Middle Black Sea Journal of Health Science / Mid Blac Sea J Health Sci

August 2022; 8(3): 349-356

RESEARCH ARTICLE

DOI: 10.19127/mbsjohs.1081086

Lactate as a Predictor for Determining Invasive Intervention Time in non-ST-Segment Acute Coronary Syndromes

Gulsah Cikrikci Isik[1(ID)], Sedanur Safak [1(ID)] , Rabia Handan Gunsay[1(ID)], Yunsur Cevik[1(ID)]

[1]Ankara Atatürk Senatoryum Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Received: 01 March 2022, Accepted: 08 June 2022, Published online: 31 August 2022

Abstract

Objective: The aim was to evaluate the correlation of lactate levels measured at admission with the urgency of intervention in patients diagnosed with non-ST-segment acute coronary syndromes (NST-ACS).

Methods: This was a prospective observational study conducted in a research hospital between March 2020 and June 2021. Patients admitted to the emergency department with chest pain and diagnosed with NST-ACS were divided into four group according to the recommendations of the European Society of Cardiology (ESC) 2015 guidelines to determine the priority of invasive intervention. Lactate levels were measured from venous blood samples. Whether there was a difference in terms of lactate levels between patients who were recommended for early invasive intervention (within 24 hours) and patients who were recommended for late invasive intervention (within 72 hours) was investigated. The sample size was estimated with G*Power and statistical analysis was performed using SPSS 22.

Results: The mean age of the group recommended for early intervention was 62±11.45 years and the mean age of the group recommended for late intervention was 61±11.89 years. The time interval between the beginning of symptoms and admission to the emergency department was similar between the groups and the median was 4 hours. GRACE scores were significantly higher in the early intervention recommended group. There was no difference in terms of lactate levels between the groups. Correlations between GRACE scores and lactate levels were statistically non-significant ($p>0.05$).

Conclusion: Lactate alone was not a good predictor for risk analyses and determination of invasive intervention time in NST-ACS patients without urgent invasive intervention indications.

Key words: non-ST-segment acute coronary syndromes, early invasive intervention, late invasive intervention, lactate

Suggested Citation: Cikrikci Isik G, Safak S, Gunsay RH, Cevik Y. Lactate as a predictor for determining invasive intervention time in non-ST-segment acute coronary syndromes. Mid Blac Sea Journal of Health Sci, 2022;8(3):349-356.

Address for correspondence/reprints:

Gulşah Cikrikci Işik

Telephone number: +90 (505) 587 3436

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E-mail: gulsah8676@gmail.com

Note: This study was applied for oral presentation at the 1st international emergency medicine congress

INTRODUCTION

Acute coronary syndromes are among the leading causes of death around the world and invasive revascularization is the most important treatment modality to improve the outcomes of these cases (1, 2). For ST-segment elevation myocardial infarction (STMI), urgent revascularization is suggested; however, for non-ST-segment acute coronary syndromes (NST-ACS), the timing of revascularization is more complex. For very high-risk patients diagnosed with refractory angina, with associated heart failure, life-threatening ventricular arrhythmias, or hemodynamic instability, the guidelines are clear and the European Society of Cardiology (ESC) recommends urgent (within two hours) coronary intervention (3). However, the optimal timing of invasive intervention is still controversial for other risk groups among NST-ACS patients because of the conflicting results of recent studies (4, 5). The current recommendations also address highly complex scores and assessments and include subjective elements for which standardization is not possible. Therefore, the search for an easily accessible and reliable predictor that will clarify this issue is ongoing.

Lactate is known as a marker of metabolic stress response, and in critically ill patients, high levels are predictive for increased mortality (6). Recent studies have demonstrated that for the stressed heart lactate is an important fuel, and in many cardiac conditions such as coronary syndromes, cardiogenic shock, or cardiac arrest, hyperlactatemia is associated with worse outcomes (7, 8).

In this study we aimed to evaluate the correlation of lactate levels measured at admission to the emergency department with the urgency of intervention in patients diagnosed with NST-ACS who were recommended for early (within 24 hours) or late (within 72 hours) revascularization according to the current guidelines. Our hypotheses were if lactate levels might be higher at the early intervention recommended group and lactate alone might be deterministic for timing of intervention.

METHODS

This study conducted in a research hospital with the approval of the local ethics committee between March 2020 and June 2021. This was a prospective observational study. Patients admitted to the emergency department (ED) with chest pain and diagnosed with NST-ACS (patients with non ST-segment elevation myocardial infarction (NSTMI) and unstable angina (UA) were included), were evaluated after examination and follow-up. These patients were subdivided into four groups according to the recommendations of the ESC 2015 guidelines (3).

Group 1 consisted of patients with at least one of the very high-risk criteria, including hemodynamic instability or cardiogenic shock, ongoing or repeated chest pain despite medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications due to myocardial infarction, acute heart failure, and recurrent dynamic ST-T wave changes. For Group 1, the guidelines clearly recommended urgent (within 2 hours) coronary intervention. Group 2 consisted of patients with at least one of the high-risk criteria, including a relevant rise or fall in troponin, dynamic ST or T wave changes, and Global Registry of Acute Coronary Events (GRACE) risk score above 140. For Group 2, the ESC recommended invasive intervention within 24 hours (early intervention). Group 3 consisted of

patients with at least one of the middle-risk criteria together with recurrent symptoms or proven ischemia in non-invasive tests. Middle-risk criteria were history of diabetes mellitus, renal failure (glomerular filtration rate of <60), congestive heart failure, early post-infarct angina, history of percutaneous coronary intervention, history of coronary artery bypass grafting, and GRACE score of 109-140. For this group, the ESC recommended late invasive intervention (within 72 hours). Group 4 consisted of patients with no risk factors and GRACE scores below 109. That group included selective patients without emergent revascularization necessity. The GRACE score is used to determine risk and mortality among acute coronary syndrome patients. The GRACE scores of these patients were calculated using an online application (MDCalc®).

As clearly stated by previous studies and guidelines for patients who require urgent (within 2 hour) invasive intervention, Group 1 was not included in the study. Since the main target of this study was to determine the predictive power of lactate in identifying the need for early (Group 2) and late (Group 3) revascularization in cases of NST-ACS, patients who did not need urgent revascularization (Group 4, patients who could be followed with a non-invasive strategy) were excluded from the study. Patients with STMI and chest trauma were also excluded.

Lactate levels were measured from venous blood samples together with blood gas analysis. Whether there was a difference in terms of lactate levels between patients who were recommended for early invasive intervention (Group 2, within 24 hours) and patients who were recommended for late invasive intervention (Group 3, within 72 hours) was investigated.

Since there was no coronary intervention laboratory in our hospital, all those patients included in the study were transferred to other hospitals. So definitive intervention timing of those cases were not known. Also study group of the patient did not affect the management of the patient in our hospital. However, because the primary goal of the study was to evaluate the difference of lactate levels between the groups which were determined according to ESC guidelines, not knowing the actual intervention time was not considered as a limitation in reaching the targeted goal.

Statistical Analysis

IBM SPSS Statistics for Windows 22.0 (IBM Corp. Armonk, NY, USA) was used for performing statistical analysis. First normal distribution of variables assessed with Kolmogorov-Smirnov test, then according to normality all variables were described in terms of mean ± standard deviation or median and interquartile range (IQR; 25-75%). Categorical variables were given as percentages. Student's t-test and Mann-Whitney U test were used to determine the statistical differences between the groups, for the parametric values and the non-parametric values, respectively. Correlations between lactate and GRACE scores were determined with Spearman's test. Values of $p<0.05$ were considered statistically significant.

G*Power for Mac OS X (version 3.1.9.2; Heinrich Heine University Düsseldorf, Düsseldorf, Germany) was used to estimate the sample size. In order to detect a medium effect size difference between the two groups (effect size: 0.5), assuming a 2-sided value of $\alpha=0.05$, we anticipated a sample size of 67

patients for each group to achieve 80% power. After those calculations, we decided to include 140 participants (70 in each group) in the study.

RESULTS

The mean age of the group recommended for early intervention was 62±11.45 years and 28 of these patients were female; the mean age of the group recommended for late intervention was 61±11.89 years and 16 of these patients were female. The time interval between the beginning of symptoms and ED admission were similar between the groups and the median was 4 hours. The frequency of comorbid conditions was also similar between the groups. GRACE scores were significantly higher in the group recommended for early intervention. The ED treatment modality of the group recommended for late intervention was generally only acetylsalicylic acid; in the group recommended for early intervention, most of the patients were given both acetylsalicylic acid and low-molecular-weight heparin. Since there was no coronary intensive care unit in our hospital, all patients were referred for further treatment. General characteristics of the patients are given in Table 1.

Table 1: General characteristics of the patients in both groups

Variables	Patients recommended for early intervention (Group 2), n=70	Patients recommended for late intervention (Group 3), n=70	p
Age, years	62±11.45	61±11.89	0.56
Gender			**0.03**
Female	28	16	
Male	42	54	
Comorbid conditions			
CAD	34	30	0.50
DM	21	22	0.86
HT	38	35	0.61
COPD	5	7	0.55
HL	11	5	0.11
Time interval (beginning of symptoms to ED arrival)	4 hours (IQR: 2-8 hours)	4 hours (IQR: 3-12 hours)	0.53
GRACE score	105±28.37	93±26.08	**0.012**
ED management			
Acetylsalicylic acid	10	66	**<0.001**
Acetylsalicylic acid + low-molecular-weight heparin	60	4	

Table 2: Blood gas analysis and lactate levels in venous blood samples

Variables	Patients recommended for early intervention (Group 2), n=70	Patients recommended for late intervention (Group 3), n=70	P
pH	7.37 (IQR: 7.35-7.41)	7.38 (IQR: 7.35-7.40)	0.56
PCO_2 (mmHg)	39.33±7.59	40.85±5.52	0.18
HCO_3 (mmol/L)	25.54±4.05	24.76±3.23	0.21
Base excess	0.85 (IQR: -2.5-3)	0.65 (IQR: -1.85-2.25)	0.87
Lactate (mmol/L)	2.20 (IQR: 1.49-2.87)	1.98 (IQR: 1.53-2.61)	0.33

Abbreviations: pCO2, partial carbon dioxide pressure; HCO3, bicarbonate; IQR, interquartile range.
Variables are given as mean ± standard deviation (if normally distributed) and median (IQR: 25-75%) (if not normally distributed).

Abbreviations: CAD, Coronary artery disease; DM, diabetes mellitus; HT, hypertension; COPD, chronic obstructive pulmonary disease; HL, hyperlipidemia; GRACE: Global Registry of Acute Coronary Events; ED, emergency department; IQR, interquartile range.

Variables are given as numbers, mean ± standard deviation (if normally distributed), and median (IQR: 25-75%) (if not normally distributed).

Blood gas analysis and lactate levels were compared between the groups. There was no difference in terms of pH levels, partial carbon dioxide pressure, bicarbonate levels, base excess, and lactate levels between the groups. Results are given in Table 2. Correlations between GRACE score and lactate levels were also checked; the results were statistically non-significant ($p>0.05$).

DISCUSSION

This study has demonstrated no difference in terms of lactate levels between NST-ACS patients recommended for early invasive intervention and those recommended for late invasive intervention. There was also no correlation between the GRACE scores and lactate levels of Group 2 and Group 3 NST-ACS patients as defined according to ESC guidelines.

Despite cardiac troponin playing an essential role in the assessment of acute coronary syndrome patients, for the NST-ACS group it is still very challenging to identify high-risk patients and invasive treatment priority and the necessity for a simple predictor still remains (9). In acute coronary syndromes, due to impaired tissue perfusion, oxygen delivery to cells is decreased and that leads cells to preferentially use glycolysis rather than oxidative phosphorylation to produce energy, which results in increased lactate production (10). Several studies have demonstrated that high lactate levels were a predictor of mortality in acute coronary syndromes (1, 6, 10). However, when those studies are analyzed, it is seen that they included high-risk patient groups with hemodynamic instability such as STMI cases or Killip class II and III heart failure (6, 10, 11). The reason for not finding a significant difference in our study might be due to the exclusion of unstable groups (STMI cases and Group 1 NST-ACS patients) and the comparison of relatively stable groups.

The normal blood lactate concentration is around 1 mmol/L and even mild increases, with values of >1.5 mmol/L, were associated with higher mortality rates in critically ill patients (12). In our study, mortality was not an outcome; however, in both groups the median lactate levels were higher than 1.5 mmol/L (2.20 mmol/L in the early intervention group and 1.98 mmol/L in the late intervention group). Although the accepted threshold values might differ between studies, lactate levels above 2 mmol/L are generally considered abnormal (13). Gjesdal et al. determined an abnormal lactate level of ≥2.5 mmol/L in their study, which analyzed blood lactate level as a predictor of short-term mortality in patients with ACS complicated with heart failure (11). In another study, Demers et al. defined the peak lactate level as 4 mmol/L during cardiopulmonary bypass in adult cardiac operations (14). From this point of view, in our study, it is demonstrated that the lactate levels of the groups were close to the abnormal limit and were even higher in the group for which early invasive intervention was recommended, as expected. However, since those values did not show a statistically significant difference between the groups, a predictive role of lactate in

determining the groups in which early or late invasive intervention should be recommended has not been demonstrated.

This study also analyzed the correlation of lactate levels and GRACE scores. In a study conducted with patients hospitalized in an intensive care unit with the diagnosis of acute coronary syndrome, a significant correlation was shown between GRACE scores and lactate levels (15). However, in that study, the sample size was small, the clinical severity of the selected ACS patients was unclear, and the strength of the correlation was quite weak (r=0.3) (15). In another study conducted with STMI patients, Hu et al. demonstrated that the combination of lactate and GRACE score was not superior to the original GRACE score alone in predicting mortality (16). In our study, there was also no significant correlation between GRACE scores and lactate levels.

Limitations

This study had some limitations. First, since invasive interventions were not performed in our hospital, all of these patients were referred and their subsequent outcomes (timing of invasive intervention, mortality, complications, etc.) could not be followed. Second, lactate level was measured just once, when the patient was first admitted to the hospital. The time interval between the onset of complaints and sample collection could not be standardized.

CONCLUSION

In this study analyzing the predictive role of lactate in the differentiation of NST-ACS patient groups for whom early (in the first 24 hours) or late (in the first 72 hours) invasive intervention was recommended, no significant difference was found between the groups in terms of lactate levels. There was also no correlation between lactate and GRACE scores. In conclusion, lactate alone was not a good predictor for risk analyses and determination of invasive intervention time in NST-ACS cases.

Ethics Committee Approval: Ethical approval was obtained from Keçiören Research Hospital with file number 2012-KAEK-15/2067 (Date 12.02.2020)

Peer-review: Externally peer-reviewed.

Author Contributions: Concept: G.C.I, Design: G.C.I, Y.C, Literature search: GCI, Data collection and Processing: G.C.I, S.S, R.H.K, Analyses and Interpretation: G.C.I, S.S, R.H.K, Writing: G.C.I, Y.C.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The author declared that this study hasn't received no financial support.

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