EAJEM-20092: Research Article

The Effect of Blood Lactate Level on Mortality in COVID-19 Positive Patients

Yeşim Işler[1], Halil Kaya[1], Melih Yüksel[1], Mehmet Oguzhan Ay[1], Şükrü Işler[2], Mehtap Bulut[1]
[1]Department of Emergency Medicine,Yuksek Ihtisas Training and Research Hospital, Health Science
[2]Department of Plastic and Reconstructive Surgery, Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey,

Objective: We aimed to investigate the relationship between increased lactate values and mortality in COVID-19 patients.
Material and Method: This study was conducted in a tertiary Training and Research hospital. According to the order of application, a total of 316 patients over the age of 18 who were admitted to the emergency department (ED) with symptoms of COVID-19 during the two months period and whose data could be completely accessed were included in the study retrospectively. Plasma lactate values and mortality within 28 days were determined.
Results: The median age of the patients was 69 years. Of the patients 53.5% were male, 72.2% had comorbidities and the most common comorbidity was COPD (13.0%). Of the patients 83.5% were hospitalized. The mean lactate value of the patients was 2.05 ± 1.45mmol / L. Mortality developed in 14.2% of the patients during the first 28 days. The 28-day mortality was significantly higher in patients with a positive Polymerase Chain Reaction (PCR) (23.8%) than that of negative PCR (8.2%) ($p < 0.001$). The lactate level was found to be significantly different in both PCR positive and negative groups in which mortality developed within 28 days ($p < 0.001$; $p < 0.001$). If the cut-off value of lactate in terms of mortality was 2.45, the sensitivity and specificity were determined as 80.0% and 81.2% respectively.
Conclusion: In patients with COVID-19 infection, the blood lactate level examined at the first admission to ED can be used as a useful screening test to predict mortality.

Keywords: COVID-19, pneumonia, lactate, mortality, pandemic,
Short Title in English: Blood Lactate Level and Mortality

Introduction

A group of unknown pneumonia cases emerged in Wuhan, China in December 2019. Most of the patients lived or worked in the local Huanan seafood wholesale market, where live wild animals were also on sale. In some patients, a clinical condition similar to acute respiratory distress syndrome (ARDS) rapidly appeared in the early stages of pneumonia. The new type of coronavirus infection with the zoonotic transition, called 2019-nCoV, has spread rapidly in China and then worldwide, causing a pandemic.

After emerging in Wuhan, Hubei province of China, the COVID-19 infection, which has rapidly spread to other countries in Asia, Pacific, Europe, and Africa, has caused a pandemic that threatens the preparation and biosafety conditions of countries worldwide (1). The world was unprepared for such a pandemic. Capacities of health facilities were insufficient.

This infection, later called COVID-19 by the World Health Organization (WHO), has caused 132.485.386 million confirmed cases and approximately 2.875.672 deaths with current data. (8 April 2021) (2)

The outbreak is still not fully under control. COVID-19 infection, which has clinical symptoms such as fever, cough, shortness of breath, myalgia, and fatigue, causes serious lower respiratory tract infections and mortality (3-6).

Due to the rapid spread of COVID-19 infection, the health infrastructure and resources of most countries have become insufficient. As a result of excessive admissions, the number of patients has dramatically increased especially in the emergency departments (ED), which has created a need to identify markers that can help us differentiate patients with serious life-threatening clinical findings and needing urgent treatment.

The usefulness of plasma lactate level measurement in EDs as an estimation for early detection of patients with tissue hypoperfusion that can cause severe sepsis and death has been reported (5). In this study, we aimed to investigate the relationship between increased lactate values and mortality in COVID-19 patients.

Materials and Methods

This retrospective cohort study started after the local ethical approval of Clinical Research Ethics Committee (2011-KAEK-25 2020 / 05-05) was obtained.

The standard data entry form including information regarding the patient's age, gender, presence of comorbid disease, plasma lactate, d-dimer, ferritin, CRP values, Polymerase Chain Reaction (PCR) testing results of oropharyngeal and nasopharyngeal swab samples, presence

of pneumonic infiltration in Computerized Thorax Tomography (CT), outcome (hospitalization, exitus, discharge) and whether there was mortality within 28 days were used. Patients over 18 years old who were admitted to ED with symptoms of COVID-19 (fever, cough, shortness of breath, diarrhea, fatigue, muscle or joint pain)between 16.03.2020 and 16.05.2020, and recorded in the hospital automation system with Covid-19 ICD-10 codes (U07. 1 and U07. 2) were screened. A total of 348patients were detected. Patients whose study data were not fully available (32 patients) were excluded. Totally 316 patients were included to the study.

The data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA) computer program. Descriptive statistics were expressed as median (IQR: 25th-75th percentiles) for continuous numerical variables while numbers and (%) for categorical variables. Kolmogorov-Smirnov test was used for the normality of data. The significance of the difference in terms of continuous numerical variables in which parametric test statistic assumptions were not provided was evaluated with Mann-Whitney U test. Chi-square and Fisher's exact tests were used to analyze whether there was a relationship between categorical variables. The ROC curve was plotted to investigate the diagnostic value of lactate. In the study, $p < 0.05$ value was considered statistically significant.

Results

A total of 316 patients were included in the study and the median (IQR: 25th-75th percentiles) age of the patients was 69 (60-78) years and 53.5% (n = 169) of the patients were male. Pneumonia was detected in Thorax Computed Tomography (CT) in 87.0% (n = 275) of the patients. Comorbidities were found in 72.2% (n = 228) of the patients. The most common comorbidity was COPD with 13.0% (n = 41). While 83.5% (n = 264) of the patients were

hospitalized, 15.8% (n = 50) were followed-up at home. Two patients (0.6%) died in ED. Mortality developed in 14.2% of the patients (n = 45) within 28 days. Distribution of patients' features are shown in Table 1. There was an increase in the mean lactate (2.05 ± 1.45 mmol / L), CRP (52.22 ± 65.90), D-dimer (2.65 ± 6.96) and ferritin (344.28 ± 524.82) values of the patients (Table 2). In the Chi-square test, a statistically significant relationship was found between PCR positivity and 28-day mortality ($p < 0.001$) (Table 3). In the Kolmogorov Smirnov test conducted to analyze the normality distribution, it was seen that the data were not normally distributed. Within this scope, Mann Whitney U test was conducted to investigate whether there was a difference between the lactate level and the 28-day mortality as well as PCR positivity / negativity. As a result of this test, lactate level was found to be significantly different in patients in both PCR positive and PCR negative groups who developed mortality within 28 days ($p < 0.001$; $p < 0.001$) (Table 3).

When the cut-off value of lactate in terms of mortality was 2.45, the sensitivity was found as 80.0%, the specificity was detected as 81.2%, and the area under the curve (AUC) was determined as 0.915(95% CI 0.876-0.955) in the ROC analysis ($p < 0.001$). If the the cut-off value of lactate in terms of mortality was 3.22, the sensitivity decreased to 57.8%, the specificity increased to 98.2% (Table 4).

Discussion

Excessive intense referral to healthcare facilities has led to the need to identify markers that can help us differentiate patients with serious life-threatening clinical findings needing urgent treatment.

Clinical, laboratory, and image findings, and factors related to the evolution of the disease and its consequences constitute critical information that must be carefully examined when a new infectious disease occurs. It is important to distinguish which COVID-19 patients

are at risk. Some patients can be safely managed as an outpatient. Reliable prognostic markers should be used to identify patients who will need more aggressive treatment. Advancing age, male gender, pre-existing coronary artery diseases (CAD), diabetes mellitus (DM), hypertension (HT), asthma, COPD, malignancies, and immunosuppressive diseases have been reported to adversely affect clinical prognosis in patients with COVID-19 (7, 8). Similarly, in our study, 53.5% (n = 169) of patients with COVID-19 were male, the mean age was 69 (min: 19 - max: 99) years, and the most common comorbidities were COPD, HT, DM, and CAD.

In a meta-analysis, clinical symptoms and findings such as fever (88.7%, 95% CI, 84.5-92.9), cough (57.6%, 95% CI%, 40.8-74.4), dyspnea (45.6%, 95% CI%, 10.9-80.4), myalgia or fatigue (29.4%, 95% CI, 19.8-39.0), sputum (28.5%, 95% CI%, 10.8-46.3) and sore throat (11%, 95% CI, 2.8-19.2) were reported in patients with COVID-19, which was statistically significant ($p < 0.001$). In laboratory tests, the decrease in albumin (75.8%, 95% CI%, 30.5-100.0), increase in C-reactive protein (58.3%, 95% CI, 21.8-94.7), increase in lactate dehydrogenase (LDH) (95% CI, 38.0-76.0), increase in Iymphopenia (43.1%, 95% CI, 18.9-67.3) and erythrocyte sedimentation rate (ESR) (41.8%, 95% CI, 0.0-92.8) were reported to be statistically significant ($p < 0.001$) (9). In our study, CRP, D-dimer, ferritin, and lactate were studied and it was seen that CRP (52.22± 65.9), D-dimer (2.66 ± 6.96), ferritin (344.29 ± 524.82) and lactate (2.05 ± 1.45 mmol / L) levels increased. In addition, lactate value over 4 mmol / L in patients with sepsis was reported to be associated with high mortality (10). As a biomarker in critical diseases and even as a therapeutic target, lactate attracts attention (11).

In patients with sepsis, widespread tissue hypoxia is found when the plasma lactate value is above 4 mmol/L, even if patients are normotensive (12). Lactate is a by-product of anaerobic cellular metabolism. In the case of hypoperfusion, blood lactate level increases due to insufficient oxygen. Since anaerobic metabolism is predominant in global hypoperfusion states or shock, lactate metabolism increases in the liver and kidneys, and as a result, the lactate level

in the blood increases. In some studies, increased lactate concentration has been associated with high mortality, irrespective of the presence of lactic acidosis (13). In our study, it was found that there was a relationship between high lactate values and mortality in patients with COVID-19. Lactate level was found to be statistically significantly different in both PCR positive and PCR negative groups in which mortality developed within 28 days ($p < 0.001$), $p = 0.004$). When the cut-off value of lactate in terms of mortality was 2.45, the sensitivity was found as 80.0%, the specificity was detected as 81.2%, and the area under the curve (AUC) was determined as 0.915 (95% CI 0.876-0.955) in the ROC analysis ($p < 0.001$).

When the first COVID-19 patients were detected in our hospital, we started to perform PCR testing to the oropharyngeal and nasopharyngeal swab samples of the patients. However, Thorax CT was performed in all patients with COVID-19 suspicion, since PCR was not concluded immediately and the accuracy rate was reported as low (30% - 60%) in the literature (5). In our study, 38.6% of the patients had positive PCR testing, and pneumonia was detected via Thorax CT in 87% of patients admitted to ED with COVID-19 symptoms. Thorax CT is a conventional, noninvasive, fast, and highly accurate imaging method. In accordance with the literature, there were characteristic CT findings (ground-glass opacification, bilateral multilobar involvement, posterior and peripheral distribution, consolidation) in our patients with COVID-19 (14). Thorax CT is considered as a routine imaging method for the monitoring and diagnosis of patients with COVID-19 pneumonia. Thorax CT may help to screen patients with suspected disease, particularly symptomatic patients with the first negative PCR scan result, and early detection of lung abnormalities (15).

Study Limitations:

The main limitations of our study were the relatively low number of patients, being retrospective, not considering lactate clearance, and not investigating the treatment methods that may affect mortality.

In conclusion, the blood lactate level examined at the first admission to ED in patients with COVID-19 can be used as a beneficial screening test to predict mortality.

References

1. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, et al. A new coronavirus associated with human respiratory disease in China. Nature. 2020;579(7798):265-9.

2- (https://covid19.who.int/) acces date: April 8, 2021

3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497-506.

4. Organization WH. Population-based age-stratified seroepidemiological investigation protocol for coronavirus 2019 (COVID-19) infection, 26 May 2020. World Health Organization; 2020.

5. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. The New England journal of medicine. 2020;382(8):727-33.

6. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020;395(10223):507-13.

7. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet (London, England). 2020;395(10229):1054-62.

8. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. Jama. 2020;323(18):1775-6.

9. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease. 2020;34:101623.

10. Nguyen HB, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. Journal of inflammation (London, England). 2010;7:6.

11. Okorie ON, Dellinger P. Lactate: biomarker and potential therapeutic target. Critical care clinics. 2011;27(2):299-326.

12. Puskarich MA, Trzeciak S, Shapiro NI, Heffner AC, Kline JA, Jones AE. Outcomes of patients undergoing early sepsis resuscitation for cryptic shock compared with overt shock. Resuscitation. 2011;82(10):1289-93.

13. Organization WH. Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases, Interim guidance, 2 March 2020. 2020.

14. Huang P, Liu T, Huang L, Liu H, Lei M, Xu W, et al. Use of Chest CT in Combination with Negative RT-PCR Assay for the 2019 Novel Coronavirus but High Clinical Suspicion. Radiology. 2020;295(1):22-3.

15. Gómez-Ramos JJ, Marín-Medina A, Prieto-Miranda SE, Dávalos-Rodríguez IP, Alatorre-Jiménez MA, Esteban-Zubero E. Determination of plasma lactate in the emergency department for the early

detection of tissue hypoperfusion in septic patients. The American journal of emergency medicine. 2018;36(8):1418-22.

TABLES

Table 1. Distribution of patients' features

	Variables	Frequency	Percentage
Gender	Female	147	46.5
	Male	169	53.5
Comorbidities	None	88	27.8
	COPD	41	13.0
	Multiple Diseases	39	12.3
	HT	37	11.7
	HT+DM	27	8.5
	DM	18	5.7
	CAD	17	5.4
	HT+CAD	12	3.8
	CRF	8	2.5
	Other	29	9.2
	Total	228	72.2
Pneumonia Findings on CT	No	41	13.0
	Yes	275	87.0
PCR	Positive	122	38.6
	Negative	194	61.4
Outcome	Hospitalization	264	83.5
	Follow up at home	50	15.8
	Exitus in the emergency service	2	0.6
28-Day Mortality	Yes	45	14.2
	No	271	85.8
	Total	316	100

CT: Computed Tomography; PCR: Polymerase Chain Reaction; HT: Hypertension; DM: Diabetes mellitus; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; CRF: Chronic renal failure

Table 2. Distribution of laboratory variables

Variables	n	Mean	Standard Deviation
Lactate	316	2.05	1.45
CRP	316	52.22	65.90
D-Dimer	316	2.66	6.96
Ferritin	316	344.29	524.82

CRP: C reactive protein; n: number

Table 3. Chi-Square and Mann Whitney U Analysis of Variables

Chi-Square Analysis

Variables			28-day mortality		Total	Chi-Square Analysis
			Yes	No		
PCR	Positive	n (%)	29 (23.8)	93 (76.2)	122 (100)	X^2 =14.778 (p < 0.001)
	Negative	n (%)	16 (8.2)	178 (91.8)	194 (100)	
	Total	n (%)	45 (14.2)	271 (85.8)	316 (100)	

Mann Whitney U Analysis

PCR	Mortality in 28 days		n	median (IQR: 25th-75th percentiles)	p
Positive	Lactate	Yes	29	2.1 (1.3-2.88)	<0.001
		No	93		
		Total	122		
Negative	Lactate	Yes	16	1.7 (1.2-2.3)	<0.001
		No	178		
		Total	194		

PCR: Polymerase Chain Reaction; **n:** Number; **IQR:** Interquartile range

Table 4. Sensitivity and specificity analysis of lactate level

AUC (95% CI)	p	Risk Fact	Cut-off	Sensitivity %	Specificity %
0.915 (0.876-0.955)	<0.001	Lactate	1.75	97.8	55.4
			2.08	95.6	67.2
			2.45	80.0	81.2
			2.75	711	90.0
			2.95	62.2	93.7
			3.22	57.8	98.2
			3.85	33.3	98.9