increased IL-6 and lactate in the first 24 h of ICU-admission of COVID-19 patients in predicting mortality rates.

2. Methodology

This study was a retrospective cohort design. This research design was chosen because it is the most suitable design for assessing an exterior of a particular clinical situation. The study was conducted in the Intensive Care Unit (ICU) of Dr. Moewardi Surakarta Hospital. The study lasted for one year, starting from March 2020 to March 2021.

The sample of this study consisted of confirmed COVID-19 patients who were treated at the ICU of Dr. Moewardi Surakarta Hospital, meeting the criteria for the selection of research subjects. The study material was deducted from the medical records of COVID-19 patients treated in the ICU during the study period who met the admission criteria.

Lactic acid and interleukine-6 (IL–6) levels were checked at the clinical pathology laboratory. 3 mL of the patient's venous blood was collected. Blood was injected into a purple-covered tube containing EDTA. Lactic acid and IL–6 levels were checked using chemo colorimetric methods. Lactic acid levels were expressed in mEq/L or mmol/L; and IL–6 levels were expressed in pg/mL.

The patient's mortality assessment was seen as the patient's condition for a maximum of 30 days after discharge from the hospital.

Statistical Analysis

Data analysis was done using IBM-SPSS computer program version 25.0. Bivariate analysis was performed using the chi-square test for nominal variables and using the unpaired t test for numerical variables. All bivariate analysis variables that had a value of $p < 0.25$ were included in the multivariate analysis with logistic regression analysis. The final result of the logistic regression is presented in the form of odds ratio (OR) and confidence interval (CI) of 95%.

4. Results

In Table 1, data on the characteristics of the research subject is obtained. There was no significant average age difference (P = 0.406) between survived and deceased patients, with the mean age in survived group was 56.09 ± 2.63 y and the mean age in deceased group was 53.36 ± 5.65 y . There was a significant mean difference in the length of stay (LoS) (P = 0.039) between survived and deceased patients with the mean of LoS in survived group was 9.6 ± 2.59 days and mean of LoS in deceased group was 6.81 ± 0.99 days. In addition, there is also levels a significant mean difference (P < 0.001) in lactate

Table 1: Characteristics of the Subjects

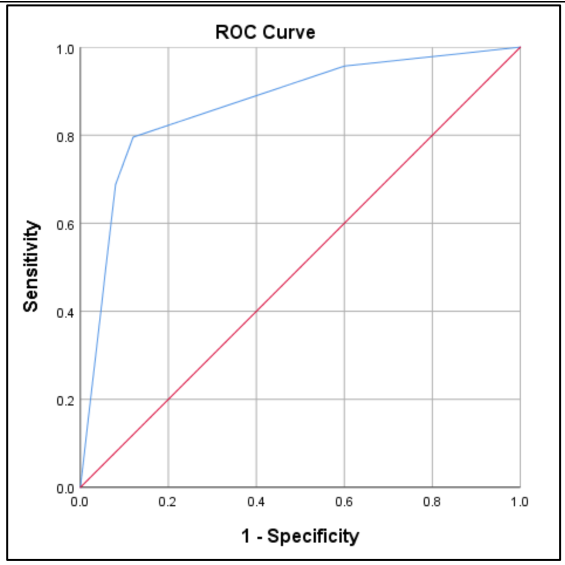
Variable	Survived	Deceased	P-value*
Age (y)	56.09 ± 2.63	53.36 ± 5.65	0.406
LoS (days)	9.6 ± 2.59	6.81 ± 0.99	**0.039***
Lactate (mmol/L)	2.37 ± 0.54	3.45 ± 0.294	**< 0.001***
IL-6 (pg/mL)	50.32 ± 14.47	161.29 ± 25.66	**< 0.001***

*Data presented as mean ± SD; * Significant difference*

Table 2: Demographic data of subjects (n = 118)

Variable	Frequency (n)	Frequency (%)
Age		
< 50 y	29	24.6%
≥ 50 y	89	75.4%
Sex		
Man	70	59.3%
Woman	48	40.7%
LoS (		
< 7 days	63	53.4%
≥ 7 days	55	40.7%
Lactate		
< 2 mmol/L	25	21.2%
≥ 2 mmol/L	93	78.8%
IL-6 (		
< 80 pg/mL	41	34.7%
≥ 80 pg/mL	77	65.3%
Status		
Survived	25	21.2%
Deceased	93	78.8%

Figure 1: ROC Curve Analysis



levels and IL-6 levels with the mean of lactate level in survived group was 2.37 ± 0.54 mmol/L and the mean of lactate level in deceased group was 3.45 ± 0.294 mmol/L. Meanwhile, the mean of IL-6 levels in survived group was 50.32 ± 14.47 pg/mL and the mean of IL-6 levels in deceased group was 161.29 ± 25.66 pg/mL.

Table 2 shows the demographic data of subjects. We divided categories based on previous studies. In epidemiological study of Lian et al.[12] at China on 465 hospitalized COVID-19 cases, we divided age into several groups, with the highest frequency being found at <50 y of age and 50 y of age. The grouping of IL-6 levels was based on a meta-analysis study by Aziz et al.[13] with the recommendation that an IL-6 levels cut-off value of > 80 pg/mL can be used to identify patients at high risk of death. The classification of length of stay

was based on a systematic review study by Rees et al.[14] who reported that length of stay < 7 days in patients outside China was associated with a high mortality rate. A total of 89 (75.4%) patients aged 50 y , 70 (59.3%) patients were male, 63 (53.4%) patients were treated for < 7 days, as many as 25 (21.2%) patients having lactate levels < 2 mmol/L, 41 (34.7%) patients had IL-6 levels < 80 pg/m, and the mortality rate was 78.8%.

Table 3: Bivariate analysis

Variable	Survived	Deceased	OR	P-value
Age				
< 50 y	8 (32%)	21 (22.6%)	1.613	0.235
≥ 50 y	17 (68%)	72 (77.4%)		
Sex				
Man	15 (60%)	55 (59.1%)	0.965	0.563
Woman	10 (40%)	38 (40.9%)		
LoS				
< 7 days	11 (44%)	52 (55.9%)	1.614	0.202
≥ 7 days	14 (56%)	41 (44.1%)		
Lactate				
< 2 mmol/L	11 (44%)	14 (15.1%)	4.434	0.003*
≥ 2 mmol/L	14 (56%)	79 (84.9%)		
IL-6				
< 80 pg/mL	22 (88%)	19 (20.4%)	28.561	< 0.001
≥ 80 pg/mL	3 (12%)	74 (79.6%)		

The results of the bivariate analysis (table 3) showed that age, sex, and length of stay did not have a significant relationship to the mortality rate (consecutive P-values: 0.235; 0.563; 0.202). It was found that lactate levels had a significant relationship (P = 0.003) to the mortality rate with an odds ratio (OR) of 4.434. There was a significant relationship of IL-6 levels (P < 0.001) to the mortality rate with an OR of 28,561. Then, we continued the bivariate analysis into a multivariate analysis.

To perform multivariate analysis, we included variables that had a P < 0.25 in the bivariate analysis. Multivariate analysis was performed using the backwards LR logistic regression test.

Table 4: Multivariate analysis

Variable	S.E.	Wald	Df	P-value	OR	CI 95%	
						Min	Max
Lactate (> 2 mmol/L)	1.145	.619	3.426	1	.064	3.143	.935
IL-6 (> 80 pg/mL)	3.235	.675	22.949	1	.000	25.41	6.764
Constant	-.920	.541	2.893	1	.089	.398	

The results of multivariate analysis (Table 4) obtained regression models to mortality variables. Length of stay falls in the first step due to its insignificant effect (OR = 1,224; P = 0.725).

The age variable falls in the second step due to its insignificant effect (OR = 1,667; P = 0.424). Variables that meet the regression model were the lactate levels (OR = 3,143; P = 0.064) as well as IL-6 levels (OR = 25.41; P < 0.001).

After conducting a logistic regression test of backwards LR and found two variables that could be predictors, we continued the analysis with the ROC curve (Figure 1) to assess the validity, sensitivity, and specificity of those variables as predictors. The curve analysis was followed by an area under the curve (AUC) analysis to assess the area, sensitivity, and specificity of the variables used as predictors.

Table 5: Results of AUC analysis

Variable	S.E.
Sensitivity	95.7%
Specificity	60%
AUC (range)	86.9% (78.9%–95%)
P-value	**< 0.001**

In Table 5, the AUC score was 86.9% with p-value <0.001. Lactate levels and IL-6 levels in this study can be used as predictors of mortality rates with a sensitivity of 95.7% and a specificity of 60%.

5. Discussion

In this study, most of the subjects (75.4%) were aged 50 y and over, with the mean age of the survived group was 56.09 ± 2.63 y and deceased group was 53.36 ± 5.65 y . In this study, there was no significant relationship between age and mortality (P = 0.235). This result was inconsistent with previous studies which showed the mortality rate in patients aged < 50 y was < 1.1% which then increased exponentially at the age of 50 y and over with a peak mortality rate at the age > 80 y .[15] In addition, Borghesi et al.[16] showed that men aged 50 y and over and women aged 80 y and over had the highest risk of lung damage.

This inconsistency may occur because the subjects in our study had mean age that was still close to 50 y . In addition, the subjects in our study were all population of Indonesia, which is a low- and middle-income country. This is supported by the study of Demombynes[17] where mortality rates by age appear flatter in low-and middle-income countries.

This study has more male subjects than female, with the percentage of male and female subjects being 59.3% and 40.7%, respectively. This study showed that there was no significant relationship between sex and mortality rates. These results are also inconsistent with previous studies, Biswas et al.[18] showed that male had a higher risk of mortality than women with a risk ratio (RR) of 1.86. Similar results were also obtained in the research of Pradhan & Olsson[19] where it was clear that male had a higher mortality rate than female.

Until now, the exact cause behind the high mortality rate of male patients has not been found when compared to female patients. This may be due to the delayed viral clearance observed in male patients with COVID-19.[20,21]

The length of stay was also observed in this study. The mean length of stay in this study for patients who survived and deceased, respectively, was 9.6 ± 2.59 days and 6.81 ± 0.99 days. Here it can be seen that there is a significant difference between patients who survived and patients who deceased (P = 0.039). These results are consistent with the study of Rees et al.[14] where the LoS of patients who deceased was generally shorter than that of patients who survived. Furthermore, this study classified the length of treatment into two groups, LoS <7 days and ≥7 days. Unlike before, after being grouped into two groups, the variable LoS did not have a significant relationship to the mortality rate.

This study also observed the relationship between lactate levels and IL-6 levels on mortality rates. Both showed a significant relationship to the mortality rate. In this study, increased lactate levels increased the risk of mortality 4.4 times. These results are consistent with previous studies where high lactate levels in COVID-19 patients increased the risk of mortality by 16 times.22 Severe infection can cause cytokine-mediated tissue damage and lactate release. Because lactate is present in lung tissue (isozyme 3), patients with severe COVID-19 infection can release large amounts of lactate into the circulation.22 This is because, in severe interstitial pneumonia, it often progresses to ARDS. In addition, lactate levels are elevated in thrombotic microangiopathy, which is associated with renal failure and myocardial injury.[22,23] In addition, lactate levels in severe cases of COVID-19 may be associated with lung damage and tissue damage. Lactate levels have also been recognized as a marker of poor prognosis in patients with COVID-19.[24]

In this study, IL-6 levels had a significant relationship and increased the risk of mortality by 28.6 times. This was consistent with previous studies.[25–27] Furthermore, we also examined the AUC score on IL-6 levels and obtained a score of 86.9% with a significance of < 0.001. IL-6 levels in this study can be a predictor of mortality rates with a sensitivity of 95.7% and a specificity of 60%. These results are consistent with the study of Gu et al.[25] where the AUC score on IL-6 levels was 90% with a sensitivity and specificity of 95% and 75.68%, respectively. Consistent results were also shown by the study of Laguna-Goya et al.[26] where the AUC score of IL-6 levels was 74% with a specificity of 89%. IL-6 as a predictor of mortality risk has been recognized and administration of IL-6 inhibitors in COVID-19 patients can reduce the risk of mortality.[28]

6. Limitations

This study is limited for being a single center study.

7. Conclusion

Raised IL-6 and lactate levels in this study can be predictors of the mortality rate of COVID-19 patients within 24 hours of ICU-admission with 95.7% sensitivity and 60% specificity.

8. Data availability

The numerical data generated during this study is available with the authors.

9. Funding

No external or industry funding was involved in this study.

10. Conflict of interests

The study was supported by the Faculty of Medicine of Sebelas Maret University and Dr. Moewardi General Hospital Surakarta. The authors declare that no conflict of interest was involved.

11. Authors contribution

The idea, writing, research, and report making is done by the first and fifth author. The second, third, and fourth author assists in drafting ideas, giving direction in research, as well as improving reports.

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