

# Relative Hyperlactatemia in the Emergency Department: A Retrospective Cohort Study

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## Original research

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# Abstract

## Objective

The clinical interpretation of lactate  $\leq 2.00$  mmol/L in emergency department (ED) patients is not well characterized. This study aims to determine the optimal cutoff value for lactate within the reference range that predicts in-hospital mortality among ED patients with initial serum lactate levels within the reference range.

## Methods

This was a retrospective study of adult patients presenting to a tertiary ED between the dates of January 1, 2014 and June 30, 2019 with an initial serum lactate level less than 2.00 mmol/L. The primary outcome was in-hospital mortality. Youden's index was utilized to determine the optimal threshold that predicts mortality. Patients above the threshold were labeled as having relative hyperlactatemia. A multivariate logistic regression was performed to determine the association between relative hyperlactatemia and in-hospital mortality. Subgroup analyses were done to further examine the interaction between relative hyperlactatemia and hospital mortality.

## Results

During the study period, 1638 patients were included. The mean age was  $66.9 \pm 18.6$  years, 47.1% of the population were female, and the most prevalent comorbidity was hypertension (56.7%). The mean lactate level at presentation was  $1.5 \pm 0.3$  mmol/L. In-hospital mortality was 3.8% in the overall population and 16.2% were admitted to the ICU. A lactate of 1.33 mmol/L was found to be the optimal cutoff that best discriminates between survivors and non-survivors. Relative hyperlactatemia was an independent predictor of in-hospital mortality (OR 1.78 CI1.18-4.03; p 0.02). Finally, Relative hyperlactatemia was associated with increased mortality in patients without hypertension (4.7% versus 1.1%; p 0.008), as well as patients without diabetes or COPD.

## Conclusion

The optimal cutoff of initial serum lactate that discriminates between survivors and non-survivors is in the ED 1.33 mmol/L. Relative hyperlactatemia is associated with increased mortality in emergency department patients, and this interaction seems to be more important in healthy patients.

## Background

The breakdown of pyruvate via the enzyme lactate dehydrogenase leads to the formation of lactate. Healthy individuals produce basal lactate levels of  $1.0 \pm 0.5$  mmol/L <sup>1,2</sup>. Normal lactate levels in the

blood usually refer to levels  $< 2$  mmol/L<sup>3,4</sup>. Current theories relate hyperlactatemia to decreased oxygen delivery and tissue malperfusion, or to impaired oxygen utilization and adrenergic stress, and both paradigm mechanisms may be compounded by impaired elimination<sup>5-10</sup>. There have been significant advances in our understanding of the physiology of lactate, and it has since become a mainstay biomarker, heavily integrated into clinical decision-making of septic patients in the emergency department<sup>11,12</sup>. Furthermore, hyperlactatemia ( $> 2.00$  mmol/L) has been associated with poor outcomes and independently predicts mortality in diverse patient populations presenting to the emergency department (ED)<sup>13</sup>. In its most recent guidelines, the Surviving Sepsis Campaign recommend using lactate levels  $\geq 4$  mmol/L to initiate IV fluid resuscitation and recommend re-measuring lactate levels if they are  $> 2$  mmol/L to monitor the response to the resuscitation<sup>8</sup>. Lactate levels within the reference range ( $\leq 2$  mmol/L) have a less clear clinical interpretation and may result in less attention given to these patients in the ED. Furthermore, there is a considerable group of patients who present in shock and have elevated in-hospital mortality rates despite having lactate levels within the normal range<sup>14</sup>. It has been proposed that this subgroup of patients with septic shock possess distinctive clinical and physiological profiles, and may have unique treatment parameter considerations<sup>15-17</sup>. Moreover, there is emerging evidence that suggests that relative hyperlactatemia (i.e. lactate above an identified threshold) has a more appropriate consideration in certain subgroups of patients, such as those with sepsis<sup>18</sup>, septic shock<sup>14,19</sup> or cancer<sup>20</sup>. The clinical interpretation of lactate  $\leq 2.00$  mmol/L in ED patients is not well characterized. This allows us to question what the best prognostic cutoff value is for lactate. One study proposed that a cutoff of 1.35 mmol/L best discriminates between survivors and non-survivors in the intensive care unit (ICU)<sup>21</sup>. Nonetheless, there is a paucity of data on this issue, particularly in the ED. This study aims to evaluate the optimal cutoff threshold for lactate that distinguishes between survivors and non-survivors and predicts in-hospital mortality among patients presenting to the ED with an initial serum lactate levels within the reference range (0.01 to 2.00 mmol/L).

## Methods

### Design and Setting

This was a retrospective cohort study of adult patients presenting to the academic ED of a tertiary care center between the dates of January 1, 2014 and June 30, 2019. All patients aged 18 years of age or older who presented to the ED and had a serum lactate level drawn had their charts queried. All patients who had an initial serum lactate level drawn and within the reference range (0.01–2.00 mmol/L) were included in the study. Exclusion criteria consisted of patients with serum lactate  $> 2.00$  mmol/L, patients who were pregnant, patients who presented with cardiac arrest and patients who had been admitted less than 10 days prior to presentation. The data collection protocol was standardized, and information was extracted from the patient's electronic medical records and anonymized. The variables collected included patient demographics and characteristics, vital signs and initial laboratory tests upon presentation to the ED, diagnosis, presence of sepsis on admission, interventions performed (renal replacement therapy,

mechanical ventilation, vasopressor use, steroid use, antibiotic administration, intravenous fluid administration), disposition, length of stay, readmission rates, in-hospital mortality and 30-day mortality rates. In this study, sepsis was defined as the presence of an infection with signs of organ dysfunction, as represented by the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score of 2 points or greater according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) guidelines<sup>22</sup>. Patient who did not meet this definition were labeled as having an infection. The study was approved by the hospital's Institutional Review Board (IRB).

## Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included mechanical ventilation, vasopressor use, steroid use, intravenous fluid administration, lengths of stay (ED, ICU and total).

## Statistical analysis

Statistical analysis was conducted with IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA). Continuous variables are presented as mean  $\pm$  standard deviation and categorical variables are presented as frequency with valid percent. Patients were stratified into survivors and non-survivors. A Youden's index was used to determine the optimal threshold that predicts in-hospital mortality, and patients above the threshold were reclassified as having relative hyperlactatemia. A multivariate logistic regression was performed to determine the association of relative hyperlactatemia and in-hospital mortality. All variables with statistical and clinical significance were included in the analysis. The variables included were age, gender comorbidities (hypertension, diabetes, dyslipidemia, chronic obstructive pulmonary disease, heart failure, immunocompromised), diagnosis category, sepsis, lymphocyte count, and white blood cells (WBC) count. We looked at the in-hospital mortality among patients with and without relative hyperlactatemia, stratified by selected subgroups. These subgroups included the following: male versus female patients; age younger than 50 years versus age older to equal to 50 years; diabetes versus no diabetes; hypertension versus no hypertension; dyslipidemia versus no dyslipidemia; coronary artery disease versus no coronary artery disease, chronic obstructive pulmonary disease (COPD) versus no COPD, congestive heart failure versus no congestive heart failure, sepsis versus no sepsis and vasopressor versus no vasopressor use.

## Results

During the study period, a total of 2692 patients were identified with lactate levels within the reference range (0.01 to 2.00 mmol/L). Of these, 868 were excluded because their initial lactate value upon ED presentation was greater than 2.00 mmol/L, 163 were excluded because they were under 18 years of age, 4 were excluded because they were pregnant, 9 were excluded because they presented with cardiac arrest and 10 were excluded because they had been recently admitted to the hospital less than 10 days prior to presentation. A total of 1638 patients were included in the study, and their characteristics are summarized in Table 1.

Table 1  
**Baseline characteristics, vital signs, laboratory values and outcomes for all patients with lactate  $\leq$  2.00 mmol/L**

Variable	Overall <i>N</i> = 1,627
	Mean $\pm$ SD
Age (years)	66.89 $\pm$ 18.61
	n, %
Sex (female)	767 (47.1)
Comorbidities	
Hypertension	921 (56.7)
Dyslipidemia	504 (31.1)
Coronary artery disease	409 (25.2)
Diabetes mellitus	473 (29.1)
CKD	229 (14.1)
ESRD	60 (3.7)
Hepatic dysfunction	16 (1.0)
COPD	167 (10.3)
Malignancy	360 (22.1)
Congestive heart failure	215 (13.2)
Diagnosis category	
Respiratory	188 (11.6)
Cardiovascular	95 (5.8)
Neurologic	53 (3.3)
Trauma	60 (3.7)
Infection	714 (43.9)
Gastrointestinal	294 (18.1)
Other medical illness	222 (13.6)
Sepsis	517 (31.8)
	Mean $\pm$ SD

<b>Variable</b>	<b>Overall</b> <b>N= 1,627</b>
Vital signs at presentation	
SBP (mm Hg)	127.48 ± 25.51
DBP (mm Hg)	69.04 ± 15.26
HR (per minute)	92.81 ± 21.57
Oxygen saturation (%)	96.26 ± 4.83
Temperature (°C)	37.33 ± 0.92
Laboratory results	
Lactate at presentation (mmol/L)	1.47 ± 0.25
Glucose (mg/dL)	129.54 ± 64.20
Creatinine (mg/dL)	1.47 ± 1.63
WBC (/cu.mm)	10903.76 ± 6699.65
pH (Arterial)	7.38 ± 0.09
INR	1.48 ± 0.88
	n, %
Outcomes	
Mechanical ventilation	51 (3.1)
Vasopressor use	69 (4.2)
Steroid use	188 (11.6)
ICU admission	264 (16.2)
30-day readmission rate	329 (22.1)
In-hospital mortality	60 (3.8)
	Mean ± SD
IV fluids in first 6 hours	1.255 ± 1.16
IV fluids in first 24 hours	1.94 ± 1.74
Length of stay (hours)	123.85 ± 261.32
ED	9.22 ± 13.37
ICU	31.96 ± 173.50

Variable	Overall
	<b>N= 1,627</b>
GPU	82.67 ± 186.17
<b>Legend</b>	
INR: international normalized ratio; BUN: blood urea nitrogen; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen; ICU: intensive care unit; IV: intravenous; ED: emergency department; GPU: general practitioner unit	

## Overall patient characteristics

The mean age was approximately  $66.9 \pm 18.6$  years. 47.1% of the population were female and the most prevalent comorbidity was hypertension (56.7%) followed by dyslipidemia (31.1%). 43.9% of patients had an infection and 31.8% of all patients had a diagnosis of sepsis. The mean lactate level at presentation was  $1.5 \pm 0.3$  mmol/L. During their hospital stay, 3.8% of the patients died, 4.2% received vasopressors, 3.1% were mechanically ventilated, and 16.2% were admitted to the ICU. The mean length of stay in the ED was  $9.2 \pm 13.4$  hours.

## ROC curve

Figure 2 demonstrates the receiver operating curve for lactate upon presentation and in-hospital mortality. The optimal cutoff that differentiates between survivors and non-survivors was found to be 1.33, and the area under the curve for that value was 0.545 (95% CI 0.477–0.614).

## Laboratory and vital signs

Youden's index was used to find the threshold that best discriminates between survivors and non-survivors and it was found to be 1.33 mmol/L. Table 2 summarizes the characteristics of patients with initial lactate levels below 1.33 mmol/L and of those with initial lactate equal to or above 1.33 mmol/L. Patients with relative hyperlactatemia (equal to or above 1.33 mmol/L) were older ( $68.8 \pm 17.8$  years vs.  $61.4 \pm 19.8$ ,  $p < 0.001$ ), had less females (45.4% vs. 51.8%,  $p = 0.027$ ), had higher rates of hypertension (59.1% vs. 49.6%,  $p = 0.001$ ), dyslipidemia (32.7% vs. 26.3%,  $p = 0.015$ ), coronary artery disease (27.0% vs. 20.0%,  $p = 0.005$ ), diabetes mellitus (31.9% vs. 21.0%,  $p < 0.001$ ), chronic obstructive pulmonary disease (11.4% vs. 7.0%,  $p = 0.011$ ) and congestive heart failure (15.9% vs. 5.6%,  $p < 0.001$ ) compared to patients with lactate levels below 1.33 mmol/L. elevated heart rates and temperatures, lower oxygen saturations, higher glucose, INR and WBC count compared to patients with lactate levels below 1.33 mmol/L.

Table 2

Patient characteristics, vital signs and laboratory values upon ED presentation for patients with lactate < 1.33 mmol/L and for patients with lactate  $\geq$  1.33 mmol/L

Variable	Lactate < 1.33 <i>n</i> = 415	Lactate $\geq$ 1.33 <i>n</i> = 1212	<i>p</i>
	Mean $\pm$ SD		
Age (years)	61.36 $\pm$ 19.78	68.79 $\pm$ 17.82	< 0.001
	n, %		
Sex (female)	215 (51.8)	552 (45.4)	0.027
Comorbidities			
Hypertension	206 (49.6)	715 (59.1)	0.001
Dyslipidemia	109 (26.3)	395 (32.7)	0.015
Coronary artery disease	83 (20.0)	326 (27.0)	0.005
Diabetes mellitus	87 (21.0)	386 (31.9)	< 0.001
Chronic kidney disease	52 (12.6)	177 (14.6)	0.307
ESRD	13 (3.1)	47 (3.9)	0.490
Hepatic dysfunction	4 (1.0)	12 (1.0)	1.000
COPD	29 (7.0)	138 (11.4)	0.011
Malignancy	88 (21.2)	272 (22.5)	0.584
Congestive heart failure	23 (5.6)	192 (15.9)	< 0.001
Diagnosis category			
Respiratory	35 (8.4)	153 (12.6)	< 0.001
Cardiovascular	14 (3.4)	81 (6.7)	
Neurologic	20 (4.8)	33 (2.7)	
Operative trauma	0 (0.0)	8 (0.7)	
Non-operative trauma	22 (5.3)	30 (2.5)	
Infection	154 (37.1)	560 (46.2)	
Gastrointestinal	97 (23.4)	197 (16.3)	
Other medical illness	73 (17.6)	149 (12.3)	

<b>Variable</b>	<b>Lactate &lt; 1.33</b> <b>n = 415</b>	<b>Lactate ≥ 1.33</b> <b>n = 1212</b>	<b>p</b>
Sepsis	105 (25.3)	412 (34)	< 0.001
	Mean ± SD		
<b>Vital signs at presentation</b>			
SBP (mm Hg)	125.52 ± 23.44	128.15 ± 26.15	0.057
DBP (mm Hg)	68.79 ± 14.17	69.13 ± 15.62	0.678
HR (per minute)	90.99 ± 20.28	93.43 ± 21.97	0.039
Oxygen saturation (%)	97.38 ± 3.70	95.88 ± 5.11	< 0.001
Temperature (°C)	37.24 ± 0.81	37.35 ± 0.96	0.024
<b>Laboratory results</b>			
Lactate at presentation mmol/L	1.11 ± 0.15	1.59 ± 1.34	< 0.001
Glucose mg/dL	117.76 ± 65.00	134.03 ± 63.36	< 0.001
Creatinine mg/dl	1.42 ± 1.97	1.49 ± 1.49	0.460
WBC /cu.mm	9861.23 ± 5961.54	11259.01 ± 6899.63	< 0.001
pH (Arterial)	7.36 ± 0.10	7.38 ± 0.09	0.073
INR	1.31 ± 0.61	1.52 ± 0.93	0.001
<b>Legend</b>			
INR: international normalized ratio; BUN: blood urea nitrogen; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen;			

Patients with relative hyperlactatemia were also more likely to have a diagnosis of sepsis (56.2% vs. 34.1%,  $p < 0.001$ ),. Furthermore. they were more likely to receive vasopressors (5.0% vs. 2.2%,  $p = 0.015$ ), steroids (13.0% vs. 7.5%,  $p < 0.001$ ), and higher volumes of IV fluids in the first 24 hours ( $2.1 \pm 1.2$ ,  $p < 0.001$ ) compared to patients with lactate levels below 1.33 mmol/L. In-hospital mortality was higher in patients with relative hyperlactatemia (4.4% vs. 1.9%,  $p = 0.029$ ) compared to patients with lactate levels below 1.33 mmol/L. The outcomes are summarized in Table 3.

Table 3

Outcomes for patients with lactate &lt; 1.33 mmol/L and for patients with lactate ≥ 1.33 mmol/L

Variable	Lactate < 1.33 <i>n</i> = 415	Lactate ≥ 1.33 <i>n</i> = 1212	<i>p</i>
	n, %		
Mechanical ventilation	11 (2.7)	40 (3.3)	0.514
Vasopressor use	9 (2.2)	60 (5.0)	0.015
Steroid use	31 (7.5)	157 (13.0)	0.003
Antibiotic use	179 (43.2)	848 (70.1)	< 0.001
ICU admission	35 (23.2)	229 (24.7)	0.681
30-day readmission rate	86 (23.8)	243 (21.6)	0.376
In-hospital mortality	7 (1.9)	53 (4.4)	0.029
	Mean ± SD		
IV fluids in first 6 hours	1.21 ± 1.08	1.27 ± 1.19	0.308
IV fluids in first 24 hours	1.58 ± 1.52	2.07 ± 1.79	< 0.001
	Mean ± SD		
Length of stay (hours)	73.62 ± 190.96	141.05 ± 279.40	< 0.001
ED	7.89 ± 12.18	9.67 ± 13.73	0.013
ICU	14.62 ± 110.22	37.90 ± 190.07	0.003
GPU	51.11 ± 134.21	93.48 ± 190.96	< 0.001
<b>Legend</b>			
ICU: intensive care unit; IV: intravenous; ED: emergency department; GPU: general practitioner unit			

Table 4

Multivariate logistic regression adjusting for multiple characteristics and outcomes with the primary outcome as in-hospital mortality and the primary exposure as relative hyperlactatemia

In-hospital mortality				
	OR	95% C.I.		p
		Lower	Upper	
Lactate > 1.33	1.78	1.18	4.03	0.02
Dyslipidemia	0.360	0.171	0.759	0.007
Congestive heart failure	6.483	3.462	12.141	< 0.001
Immunocompromised	2.544	1.179	5.492	0.017
Stepwise: age, gender (reference: male), hypertension, diabetes, dyslipidemia, COPD, heart failure, immunocompromised, diagnostic category: respiratory; cardiovascular; neurologic; trauma; sepsis; gastrointestinal; lymphocyte count, WBC count				

## Multivariate logistic regression

After adjusting for the multiple confounding variables such as age, gender, laboratory results and comorbidities, we found that patients with relative hyperlactatemia had a 1.78 greater odds of in-hospital mortality (95% CI 1.18–4.03;  $p = 0.02$ ) than patients without.

## Subgroup analysis

The association between relative hyperlactatemia and mortality in various subgroups is demonstrated in Table 5. Relative hyperlactatemia was associated with increased hospital mortality consistently across the different subgroups, however the difference was only statistically significant in patients without hypertension (4.7% versus 1.1%;  $p 0.008$ ), patients without diabetes (4.2% versus 1.0%;  $p 0.01$ ), patients without dyslipidemia (5.4% versus 1.5%;  $p 0.008$ ) and patients without COPD (4.3% versus 1.8%;  $p 0.04$ ).

Table 5

- In-hospital mortality among patients with lactate < 1.33 mmol/L and patients with lactate > 1.33 mmol/L stratified by different patient subgroups

Patient subgroup		Lactate < 1.33 mmol/L	Lactate ≥ 1.33 mmol/L	p-value
Age	< 50	1 (1.0)	7 (3.6)	0.27
	≥ 50	6 (2.3)	46 (4.6)	0.09
Sex	Male	4 (2.2)	29 (4.5)	0.18
	Female	3 (1.6)	24 (4.4)	0.08
Diabetes	Yes	4 (5.3)	19 (5.0)	0.92
	No	3 (1.0)	34 (4.2)	0.01
HTN	Yes	5 (2.7)	30 (4.3)	0.33
	No	2 (1.1)	23 (4.7)	0.03
Dyslipidemia	Yes	3 (3.1)	9 (2.3)	0.65
	No	4 (1.5)	43 (5.4)	0.008
Immunocompromised	Yes	0 (0.0)	11 (7.6)	0.45
	No	7 (2.0)	41 (4.0)	0.08
CAD	Yes	2 (2.7)	20 (6.3)	0.23
	No	5 (1.7)	33 (3.8)	0.09
COPD	Yes	1 (3.4)	8 (5.8)	0.61
	No	6 (1.8)	45 (4.3)	0.04
CHF	Yes	0 (0.0)	25 (13.2)	0.07
	No	7 (2.1)	28 (2.8)	0.46
Sepsis	Yes	3 (2.4)	34 (5.9)	0.11
	No	3 (1.4)	14 (3.2)	0.17
Vasopressors	Yes	1 (11.1)	9 (15.3)	0.74
	No	6 (1.7)	44 (3.9)	0.046

## Discussion

The results of this study have shown that lactate levels of 1.33 mmol/L were found to have the optimal threshold to discriminate between survivors and non-survivors. Furthermore, relative hyperlactatemia

(1.33 mmol/L to 2.00 mmol/L) patients had 1.78 times greater odds of dying than patients with lactate < 1.33 mmol/L. The overall hospital mortality in our population was 3.8, with the relative hyperlactatemia subgroup having a higher mortality rate of 4.4% in patients with initial lactate  $\geq$  1.33 mmol/L, compared to 1.9% in patients with initial lactate < 1.33 mmol/L. Similar results were demonstrated in a study by Rishu et al. who looked at a discriminatory level of lactate in an intensive care unit and found that a cutoff value of 1.35 mmol/L adequately discriminated between survivors and non-survivors<sup>21</sup>. In addition, they also found that mild hyperlactatemia was an independent predictor of hospital mortality (OR 1.60; 95% CI 1.29–1.98). Defining hyperlactatemia as a serum lactate level greater than or equal to 2.00 mmol/L insinuates that lactate values between 1.00 and 2.00 mmol/L can be interpreted as normal<sup>22,23</sup>. Historically, authors have used the cutoff of 1.3 mmol/L to define hyperlactatemia<sup>2,24</sup>. Over the years, the reference ranges for hyperlactatemia have varied from lactate > 1.5 mmol/L to lactate > 2.5 mmol/L<sup>15,19,25</sup>. Following this, a number of studies found an increased mortality risk when using the cutoff lactate of > 2.0 mmol/L<sup>26,27</sup>. This led to the gradual adoption of 2.0 mmol/L as the cutoff that defines the reference range in contemporary literature and in the latest national and international guidelines<sup>1,22</sup>.

In our study, when we looked at the mortality among septic patients, relative hyperlactatemia patients had a higher mortality (4.4% versus 1.9%). They were also more likely to receive more antibiotics, vasopressors and IV fluids at 48 hours. A study by Trzeciak et al. found 70% of patients diagnosed with an infection had lactate levels below 2.00 mmol/L and a mortality rate of 15%<sup>28</sup>. Recent evidence suggests that even mild hyperlactatemia in patients with septic shock is predictive of mortality<sup>16,19,29,30</sup>. Furthermore, Shetty et al. found that patients with lactate levels between 1.00 to < 2.00 mmol/L had increased in-hospital mortality (OR 2.93) compared to patients with lactate levels < 1.00 mmol/L<sup>27</sup>. All of these studies are in line with our results which show that relative hyperlactatemia patients had 1.78 times greater odds of in-hospital mortality. Despite all this evidence, there remains a knowledge gap surrounding mild hyperlactatemia in the ED and it is still unknown whether patients with mild hyperlactatemia should be treated differently. Without a more nuanced understanding of lactate levels below the reference range of 2.00 mmol/L, ED physicians may be falsely reassured.

Similar to our results, Rishu et al. in the ICU specifically sought to determine the cutoff for lactate within the reference range that has the greatest prognostic value<sup>21</sup>. Using the Youden index, they found that the optimal cutoff was 1.35 mmol/L, and that relative hyperlactatemia above that cutoff was associated with increased hospital mortality (OR 1.60). This study adds stronger evidence that a lactate within the normal range should be interpreted cautiously as it may still be associated with an increased mortality.

Finally, it is also interesting that amongst the subgroup analysis, relative hyperlactatemia patients without any comorbidities were found to have a statistically significant increased mortality when compared to “normal” lactate levels. This is an important finding as it illustrates the important prognostic value of relative hyperlactatemia in healthy individuals versus patients with comorbidities. A possible

explanation could be due to the fact that patients with comorbidities are sicker at baseline and tend to raise their lactate more easily in the setting of an acute illness.

## Limitations

To the best of our knowledge, this investigation is the first to explore mild hyperlactatemia in a population of adult ED patients. It is important to note that our results have shown that relative hyperlactatemia patients were older and had higher rates of comorbidities, laboratory derangements, vasopressor use, steroid use, in-hospital mortality and IV fluid use. Our strengths include the large sample size and the standardized lactate measurement in the same laboratory for all patients. This study is limited by its retrospective nature and is thus prone to selection bias. Second, our inclusion criteria were restricted to patients on whom there was a clinical decision to draw a serum lactate level, and this also might have introduced a selection bias. Third, since the data pertains to a single center there may be limitations to the generalizability of the findings. In an attempt to minimize information bias, the authors held multiple meetings to ensure correct patient identification and underwent training to standardize the rigorous data abstraction protocol. The data collected is insufficient to define the most likely etiology of the mild hyperlactatemia or the effect of early interventions in patients with mild hyperlactatemia on clinical outcome although this was beyond the scope of this study.

## Conclusion

The optimal cutoff of initial serum lactate within the reference range that discriminates between survivors and non-survivors is in the ED 1.33 mmol/L. Relative hyperlactatemia is associated with increased in-hospital mortality in patients presenting to the ED regardless of diagnosis or co-morbidities. Further studies are required to determine the optimal management to patients with mild hyperlactatemia.

## Declarations

**Ethics approval and consent to participate:** Approved by the Institutional Review Board and carried out in accordance with the recommendations provided. The research was performed according to ethical principles and in compliance with all prevailing and applicable laws, rules and regulations and policies regarding the protection of human subjects and research conduct as outlined by the declaration of Helsinki. Subject privacy and data confidentiality were of paramount concern at all times, and every effort was made to protect subjects' rights and welfare.

**Contribution:** GAD, RBC, SJ have made substantial contributions to conception and design of the study . NM, RAA, KAD, NK, RS, and SJ were involved in acquisition of data, data entry, and data cleaning. MK and HT were involved in analysis and interpretation of data. RBC, GAD, SJ, and RS and have been involved in drafting the manuscript. RBC, GAD and HT were involved in revising manuscript critically for important intellectual content. All authors contributed substantially to its revision. GAD and RBC take responsibility for the paper as a whole.

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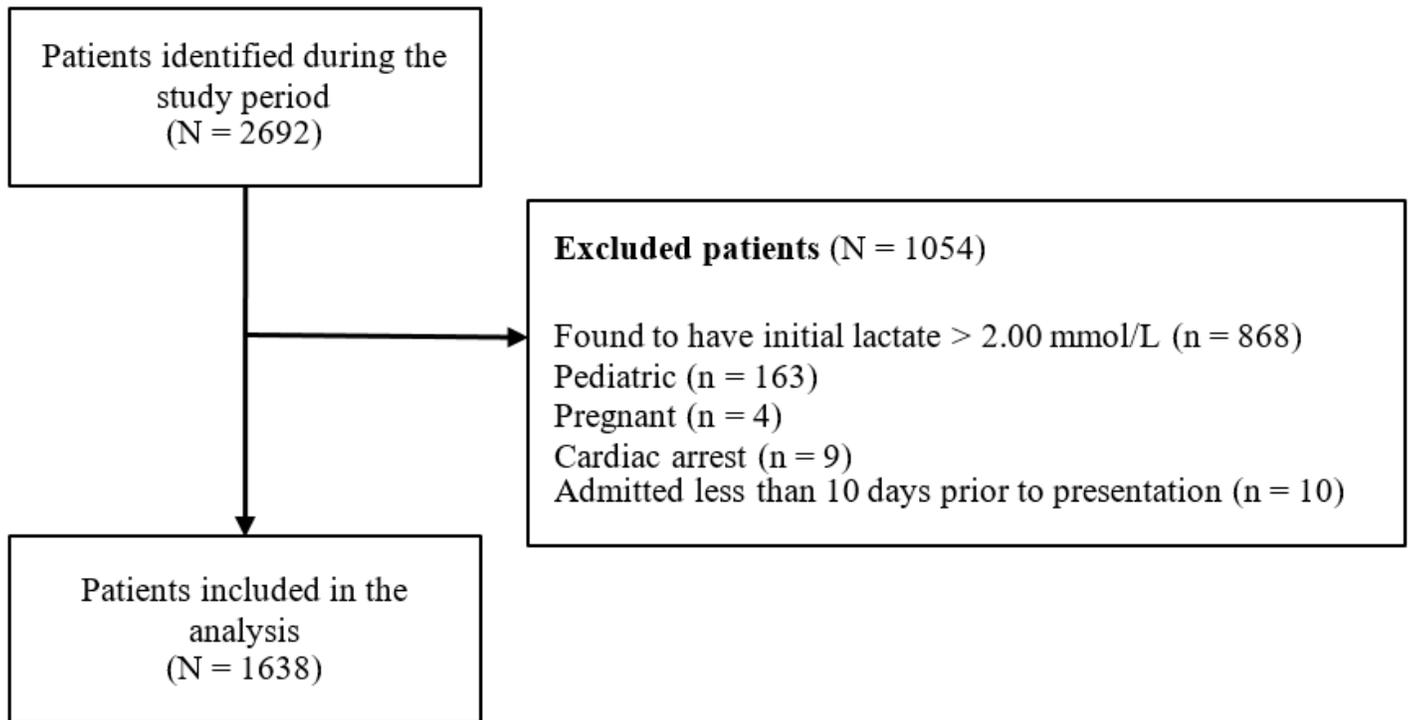
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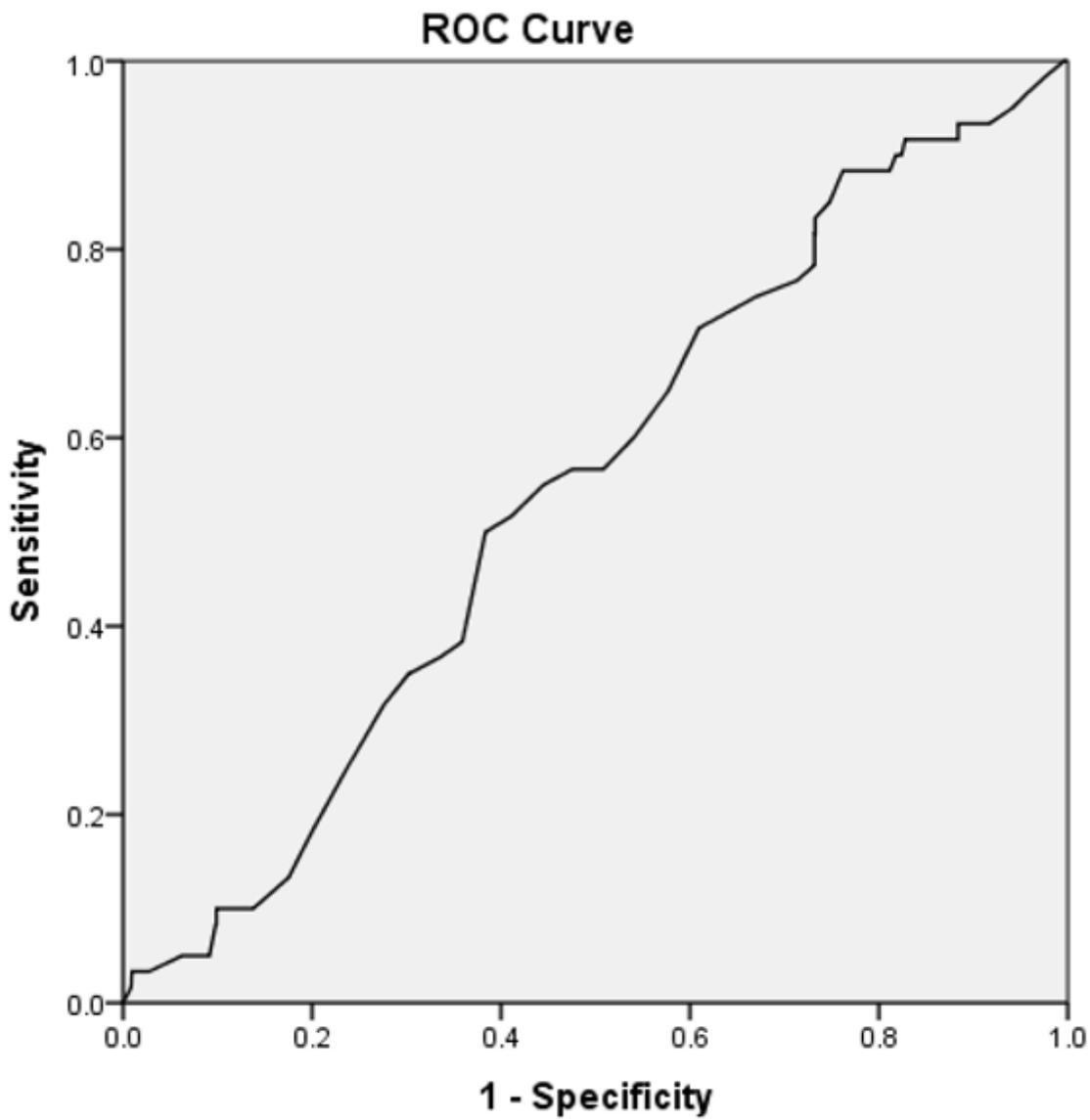
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## Figures



**Figure 1**

Flow diagram of patient selection



Diagonal segments are produced by ties.

Figure 2

Receiver operating curve and area under the curve.

## Supplementary Files

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