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Progress in the Study of Laboratory Indicators Related to Acute Pancreatitis

Jiacheng Song[1,2,3], Xiaoping Tan[1,2,3*]

[1]Department of Gastroenterology, First Hospital of Yangtze University, Jingzhou, China
[2]Digestive Disease Research Institution, Yangtze University, Jingzhou, China
[3]Clinical Medical College, Yangtze University, Jingzhou, China
Email: *tanxiaohua222@163.com

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Abstract

Acute pancreatitis (AP) is one of the more common gastrointestinal diseases in clinics and is characterized by rapid progression, many complications, and high mortality. When it develops into severe pancreatitis, its prognosis is poor. Therefore, early assessment of the degree of inflammatory response plays a crucial role in the treatment plan and prognosis of patients. More and more studies have shown that the levels of D-dimer (D-D), angiotensin-2 (Ang-2), phosphate, heparin-binding protein (HBP), retinol-binding protein-4 (RBP4), and osteoblastic protein (OPN) are closely related to the severity of acute pancreatitis and can be used as effective indicators for early assessment of AP. In this paper, the research progress of the above indicators in assessing the severity of AP is summarized.

Keywords

Acute Pancreatitis, Laboratory Indicators, Progression, Assessment

1. Introduction

Acute pancreatitis is an inflammatory disease in which the pancreas itself suffers from alveolar cell death. The causes of acute pancreatitis are as follows: obstruction of the pancreatic duct by gallstones, alcohol, hyperlipidemia, drugs, and post-operative ERCP. The clinical condition and course of the disease vary, and it is difficult to predict the course of the disease in its early stages. About 80% of patients with AP have mild, self-limited disease, with the inflammation usually subsiding within 1 week. About 20% of patients with AP have necrosis of pancreatic and peripancreatic tissues, or systemic multi-organ failure and death,

*Corresponding author.

with a mortality rate of 20% - 40%. According to global epidemiologic surveys, the disease occurs in 34 cases per 100,000 people worldwide each year, and the incidence is increasing year by year [1] [2] [3] [4]. The incidence of the disease is increasing year by year. Acute pancreatitis, as one of the global disease burdens, is gradually jeopardizing the health of people all over the world. The key to this disease is how to predict the severity and progression of the disease at an early stage and how to reduce the mortality rate after the disease. According to the findings of clinical research, certain laboratory indicators play a role in predicting the early severity of acute pancreatitis. In this article, we will review some of the laboratory indicators that can predict the early severity of acute pancreatitis.

2. Laboratory Indicators to Assess AP

2.1. D-Dimer (D-D)

In SAP, the development of severe systemic inflammation can result in systemic vascular injury and endothelial dysfunction throughout the province, leading to the development of DIC and the formation of thrombi in the microcirculation. Activation of fibrinolysis secondary to coagulation activation can lead to an elevated concentration of fibrin/fibrinogen degradation products, including D-dimers. Wan Wan *et al.* [5] showed that serum D-dimer level is an independent correlate of AP prognosis and complications (APFC, ANC, pancreatic necrosis, infected pancreatic necrosis, organ failure, persistent organ failure, ICU stay, and mortality). For the prediction of SAP, the area under the curve for serum D-dimer levels was 0.714. When the optimal cutoff value of 2.5 mg/L was used for the prediction of SAP, the prognosis of patients with >2.5 mg was worse than that of patients with <2.5 mg/L. The results of this study showed that the prognosis of patients with SAP was worse than that of those without SAP. Xu Qingfang *et al.* [6] found a positive correlation between D-dimer and AP severity. The sensitivity and specificity of serum D-dimer for early prediction of the severity of biliary pancreatitis at a critical value of 1.170 were 0.906 and 0.832, and the area under the ROC curve was 0.925, respectively. This indicates a high diagnostic value and suggests that the level of D-dimer is an effective indicator for identifying the severity of BAP. Wang Yan *et al.* [7] found that D-dimer was an independent risk factor for determining the severity of acute pancreatitis, with an area under the ROC curve AUC of 0.72. Li Mengke *et al.* [8] found that the AUC of D-dimer was 0.72, the optimal cut-off value was 1.43 μg/L, the sensitivity was 0.58, and the specificity was 0.79, indicating that D-dimer can be used as a predictor of the severity of AP and has good diagnostic efficacy. Xue *et al.* [9] showed that D-dimer was an independent predictor of pancreatic necrosis. The ROC curve was constructed with D-dimer, which predicted the occurrence of pancreatic necrosis in patients with acute pancreatitis, with an AUC of 0.786, an optimal cut-off value of 2.08, and a sensitivity and specificity of 75.86% and 70.8%, respectively. Cui Huning [10] *et al.* showed that, according to multifactorial logistic regression analysis, elevated levels of D-dimer were a risk factor for

SAP in patients with AP, and ROC curve analysis showed an AUC of 0.86, a best cut-off value of 2.28, and sensitivity and specificity of 82.50% and 78.30%, respectively, which could indicate that D-D could predict the severity of the disease in patients with AP. In conclusion, D-dimer has a certain diagnostic value in predicting the severity of acute pancreatitis.

2.2. Angiopoietin 2 (Ang-2)

Ang-2 is an important family of vascular growth factors, consisting of angiotensin-1, angiotensin-2, angiotensin-3, and other members. Among them, Ang-2 is a protein composed of 496 amino acids. Angiotensin 2 is pre-synthesized in endothelial cells, and after synthesis, it is stored in Weibel-Palade vesicles. When endothelial cells are stimulated and activated by hypoxia and inflammatory mediators (histamine, 5-hydroxytryptophan, and superoxide), Ang2 is rapidly released in an autocrine form and binds to the Tie2 receptor, resulting in the movement of pericytes from vascular structures and detachment from the vascular basement membrane structure. Vascular basement membrane structure, so that the stability of blood vessels is weakened and vascular permeability is increased. For example, acute myocardial infarction and ARDS are closely related to the elevated concentration of Ang-2, which shows that Ang-2 has an important role in vascular stability and permeability as well as the inflammatory response. [11] [12] Sporek *et al.* [13] showed that Ang-2 was a significant predictor of AKI and renal failure and that serum Ang-2 may be a relevant predictor of AP severity, especially the development of AP renal syndrome. Zhang *et al.* [14] showed that Ang-2 could differentiate between patients with SAP who developed POF and those with MAP (AUC = 0.88) and MSAP (AUC = 0.74). In addition, according to multivariate logistic regression, elevated Ang-2 was shown to be an independent predictor of the development of POF in patients with AP. Dumnicka *et al.* [15] showed that Ang-2 was the best predictor of SAP and that a critical Ang-2 value of 5.92 ng/mL at 24 hours after the onset of AP symptoms predicted SAP with a sensitivity of 100% and a specificity of 92%. Lv Yongcai *et al.* [16] showed that on day 1, Ang-2 predicted POF value better than traditional predictors, with a sensitivity of 83.30%, a specificity of 68.40%, and an AUC of 0.738 when its cut-off value was 126.44 μg/L, whereas Ang-2 predicted PN value as the best single biochemical indicator when the cut-off value of Ang-2 was 130.9 μg/L, it had a sensitivity of 77.3%, a specificity of 73.6%, and an AUC of 0.703. According to a systematic evaluation and meta-analysis by Lv *et al.* [17] the results of a systematic evaluation and meta-analysis showed that Ang-2 had high diagnostic accuracy for AP combined with OF; the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of combined OF were 0.93, 0.85, 6.40, and 0.08, respectively. the AUC = 0.95, and the optimal prediction time of Ang-2 might be 24 - 72 h after the onset of AP. Huang *et al.* [18] conducted a prospective study showing that Ang-2 was an accurate early predictor of SAP, AGI, and intestinal barrier dysfunction, and Ang-2 was effective in predicting SGI with an AUC of 0.916, sensitivity of 93.8, and specificity of

82.6%. The optimal Ang-2 cut-off value for determining SGI was 11.49 ug/L. also predicted MODS with an AUC of 0.980 and a cut-off value of 11.76 0.952. The mortality rate of patients with SAP was significantly elevated when serum Ang-2 concentration was >15.31 ug/L (sensitivity 100%, specificity 87.3%). Therefore, serum Ang-2 levels play an important role in the occurrence and development of AP, are involved in the progression of AP through the regulation of blood circulation and pancreatic microcirculation, and are considered to be a promising biochemical indicator for predicting the early severity of AP.

2.3. Serum Phosphate

Phosphate is a substance essential to life. Bone and teeth account for the vast majority of phosphate; the rest of the phosphate is mainly distributed in the cell, while only a very small amount exists in the extracellular fluid. Phosphate is the nucleotide backbone of the biological genetic material DNA, RNA, and ATP, the most direct energy source material in living organisms. Phosphate is one of the important components that make up the cell membrane [19]. In the serum, phosphate needs to be maintained in a certain normal concentration area; exceeding or falling below its normal range will lead to adverse effects on the body and organ function [20]. The body's high level of phosphate concentration can be reduced through a number of factors, such as High levels of phosphate in the body can cause cellular damage by inducing programmed endothelial cell death. [21] Mazzini *et al.* [22] showed that serum phosphate levels were higher in patients with severe AP and were correlated with severity. Abdellah *et al.* [23] first evaluated the predictive role of baseline serum phosphorus on mortality in acute pancreatitis (AP) in the intensive care unit (ICU) and concluded that phosphate is an independent prognostic factor for AP mortality and that phosphate is the single most valuable routine laboratory test for predicting mortality in AP and can predict mortality in AP independently of other known factors. The sensitivity and specificity for predicting mortality were 0.58 and 0.78, respectively, when the threshold value was 3.78 mg/dl. Its AUC was 0.7. However, future prospective studies are needed to confirm these results. Fischman *et al.* [24] found that hyperphosphatemia on admission was independently associated with increased 30-day mortality in patients with acute pancreatitis and that hyperphosphatemia was a statistically significant independent predictor of early mortality. Serum phosphatase is readily available in the clinic and can be obtained by automated measurements, but there is a lack of prospective clinical studies to validate its predictive credibility.

2.4. Heparin Binding Protein (HBP)

Also known as antimicrobial peptide (azurocidin) or cationic antimicrobial protein 37 kDa/CAP37, has a molecular weight of 37 kDa and belongs to the class of serine proteases. According to research, HBP has an important function and a very significant role in neutrophil-mediated regulation of vascular endothelial permeability and vascular leakage. The site of HBP synthesis is in neutrophils,

and after synthesis, it is stored in the azurocidinophilic granules and secretory vesicles of the neutrophils. Under the action of various types of stimulating factors (bacterial-produced substances, inflammatory cytokines, and chemokines), it is found in the blood circulation of the body. Neutrophils can firmly adhere to vascular endothelial cells, leading to the activation of neutrophils. In the process of adhesion, HBP released by neutrophils can bind with glycosaminoglycans on the vascular endothelium, causing structural changes in the endothelial cell skeleton, leading to the entry of vascular fluids and inflammatory cells into the inflammatory site through the vascular endothelial gap and their accumulation therein, and thus expanding the systemic inflammatory response of the body. As a powerful chemotactic agent, the chemotactic effect of HBP is especially pronounced on monocytes and macrophages, and the effect on macrophages is most obvious. HBP acts as a powerful chemotactic agent, especially on monocytes and macrophages. According to some studies, HBP can also be evaluated as an early biomarker of sepsis severity, and in patients with sepsis, it can predict the progression of organ dysfunction as well as the pathologic course of circulatory failure, respiratory failure, and acute kidney injury. Plasma HBP levels higher than 15 - 30 ng/mL are associated with mortality and organ failure in sepsis [25] [26] [27]. Acute pancreatitis, as an inflammatory response, has been found to be associated with HBP and AP in recent years. Martina *et al.*'s [28] study found that HBP concentrations were generally elevated in AP and was the first study to analyze HBP levels in AP, but there was no significant difference in HBP levels between the severity groups, and the area under the curve (AUC) of HBP for predicting moderately severe or severe AP was 0.455, which was a poor predictor. Shu *et al.* [29] showed that HBP levels were significantly elevated in SAP patients compared to other classification groups, and when HBP levels were ≥7 ng/ml, the specificity for predicting POF was 74%, the sensitivity was 90%, and the AUC was 0.82, which suggests that HBP is a useful marker for predicting severe AP. Li Yu [30] *et al.* showed that HBP level had a significant increase in acute pancreatitis co-infection, and the area under the curve (AUC) of HBP for predicting acute pancreatitis co-infection was 0.835, with a critical value of 33.99, a sensitivity of 84.6%, and a specificity of 78.4%, which was a good prediction. Xie Songling *et al.* [31] showed that the AUC of HBP for assessing the severity of AP was 0.825, with a sensitivity of 75.3% and a specificity of 85.2%. It is valuable for the early diagnosis of SAP. Wang Qi *et al.* [32] showed that the sensitivity and specificity of serum HBP in early prediction of SAP complicated with ACS (abdominal compartment syndrome) at the optimal threshold of 42.57 ng/ml were 87.1% and 84.2%, respectively. HBP in AP is still relatively poorly reported, and more data and trials are needed to demonstrate its validation for predictive ability.

2.5. Retinol-Binding Protein-4 (RBP4)

RBP4 is a member of the lipid transport protein family. Its molecular weight is

about 21 kilodaltons (kDa). RBP4 is synthesized more in the liver and only 20% in adipose tissue. RBP4 is the only known vitamin A-specific transporter protein, which has the function of regulating the level of retinol body circulation. And it can transport retinol from storage sites to target tissues. Binding of retinol to RBP4 increases its hydrophilicity, and free RBP4 has a low molecular weight and is easily filtered in the glomerulus. Normally, retinol-bound RBP4 (HoloRBP) further binds to transthyretin protein (TTR) to form a retinol transporter complex, so it prevents HoloRBP from being filtered through the glomerulus, and RBP4 is known as an adipokine. Involved in energy metabolism, insulin signaling, and insulin resistance, it is considered a biomarker of insulin resistance and metabolic syndrome. It plays a crucial role in growth, vision, and metabolic diseases [33]-[38]. A recent study illustrated that RBP4 may be related to the severity of acute pancreatitis. Han [39] In an experimental study, RBP4 was shown to be an independent risk factor for the complication of acute lung injury (ALI) and necrotic material accumulation (ANC) in patients with AP, and the sensitivity and specificity of early prediction of ALI were 59.70% and 96.50%, respectively, with an AUC of 0.829 at a critical value of 30.45 mg/L. The sensitivity and specificity of early prediction of ANC were 0.829 at a critical value of 28.35 mg/L. The sensitivity and specificity of early prediction of ANC were 0.829 at a critical value of 28.35 mg/L. The sensitivity and specificity of ANC were 61.20% and 95.50%, respectively. The ability of RBP4 to predict AP complications is good and may be a potential therapeutic target for AP, which needs to be validated by a large number of sample sizes and trials. Prospective studies are also needed to examine trends in phosphate throughout the course of the disease and to determine its role in the adverse outcomes of acute pancreatitis.

2.6. Osteopontin (OPN)

OPN is also known as Bone Sialic Acid Protein 1 (BSP-1) and Early T-lymphocyte Activating Protein 1 (ETA-1). It is a highly phosphorylated glycosphingolipid protein, consisting of about 314 amino acids, and OPN is negatively charged and highly acidic. It is an extracellular matrix protein involved in a variety of physiological functions and pathological states and is widely found in a variety of tissues, such as the kidney, brain, bone marrow, lungs, etc. OPN can stimulate the body to produce a variety of inflammatory mediators, thereby activating inflammatory cells in the body and promoting the progression of inflammation in tissue injury, metabolic disorders, or cancerous lesions. In addition, OPN can participate in a variety of pathophysiological processes, such as mineralization, inflammation, immune response, and wound healing, and plays an important role in tissue remodeling [40] [41] [42] [43]. Swärd *et al.* [44] showed that OPN levels at admission were higher in patients with AP complicated by organ failure than in patients without organ failure. In addition, OPN on admission was associated with increased severity of pancreatitis, and OPN on admission was found to be an independent predictor of organ failure by multivariate logistic regression analysis. The area under the ROC curve for OPN on admission to predict

organ failure was 0.76. Rao *et al.* [45] found no significant difference in mean plasma OPN levels in patients with AP complicated by persistent organ failure compared with those without persistent organ failure, but OPN levels were significantly higher in patients who died compared with those who survived. The sensitivity and specificity for predicting mortality when the admission OPN cutoff value was 25 ng/mL were 75% and 92.7%, respectively, with an AUC of 0.823. Wirestam *et al.* [46] found that OPN levels at admission did not predict AP severity, but OPN was a relevant biomarker reflecting AP tissue damage. In conclusion, regarding the OPN level to predict SAP severity, organ failure, and mortality, despite these limitations, our results suggest that OPN is a promising biomarker reflecting AP tissue injury. OPN increased over time, suggesting that serial OPN measurements may be useful for the early detection of high-risk patients. Nevertheless, the clinical value of OPN needs to be further evaluated in larger cohorts.

2.7. Atherogenic Index of Plasma (AIP)

Hypertriglyceridemia (HTG) is the third-leading cause of acute pancreatitis (AP). Free fatty acids are lipotoxic substances produced by biochemical reactions of triacylglycerols in living organisms, and their lipotoxicity contributes to the development of acute pancreatitis (AP) by stimulating an inflammatory response, leading to multiple systemic organ failure, and causing necrotic adenohypophysial cell death [47]. High-density lipoprotein (HDL) has multiple functions, including reverse cholesterol transport (RCT), anti-inflammatory effects, antioxidant effects, as well as vascular protection and antithrombotic functions [48]. A prospective study by Ana *et al.* [49] conducted a prospective study showing that reduced HDL-C levels can be used to predict the risk of mild to severe acute pancreatitis (AP) complicating multiorgan failure within 48 hours of hospitalization in the emergency department. The plasma atherogenicity index (AIP) is a biomarker of events presumably leading to atherosclerosis and cerebrovascular disease, and the AIP is a means of wide-ranging screening that is characterized as rapid, efficacious, noninvasive, and cost-effective [50]. TG and HDL are the two important components of AIP, which are calculated as log (TG/HDL-C).Cho *et al.* [51] conducted a prospective study, and multifactorial analysis showed that AIP was an independent predictor of SAP, with a significant correlation between the two, and when predicting SAP, AIP (AUC = 0.709) > HDL (AUC = 0.683) > TG (AUC = 0.371) ,suggesting that AIP is a simple, convenient, and novel biomarker for the prediction of SAP. Pan Yang *et al.* [52] found that AIP was an independent risk factor for SAP, and AIP predicted SAP with a cutoff value of 0.694, a sensitivity of 77.2, and a specificity of 58.4. Its area under the curve contrasted with AIP (AUC = 0.706) > TG (AUC = 0.700) > HDL (AUC = 0.396). JI Qi *et al.* [53] A study of 214 cases of acute pancreatitis prediction found that AIP was likewise an independent risk factor for SAP and had an optimal cutoff value of 0.545, a sensitivity of 0.692, and a specificity of 0.669. AIP (AUC = 0.725) > TG (AUC = 0.611) > HDL (AUC = 0.604). For

hyperlipidemic pancreatitis prediction, the best cutoff value was 1.015, the AUC was 0.808, the sensitivity was 0.692, and the specificity was 0.711. Similarly, JI Qi *et al.* [54] again found that sHTG-AP had greater AIP values than the non-sHTG-AP group and that AIP was a risk factor for sHTG-AP patients and was positively correlated with severity. The optimal cutoff value for AIP prediction of sHTG-AP was 1.095, and the lower curve of AIP was 1.692 with a specificity of 0.611. and the area under the curve of AIP was 0.759 with a sensitivity of 0.821 and a specificity of 0.627, respectively. The above results were similar to those of Pan Yang and Cho, which proved that the predictive ability of AIP was better compared to the single factors TG or HDL. The sample sizes of the relevant studies were small, and the results of the analysis may be biased. In the future, prospective, multicenter, large sample size studies are needed to further validate the correlation and predictive value of AIP and AP and to incorporate AIP into the existing predictive scoring system with a view to providing assistance in the early diagnosis and treatment of AP.

3. Wrap-Up

In summary, commonly used clinical laboratory indicators are closely related to AP prognosis, are simple to use, and are potential clinical predictors. Various laboratory indices have their own advantages in the assessment of AP prognosis, but they have their own limitations due to the different subjects, small sample sizes, different target outcomes, and the fact that some of the studies were not compared with the existing scoring systems, and it is difficult to identify laboratory indices that can replace the traditional scoring systems. In addition, the predictive value of a single laboratory index is limited and susceptible to other diseases. With the development of science and technology, it is expected that the dilemma of early assessment of AP progression in clinical practice can be solved in the future.

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Conflicts of Interest

There are no interests and disputes in this article.

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