Research Article

Abdussamed Vural*, Mahmut Karapehlivan, Turgut Dolanbay, Mustafa Oguz Cumaoglu, Ahmet Yunus Hatip, Yakup Cetinkaya and Adnan Unalan

4-h mean lactate clearance as a good predictor of adverse outcome in acute cardiogenic pulmonary edema: a pilot study

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Abstract

Objectives: This pilot study aimed to evaluate the efficacy of the 4-h mean lactate clearance (LACclr) level as a predictive factor for in-hospital outcomes, 30-day mortality, and treatment success in patients with acute cardiogenic pulmonary edema (ACPE), a significant clinical form of acute heart failure (AHF).

Methods: A total of 44 patients diagnosed with acute pulmonary edema were included in the study. The patients were divided into two groups based on lactate levels and negative outcomes, and lactate and LACclr levels and negative outcomes were analyzed using statistical tests such as Fisher's exact test, Student's t-test, Mann-Whitney U test, and Receiver operating characteristic (ROC) analysis.

Results: The results indicated a statistically significant difference in the total hospitalization length of stay according to whether the patients had a negative outcome (intubation and in-hospital mortality) (p=0.033). Additionally, the area under the curve (AUC) value for 4-h mean LACclr was 0.795 in all patients, which was statistically significant in predicting 30-day mortality (p=0.033). The optimal cut-off value for the 4-h mean LACclr in predicting 30-day mortality was found to be 5.57 %, with 80 % sensitivity and 66.7 % specificity. The threshold to rule out 30-day mortality for all patients was 18.85 with 100 % sensitivity and 30.2 % specificity (AUC, 0.795 95 % CI [0.546–1.000], p=0.033).

Conclusions: These findings suggest that the 4-h LACclr level, calculated within 4 h of emergency department (ED) presentation, can be used as a predictive indicator for needing intubation, in-hospital mortality, and 30-day mortality and to identify patients at higher risk for adverse outcomes.

Keywords: acute heart failure; acute pulmonary edema; cardiogenic; lactate; lactate clearance; prognosis

Introduction

Acute heart failure (AHF) is defined as a marked escalation in clinical symptoms or a sudden decrease in cardiac reserves requiring urgent therapy [1]. Acute cardiogenic pulmonary edema (ACPE), one of the most dramatic clinical forms of AHF, is an acute respiratory distress associated with rapid transudative fluid development in the pulmonary interstitium and alveoli, which often occurs in elderly patients. Pathophysiologically, ACPE is characterized by elevated pulmonary capillary pressure, which results from dysfunction of the left ventricle, either systolic or diastolic [2]. The leading etiology of ACPE is acute myocardial infarction (AMI)-induced left ventricular failure [3]. This condition causes myocardial damage, leading to a decrease in cardiac functional reserve. In addition, hypertensive emergencies lead to increased venous and pulmonary capillary pressures [4].

***Corresponding author: Abdussamed Vural**, Department of Emergency Medicine, School of Medicine, Niğde Ömer Halisdemir University, Niğde, Türkiye, E-mail: abdussamedvural@gmail.com. https://orcid.org/0000-0003-4506-916X
Mahmut Karapehlivan, Department of Biochemistry, School of Medicine, Kafkas University, Kars, Türkiye. https://orcid.org/0000-0003-0408-534X
Turgut Dolanbay and Mustafa Oguz Cumaoglu, Department of Emergency Medicine, School of Medicine, Niğde Ömer Halisdemir University, Niğde, Türkiye. https://orcid.org/0000-0002-4092-1192 (T. Dolanbay). https://orcid.org/0000-0003-4245-1101 (M.O. Cumaoglu)
Ahmet Yunus Hatip, Department of Emergency Medicine, Isparta Training and Research Hospital, Isparta, Türkiye. https://orcid.org/0000-0002-7595-2175
Yakup Cetinkaya, Department of Cardiology, School of Medicine, Niğde Ömer Halisdemir University, Niğde, Türkiye. https://orcid.org/0000-0002-0689-7221
Adnan Unalan, Department of Biostatistics, School of Medicine, Niğde Ömer Halisdemir University, Niğde, Türkiye. https://orcid.org/0000-0002-9187-9713

When cardiac arrhythmia, conduction abnormalities, or vasoconstriction cause more afterload and hypervolemia causes more preload, the heart's ability to work is weakened.

These pathophysiological changes cause fluid to shift from the pulmonary capillaries to the interstitial spaces of the lung and alveolar spaces [5]. In clinical practice, patients with this condition usually present to the emergency department (ED) with severe episodes of dyspnea and hypoxia (SO_2<90 %) [6]. Rapid assessment and treatment of patients are vital for reducing the risk of respiratory failure and cardiovascular collapse.

Lactate is produced in the absence of oxygen as a byproduct of cellular metabolism and is indicative of tissue hypoxia and impaired perfusion. Although lactate levels are usually used in critically ill patients, mostly in shock, they can be elevated for several reasons [7]. Elevated blood lactate levels are strong prognostic markers for tissue hypoperfusion and are often used in therapeutic decision-making. This is an important part of evaluating the success of the treatment. Kawase et al. [8] reported that higher lactate levels on admission were associated with worse in-hospital mortality in patients with acute decompensated heart failure (HF) with and without acute coronary syndrome (ACS). Bakker et al. [9] indicated that measuring serial blood lactate levels could effectively serve as a predictor of multiple organ failure and mortality in patients with septic shock. In contrast to a single lactate level reflecting an instantaneous static state, Scott et al. [10] highlighted in a study on cardiac failure that serial measurements of lactate concentrations and dynamic changes in lactate levels may be more useful in indicating patient prognosis, arguing that 0–2 h lactate clearance (LACclr), is a good marker for prognosis prediction. However, no study has evaluated in-hospital clinical outcomes and treatment effectiveness in patients treated for ACPE in the ED after the first critical 4 h, the most intensive period of treatment. In this context, a single lactate or LACclr measurement in the early period in the ED may be insufficient to serve as a predictor of clinical outcome or treatment efficacy over time. In a systemic review published by Vincent et al. on lactate kinetics [11], decreasing lactate levels over time were consistently associated with lower mortality rates in critically ill patients. However, the authors suggested the use of a dynamic evaluation of serial lactate concentrations, regardless of the initial value, as lactate levels change, and these changes are relatively slow. Therefore, their recommendation was to measure lactate levels every 1–2 h for follow-up in acute conditions.

However, the question of which lactate clearance time interval is a good predictor of patient prognosis remains unclear. This study argues that the initial lactate levels before treatment in acute cardiogenic pulmonary edema are insufficient to assess resuscitation in these patients.

In light of the literature mentioned above, there is a need for better indicators that can be used to predict the clinical outcomes and treatment efficacy in critically ill emergency patients with ACPE. Studies of HF have often focused on unclassified HF. The present study is the first prospective study of 4-h LACclr in patients followed up at an AHF clinic in the ED.

The main objective of this study was to assess the predictive value of the 4-h mean LACclr level for in-hospital mechanical ventilation, in-hospital mortality, and 30-day mortality in patients with ACPE.

Materials and methods

Ethical aspects

This prospective cross-sectional study was approved by the Non-Interventional Ethics Committee of the Niğde Ömer Halisdemir University Faculty of Medicine (dated 10/11/2022 and numbered 2022/99). During the enrollment phase, the informed consent form was signed by the patients themselves (if they were able to sign the form) or by their primary relatives.

Patients and study design

A total of 44 patients who were diagnosed with acute cardiogenic edema and met the inclusion criteria provided informed consent to participate in the pilot study. These individuals were followed up in the ED of our third-level hospital, Niğde Ömer Halisdemir Training and Research Hospital.

The mean LACclr level was obtained by averaging the clearance sum of arterial blood lactate values measured consecutively at the initial point after 1, 2, and 4 h. Within the first 2 h, a cardiologist evaluated patients who continued their follow-up and treatment in the ED using echocardiography (ECHO). Therefore, we aimed to determine the etiological causes of ACPE. Additionally, the cardiologist planned the hospitalization of patients and ensured their follow-up in the intensive care unit (ICU) or ward. The patients were divided into two groups based on their initial lactate levels (before treatment), <4 mmol/L and ≥4 mmol/L, and their 4-h mean lactate levels, normal (<2 mmol/L) and high (≥2 mmol/L). They were also categorized into two groups based on negative outcomes, and statistical comparisons were performed between these groups.

Inclusion and exclusion criteria

The study included individuals who were 18 years or older and sought medical care at the ED within the ACPE clinic. The diagnosis of AHF was based on the 2021 European Society of Cardiology (ESC) diagnostic guideline [12]. ACPE was defined as sudden symptoms, an oxygen saturation level below 90 % on room air before emergency treatment, and/or confirmed alveolar or interstitial edema on chest radiographs, severe respiratory distress, crackling sounds in the lungs, or orthopnea [13]. Patients who met these criteria were included in the study. Patients with cardiogenic shock, need for a pacemaker or intra-aortic balloon pump, ST-segment elevation MI (STEMI), signs of serious infection, brain natriuretic peptide (BNP) values <100 pg/mL, malignant ventricular arrhythmias, or NSTEMI who underwent emergency angiography after not completing the 4-h follow-up period were excluded from the study. Patients with end-stage liver and kidney failure and malignancies were excluded from the study. In addition, patients who did not volunteer in the study were under the age of 18 years, were pregnant, whose lactate measurements could not be performed during the monitored period, or whose lactate measurements were interrupted within the first 4 h were excluded.

Application

Blood concentrations of arterial lactate were obtained during ED admission at 1, 2, and 4 h. The 4-h mean LACclr value was calculated using the following formula:

4-h mean LACclr=[((initial lactate − first-hour lactate)/initial lactate + (first-hour lactate − second-hour lactate)/first-hour lactate + (second-hour lactate − fourth-hour lactate)/second-hour lactate))/3] × (%). Other calculated LACclr values were determined in accordance with this formulation.

Lactate levels were monitored by hourly blood sampling and analyzed electrochemically using a Radiometer ABL800 Flex® lab analyzer (Kopenhag, Denmark), which was specifically designed for blood gas analysis. Additionally, a Roche Cobas® e 601 hormone analyzer (Kobe, Japan), Roche Cobas® c 501 biochemistry analyzer (Kobe, Japan), and XN-1000 hemogram analyzer (Kobe, Japan) from Sysmex Corporation were employed for comprehensive biochemical and hematological analyses, ensuring a thorough examination of lactate levels and associated parameters in the study. All patients in the emergency critical care unit were treated according to the established protocols. The standard treatment protocol to ensure hemodynamic stability was as follows: (I) patients admitted to the ED with acute dyspnea and signs of overload (a clinical picture of pulmonary edema) will be rapidly monitored in the critical care unit, and their vital signs will be recorded. A detailed physical examination of the patients will be performed by a competent emergency medicine specialist, and symptomatic treatment will be initiated without wasting time for a possible diagnosis, in line with clinical prediction (the first stage in which inclusion or exclusion criteria are applied). (II) Regardless of the underlying etiology, the drugs and applications to be used to provide hemodynamic stabilization are as follows: nitroglycerin derivatives for high blood pressure, diuretics, morphine (low dose), O_2 support (target SO_2>90), fluid support if needed, control of electrolyte imbalance, inotropic infusion support with dopamine if needed, and non-invasive mechanical ventilation (NIMV) support will be provided. (III) The criteria for patients on NIMV are as follows [10]: tachypnea≥25/min, pH 7.10–7.35, and pCO_2>50 mmHg; indications for discontinuation of NIMV are normal mental status, hemodynamic stability, respiratory rate<25/min, absence of assistive respiratory muscles and paradoxical abdominal movements, arterial pH>7.33, pCO_2<70 mmHg, and pO_2>55 mmHg.

The primary negative endpoints of our study were in-hospital mortality and adherence to endotracheal intubation/invasive mechanical ventilation (IMV). The primary positive endpoint was hospital discharge, without the need for IMV.

Statistical analysis

Continuous data and descriptive statistics are expressed as means with standard deviations (SD) or medians with interquartile ranges (IQR, 25–75). Categorical variables are presented as numbers and percentages. Fisher's exact test was used in the chi-squared ($\chi 2$) analysis to test for significant differences between the study groups in terms of lactate levels and negative outcomes. Student's t-test was used to compare the means of continuous variables for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Pearson or Spearman correlation analysis was used to evaluate the relationship between continuous variables. The primary endpoints were dependent, and the 4-h mean LACclr level was the independent variable. We determined how well the 4-h mean LACclr could predict endpoints by measuring the area under the curve (AUC) through Receiver operating characteristic (ROC) analysis. The normality of the data distribution was assessed using the Shapiro-Wilk (S-W) test according to the sample size and power. All statistical analyses were conducted at a 95 % confidence level, and p-values less than 0.05 were

considered statistically significant. SPSS (IBM SPSS Statistics Version 22, SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

The study included 44 patients who met the inclusion criteria. The mean age of the patients was 70.8 ± 8.5 years, and the female and male percentages were 56.8 and 43.2 %, respectively. All patients (n=44) had hypertension (HT), 75 % (n=33) had coronary artery disease (CAD), 68.2 % (n=30) had diabetes mellitus (DM), 38.6 % (n=17) had HF, 20.5 % (n=9) had atrial fibrillation (AF) and chronic obstructive pulmonary disease (COPD), and 25 % (n=11) had chronic renal failure (CRF). Half of the patients (n=22) followed up in the critical unit of the ED received NIMV support. At the end of the 4-h follow-up period, three patients (6.8 %) were intubated. The median (IQR 25–75) lengths of ICU and ward hospitalizations were 2 (1–3) and 4 (3–6), respectively. There was no significant difference in ICU length of stay according to whether the patients had a negative outcome (intubation and/or in-hospital mortality), whereas there was a statistically significant difference in the total length of hospitalization (p=0.033) (Table 1). Eight patients (18.2 %) required invasive endotracheal intubation, and mortality occurred in three patients (6.8 %). A positive outcome (discharge from the hospital without needing IMV) was observed in 81.8 % (n=36) of patients. The 30-day mortality rate was 11.4 % (n=5). The demographic and clinical data of the patients are presented in Table 1. There were no statistically significant differences (p>0.05) in the in-hospital negative outcome, need for NIMV, or 30-day mortality in patients divided into two groups according to 4-h mean LAC levels (<2 mmol/L and ≥2 mmol/L) and initial lactate levels (<4 mmol/L and ≥4 mmol/L). Table 2 presents this relationship. When in-hospital mortality rates of patients were compared according to lactate levels and/or mean LACclr, no statistically significant difference was found between those who died and those who were discharged for initial lactate, 4-h mean lactate, LACclr 0–1 h, LACclr 0–2 h, and 4-h mean LACclr (p=0.913, p=0.397, 0.494, p=0.408, p=0.055, respectively). On the other hand, in 30-day mortality, LACclr 0–2 h and 4-h mean LACclr values showed a significant difference between the groups (p=0.013 and p=0.005, respectively). This relationship is presented in Table 3. Furthermore, the LACclr values at 0–2 h and 4-h mean LACclr were significantly different from the other indicators between the groups categorized according to the need for endotracheal intubation (p=0.024 and p<0.001, respectively). Table 4 presents this relationship. The mean values of aspartate aminotransferase (AST, IU/L) and alanine aminotransferase (ALT, IU/L) were 26.61 ± 16.04 and 20.53 ± 13.10, and the median values (IQR, 25–75) were 22.50 (16.25–32.75) and 16.50 (13–24), respectively. The mean creatinine (mg/dL) value of the patients was 1.40 ± 0.60) and the median value (IQR, 25–75) was 1.21 (0.98–1.67). AST, ALT, and creatinine levels were not significantly associated with the need for IMV, in-hospital mortality, or 30-day mortality in patients with and without negative outcomes (p>0.05). In the correlation analysis of continuous variables, a negative correlation was found between pH and total length of hospitalization, as well as between hemoglobin and Pro BNP (r=−0.0312, p=0.039; r=−0.453, p=0.002, respectively) and a positive correlation between troponin and Pro BNP (r=0.434, p=0.003). The optimum cut-off value of 4-h mean LACclr for predicting 30-day mortality was 5.57 %, with 80 % sensitivity and 66.7 % specificity (p=0.033). In addition, the optimum cut-off value of 2-h (0–2 h) LACclr in predicting 30-day mortality was 17.26 % with the same sensitivity and specificity. However, this result was not statistically significant (p=0.064). The ROC analysis results are shown in Figure 1. Furthermore, the threshold to rule out 30-day mortality for all patients was 18.85 with 100 % sensitivity and 30.2 % specificity (AUC, 0.795 95 % CI [0.546–1.000], p=0.033).

Discussion

In this study, we investigated the relationship between the mean serum LACclr levels in the first 4 h after the initiation of treatment and prognosis in patients with ACPE. To our knowledge, this is the first prospective study to show that the 4-h mean LACclr level strongly predicts 30-day mortality in patients with ACPE. The main finding of our study was that patients with a negative in-hospital outcome or mortality within the first 30 days had a statistically lower 4-h mean LACclr rate than those without a negative outcome or mortality. There are many studies on lactate levels in critically ill patients in the literature [14–20]. However, limited studies attempt to explain the role of changes in initial lactate levels or LACclr concentrations on prognosis in AHF [21, 22].

Scott et al. [10] emphasized that serial measurements of lactate concentrations may be more useful in indicating prognosis; they argued that 0–2 h LACclr is a good marker for predicting prognosis. Bosso et al. also investigated how the 24-h time-weighted mean lactate level in AHF affects prognosis. They found that patients with values above 1.6 and 2.79 mmol/L had poor and worse outcomes compared to patients with values below 1.6 and 2.79 mmol/L [21].

Table 1: Demographic and clinical features of the patients.

Variables	Total (n=44)	Clinical output		p-Value
		Negative (n=8)	Positive (n=36)	
Sex, n (%)				
Male	19 (43.2)	5 (62.5)	14 (38.9)	0.262
Female	25 (56.8)	3 (37.5)	22 (61.1)	
Age, years, mean ± SD	70.8 ± 8.5	75.1 ± 5.5	69.9 ± 8.9	0.116
Comorbid diseases, n (%)				
HT	44 (100)	8 (100)	36 (100)	NA
DM	30 (68.2)	6 (75)	24 (66.7)	1.000
CHF	17 (38.6)	2 (25)	15 (41.78)	0.455
CAD	33 (75)	7 (87.5)	26 (72.2)	0.656
COPD	9 (20.5)	2 (25)	7 (19.4)	0.659
CRF	11 (25)	2 (25)	9 (25)	1.000
AF	9 (20.5)	1 (12.5)	8 (22.2)	1.000
Vitals, mean ± SD or median (IQR)				
Systolic BP, mmHg	163.8 ± 26.8	159.4 ± 25.1	164.7 ± 27.4	0.615
Diastolic BP, mmHg	100 (17.5)	93.1 ± 10.3	100 (20)	0.319
In-hospital negative output, n (%)				
Intubation	8 (18.2)	8 (100)		
Mortality	3 (6.8)	3 (100)		NA
Interventions in ED, n (%)				
NIMV	22 (50)	5 (100)	14 (38.9)	0.016
Intubation at 4 h	3 (6.81)	3 (37.5)	22 (61.1)	
LOS, median (IQR 25–75)				
ICU, days	2 (1–3)	3 (2.25–4.75)	1.5 (1–2)	0.22
In-hospital, days	4 (3–6)	6 (5–7)	3 (3–6)	0.033
30-day mortality, n (%)	5 (11.4)	5 (62.5)	3 (8.1)	<0.001

The significance level is set at 0.05. n=42, with two of the total patients (n=44) having censored data for 30-day mortality. LOS, length of stay; NIMV, non-invasive mechanical ventilation; BP, blood pressure; NA, not applicable; IQR, interquartile range; SD, standard deviation; HR, heart rate; ED, emergency department; ICU, intensive care unit; HT, hypertension; DM, diabetes mellitus; CHF, chronic heart failure; CAD, coronary heart disease; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; AF, atrial fibrillation.

Table 2: Clinical adverse outcomes of patients based on 4-h mean lactate and initial lactate.

Variables	4-h mean lactate				p-Value
	<2 mmol/L		≥2 mmol/L		
Adverse outcomes	Yes	No	Yes	No	
Endotracheal intubation	2	18	6	18	0.259
In-hospital mortality	1	19	2	22	0.570
Need for NIMV	7	13	12	9	0.215
30-day mortality	1	18	4	19	0.673
Variables	**Initial lactate**				**p-Value**
	<4 mmol/L		≥4 mmol/L		
Adverse outcomes	Yes	No	Yes	No	
Endotracheal intubation	7	28	1	8	0.474
In-hospital mortality	2	33	1	8	0.506
Need for NIMV	13	20	6	2	0.115
30-day mortality	4	29	1	8	1.000

The significance level is set at 0.05. NIMV, non-invasive mechanical ventilation.

However, we believe that lactate levels or clearance rates measured in a very short or relatively long period of time may be insufficient as predictors of treatment success or negative outcomes in serious clinics such as ACPE requiring intensive resuscitative treatment and follow-up. In the model we applied in our study, we proposed that the most appropriate time period for LACclr evaluation in this patient group is the first 4-h period when the treatment is applied most intensively and that the mean rate of change in lactate levels obtained hourly or bi-hourly during this period will be more useful in predicting in-hospital negative outcomes and 30-day mortality. In the current study, the 4-h mean LACclr was statistically more significant than the 2-h mean LACclr in predicting 30-day mortality and intubation requirement. As known, metabolic alterations such as increased glycolysis and catecholamine-stimulated Na-K pump activity can contribute to elevated blood lactate concentrations [23]. Reduced lactate clearance, primarily as a result of liver hypoperfusion, can also lead to elevated blood lactate levels [24].

However, this study revealed that the median values of liver and renal function tests were within normal limits, suggesting no significant abnormalities that could impact lactate clearance. Furthermore, no notable discrepancy was observed between the groups in terms of AST, ALT, and creatinine levels with respect to poor clinical outcomes.

The in-hospital mortality rates of patients with AHF are difficult to determine because the causes, severity, and treatment protocols are highly variable. According to the results of large-scale clinical trials, in-hospital and 1-year mortality rates vary widely, ranging from 4 % to nearly 40 % [25–28]. High in-hospital mortality rates of 10–20 % have been reported for ACPE, particularly when associated with ACS. However, studies on in-hospital mortality rates in patients with ACPE but without AMI are limited. In our study,

Table 3: 30-day mortality according to different lactate levels and lactate clearances.

Variables	30-day mortality	n	Mean	SD	CI (%95) of the difference		p-Value
					Lower	Upper	
Initial lactate concentration, mmol/L	Yes	5	2.90	1.03	−1.56	1.37	0.90
	No	37	2.99	1.57			
4-h mean lactate, mmol/L	Yes	5	2.77	0.86	−0.59	1.5	0.39
	No	37	2.32	1.11			
LACtclr 0–1 h, %	Yes	5	18.23	15.86	18.16	12.96	0.737
	No	37	20.83	16.19			
LACtclr 0–2 h, %	Yes	5	−4.91	43.95	−56.16	−7.03	0.013
	No	37	26.68	22.54			
4-h mean LACclr, %	Yes	5	−6.42	17.66	−29.59	−5.68	0.005
	No	37	11.21	11.68			

The significance level is set at 0.05. LACtclr, lactate clearance; CI, confidence interval.

Table 4: Needing intubation according to different lactate levels and/or lactate clearances.

Variables	Need for intubation	n	Mean	SD	CI (95 %) of the difference		p-Value
					Lower	Upper	
Initial lactate concentration, mmol/L	Yes	8	2.58	0.98	−1.64	0.69	0.417
	No	36	3.06	1.55			
4-h mean lactate, mmol/L	Yes	8	2.55	0.83	−0.62	1.07	0.592
	No	36	2.33	1.12			
LACtclr 0–1 h, %	Yes	8	17.55	14.38	−16.80	8.78	0.531
	No	36	21.55	16.56			
LACtclr 0–2 h, %	Yes	8	−9.38	39.18	−72.75	−6.91	0.024
	No	36	30.45	17.22			
4-h mean LACtcl, %	Yes	8	−8.31	13.76	−29.87	−13.24	<0.001
	No	36	13.24	9.76			

The significance level is set at 0.05. LACtclr, lactate clearance; CI, confidence interval; SD, standard deviation.

the in-hospital mortality rate was 6.8 %, and the 30-day mortality rate was 11.4 %, which is consistent with the literature. In a study by Zymliski et al., patients with AHF were analyzed in two groups according to lactate levels ≤2 mmol/L and >2 mmol/L, and 1-year mortality was found to be statistically significant in patients with high lactate levels [29]. However, in the present study, no significant difference was found between the patients in terms of early prognosis in terms of in-hospital and 1-month mortality at both the 2 mmol/L and 4 mmol/L thresholds.

In a study by Regnier et al., the AUC values for initial LACclr and 2-h LACclr in terms of mortality were found to be 0.78 and 0.70 for all patients [30]. In the study by Odom et al., these two values were found to be 0.88 and 0.78, respectively, in patients with >4 mmol/L, and these values were reported to be independent predictors for early (48 h) and late mortality [18].

In our study, the AUC value was 0.526 for the initial lactate level and 0.682 for the mean 4-h lactate in all the patients. However, these two values were not statistically significant in terms of 30-day mortality. In contrast, the AUC value for 4-h mean lactate level was 0.795 in all patients, which was statistically significant in predicting 30-day mortality. Even so, the AUC value for 2-h LACclr (0–2 h) was 0.756 in all patients, which was not statistically significant in predicting the 30-day mortality.

The ESC 2021 guidelines highlight the ongoing need for evidence-based biomarkers to enhance the diagnosis, treatment, and prognosis of patients with AHF, thereby improving organ perfusion and influencing clinical outcomes. ESC has suggested various biomarkers to identify the etiologic causes of AHF or to exclude the diagnosis when suspected, such as pro-BnP, NT-proBnP, troponin, procalcitonin, D-dimer, thyroid stimulating hormone (TSH), and lactate. For instance,

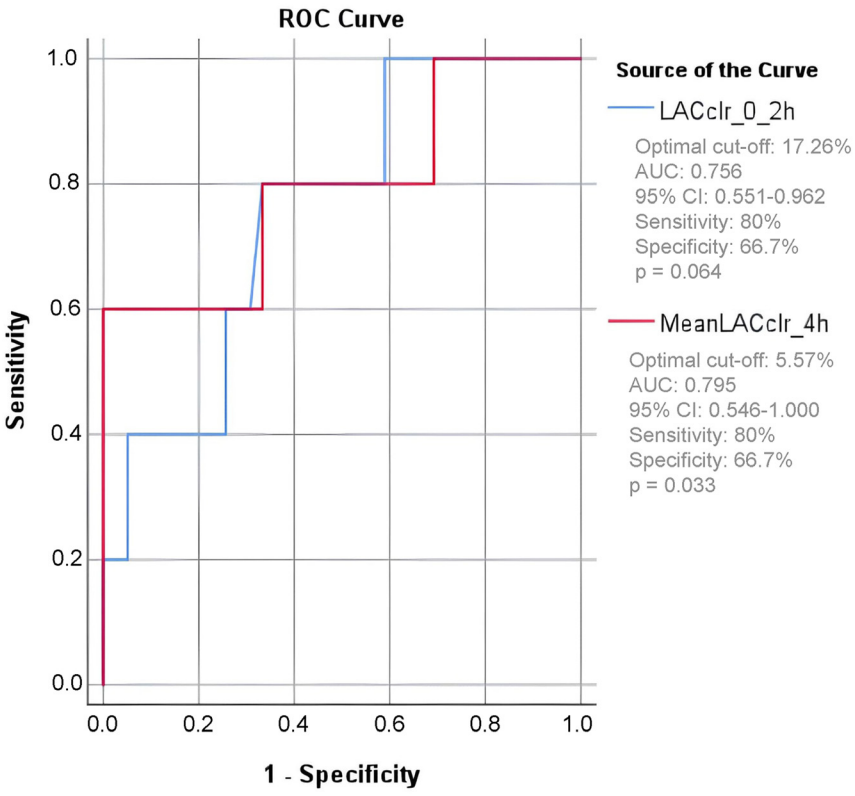

Figure 1: ROC curves of 4-h mean LACclr and 2-h LACclr (0–2 h) to predict 30-day mortality. ROC, receiver operating characteristic; LACclr, lactate clearance. According to the figure, the optimal cutoff value for 4-h LACclr in predicting 30-day mortality was 5.57 %, with a sensitivity of 80 % and specificity of 66.7 % (p=0.033). For 2-h LACclr, the optimum cutoff value was 17.26 %, but it was not statistically significant (p=0.064).

troponin is used to diagnose ACS, D-dimer to detect or exclude pulmonary embolism, BNP to exclude non-cardiogenic causes, procalcitonin to identify infections, ferritin to assess anemia, and TSH to assess thyroid function [12]. Among these, lactate has emerged as a promising marker for assessing tissue perfusion, particularly in acute decompensated HF. Lactate monitoring, when combined with clinical assessment and vital signs, is expected to play a significant role in the management of acute severe pulmonary edema. Its potential utility lies in helping clinicians comprehensively assess the tissue perfusion status, contributing to more effective patient care and improved outcomes.

Palazzuoli et al. showed in their clinical studies that erythropoietin supplementation in patients with cardiorenal anemia increased BNP levels [31]. In our study, a statistically significant negative correlation was found between hemoglobin and BNP levels. Although high BNP and low hemoglobin levels are expected in patients with severe HF, correcting anemia can alleviate the symptoms of shortness of breath in patients with HF. In addition, Troponin and BNP provide potential utility as screening methods for identifying individuals at an elevated risk of chronic HF [32]. In the current study, a positive correlation was found between troponin and BNP levels. In this respect, these two markers may be important in screening for new HF as well as existing HF. This study focused on in-hospital mortality, intubation rates, and 30-day mortality as the primary endpoints. Future studies should consider additional outcome measures, such as long-term survival, quality of life, and healthcare utilization. Further validation of the findings through prospective, randomized controlled trials or meta-analyses is essential to confirm the predictive value of 4-h mean lactate clearance in patients with ACPE.

Limitations of the study

This study had some major limitations. First, it prevented the extrapolation of the results to the general adult population. A small sample size gives a result that may not be sufficiently powered to detect differences between groups, and the study may turn out to be falsely negative, leading to a type II error. Second, the study assessed in-hospital negative outcomes, such as the need for intubation, mortality, and 30-day mortality, which may not reflect medium- or long-term mortality predictions. Third, the physicians managing the patients were not blinded to the sequential lactate measurements, which could have introduced bias in patient selection. However, efforts were made to minimize bias by strictly adhering to the established study protocol for all clinical decisions and laboratory results. Large-scale studies,

including strategies to control for confounding factors, are needed to isolate the effect of 4-h mean LACclr on clinical outcomes.

Conclusions

This study sheds light on the predictive potential of mean serum LACclr levels during the initial 4 h of treatment in patients diagnosed with ACPE. This pilot study marks the first endeavor of its kind, demonstrating a robust correlation between the 4-h mean LACclr level and 30-day mortality among patients with ACPE. Notably, patients who experience unfavorable outcomes during their hospital stay, particularly those who pass away within the first 30 days, often demonstrate a substantially lower 4-h mean LACclr than those who do not experience such adverse outcomes. The optimum cut-off value of 4-h mean LACclr for predicting 30-day mortality was 5.57 % with 80 % sensitivity and 66.7 % specificity. The threshold for ruling out 30-day mortality for all patients was 18.85, with 100 % sensitivity and 30.2 % specificity. Although prior studies have investigated lactate dynamics in critically ill populations, research exploring the impact of fluctuations in initial lactate levels or LACclr concentrations on the prognosis of AHF, particularly ACPE, remains scarce. Our study underscores the significance of serial lactate measurements and the dynamic changes in lactate levels over time, suggesting their potential superiority over isolated static measurements in prognostic assessments. In conclusion, in patients presenting with ACPE, 4-h LACclr calculated within the first 4 h after ED presentation may be used as a predictive indicator for in-hospital and 30-day mortality. In addition, in this patient group, 4-h LACclr may be a useful index for identifying patients with a higher risk of adverse outcomes that may require aggressive treatment in patients admitted from the ED to the ICU or ward. While the 4-h mean LACclr showed promising predictive value, further validation through clinical randomized studies is essential to confirm its efficacy as an index of adverse outcomes in patients with ACPE.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).
Informed consent: The patients or their primary relatives signed an informed consent form during the enrollment period.
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