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Original Research

The relationship of lactate clearance with mortality in COVID-19 pneumonia

Lactate clearance predicts mortality in COVID-19

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Abstract
Aim: In our study, we investigated the relationship of lactate clearance with disease severity and predictive mortality in patients with COVID-19 infection, which can lead to high mortality such as acute respiratory distress syndrome.
Material and Methods: The vital signs, demographic data and laboratory results of the patients who were diagnosed with COVID-19 pneumonia according to the results of CT and PCR analysis were recorded in the patient forms. Hospitalization status, intensive care requirements and disease outcomes of the patients were noted. Lactate clearance was calculated with the values at the time of admission to the emergency department and at the 6th hour. Data analyzes were performed in terms of the need for intensive care and its power to predict mortality.
Results: Data from 439 patients were analyzed for the study, and data from 318 patients who met the inclusion criteria were analyzed. The ROC analysis was performed to determine the value of lactate clearance in demonstrating mortality. When the areas under the curve were examined to test the power of LC in predicting survival, it was observed that the sensitivity was 82.76% and 75.69%.
Discussion: In our study, the power of LC to predict survival according to the severity of the infection in people with COVID-19 infection was examined and it was observed that it could significantly predict survival, especially in patients hospitalized in the intensive care unit. Therefore, this method, which is easy to apply, reproducible, non-invasive and cost-effective, can be recommended to predict the prognosis in patients with COVID-19 infection.

Keywords
COVID-19, Mortality, Lactate Clearance

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Introduction

On March 11, 2020, the World Health Organization declared the COVID-19 infection caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) as a pandemic (available at: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10). COVID-19 infection may progress asymptomatically or cause mortality by causing acute respiratory distress syndrome (ARDS) [1]. The pandemic has been partially brought under control thanks to increased personal protection measures and widespread vaccination. On the other hand, the emergence of new variants of the virus makes it difficult to completely control the pandemic.

While some of the COVID-19- infected patients are being treated at home, some of them are being treated in wards and intensive care units according to their clinical status. The vast majority of hospital admissions due to COVID-19 are carried out by emergency services. This situation has created a huge burden on the emergency services. Critical patient management in the emergency department is a complex and dynamic process, as in other units. It is necessary to quickly grasp the clinical condition of the patient and to initiate serial intervention. Therefore, there is a need for easily calculable risk markers that can predict disease severity and provide patient triage in a short time.

Lactate is formed as a result of the reduction of pyruvate in the human body by the enzyme lactate dehydrogenase [2]. In a healthy person, the plasma lactate level is less than 2 mmol/L. In cases of hypoxia or hypoperfusion, plasma lactate level increases rapidly [3,4]. The concentration of lactate, which can be measured with a blood gas analyzer, is an easily measurable marker that shows the perfusion disorder of the tissues independently of blood pressure [5].

Many studies have shown that high serum lactate levels are associated with poor outcomes in patients with septic shock [6,7]. A high lactate value is a significant parameter in the estimation of mortality. However, lactate levels may be normal in some diseases that can be mortal. Therefore, there is a need for a more effective mortality indicator than the measurement of lactate alone in patients who require close follow-up, need aggressive treatment, and whose immediate metabolic status may vary. This has led to the investigation of the usability of lactate clearance rate, namely lactate clearance (LC), in critically ill care [3].

Therefore, in our study, we investigated the relationship of LC with disease severity and predicting mortality in patients with COVID-19 infection, which can lead to high mortality such as ARDS.

Material and Methods

Our study was designed as a retrospective and observational study. Patients who applied to the 3rd Stage University Hospital emergency service, which served as a pandemic center between March 2021 and March 2022, were included. Demographic characteristics, laboratory parameters and disease outcomes of patients with confirmed COVID-19 diagnosis in the emergency department were analyzed. The power of the data in predicting ICU admission and mortality was calculated.

The study included patients over the age of 18, who presented with symptoms suggestive of COVID-19 pneumonia, had a positive Polymerase Chain Reaction (PCR) test result, and had COVID-19 pneumonia confirmed by Computed Tomography (CT). Patients with comorbidities that may cause lactate elevation such as chronic liver disease, severe anemia, and severe dehydration symptoms in their medical history, patients with an active lung tumor and pulmonary edema, whose medical information could not be reached, or who had missing laboratory data were excluded from the study (Figure 1).

The data of the patients who met the study criteria were collected through the hospital information system. The vital signs, demographic data and laboratory results of the patients who were diagnosed with COVID-19 pneumonia according to the results of CT and PCR analysis were recorded in the patient forms. Hospitalization status, intensive care requirements and disease outcomes of the patients were noted. Lactate clearance was calculated with the values at the time of admission to the emergency department and at the 6th hour. Data analyzes were performed in terms of the need for intensive care and its power to predict mortality.

Approval for the study was granted by the Izmir Katip Celebi University Ethics Committee (no. 0287). The study conformed to the provisions of the 1995 Declaration of Helsinki.

Statistical analysis

Data were evaluated in IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA), Medcalc and JASP statistical package programs. Descriptive statistics were given as $\bar{x}$(mean), ss (Standard Deviation) values. In addition, the homogeneity of variances, which is one of the prerequisites of the parametric tests, was checked with the Levene test. Normality assumption was checked with the "Shapiro-Wilk" test. In order to evaluate the differences between the two groups, the "Two Independent Samples t-test" was used. The "Roc Curve" analysis method was used to compare the diagnostic performances of two or more diagnostic or laboratory tests. When the relationship between two quantitative variables was required to be examined, the "Spearman rho" coefficient was used because the data did not meet the normal distribution conditions. The Chi-square test was used for the analysis of categorical data. A p-value of <0.05 was considered statistically significant.

Results

Data from 439 patients were analyzed for the study, and data from 318 patients who met the inclusion criteria were analyzed (Figure 1). Of the patients included in the study, 138 (43.4%) were female and 180 (56.6%) were male. The mean age of the patients was 72.57±14.54 years. The in-hospital mortality rate was 47.5%.

In the ROC analysis performed to determine the value of lactate clearance in demonstrating mortality, the area under the curve was found to be 0.573 (57.3%) for clearance and was statistically significant (p=0.023). The cut-off value for determining survival was accepted as ≤-38.89 (Table 1) (Figure 2). In the analyzes performed according to the clearance categories for mortality, the respiratory rate was found to be higher in the group with low clearance than in the group with higher clearance (p=0.021). Systolic blood pressure value was higher in the group with LC >-38.89 (p=0.026). SPO2 and PaO2 values were found to be statistically higher in the group with clearance ≤-38.89 (p=0.007, p=0.011, respectively). While the first lactate measurement was increased in the group with LC >-38.89 (p=0.003), the 6th-hour lactate value was also statistically higher in the LC ≤-38.89 group (p<0.001). Other variables did not differ statistically according to the cut-off value (p>0.05) (Table 2). When the data of all patients were included, a statistically significant negative correlation was observed between the respiratory rate, SPO2, PaO2, lactate 0 hours and lactate 6-hour values and clearance. No significant relationship was found in other variables (Table 3). When the areas under the curve were examined to test the power of LC in predicting survival, it was observed that the sensitivity was 82.76% and 75.69%, respectively, while the specificity was 32.4% and 37.21% in outpatients and ward patients (p=0.213, p=0.092, respectively). In terms of predicting survival in intensive care patients, the sensitivity was 40.56%, while the specificity was 76.88% (p=0.018) (Figure 3).

Table 1. Mortality Roc Analysis

	Area under the curve (AUC)	Std. Fail	p	Area under the curve (AUC) 95% Confidence limits		Sensitivity	Specificity	Cut off value
				Lower limit	Upper limit			
Clearance	0,573	0,032	0,023	0,51	0,636	26,49	86,63	≤-38,89

Table 2. Comparisons by Clearance Categories for Mortality

	Groups		z	p
	>-38,89 M(IQR)	≤-38,89 M(IQR)		
Age	73,0 (26,0)	75,0 (19,0)	0,095	0,924
Systole	123,0 (24,0)	125,0 (20,0)	2,23	0,026
Diastole	70,0 (20,0)	73,0 (18,0)	1,732	0,083
Pulse	86,0 (19,0)	88,0 (20,0)	0,543	0,272
Respiration Rate	17,0 (7,0)	23,0 (12,0)	2,198	0,021
Body Temperature	36,7 (0,4)	36,7 (0,3)	1,069	0,285
pH	7,4 (0,1)	7,4 (0,1)	0,451	0,652
SPO2	92,4 (13,8)	88,6 (28,1)	2,711	0,007
PaO2	64,0 (56,0)	58,0 (41,9)	2,558	0,011
Lactate 0	1,4 (1,1)	1,6 (1,6)	2,923	0,003
Lactate 6	2,7 (3,1)	1,3 (1,1)	6,821	<0,001
CRP	128,0 (164,3)	98,0 (125,1)	1,447	0,148
Leukocyte	9,3 (7,8)	9,8 (8,1)	0,373	0,709
Neutrophil	7,6 (6,8)	7,8 (7,5)	0,254	0,799
Lymphocyte	0,7 (0,8)	0,9 (0,8)	1,207	0,228

M: Median, IQR: Interquartile range, z: Mann-Whitney U test

Table 3. Correlations by Clearance Categories

	Whole Group		>-38,89		≤-38,89	
	rho	p	rho	p	rho	p
Age	-0,027	0,633	-0,071	0,256	0,327	0,01
Systole	0,055	0,33	-0,108	0,406	-0,041	0,51
Diastole	0,086	0,128	0,129	0,323	0,022	0,722
Pulse	0,066	0,24	-0,224	0,083	0,081	0,193
Respiration Rate	-0,135	0,016	-0,051	0,695	-0,143	0,022
Body Temperature	-0,113	0,044	-0,234	0,07	-0,096	0,126
pH	-0,07	0,213	0,137	0,291	-0,144	0,021
SPO2	-0,261	<0,001	-0,279	0,029	-0,23	<0,001
PaO2	-0,244	<0,001	-0,242	0,06	-0,214	0,001
Lactate 0	0,337	<0,001	0,233	0,071	0,34	<0,001
Lactate 6	-0,45	<0,001	-0,248	0,054	-0,302	<0,001
CRP	-0,073	0,195	0,064	0,624	-0,032	0,605
Leukocyte	-0,03	0,594	0,154	0,237	-0,075	0,232
Neutrophil	-0,073	0,192	0,155	0,232	-0,106	0,09
Lymphocyte	0,067	0,233	-0,15	0,249	0,037	0,556

rho: Spearman's Correlation Coefficient

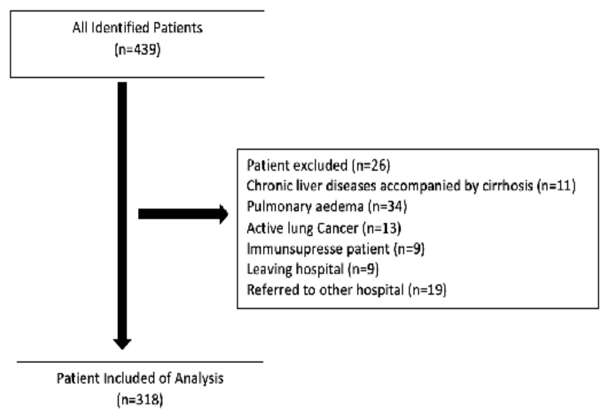

Figure 1. Consult Diagram

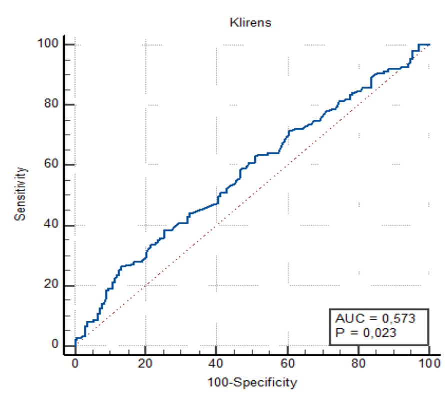

Figure 2. Mortality Roc Analysis

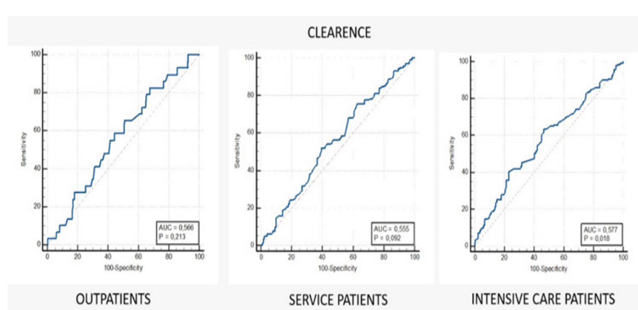

Figure 3. Roc Analysis of Patients by Outpatient, Service and Intensive Care

Discussion

In our study, the power of LC to predict survival according to the severity of the infection in people with COVID-19 infection was examined and it was observed that it could significantly predict survival, especially in patients hospitalized in the intensive care unit. Therefore, this method, which is easy to apply, reproducible, non-invasive and cost-effective, can be recommended to predict the prognosis in patients with COVID-19 infection.

The COVID-19 pandemic has started to lose its effect with vaccination, but has increased its momentum again recently due to the decrease in vaccination and the relaxation of social isolation measures. In parallel with this, patient admissions showing signs of COVID-19 such as fever, cough and respiratory distress have been increasing recently. For this reason, it is extremely important to identify and triage patients with poor prognosis in areas such as the emergency department, where the patient density is already high.

Recently, lactate level, decrease in follow-up lactate values and predictive aspect of mortality in different disease groups of LC have been investigated and it has been observed that it is a useful parameter. Reducing the lactate value is also recommended in recent guidelines and it is accepted that it is one of the important parameters of tissue perfusion improvement. On the other hand, the effect of LC on mortality has not been studied in patients with COVID-19 infection, which causes mortal conditions such as ARDS. COVID-19 infection is more mortal especially in elderly patients. The mean age of the patients in our study was 72 and the in-hospital mortality was 47.5%, which is consistent with this information.

The cut-off value of LC in terms of predicting mortality was 38.89. When the respiratory rate, SPO2, PaO2, lactate at 0 hours and 6th-hour lactate values are examined, a negative correlation with LC is observed. According to data obtained from other studies, survival is expected to increase in patients with high LC, and this negative correlation also supports the study hypothesis. In addition, the role of LC in predicting mortality was also examined in septic patients, and it was observed that it could predict survival in the septic shock patient group [8]. In another study by Marty et al. involving 91 intensive care unit patients with septic disease, it was observed that increasing LC by 20% significantly reduced 28-day mortality [9].

In another study emphasizing the importance of lactate in terms of reflecting mortality, 2 groups of patients were recruited. The target was to reduce the lactate value by more than 20% within 2 hours in one group, and achieve a central venous oxygen saturation of 70% in the other group. In the analyzes performed, it was observed that mortality was significantly lower in the group in which lactate was reduced [10]. In another study by Jansen et al., correction of LC and central venous oxygen saturation together reduced the mortality rate by 9.6% [10]. In our study, mortality in intensive care patients with high LC was lower and the power of LC to predict survival was significantly higher, which is in line with the literature.

The specificity of LC in predicting mortality in all diseases causing mortality was between 52-84%, and it was found to be 76% in our study [11]. Consistent with other causes of mortality, LC also predicts survival well in patients with COVID-19.

The most important limitation of our study is its single-center and retrospective design. The data of the patients were recorded considering their first application. These dynamic parameters are likely to vary according to disease severity and response to treatment. Although the results are reliable, multicenter clinical studies with more patients are needed.

Conclusion

The LC significantly reflects the probability of survival in patients with COVID-19 infection, especially during ICU admission. Since it is an easily applicable, inexpensive and reproducible test, it can be used as a useful parameter to predict the prognosis for people with COVID-19 infection in the emergency department.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflicts of interest.

References

1. Zhou F, Yu T, Du R. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054–62.
2. Philp A, Macdonald AL, Watt PW. Lactate- a signal coordinating cell and systemic function. J Exp Biol. 2005;208(24):4561-75.
3. Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of allcause mortality in critically ill patients: a systematic review and meta-analysis. Crit Care Med. 2014; 42(9): 2118-25. .
4. Vernon C, Le Tourneau JC. Lactic acidosis: recognition, kinetics and associated prognosis. Crit Care Clinics. 2010; 26(2):255-83.
5. Houwink AP, Rijkenberg S, Bosman RJ, van der Voort PH. The association between lactate, mean arterial pressure, central venous oxygen saturation and peripheral temperature and mortality in severe sepsis: a retrospective cohort analysis. Crit Care. 2016;20:56.
6. Khodashahi R, Sarjamee S. Early lactate area scores and serial blood lactate levels as prognostic markers for patients with septic shock: a systematic review. Infectious Diseases. 2020; 1–13.
7. Kim YA, Ha E-J, Jhang WK. Early blood lactate area as a prognostic marker in pediatric septic shock. Intensive Care Med. 2013;39(10):1818–23
8. Şeyhoğlu D T, Akdeniz Y S, İpekci A, İkizceli İ. The Effect of Lactate and Lactate Clearance on Mortality in Sepsis Patients Admitted to the Emergency Department. Phnx Med J. 2022; 4(1): 5-12.
9. Marty P, Roquilly A, Vallée F, Luzi A, Ferre F, Fourcade O, et al. Lactate clearance for death prediction in severe sepsis or septic shock patients during the first 24 hours in Intensive Care Unit: an observational study. Ann. Intensive Care. 2013;3(3):1-7.
10. Jansen TC, van Bommel J, Schoonderbeek FJ, Sleeswijk Visser SJ, van der Klooster JM, Lima AP, et al. Early lactate-guided therapy in intensive care unit patients: a multicenter, open-label, randomized controlled trial. Am J Respir Crit Care Med. 2010;15;182(6):752-61.
11. Zhang Z, Xu X, Chen K. Lactate clearance as a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review study protocol. BMJ Open. 2014; 4:e004752.

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