

## Original Article

# Prognostic significance of ischemia-modified albumin for severe acute pancreatitis

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**Abstract:** *Background:* Severe acute pancreatitis (SAP) is characterized by the noxious combination of severe systemic inflammation and hypoperfusion and oxidative stress. Ischemia-modified albumin (IMA) was recognized as a novel marker of oxidative stress and ischemia. The purpose of this study was to evaluate serum IMA level in patients with SAP and analyze its prognostic significance. *Methods:* A total of 72 patients with SAP were enrolled. Serum IMA level was measured within 24 hours of the onset of SAP, and baseline characteristics were recorded. The BISAP, APACHE II and SOFA scores were calculated. Multivariate logistic regression and receiver operating characteristic curve analyses were used to evaluate predictive ability of LMA for in-hospital mortality of SAP. Kaplan-Meier analysis was further used to compare in-hospital mortality difference between high LMA and low LMA. *Results:* The overall in-hospital mortality rate of all 72 SAP patients was 23.6%. Non-survivor group had higher serum IMA ( $107.2 \pm 10.8$  VS  $88.4 \pm 11.9$ ,  $P < 0.05$ ) than survivor group. Otherwise, the optimal cutoff levels for the IMA predicting in-hospital mortality of patients with SAP was 112 U/ml using a sensitivity of 77.4% and a specificity of 76.2% as optimal conditions (AUC, 0.734; 95% CI: 0.615-0.852;  $P = 0.002$ ). IMA level also was confirmed as an independent prognostic factor for SAP in multivariate analysis. Patient with high IMA level ( $\geq 112$  U/ml) had poorer survival rate than low IMA ( $< 112$  U/ml) in log-rank test of Kaplan-Meier survival analysis ( $P < 0.05$ ). *Conclusions:* Serum IMA level can be considered as an independent predictor for in-hospital mortality of patients with SAP.

**Keywords:** Ischemia-modified albumin, severe acute pancreatitis, mortality, prognosis

## Introduction

Severe acute pancreatitis (SAP) is an acute inflammatory process of pancreas involving of local tissues and remote organs and complicating organ failure and/or local complications, which remains the most frequent gastrointestinal presentation to emergence units, with rising incidence and high mortality rate [1-3]. Despite advances in the comprehensive management, prognosis of SAP is far from satisfying [4]. Stratification of the patients though identifying prognosis is important for providing individualized therapeutic interventions for patients with different risk level, thus improving clinical efficacy of SAP [5].

One of the most important pathophysiologic mechanisms leading to early mortality of SAP is the noxious combination of severe systemic inflammation and hypoperfusion [6]. It has been reported that tissue hypoperfusion and

oxidative stress can result to overproduction of reactive oxygen species (ROS), which play prominent roles in the mechanism of inflammatory responses during SAP [7-9]. Furthermore, the overproduced ROS was able to directly or indirectly damage cell and tissues and result in organ dysfunction and histological changes, thus lead to the development of multiple organ failure and death [10, 11]. Early recognition of the above progress may be helpful for risk stratification and timely clinical intervention.

Ischemia-modified albumin (IMA), a novel marker of oxidative stress and ischemia, is a metabolic variant of protein results from altering binding capacity of albumin for transition metals during acute ischemic conditions [12]. It has been recognized that elevated IMA levels in most patients with different types of ischemic diseases [13-15]. Moreover, IMA has prognostic significance in patients with end-stage renal diseases and acute coronary diseases [16, 17].

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**Table 1.** Correlation between clinicpathologic characteristics and in-hospital mortality in patient with severe acute pancreatitis

Characteristics	Total (n=72)	Survivors (n=55)	Non-survivors (n=17)	P
Male	53 (73.6%)	40 (72.7%)	13 (76.5%)	
Age (y)	53.4±11.2	52.1±12.8	55.2±13.0	0.579
BMI (kg/m <sup>2</sup> )	26.2±2.3	26.3±2.6	26.5±1.5	0.764
Length of stay (d)	23.2±18.2	24.5±17.3	18.4±13.8	0.885
Pain-to-admission time (h)	11.4±8.3	12.5±6.5	9.8±4.2	0.112
Etiology				0.095
Biliary	22 (30.6%)	11 (20.0%)	8(58.8%)	
Alcoholic abuse	39 (54.2%)	34 (61.8%)	7 (29.4%)	
Hyperlipidemia	11 (15.2%)	9 (16.4%)	2 (11.8%)	
Comorbidity				0.655
Hypertension	26 (36.1%)	19 (34.6%)	7 (41.2%)	
Diabetes Mellitus	28 (38.9%)	23 (41.8%)	5 (29.4%)	
Fatty Liver	18 (25.0%)	13 (23.6%)	5 (29.4%)	
Treatment				0.001
Conservative	41 (56.9%)	38 (69.1%)	3 (17.6%)	
Percutaneous drainage	12 (16.7%)	6 (10.9%)	6 (35.3%)	
Surgery	19 (26.4%)	11 (20.0%)	8 (47.1%)	
Laboratory data				
IMA	96.3±12.6	88.4±11.9	107.2±10.8	<0.001
Albumin (g/L)	31.2±5.3	32.6±6.2	26.8±5.2	<0.001
CRP (mg/L)	112.5±89.8	92.4±84.5	152.5±200.8	0.079
APACHE II score	16.1±5.8	13.2±6.2	22.1±8.7	<0.001
SOFA score	8.1±4.8	6.8±4.8	9.7±4.2	0.028
BIASP score	2.5±1.8	2.0±1.1	2.8±1.2	0.012

BMI, body mass index; IMA, ischemia-modified albumin; CRP, C-reactive protein; BISAP, the Bedside Index of Severity in Acute Pancreatitis score; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment score.

For patients with SAP, IMA level may be used to quantify the degree of ischemia and oxidative stress in process of severe systemic inflammation and predict the prognosis. However, there was no data regarding the prognostic value of IMA levels in patients with SAP. In this study, we try to study IMA levels in patients with SAP and analyzed its prognostic significance.

### Materials and methods

#### Patients

This prospective study enrolled seventy-two consecutive patients with SAP admitted to Emergency Department in the First Affiliated Hospital of Xin-Xiang Medical University from July 1, 2014, to July 1, 2016. The diagnosis of SAP was made by according to the criteria proposed by revised Atlanta 2012 classification

diagnosis of SAP [18]. The inclusion criteria were clinically confirmed SAP, age older than 18 years, and life expectancy of more than 24 hours. Patients were excluded if they had other ischemic diseases, severe cardiac or neurological disorders, malignant disease, chronic inflammatory disease, acute and chronic infective disease, preexisting organ failure, chronic obstructive airways disease and immunosuppressive disorders. In addition, patients had extremely low or high serum albumin levels (<20 or >55 g/L) were also excluded [19, 20]. Written informed consent was obtained from individual patients and subjects. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xin-Xiang Medical University.

#### Clinical assessment

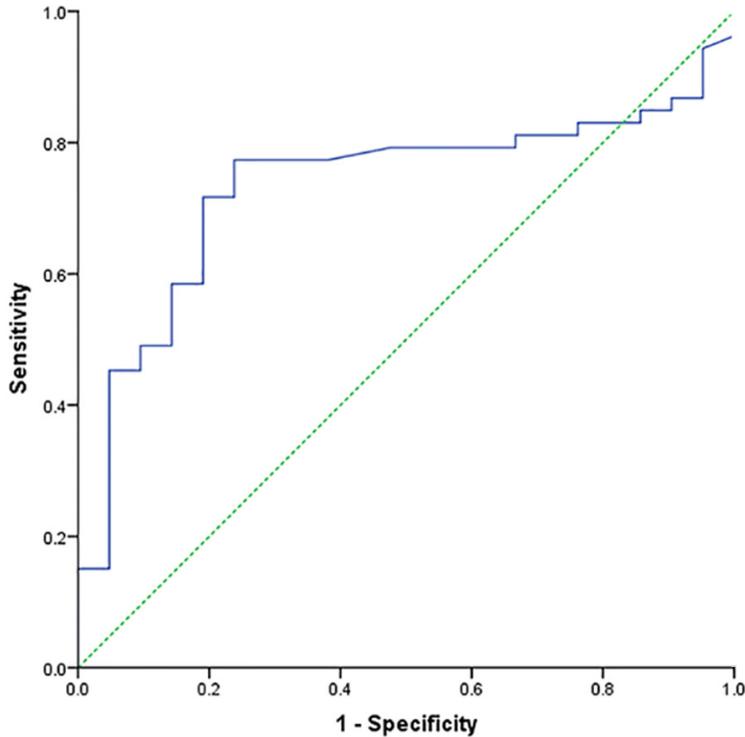
Demographic characteristics of all patients was recorded by one physician

and furtherly check by another physician, such as age, gender, body mass index (BMI), length of stay, the duration between onset of pain and hospital-admission, etiology of SAP, comorbidity, types of treatments and laboratory data including serum albumin and C reactive protein (CRP). The Bedside Index of Severity in Acute Pancreatitis (BISAP), Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated [21-23]. All patients received appropriate medical therapy and were followed until discharge from the hospital or hospital death. Outcome was assessed as in-hospital mortality.

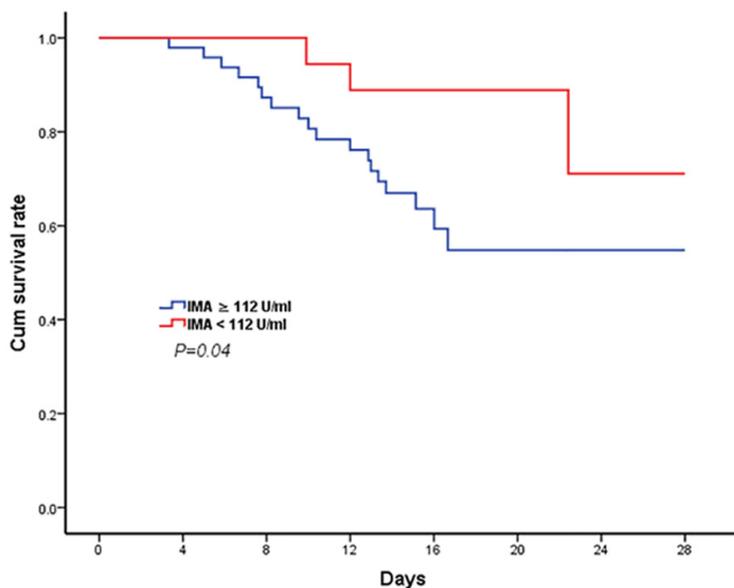
#### Measurement of IMA

5 ml peripheral venous blood samples of all patients were obtained and stored in a serum

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**Figure 1.** Receiver-operator characteristic curve for IMA. The areas under the curve were 0.734 with a 95% confidence interval (95% CI) for the area between 0.615 and 0.852,  $P=0.002$ .



**Figure 2.** Kaplan-Meier estimates of in-hospital mortality for patients with SAP. (In-hospital mortality rate in  $IMA \geq 112$  U/ml, 11.5%; in  $IMA < 112$  U/ml, 37.5%,  $P=0.004$ ).

tube with the inert separation gel and clot activator within 24 hours of the onset of SAP. After

centrifugation, the serums were decanted and measured immediately by a commercially available albumin cobalt test kit (Yikang Science Technique Development Co, Changsha, China) according to the manufacturer's instructions and using their reagents and equipment.

### Statistical analysis

Analyses were performed with SPSS 20.0 (IBM, USA).  $P < 0.05$  (two sided) was considered statistically significant. Data for categorical variables are expressed as a percentage and continuous variables as mean  $\pm$  SD. The  $\chi^2$  test or Fisher's exact test was used to compare categorical variables while continuous variables were analyzed by independent student's t test. The receiver operating characteristic (ROC) curves was used to establish cutoff value of serum IMA level that optimally predicted in-hospital mortality, and calculate corresponding area under curve (AUC) and 95% CI, the sensitivity and specificity. The variables associated with in-hospital mortality at  $P < 0.05$  on univariate analysis were enrolled in multivariate logistic regression analyzes to determine independent predictor of and in-hospital mortality. The survival curve was studied in Kaplan-Meier analyses by using the log-rank test.

## Results

### Patient characteristics

Baseline clinicopathologic characteristics of 72 patients with SAP are shown in **Table 1**.

There were 53 males and 19 females, with  $53.4 \pm 11.2$  years average age. The mean duration from admission to death or

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**Table 2.** Multivariate logistic regression analysis of risk factors associated with in-hospital mortality in patients with severe acute pancreatitis

	OR	95% CI		P
		Lower bound	Upper bound	
IMA level	3.521	1.281	5.223	0.021
Albumin level	1.012	0.722	2.251	0.832
APACHE II score	1.320	1.052	1.691	0.006
SOFA score	0.820	0.458	1.224	0.352
BIASP score	2.421	1.252	4.588	0.032

OR, odds ratio; 95% CI, 95% confidence interval; IMA, ischemia-modified albumin; BISAP, the Bedside Index of Severity in Acute Pancreatitis score; APACHE II, Acute Physiology and Chronic Health Evaluation II score; SOFA, Sequential Organ Failure Assessment score.

discharge was 23.2±18.2 days. The most frequently etiology of SAP was Alcoholic abuse, accounted for 39 of 72 patients.

### *Prognostic significance of IMA for patients with SAP*

The overall in-hospital mortality rate was 23.6% (17/72). According to the ROC curve analysis, the optimal cutoff levels for the IMA predicting in-hospital mortality of patients with SAP was 112 U/ml using a sensitivity of 77.4% and a specificity of 76.2% as optimal conditions (AUC, 0.734; 95% CI: 0.615-0.852; P=0.002) (**Figure 1**).

According to optimal cutoff levels of the IMA, all 72 patients with SAP were divided into high IMA ( $\geq 112$  U/ml) group and low IMA ( $< 112$  U/ml) group. Kaplan-Meier survival analysis showed that the in-hospital mortality rate of high IMA group was significant higher than the low IMA group (37.5% VS 11.5%,  $p=0.04$ ) (**Figure 2**).

### *Factors predicting mortality*

On univariate analysis (**Table 1**), we found that treatment, serum IMA, albumin and CRP level, APACHE II, SOFA and BIASP score were associated with in-hospital motility of patients with SAP. Patients in non-survivor group had higher serum IMA (107.2±10.8 VS 88.4±11.9,  $P<0.05$ ) than survivor group (**Table 1**). Furthermore, APACHE II, SOFA and BIASP score of non-survivor group also higher than survivor group (all  $P<0.05$ , **Table 1**). However, patients in non-survivor group had poorer serum albu-

min level than survivor (26.8±5.2 VS 32.6±6.2,  $P<0.05$ ) (**Table 1**). Otherwise, non-survivor group got more frequent invasive treatments including percutaneous drainage and surgery than survivor ( $P<0.05$ ).

A multivariate analysis enrolled serum IMA level, serum albumin level, APACHE II, SOFA and BIASP score into the COX regression model to identify independent predictive factors for in-hospital mortality SAP. The result showed that serum IMA level (OR, 3.521; 95% CI, 1.281-5.223;  $p<0.05$ ) and APACHE II score (OR, 1.320; 95% CI, 1.052-1.691;  $p<0.05$ ) and BIASP score (OR, 2.421; 95% CI, 1.252-4.588;  $p<0.05$ ) were the independent prognostic factors (**Table 2**).

## Discussion

In this study, we prospectively analyzed the serum IMA level of patients with SAP, and found that patients died during hospitalization had a significant higher IMA level than survivor, and that IMA level was a useful and independent predictor of in-hospital mortality in patients with SAP. Furthermore, high IMA was significantly associated with poorer survival than low IMA in the Kaplan-Meier survival analysis. Therefore, we confirmed that the serum IMA level can be examined for optimal risk stratification of individual patients with SAP, and serum IMA level can serve as a biomarker for predicting in-hospital mortality of patients with SAP.

Severe systemic inflammatory, tissue hypoperfusion, and subsequent oxidative stress are common in severe acute pancreatitis [24-26]. Then, oxidative stress induces overproduction of ROS and increasing release of oxygen free radicals, thus resulting in IMA formation in vivo by oxidative modification of serum albumin [27, 28]. Otherwise, IMA, as an easily and inexpensively measurable biomarker generated under ischemic and oxidative conditions, has been proved that increased in several disorders concerning oxidative stress, such as sepsis and myocardial ischemia [29, 30]. In this study, the mean IMA level in patients with SAP was 96.3 ±12.6 U/mL, which is high.

The development of tissue ischemia and oxidative damage in setting of SAP would lead to mitochondria dysfunction, multiple organ failure, and death. Furthermore, the severity of tissue ischemia and oxidative stress is directly

associated with early mortality [31]. Thus, IMA level, as a factor directly reflecting oxidative stress, was also confirmed as a potential prognostic biomarker in other diseases involved with tissue ischemia or oxidative stress. Yin et al [32] suggested that serum IMA level was associated with short-term mortality of patients with severe sepsis. Ma et al [33] concluded from their study that IMA was a clinically potential new marker for diagnosing doxorubicin-induced myocardial injury, and is helpful to predict long-term impairment of cardiac function. In current study, we first explore prognostic significance of IMA in patients with SAP, and found that serum IMA level was significantly associated with in-hospital mortality of patients with SAP.

For patient with SAP, local complications and organ failure resulting from severe systemic inflammation and oxidative stress is common and is furtherly associated with high mortality. The current study demonstrated for the first time that serum LMA level was an independent marker of in-hospital mortality in SAP patients comparing with other predictors including BISAP score, APACHE II score and SOFA score. In-hospital mortality rate was higher for patients with high IMA level ( $\geq 112$  U/mL) than with lower levels, so physicians should be aware of the short-term mortality for a high LMA level and provide early and proactive intervention to decrease IMA level. However, IMA level is not a direct contributor to poor outcomes, but a marker of severe oxidative stress and tissue ischemia. Targeting the original abnormal process might be a reasonable strategy to decrease IMA levels, such as correcting tissue ischemia and mitochondrial target therapy [34].

Several limitations may influence the interpretation of the results of this study. One limitation is the single center and limited subjects and a relatively short follow-up period. A large-scale, multicenter, prospective study should be conducted to confirm long-term results and obtain more definite evidence. Furthermore, we analyzed the cutoff levels of the IMA level though ROC curve in a small cohort, may imply some overestimation [35]. Thus, the results of this study may not be comparable with those of other studies. A meta-analysis including various LMA validation studies may be required

to confirm more definite cutoff values for the LMA.

In conclusion, the serum LMA level is increased in critically ill patients with SAP. As a biomarker of oxidative stress and ischemia, serum IMA level may be a useful independent predictor of short-term mortality for patients with SAP.

### Disclosure of conflict of interest

None.

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