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Research Article

PREDICTIVE VALUE OF BLOOD URIC ACID LEVELS IN SEVERE ACUTE PANCREATITIS

Li Minghui

[1]Chongqing Medical University, Chongqing, China

Wang Xiaoyu

[2]Department of Critical Care Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, China

Abstract

Acute pancreatitis (AP) can manifest as a severe, life-threatening condition, and early identification of patients at risk of progression to severe acute pancreatitis (SAP) is crucial. This study explores the potential of blood uric acid (UA) levels as a marker for assessing disease severity and predicting prognosis in SAP patients. The research aims to provide a practical and efficient method for identifying high-risk patients and guiding timely interventions.

Keywords: acute pancreatitis, severe acute pancreatitis, uric acid, disease severity, prognosis

Introduction

Acute pancreatitis (AP) is essentially an inflammatory disease[1].With aggressive treatment, most patients with AP will be in remission within a week, but 20-30% of patients will progress to severe acute pancreatitis (SAP) with multi-organ failure and local or systemic complications, with a mortality rate of 8% to 25%[2] .Early identification of patients with more severe SAP can help guide physicians to more intensive monitoring and timely intervention[3]. Currently, the scoring systems commonly used to predict the severity and prognosis of SAP disease include the Acute Physiology and Chronic Health Evaluation (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score, and modified Marshall score, but they are impractical due to the calculate complexity[4-8].

UA is the end product of purine metabolism in the body. Hyperuricemia has been linked to the development and progression of inflammation in several diseases, including cardiovascular disease, diabetes, acute and chronic kidney disease, and acute respiratory distress syndrome[9-11]. As a prognostic marker, UA is highly correlated with disease severity and mortality in the development of myocardial infarction, pulmonary hypertension, diabetic nephropathy, chronic obstructive pulmonary disease, and sepsis[12-17]. Elevated admission UA levels are often observed in patients with SAP. However, the role of UA in assessing disease severity and predicting prognosis in SAP patients has not been investigated.

Therefore, this study aimed to investigate the correlation between blood uric acid and disease severity, complications, and prognosis in patients with SAP.

1. Materials and Methods

2.1 Participants

Clinical data of 294 patients with SAP admitted to the intensive care unit of The First Affiliated Hospital of Chongqing Medical University from 2013 to 2020 were collected retrospectively. All patients were diagnosed by the 2012 Atlanta International Consensus[8]. SAP was defined as patients with AP presenting with persistent organ failure (≥48 hours). Exclusion criteria: (1) recent history of oncological radiotherapy or

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chemotherapy; (2) patients with stage III-IV chronic kidney disease and gout; (3) patients under the age of 18; (4) patients who were pregnant, lactating, with incomplete data, abandoned and transferred (Figure 1).

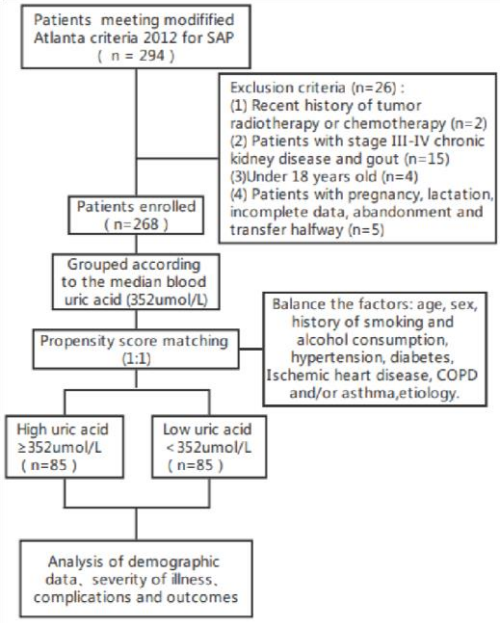

Figure 1 The flow chart.

2.2 Ethics Approval

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

2.3 Data Collection and Assessments

General information on admission was collected in the medical record system, including gender, age, etiology, smoking, drinking, and co-morbidities. Acute Physiology and Chronic Health Assessment (APACHE II) score, Sequential Organ Failure Assessment (SOFA score), and Modified Marshall score were completed within 24 hours of admission. Observed tests include admission blood uric acid (UA), creatinine (CREA), and calcitonin (PCT). Complications include abdominal hemorrhage, infected pancreatic necrosis (IFN), and intra-abdominal hypertension (IAH) occurring during hospitalization. Criteria for abdominal hemorrhage: Significant hemodynamic deterioration and/or a sharp drop in hemoglobin concentration >20g/L due to an abdominal bleeding event during or after AP, abdominal hemorrhage on ultrasound, CT, or bloody turbid fluid on laparotomy[18]. Criteria for IFN: Bacteria and/or fungi cultured in peritoneal lavage or peripancreatic puncture fluid or gas within the collection seen on enhanced CT of the abdomen[8]. Criteria for IAH: Intra-abdominal pressure (IAP) ≥ 12 mmHg[19].During hospitalization, treatment such as mechanical ventilation and hemofiltration were recorded, as well as prognoses such as ICU stay, duration of hospitalization, and mortality.

2.4 Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software (SPSS Inc, Armonk, NY) and GraphPad Prism 9.0 (GraphPad Software, San Diego, California). Continuous variables are expressed as medians (quartiles) for non-normally distributed variables (Kolmogorov Smirnov test), and the MannWhitney U test

was used to compare two groups. Categorical variables are presented as count (proportion) and were compared using the chi-square test. Propensity score matching (PSM) was performed to control for the baseline characteristics and clinical conditions between the two groups at a ratio of 1:1. The Wilcoxon signed-rank test and McNemar test were used to compare the continuous variables and categorical variables between the two groups in the propensity score-matched population. Spearman's correlation analysis was used to determine whether uric acid levels correlated with disease severity and prognosis, with $r > 0$ being a positive correlation and $r < 0$ being a negative correlation. The area under the curve (AUC) and 95% confidence interval were calculated to determine the optimal threshold value for UA based on the trade-off between sensitivity and specificity. $p<0.05$ was considered a statistically significant difference.

3. Results

3.1 Patient Characteristics

A total of 268 patients with SAP were included in this study, 174 males and 94 females, with a median age of 48 years (38.5 - 59 years). The etiological classification includes 147 patients (55%) with hyperlipidemic SAP, 73 patients (27%) with cholestatic SAP, 6 patients (2%) with alcoholic SAP, and 42 patients (16%) with unknown causes. The group was divided into a high UA group (≥352umol/L, n=132) and a low UA group (<352umol/L, n=136) based on median UA levels on admission. We discovered significant differences in baseline characteristics and clinical conditions between the two groups across the research population, including age, gender, smoking, alcohol use, diabetes, and etiology. To balance the heterogeneity between the two groups, we used propensity score matching (1:1), and there were no differences in baseline information between the 85 pairs of patients after propensity score matching.

There was no statistical difference in the incidence of ARDS, AKI, or the need for mechanical ventilation between the two groups ($P > 0.05$), but more patients in the high UA group required continuous renal replacement therapy than in the low UA group (74 vs. 62, $P = 0.026$) (Tables 1).

Table 1. Comparisons of baseline in the propensity score-matched population

Parameters	High uric acid (n=85)	Low uric acid (n=85)	P value
Age, year	48(39-59)	48(42-59)	0.657
Sex, Male	60 (70.59)	61 (71.76)	1.000
Etiology, n (%)			
Hyperlipidemia	43 (50.59)	42 (49.41)	1.000
Biliary	26(30.59)	26(30.59)	1.000
Alcoholic	2(2.35)	2(2.35)	1.000
Others	14(16.47)	15(17.65)	1.000
History, n (%)			
Cigarette	43 (50.59)	45 (52.94)	0.839
Alcohol	42 (49.41)	48 (56.47)	0.286
Co-morbidities, n (%)			
Hypertension	24 (28.24)	24 (28.24)	1.000

Diabetes mellitus	24 (28.24)	22 (25.88)	0.832
Ischemic heart disease	6(7.06)	6(7.06)	1.000
COPD and/or asthma	1(1.18)	1(1.18)	1.000
Laboratory investigations	2(2.35)	4(4.71)	0.687
CREA, umol/l	132(83-254)	68.5 (55.5 - 88)	**0.000**
PCT, ng/ml	8.84 (2.4 - 22.57)	1.815 (0.6 - 6.065)	**0.000**
Complication, n (%)			
ARDS	84 (98.82)	79 (92.94)	0.125
AKI	33 (38.82)	31 (36.47)	0.868
Intra-abdominal hemorrhage	10 (11.76)	6(7.06)	0.454
IFN	20 (23.53)	8 (9.41)	**0.029**
IAH	44 (51.76)	43 (50.59)	1.000
Treatment, n (%)			
Need for CRRT	74(87.06)	62 (72.94)	**0.026**
Need for MV	77 (90.59)	74(87.06)	0.629
Disease severity score			
APACHE II score	16(12-21)	13(10-16)	**0.001**
SOFA score	6(4-8)	4(3-6)	**0.011**
Modified Marshall score	3(3-5)	3(2-4)	**0.012**
BISAP score	3(2-3)	3(2-3)	0.650
Clinical outcomes			
ICU stay	12(6-18)	7(4-13)	**0.004**
Duration of hospitalization	25(16-37)	21 (14-25.5)	**0.004**
Death, n (%)	15(17.65)	9 (10.59)	0.238

Data were presented as median (range) and n (%). The comparison was determined by Wilcoxon symbolic rank test and McNemar test. $p < 0.05$ was statistically significant.

3.2 Associations of uric acid levels with clinically relevant outcomes

The index of renal impairment (CREA) was higher in the high UA group versus the low UA group (P<0.05) and there was a positive correlation between UA and CREA (r=0.42, P=0.000). We also measured the expressions of inflammation markers (PCT), and the results revealed a statistical difference in PCT levels between the two groups (P<0.05) and that there was a correlation between UA and PCT (r=0.17, P=0.000).

APACHE II score, SOFA score, and modified Marshall score were higher in the high UA group than in the low UA group (P<0.05), and there was a positive correlation between UA and APACHE II score (r=0.21,

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P=0.006, Fig. 2A), SOFA score (r=0.22, P=0.005, Fig. 2B), and modified Marshall score (r=0.22, P=0.005, Fig. 2C). The high UA group had significantly longer ICU stay (P=0.004) and duration of hospitalization (P=0.004) than the low UA group, and there was a positive correlation between high UA and ICU stay (r=0.21, P=0.007, Fig. 2D) and duration of hospitalization (r=0.42, P=0.000, Fig. 2E) (Table 2). Mortality was higher in the high UA group than in the low UA group (17.65% vs. 10.59%, P=0.238), although there was no statistical difference.

Table 2 Associations of uric acid levels with clinically relevant outcomes

Parameters	rs coefficient	P value
CREA	0.42	0.000
PCT	0.17	0.025
APACHE II score	0.21	0.006
SOFA score	0.22	0.005
Modified Marshall score	0.22	0.005
ICU stay	0.21	0.007
Duration of hospitalization	0.42	0.000

The correlation was determined by Spearman test, and P < 0.05 was considered significant.

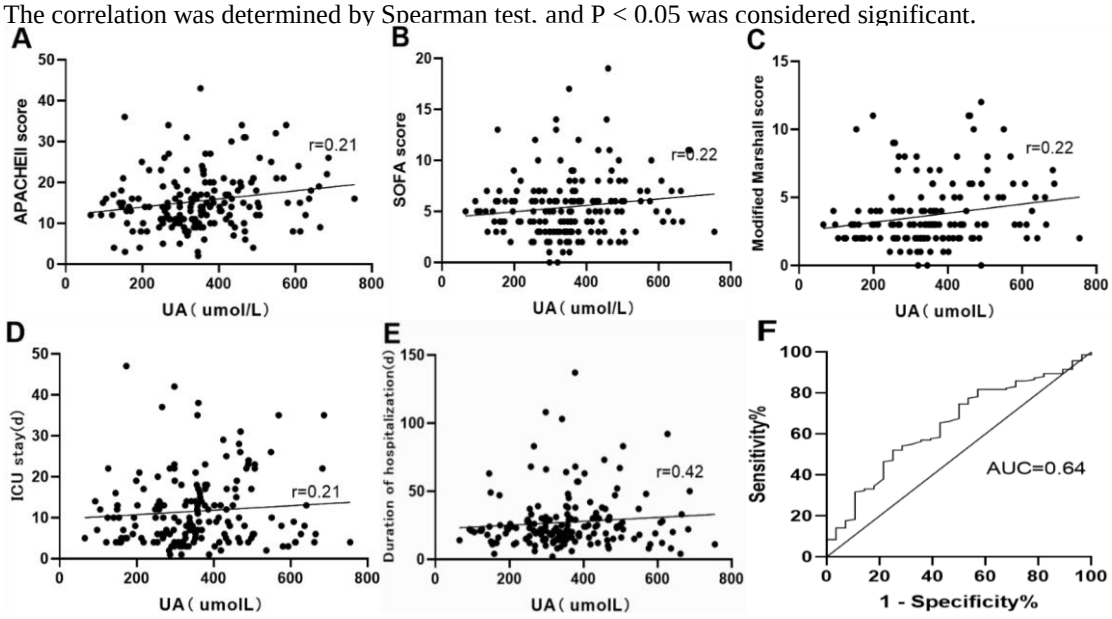

Figure 2. Correlation of UA with APACHE II score(A), SOFA score(B), ModifiedMarshall score(C), ICU stay (D), Duration of hospitalization(E).ROC curves of UA levels for predicting IFN in patients with SAP(F).Abbreviation: CRRT, continuous renal replacement therapy.MV, mechanical ventilation.

3.3 Comparison of the predictive value between UA levels and other indexes for infectious pancreatic necrosis in patients with SAP

The incidence of abdominal hemorrhage and intra-abdominal hypertension did not differ statistically between the two groups, but the incidence of infected pancreatic necrosis was higher in the high UA group

than in the low UA group (20 vs. 8, P=0.029). The ROC curves were plotted for each index to predict IFN in SAP patients, and the sensitivity, specificity, and AUC were calculated. the AUCs of UA, APACHE II score, SOFA score, and modified Marshall score for infected pancreatic necrosis were 0.642 (Fig. 2F), 0.690, 0.601, and 0.611, the predictive ability of UA was similar to that of APACHE II score, SOFA score, and modified Marshall score, and with a cut-off value of 258.5 umol/L. The capacity to predict IFN was improved by combining UA and those disease scores. (Table 3).

Table 3 Diagnostic efficiency of UA, APACHE II score, SOFA score, Modified

Parameters	Sensitivity	Specificity	AUC (CI 95%)	Cut-off value	P value
UA	0.893	0.246	0.642 (0.535-0.75)	258.5	0.017
APACHE II score	0.714	0.648	0.690 (0.587-0.792)	15.5	0.002
SOFA score	0.714	0.451	0.601 (0.483-0.719)	4.5	0.091
Modified Marshall score	0.321	0.915	0.611 (0.484-0.737)	6.5	0.065
UA+APACHE II score	0.893	0.521	0.721 (0.625-0.816)	-	0
UA+SOFA score	0.821	0.465	0.662 (0.557-0.767)	-	0.007
UA+Modified Marshall score	0.786	0.486	0.662 (0.549-0.775)	-	0.007

Receiver operating characteristic curve analysis of uric acid and other indexes for predicting infectious pancreatic necrosis in patients with SAP.

4. Discussion

In our study, the prevalence of hyperlipidemic SAP was 54%, higher than in a recent study in China (40.82%)[20], which may be related to local dietary habits (high-fat diet). The analysis revealed that patients with high UA needed longer hemofiltration and mechanical ventilation; UA has positively correlated with CREA, PCT, disease severity, ICU stay, and overall hospital days; and UA had predictive value for IFN comparable to well-known scoring systems like the APACHE II score, SOFA score, and modified Marshall score.

UA is a purine metabolite, 80% of which is produced by nucleoside metabolism in human cells and 20% is obtained from food[21]. The kidneys excrete the majority of UA (65-75%), while the intestine excretes the remaining (25-35%)[22]. In this study, UA was positively correlated with markers of renal impairment (CREA), which may be explained that SAP often caused AKI and led to reduced renal excretion of UA through systemic inflammatory responses and hypovolemia.

Previous research has shown that UA causes endothelial dysfunction by inducing oxidative stress and inflammatory responses that damage the intrarenal microvasculature, reduce endothelial NO levels, and inhibit epithelial cell proliferation and migration, thereby reducing renal blood flow and glomerular filtration rate (GFR)[23-24].Uric acid not only causes oxidative stress in human vascular endothelial cells, but it also stimulates endothelial cells to produce ICAM-1, IL-1, and other inflammatory factors via the renin-angiotensin system (RAS), promoting endothelial cell senescence and apoptosis[25-26]. In our study, more patients in the high UA group required continuous renal replacement therapy than in the low UA group.

UA causes oxidative stress in cells, as well as the activation of various intracellular signaling pathways[22]. High blood uric acid modulates the leukocyte response to inflammatory patterns via epigenetic modifications such as histone methylation, promoting the release of pro-inflammatory cytokines such as IL-1b and IL-6, inhibiting the release of IL-1Ra, increasing ROS production, stimulating chemotaxis, and activating the NF-kB and mitogen-activated protein kinase pathways[27-29]. It has been shown that elevated serum uric acid levels are associated with high-sensitivity C-reactive protein(hs-CRP), tumor necrosis factor-α(TNF-α), superoxide anion (O_2-), and hydrogen peroxide (H_2O_2)[30-31]. In this study, we also discovered a link between serum UA levels and the inflammatory marker PCT.

In terms of the value of UA as a marker of disease severity and prognosis, previous research has shown that hyperuricemia is significantly linked to a higher risk of 90-day all-cause mortality and AKI incidence in patients with sepsis in the ICU[17]. A retrospective study showed a positive linear relationship between UA at non-crystalline but higher than normal levels and the incidence of AKI and the need for dialysis during hospitalization in patients with various diseases[32]. Another study discovered that among ARDS patients intubated in the ICU for mechanical ventilation, a larger proportion of patients in the high UA group (3.0 mg/dL) died of septic shock, and high UA levels were substantially related to higher in hospital mortality[11]. In this study, UA levels were positively correlated with disease severity, ICU stay, and total hospital durations, but not with mortality. The possible mechanism for this is that high blood UA may lead to increased systemic inflammatory response and pancreatic microcirculation disorders by enhancing the production of pro-inflammatory mediators and inhibiting the anti-angiogenic effect of cellular NO production in vivo, which in turn affects the disease severity and prognosis of SAP.

Infectious pancreatic necrosis and septic complications are major clinical problems leading to high mortality in the late phase of AP (after 14 days of onset). In a retrospective study involving 711 patients with AP, intra-abdominal pressure (IAP), acute physiology and APACHE II score, CTSI, SAP, and admission to ICU were identified as risk factors for predicting abdominal infection[33]. In another study of 163 SAP patients, the extensive anatomical spread of necrotic material, AP due to interventional procedures, bacteremia, and open abdominal treatment were identified as independent risk factors for IPN[34]. In our study, the AUC, sensitivity, and specificity of UA levels for predicting IFN were 0.642 (95% CI= 0.535-0.75), 0.893, and 0.246, respectively, which were comparable to the AUCs of commonly used scoring systems such as APACHE II score, SOFA score, and modified Marshall score, and UA improved the AUC of the above scoring systems for predicting IFN when combined. But those scores had limited predictive power for IFN in the current study, with AUCs mostly between 0.6 and 0.7, which was consistent with other studies' findings[35]. Considering that the above indexes were collected within 24 hours after admission, APACHE II score, SOFA score, and modified Marshall score primarily reflected the severity of systemic inflammatory reaction at the time of admission and had low efficacy in assessing local complications later. The possible mechanism of UA level in predicting IFN is that uric acid damages vascular endothelial cells through inflammatory response and

oxidative stress, leading to increased permeability of mesenteric vessels and intestinal wall[36-38], exacerbates intestinal edema and intestinal bacterial migration, and increases the risk of IFN.

Our study has the following limitations. First, this study was retrospective; however, we performed propensity score matching to achieve balanced comparable baseline information between groups; second, the data in this study were only from one tertiary hospital and could not be generalized to other institutions, and a multicenter study with larger sample size is required; and finally, this study focused only on admission to UA and did not follow up on the value of its dynamics for the assessment of SAP conditions.

5. Conclusions

In conclusion, SAP patients admitted with high UA level have higher disease severity and longer hospital stay, and UA level is associated with IFN in SAP patients. It is suggested that UA level can be used as a convenient indicator of disease severity and IFN risk in SAP patients.

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Abbreviations

AP: acute pancreatitis

SAP: severe acute pancreatitis

UA: uric acid

CREA: creatinine

PCT: calcitonin

APACHE II: Acute Physiology and Chronic Health Evaluation score

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SOFA: Sequential Organ Failure Assessment score

IFN: infected pancreatic necrosis IAH: intra-abdominal hypertension hs-CRP: high-sensitivity C-reactive protein

TNF-α: tumor necrosis factor-α

O_2-: superoxide anion

H_2O_2: hydrogen peroxide

GFR: glomerular filtration rate