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Elevated venous lactate level as an early predictive marker of organ failure in acute pancreatitis: a retrospective study

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Abstract. – OBJECTIVE: The aim of this study was to elucidate the relationship between venous lactate levels and the severity of acute pancreatitis (AP).

PATIENTS AND METHODS: Retrospective data analysis was conducted on patients diagnosed with acute pancreatitis. The comparative assessment encompassed baseline characteristics, laboratory data, illness severity, local consequences, and organ failure instances. This comparison was performed between patients exhibiting normal serum lactic acid levels (HL) and those displaying elevated HL levels. The association between serum HL levels and other pertinent clinical markers was investigated using linear regression. Logistic regression analysis was employed to evaluate the utility of elevated serum lactate levels in identifying high-risk groups.

RESULTS: Significantly elevated serum HL levels were observed in patients with moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP) in contrast to those with mild acute pancreatitis (MAP) ($p<0.01$). Multivariate logistic analysis demonstrated that higher lactate levels independently predicted organ failure (95% CI 0.738-0.902, $p<0.05$). Receiver operating characteristic (ROC) curve analysis indicated that the lactate (LAC) cut-off value of 2.45 mmol/L yielded sensitivity and specificity values of 76.5% and 79.1%, respectively, for predicting AP-associated organ failure. The corresponding area under the curve (AUC) was 0.820.

CONCLUSIONS: In AP patients, elevated serum HL levels signify disease severity and hold predictive potential for assessing the risk of organ failure.

Key Words:
Venous lactate level, Predictive marker, Acute pancreatitis.

Introduction

Acute pancreatitis (AP) precipitates both local and systemic inflammatory response syndromes (SIRS), culminating in the potential for hospitalization due to gastrointestinal disorders[1]. This condition is categorized into three distinct classes: mild AP (MAP), moderately severe AP (MSAP), and severe AP (SAP)[2].

In the event of an early determination of the severity of AP, medical practitioners can implement targeted interventions such as fluid resuscitation, enteral nutrition[3,4] and antibiotic therapy[5]. These interventions hold the potential to substantially mitigate the incidence of complications, enhance overall prognosis, and curtail mortality rates[6]. Previous investigations[7-9] have underscored the association between elevated serum markers and the severity of AP, including but not limited to white blood cell count (WBC), C-reactive protein (CRP), procalcitonin (PCT), blood urea nitrogen (BUN), age, lactate dehydrogenase (LDH), and hematocrit. Furthermore, the predictive efficacy pertaining to localized pancreatic complications and organ failure remains suboptimal, necessitating the identification of novel markers. Lactic acid (HL), an end product of glycolysis, is regarded as a pivotal indicator of tissue hypoxia. The elevation of HL levels might be attributed to heightened mucosal permeability in patients[10]. The release of HL within the intestines may manifest earlier in specific segments of the gastrointestinal tract[11]. Severe acute pancreatitis (SAP) patients often experience pronounced intra-abdominal pressure, a factor that frequently exerts an impact on intestinal blood circulation. The impairment of intestinal wall metabolism can be attributed to the overarching influence of systemic inflammation[11,12]. Consequently, this can pave the way for bacterial translocation, a pivotal event believed to be instrumental in instigating pancreatic tissue necrosis and eventual organ failure[13,14].

For medical practitioners, the early detection of intestinal hypoperfusion or metabolic alterations

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during the clinical course of the disease holds profound significance. Notably, serum venous lactate levels have demonstrated the potential to prognosticate SAP, mortality, and admission to the intensive care unit (ICU)[15]. However, comprehensive insights pertaining to the relationship between serum venous lactate levels and the occurrence of organ failure remain limited.

Patients and Methods

Definitions

At least 2 of the following 3 points were used to diagnose acute pancreatitis: (1) persistent abdominal pain, (2) serum amylase at least three times the upper limit of the normal value, (3) findings consistent with AP on contrast-enhanced CT (CECT), magnetic resonance imaging (MRI), or ultrasound.

Patients

Consecutive patients diagnosed with acute pancreatitis at the Affiliated Hospital of Yangzhou University from January 2013 to October 2018 were enrolled. To be eligible for the study, patients had to meet the following criteria: abdominal pain starting no more than 72 hours before hospital admission, age 18 or older, venous HL levels measured within 2 hours of collecting other blood samples within 24 hours, and comprehensive medical records available. The primary outcomes under investigation encompassed the occurrence of local complications and organ failure.

The typical range for serum lactic acid is between 0.5 and 1.5 mmol/L. Patients whose lactic acid levels were ≤1.5 mmol/L were categorized into the normal lactic acid group, while those with levels >1.5 mmol/L were classified into the high lactic acid level group.

Statistical Analysis

The statistical analyses were performed using IBM SPSS, version 26.0 (IBM Corp., Armonk, NY, USA). Student's *t*-tests and Mann-Whitney U tests were employed for continuous variables, and results are presented as means accompanied by their corresponding standard deviations (SD). For categorical variables, Chi-square tests were utilized. The predictive accuracy of laboratory tests was evaluated through the area under the curve (AUC) analysis, sensitivity, and specificity tests, along with the calculation of a 95% confidence interval (CI). Logistic regression analyses were conducted to investigate the various indicators further. Multivariate analysis was carried out using a Cox regression model. A significance level of $p<0.05$ was deemed statistically significant. Significance levels are denoted as follows: $*p<0.05$, $**p<0.01$, $***p<0.001$.

Results

Demographic Characteristics of Participants

A total of 446 patients diagnosed with AP were included in the study (Table I). Within the normal serum HL group, the mean age was 51.9 years, with 63.2% of the patients being males. In contrast, the high serum HL group had an average age of 52.6 years, with 87.6% of the patients being males.

Table I. Demographic characteristics of participants.

Variable	Total (N=446)	Normal LAC (N=204)	High LAC (N=242)	*p*-value
Sex, male, N (%)	341 (76.5%)	129 (63.2%)	212 (87.6%)	0.493
Age, years (S±D)	52.23±16.37	51.88±16.06	52.62±16.76	0.415
Smoke, N (%)	141 (31.6%)	58 (28.4%)	83 (34.3%)	0.834
Alcohol, N (%)	95 (21.3%)	43 (21.1%)	52 (21.5%)	0.089
Comorbidities, N (%)				
Fatty liver disease N (%)	275 (61.7%)	117 (57.4%)	158 (65.3%)	0.098
Diabetes, N (%)	72 (16.1%)	28 (13.72%)	44 (18.2%)	0.135
Hypertension, N (%)	35 (7.8%)	16 (7.8%)	19 (7.9%)	0.237
CHD, N (%)	14 (3.1%)	11 (5.4%)	3 (1.2%)	0.058
Preclinical pancreatitis, N (%)	106 (23.8%)	47 (23.0%)	59 (24.4%)	0.565
Chronic pancreatitis, N (%)	4 (0.9%)	2 (1.0%)	2 (0.8%)	0.335
Pathogenesis				0.138
Biliary, N (%)	140 (31.4%)	67 (32.8%)	73 (30.2%)	
Alcoholic, N (%)	44 (9.9%)	21 (10.3%)	23 (9.5%)	
HTG, N (%)	168 (37.7%)	62 (30.4%)	106 (43.8%)	

Lactate (LAC); hypertriglyceridemia (HTG).

The Comparisons of Biochemical Parameters Between Normal HL Group and High HL Group

Regarding laboratory assessments, notable distinctions were observed between the two groups concerning variables such as white blood cell count, neutrophil count, hematocrit, aspartate aminotransferase, lactate dehydrogenase, and CRP percentage ($p<0.05$) (Table II). In the realm of disease severity and prognostic implications, the high lactate group exhibited a heightened classification within the Atlanta Classification system, elevated BISAP and RANSON scores, an augmented susceptibility to SIRS, and an increased propensity for local pancreatic complications and organ failure ($p<0.05$). These disparities demonstrated statistical significance (Table III).

Correlation Between LAC and Clinical Indicators

Further linear regression analysis between lactate and other clinical indicators showed that lactate has a significant correlation with advanced age (age greater than 60 years) (95% CI 0.017-0.530, $p=0.037$), SIRS (95% CI 0.075-0.151, $p=0.00002$), local pancreatic complications (95% CI 0.047-0.103, $p=0.00002$), organ failure (95% CI 0.068-0.137, $p=0.0004$), Atlanta classification (95% CI 0.120-0.200, $p=0.0001$), Bedside index for severity in acute pancreatitis (BISAP) score (95% CI 0.225-0.382, $p=0.00001$), RANSON score (95% CI 0.206-0.365, $p=0.0001$), white blood cell count (95% CI 0.559-1.242, $p=0.0001$), neutrophils cell percentage (95% CI 1.231-3.069, $p=0.0002$) and LDH (95% CI 1.975-2.386, $p=0.0001$) ($p<0.05$).

Table II. The comparisons of biochemical parameters between groups.

Variable	Normal LAC (N=204)	High LAC (N=242)	*p*-value
WBC*10^9/L (S±D)	9.7±4.0	13.5±5.0	<0.001***
NEUT% (S±D)	76.0±14.5	82.4±11.05	<0.001***
HCT% (S±D)	40.3±5.9	42.9±5.9	<0.001***
ALT, U/L (S±D)	93.2±147.5	105.3±153.3	0.399
AST, U/L (S±D)	92.7±159.6	124.8±182.3	0.048*
GGT, U/L (S±D)	153.1±222.8	194.5±266.2	0.079
ALP, U/L (S±D)	119.8±130.4	122.2±128.5	0.845
LDH, U/L (S±D)	229.8±194.9	273.4±174.6	0.013*
Cr, mmol/L	64.3±30.7	67.0±31.3	0.355
BUN, mmol/L (S±D)	4.8±1.77	4.7±2.30	0.595
GLU, mmol/L (S±D)	10.3±8.01	9.6±7.9	0.773
CRP (S±D)	42.8±66.9	87.5±117.4	<0.001***

White blood cell count (WBC), C-reactive protein (CRP), blood urea nitrogen (BUN), lactate dehydrogenase (LDH), hematocrit (HCT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), Lactate (LAC), Neutrophil (NEUT), Creatinine (Cr), Serum glucose (GLU). *$p<0.05$, ***$p<0.001$.

Table III. Biochemistry characteristics of participants.

Variable	Normal LAC (N=204)	High LAC (N=242)	*p*-value
Atlanta Classification MAP, N (%)	169 (82.8%)	156 (64.3%)	<0.001***
MSAP, N (%)	24 (11.9%)	66 (27.3%)	
SAP, N (%)	11 (5.3%)	20 (8.4%)	
BISAP scores			<0.001***
<2, N (%)	180 (88.2%)	168 (69.4%)	
≥2, N (%)	24 (11.8%)	74 (30.6%)	
RANSON scores			<0.001***
<3, N (%)	184 (90.2%)	176 (72.7%)	
≥3, N (%)	20 (9.8%)	66 (27.3%)	
Outcome			
SIRS, N (%)	27 (13.2%)	70 (28.9%)	<0.001***
Local complications, N (%)	11 (5.4%)	37 (15.3%)	<0.001***
Organ failure, N (%)	9 (4.4%)	31 (12.8%)	<0.001***

Lactate (LAC), Mild AP (MAP), moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP), systemic inflammatory response syndromes (SIRS). ***$p<0.001$.

Lactate and the Severity of APs

Serum venous HL levels were positively correlated with the Atlanta grade and were higher in patients with SIRS and organ failure (Figures 1-3).

Lactate as an Independent Risk Factor for Organ Failure

Logistic regression analysis was performed on all laboratory data. It was found that lactate level >2.45 mmol/L was an independent risk factor for organ failure (Figure 4). The AUC of >2.45 mmol/L at admission for predicting AP organ failure was 0.820 (95% CI 0.738-0.902), with a sensitivity of 76.5% and a specificity of 79.1%. Therefore, in this study, a lactate level >2.45 mmol/L

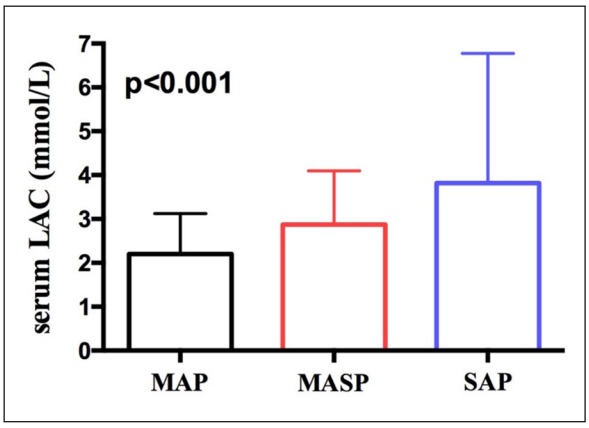

Figure 1. Serum LAC levels between patients with different disease severity.

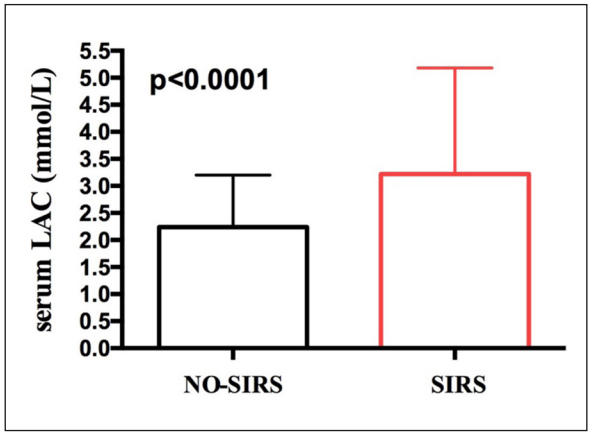

Figure 2. Serum LAC levels in NO-SIRS and SIRS.

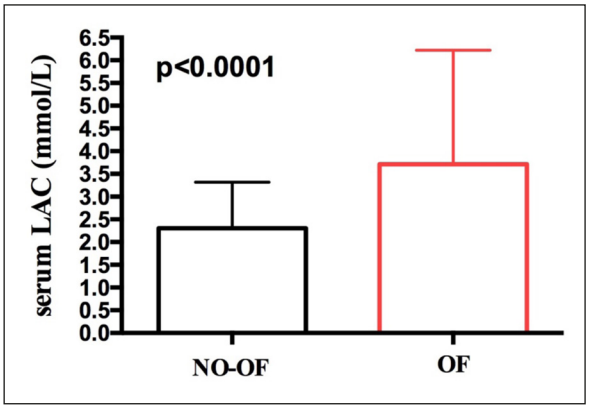

Figure 3. Serum LAC levels in patients without organ failure (NO-OF) and organ failure (OF).

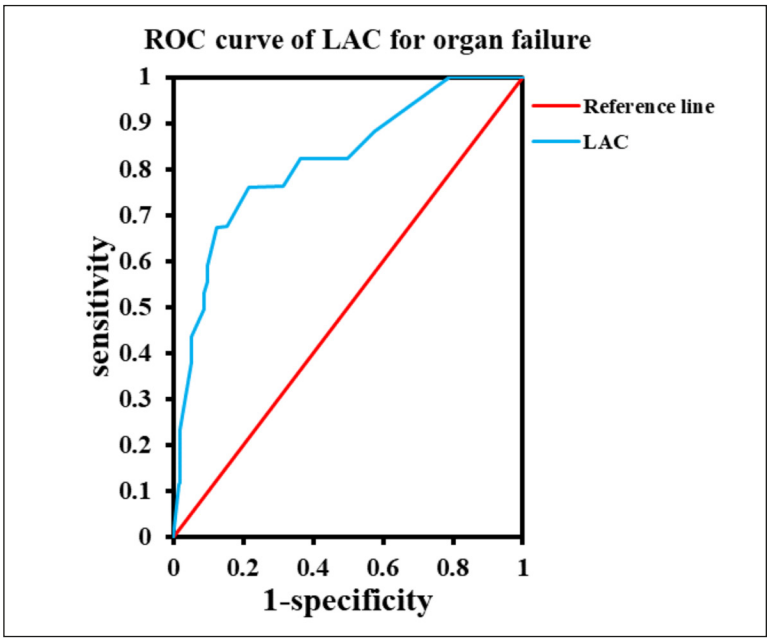

Figure 4. AUROC analysis of LAC in patients with AP and organ failure. AUC=0.820; $p<0.001$; 95% CI 0.738-0.902.

was identified as the cutoff value for diagnosing organ failure in AP (Table IV).

Discussion

Our investigation underscores a statistically significant differentiation in serum venous HL levels among the MAP, MSAP, and SAP groups, thereby signifying the capability of HL levels to reflect the severity of AP. Furthermore, serum venous HL levels exhibited a positive correlation with the Atlanta classification grade and were notably elevated in patients afflicted with SIRS and those experiencing organ failure. Moreover, our findings reveal that serum venous HL levels hold the potential as a straightforward yet efficacious predictor of organ failure in individuals presenting with acute pancreatitis upon admission.

In the current study, in approximately 80% of cases, AP presents with a mild form characterized by edema. However, nearly 20% of patients develop a severe or intricate trajectory of the disease, marked by either delayed or early systemic and local complications. The mortality rate associated with severe pancreatitis can ascend to 50%, whereas the collective mortality rate encompassing all forms of pancreatitis ranges between 2% and 5%[16].

One of the pivotal determinants impacting mortality in AP is the occurrence of organ failure and tissue infection in the peripancreatic region[17]. Illustrative instances of localized complications encompassing pancreatic pseudocyst, walled-off necrosis (WON), and pancreatic duct disruption syndrome (DPDS) have the potential to significantly contribute to elevated morbidity and mortality rates[18]. Nevertheless, the dearth of optimal early prognostic indicators remains conspicuous in predicting organ failure. Recent years have witnessed investigations[19] into predictors of pancreatic infection occurrence and progression in AP, with markers such as CRP, PCT, and LDH levels garnering attention. Our study underscores the substantial association between elevated venous HL levels and the severity of pancreatitis, as well as their prognostic relevance for organ failure.

In addition, serum HL levels hold the potential to foster the creation of novel predictive scores. Notably, they exhibit an AUC of 0.79 for the prediction of SAP and an impressive AUC of 0.8710 for prognosticating mortality, as demonstrated in the year 2017. A study conducted in 2019 by Shu et al[20] discovered a significant correlation. In the context of MSAP, patients with elevated arterial HL levels displayed an augmented incidence of pancreatic infection in comparison to those with normal arterial HL levels ($p<0.01$).

Moreover, we determined that venous lactate levels exceeding 2.45 mmol/L [Hazard Ratio (HR): 5.27, 95% CI 0.738-0.902; $p<0.01$] constituted an independent risk factor for organ failure. Elevated venous HL levels represent a crucial hallmark of ischemia and hypoxia. In the context of AP patients, the primary mechanism underlying the translocation of intestinal flora hinges on the impairment and dysfunction of the intestinal barrier, spurred by ischemia and hypoxia-induced damage[21,22]. Evidently, numerous experimental investigations[23] underscore that pancreatic tissue infection primarily stems from the translocation of intestinal bacteria. Furthermore, emerging research[24] alludes to the blood HL level as a potential marker for SIRS severity within the context of sepsis. This systemic inflammation curtails immune function and the body's capacity to eradicate pathogens,

Table IV. Multivariate analysis of risk factors for organ failure in AP.

Multivariate analysis	OR	Odds Ratios (95% CI)	*p*-value
Age	1.013	0.996,1.031	0.140
Male sex	1.478	0.876,2.491	0.143
Smoking	0.979	0.522,1.838	0.948
Alcohol	0.962	0.461,2.011	0.919
Diabetes on admission	1.001	0.990,1.012	0.854
WBC	0.975	0.883,1.075	0.607
NEUT	0.959	0.905,1.015	0.150
LAC	0.749	0.562,0.998	0.048**
LDH	1.000	0.997,1.003	0.768
HCT	1.021	0.971,1.073	0.418

White blood cell count (WBC), lactate dehydrogenase (LDH), hematocrit (HCT), Neutrophil (NEUT), Lactate (LAC). ** $p<0.01$.

consequently rendering pancreatic tissue susceptible to infection by intestinal bacteria[25]. Notably, in the presence of an infection, white blood cells escalate anaerobic glucose metabolism, thereby further elevating lactate levels[26,27].

Recommendations

First, the extensive scope of our sample selection spans a duration of 7 years, effectively mitigating the influence of selection bias. Second, this study pioneers the examination of the correlation between serum venous HL levels and the severity of AP. Importantly, we have established HL levels as an independent risk factor for the onset of organ failure. Third, the equivalence in baseline HL levels between the normal and high HL groups, without any statistically significant disparity, significantly attenuated selection bias. Fourth, to circumvent the influence of confounding factors such as CRP, LDH, white blood cell count, neutrophil percentage, etc., we conducted a comprehensive multivariate logistic regression analysis.

Nonetheless, our study is not devoid of limitations. Firstly, the retrospective nature of our investigation renders it susceptible to selection bias. In response, we adopted rigorous inclusion criteria and augmented our sample size to ameliorate this bias. Secondly, as lactate levels at the time of admission were not available for all AP patients, their data were excluded from our analysis. Despite these inherent limitations, the findings remain a valuable predictive indicator for early identification of the risk of organ failure in individuals with AP.

Conclusions

Our findings underscore the potential of blood HL as an early predictive marker for organ failure within the realm of AP. Nevertheless, to establish the robustness of this discovery, further comprehensive studies are imperative.

Ethics Approval

Ethics Committee approval was obtained from the Institutional Ethics Committee of "The First Affiliated Hospital of Soochow University" (acceptance number: FAHSU251) to start the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consent was obtained from each patient to publish the data.

Authors' Contributions

SX, NW, GY, YD, and CX designed the research, analyzed the data and wrote the manuscript, collected and recorded the demographic, clinical, and laboratory data, and performed the statistical analysis. All authors read and approved the final manuscript.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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