RESEARCH LETTER

The Use of Lactate-Capillary Refill Time Product as Novel Index for Tissue Perfusion in Patients with Abdominal Sepsis: A Prospective Observational Study

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Introduction

Septic shock is a life-threatening condition with mortality rate of up to nearly 40%. Septic shock is characterized by altered microcirculation that leads to tissue hypoperfusion and ultimately multi-organ dysfunction. Hence, maintenance of adequate tissue perfusion is the mainstay of resuscitation of patients with septic shock.[1]

Serum lactate is still considered the gold standard for evaluation of tissue perfusion.[2,3] Thus, according to the latest definition, elevated serum lactate, as an indicator of tissue hypo-perfusion, is required for diagnosis of septic shock.[4] However, the use of lactate in follow-up during resuscitation is limited by its slow kinetics even in survivors.[5] Capillary refill time (CRT) is a simple method for peripheral perfusion evaluation that showed good performance for guiding resuscitation[6] and was recently introduced as a surrogate to serum lactate level in the surviving sepsis campaign guidelines.[7] Each of the two parameters, CRT, and serum lactate, showed good performance as perfusion index. Serum lactate represents a marker of global tissue perfusion which is elevated in all types of dysoxia while CRT is mainly prolonged in cases of circulatory failure. We hypothesized that combination of the two parameters could improve their predictive ability.

Intra-abdominal sepsis is the second most common cause of sepsis after pulmonary sepsis and the associated mortality rate > 40%.[8] Furthermore, patients with intra abdominal sepsis usually require emergency laparotomy for source control of infection making them more vulnerable postoperatively.[9]

Thus, this study aimed to evaluate the accuracy of lactate-CRT product in predicting mortality in patients with septic shock after emergency laparotomy.

Patients and Methods

This prospective observational study was conducted in the surgical intensive care unit (ICU) of Cairo University Hospital after Research Ethics Committee approval (N182022) and clinical trial registration (NCT05289388) between March and June 2022. Written informed consent was obtained from patients' proxy before the enrolment.

We consecutively included adult (>18 years) patients with clinically suspected septic shock according to the latest definition of septic shock (sepsis-3)

> hypotension in a patient with sepsis requiring vasopressor therapy to maintain mean arterial pressure above 65 mmHg despite adequate fluid resuscitation in addition to elevated serum lactate level. (above 2 mmol/L)[4]

Patients with metastatic cancer, patients with expected death within 24 h, and patients with sepsis due to non-abdominal source were excluded from the study. We did not include patients with advanced liver disease (Child B or C liver

cirrhosis) or kidney disease (estimated glomerular filtration rate <30 mL/min/1.73m^2) into our study. Patients were managed according to the latest surviving sepsis campaign guidelines[7] and fluid therapy was according to the institutional local protocols.[10] All patients were followed up until discharge from the ICU or death.

On ICU admission, arterial blood gas sample, including serum lactate (blood gas analysis device GEM premier 300, Instrumentation Laboratory, Bedford, MA, USA), was obtained. Capillary refill time was evaluated by a single physician (defined as the time for finger nailbed to regain its color after applying a pressure to the nailbed that caused blanching). Both variables, serum lactate and CRT, were also measured 6 and 12 h after admission. Lactate-CRT index was calculated as the product of the two variables.

The primary outcome was the ability of Lactate-CRT index in predicting in-hospital mortality.

Other outcomes included the ability of CRT, serum lactate in predicting in-hospital mortality. Collected data included the Acute Physiology and Chronic Health Evaluation (APACHE) II score, mean arterial pressure, heart rate, respiratory rate, Glasgow coma scale, arterial pH, serum sodium, potassium, creatinine, and white cell count all obtained at ICU admission.

Sample Size

We calculated our sample size using MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium) to detect the accuracy of Lactate-CRT index in prediction of mortality. Assuming that the mortality rate in patients with septic shock is 40%, a sample size was calculated to detect an area under receiver operating characteristic curve (AUC) of 0.8, with null hypothesis at 0.5. A minimum number of 34 patients, with at least 14 mortality cases, would be needed for a study power of 90% and an alpha error of 0.05.

Statistical Analysis

Statistical analysis was conducted using the MedCalc Software version 14 and Statistical package for social science (SPSS) software, version 26 for Microsoft Windows (Armonk, NY, IBM Corp). Patients were divided into survivors and non-survivors. Normality of numerical data were assessed using the Shapiro–Wilk test. Data were expressed as frequencies (%), means (with standard deviation), or medians (with quartiles). To evaluate the ability of each of Lactate-CRT index, lactate, and CRT to predict mortality, receiver operating characteristic curves were constructed and the AUCs were calculated. The best cut-off value was calculated using the Youden's index and the corresponding sensitivity, specificity, positive and negative predictive values are presented. The AUCs were compared using the Hanley–McNeil test. Logistic regression analysis was performed to identify the odd ratio and 95% confidence interval (CI) for each of CRT, serum lactate and lactate-CRT index at each timepoint to predict in-hospital mortality. A multivariate analysis was performed including the serum lactate and CRT without the lactate-CRT index since the lactate-CRT index is the product of both variables. The level of significance was set at $P < 0.05$ for two-tailed tests.

Results

Thirty-six patients were screened for eligibility; and 2 patients were excluded for not fulfilling the inclusion criteria. Thirty-four patients were included and were available for the final analysis. The included patients had a mean age of 54 ±13 years and 15/34 (44%) were males. The median (quartiles) length of ICU stay was 6 (3, 11) days and 15/34 (44%) patients had died (Table 1). All the included patients were recruited after surgical source control, and 6/34 (18%) patients required reoperation.

The CRT, serum lactate, and lactate-CRT index at the time of admission were not able to predict patient's mortality (AUC [95% CI]: 0.64 [0.45 −0.79], 0.58 [0.40–0.75], 0.61 [0.42–0.77], respectively). However, both 6- and 12-h serum lactate and CRT were able to predict patient's mortality and the accuracy was slightly improved when the CRT-lactate index was used with AUC (95% CI) of 0.82 (0.65–0.93), and 0.85 (0.69–0.95) at 6- and 12-h, respectively. (Table 2) (Supplementary Figure 1) Comparison of CRT, serum lactate, and lactate-CRT index AUCs showed no statistical significance.

Table 1 Demographic Data, Hemodynamic and Physiologic Characteristics, and Outcome Data. Data Presented as Mean (Standard Deviation), Median (Quartiles), and Frequency (%)

Demographic Data	
Age (years)	54 (13)
Male sex	15 (44%)
Comorbidity (%)	
Hypertension	8 (24%)
Diabetes mellites	13 (38%)
Mild to moderate Chronic kidney disease*	3 (9%)
Acute kidney injury	3 (9%)
Clinical data	
Hear rate (beat per minute)	119 (17)
Mean arterial pressure (mmHg)	43 (9)
Respiratory rate (breath per minute)	22 (20, 28)
Glasgow coma scale	14 (13, 15)
APACHE II score	15 (12, 18)
Laboratory data	
pH	7.27 (0.12)
Sodium (mmol/L)	137 (6)
Potassium (mmol/L)	4.1 (0.6)
Creatinine (mg/dL)	1.4 (1.1, 1.7)
White cell count (x10^9/L)	20.7 (7.5)
Perfusion indices	
CRT (s)	
0	3.0 (1.8, 3.0)
6 h	2.0 (1.0, 4.0)
12 h	2.0 (1.0, 4.0)
Lactate (mg/dL)	
0	2.9 (2.4, 4.0)
6 h	2.5 (2.0, 3.7)
12 h	2.5 (1.5, 4.2)
Lactate-CRT index (s. mmol/L)	
0	7.8 (3.6, 12.1)
6 h	4.9 (2.1, 15.0)
12 h	5.5 (1.7, 13.1)
Outcomes	
Length of stay (days)	6 (3, 11)
Days of mechanical ventilation (days)	2 (1, 4)
Death	15 (44%)

Note: *Estimated glomerular filtration rate 30–89 mL/min/1.73m^2.
Abbreviations: APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II, CRT: capillary refill time.

Univariate analysis for the perfusion indices revealed that only the CRT is a predictor for in-hospital mortality; however, none of the perfusion indices was identified as an independent risk factor for in-hospital mortality in the multivariate analysis. (Supplementary Table 1)

Table 2 AUC Analysis for the Ability of CRT, Serum Lactate, and Lactate-CRT Index in Predicting in-Hospital Mortality

	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Cut-Off
6 h						
CRT	0.79 (0.62–0.91)	93 (68–100)	58 (34–80)	64 (41–83)	92 (62–100)	>1 s
Serum Lactate	0.80 (0.62–0.92)	93 (68–100)	53 (29–76)	61 (39–80)	91 (59–100)	>2 mmol/L
Lactate-CRT index	0.82 (0.65–0.93)	93 (68–100)	63 (38–84)	67 (43–85)	92 (64–100)	>3.4 s. mmol/L
12 h						
CRT	0.83 (0.67–0.94)	93 (68–100)	74 (49–91)	74 (49–91)	93 (68–100)	>1 s
Serum Lactate	0.83 (0.66–0.94)	100 (78–100)	68 (43–87)	71 (48–89)	100 (75–100)	>2.1 mmol/L
Lactate-CRT index	0.85 (0.69–0.95)	100 (78–100)	63 (38–84)	68 (45–86)	100 (74–100)	>2.1 s. mmol/L

Abbreviations: AUC, area under receiver of operating characteristics; CI, confidence interval; CRT, capillary refill time; NPP, negative predictive value; PPV, positive predictive value.

Discussion

We found that both parameters, CRT, and serum lactate, at 6- and 12-h, were able to predict patient's mortality and the combination of the two parameters slightly improved the accuracy.

Serum lactate is the gold standard in shock definition.[3] The use of peripheral perfusion markers could predict outcomes and guide fluid resuscitation in septic shock[3,11] and after major abdominal surgery.[12] In a recent randomized controlled trial, the ANDROMEDA SHOCK trial,[6] the use of CRT for guiding resuscitation showed better outcomes than lactate. Thus, the latest guidelines introduced the CRT for the first time as a marker of peripheral perfusion in patients with sepsis.[7] However, the CRT is a marker of poor oxygen delivery due to circulatory shock only and not due to other causes of poor oxygen delivery such as anemia and hypoxia. On the other hand, serum lactate is a global marker of dysoxia whatever the cause of impaired oxygen delivery. Serum lactate has several limitations such as being elevated in several aerobic conditions (liver impairment, infections, and convulsions); and having slow dynamics.[13] Hernandez et al had found that 50% of the survivors of septic shock had persistently elevated lactate 24 h after resuscitation.[14] Thus, the use of a combined index was hypothesized to provide a more comprehensive marker than the use of either marker alone.

We found that 6- and 12-h measurements of peripheral perfusion markers have better predictive values than the early admission markers. The low accuracy of the early measurements might be because all patients in our study were admitted after performing major abdominal surgery with prolonged time and major fluid shifts, and the markers of perfusion might had been affected by residual anesthesia and possible hypothermia. The cutoff value of the CRT was low and lies within the normal range. However, our results showed that this value has good negative rather than positive predictive value. Therefore, it is still useful as a screening tool to pick-up patients with predicted favorable outcomes.

Our study is a hypothesis-generating report that aimed to introduce the lactate-CRT index as a possible novel parameter for evaluation of peripheral perfusion in abdominal sepsis. The results showed slight improvement in the AUC with the use of lactate-CRT index compared to either of its components. However, future larger studies might show better predictive values in larger number of patients.

Our study had some limitations. It is a single center. We only included patients with abdominal sepsis post emergency laparotomy; hence, future studies are warranted to confirm our cutoff values and validate this index in other populations.

Conclusion

In conclusion, the use of lactate-CRT index, 6- and 12-h after ICU admission, slightly improved the performance of either of its components in predicting outcomes in patients with abdominal sepsis.

Abbreviations

APACHE II, Acute Physiology and Chronic Health Evaluation; AUC, area under receiver operating characteristics curve; CI, confidence interval; CRT, capillary refill time; ICU, intensive care unit; NPV, negative predictive value; PPV, positive predictive value.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author (Dr. Ahmed Hasanin, email: ahemdmohamedhasanin@gmail.com) upon reasonable request after permission of Cairo university.

Ethics Approval and Informed Consent

We conducted this study in accordance with Declaration of Helsinki and the Research Ethics Committee of Cairo University approved the conduction of this study (N182022). Written informed consent was obtained from all patients before the enrollment.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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