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Research Progress of Serological Markers Related to Infection in Acute Pancreatitis

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Abstract: ***Acute pancreatitis (AP) is a common acute abdominal disease in clinical practice. Its essence is a chemical inflammation. However, during its occurrence and development, it is often accompanied by infection in or around the pancreas. The severity of infection is of great significance for judging the severity of acute pancreatitis. In recent years, some infection-related serological markers have been used to assist in judging the severity of acute pancreatitis. This article reviews the research progress of infection-related serological markers in predicting the severity and prognosis of acute pancreatitis.***

Keywords: Acute pancreatitis, Serological infection markers, Severity of pancreatitis**.**

1. Introduction

Acute pancreatitis (AP) is an acute inflammatory disease in which pancreatic enzymes are activated within the pancreas due to various causes, leading to autodigestion of pancreatic tissue, resulting in inflammation, edema, bleeding, and even necrosis. The condition of acute pancreatitis can range from mild to severe, and approximately 20% of patients can progress to severe acute pancreatitis (SAP) [1]. SAP is a life-threatening condition. Pancreatic tissue can experience bleeding and necrosis, often followed by intra-abdominal infection, and can even cause multiple organ failure (MOF), with a certain mortality rate [2]. Detection of infection-related serological markers is a rapid, simple, and objective examination method that can provide key information about the inflammatory response and the degree of infection, helping clinicians assess the condition, formulate treatment plans, and monitor treatment effectiveness. Commonly used clinical serological infection markers include white blood cell (WBC) count, neutrophil (NEU) percentage, C-reactive protein (CRP), procalcitonin (PCT), interleukin 6 (IL-6), etc. These markers can, to a certain extent, reflect the severity of pancreatic or systemic inflammation, but they lack specificity in predicting the progression, complications, and prognosis of AP. Therefore, exploring and discovering new serological infection markers with high sensitivity and specificity is of great significance for improving the accuracy of AP diagnosis and treatment and formulating individualized treatment plans. This article reviews the progress of new serological infection markers in predicting the progression of AP and evaluating the severity of AP in recent years.

2. Heparin-Binding Protein (HBP)

HBP is a protein secreted by mature neutrophils. It can affect the permeability of the vascular wall by regulating the function of vascular endothelial cells, also regulate the function of the mononuclear-macrophage system cells and promote their activation of the related inflammatory response. It can also promote the chemotaxis and adhesion of neutrophils and participate in the migration and aggregation of inflammatory cells [3. In addition, it can regulate apoptosis through the mitochondrial pathway and is one of the earliest markers to increase in bacterial infections [4]. In an observational cohort study, it was found that the serum HBP level in the SAP group was significantly higher than that in the non-SAP group. The serum HBP level increased significantly when SAP patients developed persistent organ failure (POF). When the serum HBP level at admission was ≥ 7 ng/ml, the sensitivity for predicting POF was 90%, the specificity was 74%, and the area under the receiver operating characteristic (ROC) curve (AUC) was 0.82 [5], suggesting that an increase in serum HBP is of certain significance for predicting SAP. In 2021, Fu Mingyue et al. found that the serum HBP level on the day of admission in SAP patients with abdominal infection was higher than that in the group without abdominal infection. The sensitivity of serum HBP level in predicting AP complicated with abdominal infection was 39.7%, the specificity was 80.2%, and the AUC was 0.739. Their study also found that the combined detection of serum HBP, IL-6, and PCT could improve the sensitivity of predicting SAP complicated with abdominal infection [6]. Zhong et al. found that a serum HBP level of ≥ 85.8 ng/ml within 3 days of admission was a useful indicator for predicting SAP, with a sensitivity and specificity of 92.2% and 88.2% respectively, and an AUC of 0.79. The combined application of serum HBP and PCT or IL-6 could improve the diagnostic ability for SAP [7]. In 2023, Kong et al. constructed a multi-factor logistic regression model composed of HBP, CRP, and PCT, with a sensitivity and specificity of 88% and 98.3% respectively, and an AUC of 0.963. This model has good discrimination and practicality for predicting the occurrence of SAP [8]. It should be noted that the specific mechanism of serum HBP in the occurrence and development of AP is not yet fully understood, and further clinical and basic research is needed in the future to gain a deeper understanding of its function and potential clinical applications.

3. Immature Granulocyte Count (IGC) and Immature Granulocyte Count Percent (IG%)

Immature granulocytes (IG) refer to a class of granulocyte precursor cells present in the peripheral blood, also known as band-shaped nuclear cells, mainly including promyelocytes,

myelocytes, and metamyelocytes. In normal healthy individuals, the content of IG% in peripheral blood is extremely low, accounting for less than 1% of the total blood granulocyte count. They usually develop and mature in the bone marrow and then enter the circulatory system, with strong phagocytic and bactericidal abilities, which can effectively eliminate pathogens. Therefore, the presence of IG in the peripheral blood is important information reflecting the severity of inflammatory and infectious diseases. Lipinski et al. found that when IG% > 0.6, it could predict the severity of AP, with a sensitivity and specificity of 100% and 98.3% respectively, and an AUC of 0.98 [9]. The ROC curve showed that IG% was more capable of predicting the severity of AP at an early stage than the systemic inflammatory response syndrome (SIRS) and WBC count [10]. Another prospective multicenter study found that when IG% increased, the incidence of acute respiratory distress syndrome (ARDS) increased significantly. The sensitivity and specificity of IG% in predicting the occurrence of ARDS were 90.8% and 60.4% respectively, and the AUC was 0.821, suggesting that IG% helps identify high-risk individuals for ARDS in AP patients [11]. In 2020, Hou Wei et al. found that when predicting the occurrence of SAP, the sensitivity of IG% at a cut-off value of 0.9 was 100%, the specificity was 93.8%, and the AUC was 0.973, which was superior to the traditional inflammatory markers WBC, NLR, and CRP [12]. In 2022, Ugurlu et al. found in their study that compared with non-SAP patients, the IG% in SAP patients increased significantly. The sensitivity and specificity of IG% in predicting the occurrence of SAP were 100% and 95.4% respectively, and the AUC was 0.995 [13]. This study also found that the IG% in SAP patients with acute kidney injury (AKI) was higher than that in those without AKI. Checking IG% at admission in SAP patients could predict the possibility of AKI in patients [14]. Currently, many studies have found that an increase in IG% is closely related to the incidence of SAP and its complications, and this indicator is easy to obtain clinically, with certain clinical application prospects. The main problem is that there is currently no consensus on what level or degree of increase in IG% is clinically significant. Therefore, when applying IG% to the clinical practice of AP, the patient's clinical symptoms, medical history, and other examination results still need to be comprehensively considered.

4. Angiopoietin-2 (Ang-2)

Ang-2 is mainly involved in angiogenesis and vascular remodeling processes. Its expression is regulated by a variety of factors, including inflammatory factors, vascular growth factors, and hypoxia. Under normal physiological conditions, the expression level of Ang-2 is relatively low. In some disease conditions, such as tumors, inflammation, trauma, and vascular lesions, the expression of Ang-2 increases significantly and promotes apoptosis and vascular atrophy by disrupting the connections between endothelial cells and perivascular cells. In one study, by measuring and comparing the serum Ang-2 levels of AP patients and the control group at admission in two sets of experimental data, in the first group (3.698 pg/ml vs. 1.001 pg/ml) and the second group (4.945 pg/ml vs. 2.631 pg/ml) cohorts, the Ang-2 level at admission in patients who developed POF was significantly higher than that in those who did not. The sensitivity for predicting the occurrence of POF was 90%, the specificity was 67%, and the AUC was 0.81, suggesting that an increased Ang-2 level at admission may be related to the early occurrence of POF in AP patients [15]. Another randomized controlled trial found that compared with non-SAP patients, the early Ang-2 level in SAP patients was higher and was related to infectious complications (including infected necrosis, bacteremia, and infectious ascites), intestinal ischemia, and death. According to the ROC curve, the cut-off values of plasma Ang-2 for predicting SAP, MOF, and infectious complications were 4.56 mg/L (sensitivity 81.1%, specificity 76.9%), 5.01 mg/L (sensitivity 72.2%, specificity 73.2%), and 4.51 mg/L (sensitivity 79.5%, specificity 76.3%) respectively. As a predictor of adverse outcomes, plasma Ang-2 was superior to many current indicators, such as the APACHE II score, CRP, lipopolysaccharide-binding protein, and PCT [16]. In 2016, Sporek et al. found that the odds ratios (OR) of serum Ang-2 for predicting AKI at 24 h, 48 h, and 72 h after admission were 1.13, 1.40, and 1.66 respectively, and the OR for predicting renal failure were 1.14, 1.38, and 1.84 respectively, suggesting that Ang-2 may be a predictor of the pancreatic-renal syndrome in AP patients [17]. A prospective study found that the cut-off values of serum Ang-2 concentration at admission for predicting acute gastrointestinal injury (AGI) from grade 1 to grade 4 were 5.10 μg/L, 11.74 μg/L, 20.09 μg/L, and 22.66 μg/L respectively, with a sensitivity of 93.8%, a specificity of 82.6%, and an AUC value of 0.916. On the other hand, in the conventional AGI assessment methods (Ranson score, APACHE II score, and CRP), there were no statistically significant differences between different grades, suggesting that Ang-2 is an early predictor of AGI and is superior to traditional biomarkers [18]. Various studies have shown that Ang-2 has a certain ability to predict the occurrence of SAP and its complications.

5. Pentraxin-3 (PTX-3)

PTX-3 and CRP belong to the pentraxin family of acute-phase reaction glycoproteins, and are mainly produced by immune cells (macrophages, dendritic cells, neutrophils, and endothelial cells). As an inflammatory regulatory protein, during inflammation, PTX3 is rapidly released extracellularly and plays multiple roles in the inflammatory process: it can promote the clearance of pathogens by binding to them and enhance the phagocytic ability of macrophages; it can also promote the recognition of pathogens by myeloid cells by activating the complement system; in addition, it can regulate the production and release of inflammatory mediators and control the degree and duration of the inflammatory response. Some studies have found that the PTX-3 level in AP patients was significantly positively correlated with WBC, HCT, and CRP. The PTX-3 level in AP patients before treatment was significantly higher than that in the control group and decreased significantly after treatment. The sensitivity and specificity of PTX-3 in differentiating the AP group from the control group were both 100%, and the AUC was 1.00 [19]. Another study showed that on the first day of admission in AP patients, PTX-3 was positively correlated with the severity of AP complicated with diabetic ketoacidosis (DKA) and was significantly higher than that in the simple DKA group and the control group, suggesting that an increase in serum PTX-3 was related to AP complicated with DKA [20]. In 2022, Bao et al. found that the serum PTX-3 at admission in AP patients

was positively correlated with the APACHE II score, and the serum PTX-3 in the death group was higher than that in the survival group, suggesting that PTX-3 has good guiding significance for the early diagnosis and prognosis assessment of SAP patients [21]. Lin Jun et al. found that the serum PTX-3 level in SAP patients with peripancreatic infection increased abnormally. Its sensitivity in predicting peripancreatic infection in SAP patients was 79.6%, the specificity was 81%, and the AUC was 0.851, with a relatively high predictive value [22]. In the inflammatory response, the presence time of PTX-3 is more persistent than that of CRP, and it reaches its peak earlier than CRP. Therefore, PTX-3 is expected to become a predictive indicator reflecting the severity of AP inflammation.

6. Neutrophil CD64

CD64 is a high-affinity receptor that binds to the Fc portion of IgG antibodies and is a member of the immunoglobulin superfamily. It is mainly distributed on the surface of antigen-presenting cells (APCs) such as monocytes, macrophages, and dendritic cells, and its expression is regulated by cytokines. Under normal physiological conditions, CD64 is expressed at a low level on the surface of neutrophils. When an infection occurs, neutrophils are stimulated by lipopolysaccharide, complement, and various cytokines, and the expression level of CD64 on the surface of neutrophils increases and remains stable for a certain period. The expression of CD64 on the cell membrane surface of neutrophils begins to increase 4 - 6 hours after the infection occurs, reaches a peak at about 22 hours, and has high sensitivity and specificity within 24 hours. Zhang et al. found in their study that the CD64 expression in SAP patients at admission was higher than that in MAP patients. The sensitivity of CD64 in predicting the severity of AP was 80%, the specificity was 66.7%, and the AUC was 0.838, which was superior to the Ranson score and the APACHE II score [23]. Wang Feng et al. also found in their study that the sensitivity of CD64 in differentiating SAP and MAP was 82.2%, the specificity was 80%, and the AUC was 0.925, all of which were superior to the APACHE II score, CRP, and IL-6, suggesting that CD64 is a potential effective indicator for evaluating the condition of AP [24]. Swatantra et al. found in 2019 that a CD64 expression > 3.9% had a sensitivity of 94.4% and a specificity of 68.4% in predicting infected pancreatic necrosis, suggesting that the expression of CD64 can be used as a useful biomarker for differentiating infected and sterile pancreatic necrosis [25]. Wang et al. found in 2022 that when diagnosing AP complicated with infection, among various clinical indicators, CD64 had the best sensitivity, which was 82.1%, while PCT had the highest specificity, which was 95.1%. Therefore, the combined diagnosis of AP complicated with infection by CD64 and PCT had a good diagnostic effect [26]. High expression of CD64 can enhance the phagocytic and killing effects of neutrophils, thus promoting the body's immune defense response. In future clinical work, neutrophil CD64 is expected to become another important serological marker for predicting SAP.

7. Soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1)

Triggering receptor expressed on myeloid cells-1 is a transmembrane immune receptor related to infection, and sTREM-1 is its soluble form. During acute inflammatory responses, sTREM-1 is expressed on the surfaces of neutrophils and monocytes/macrophages, released into blood or body fluids. It appears early and has a relatively short half-life, and it can enhance the inflammatory response through signal transduction pathways. sTREM-1 can induce the production and release of inflammatory mediators, which can further promote the activation of immune cells and the persistence of the inflammatory response. However, sTREM-1 is rarely or not expressed in non-infectious inflammatory diseases, suggesting that it can be used as an indicator for diagnosing infections and monitoring disease progression. Yasuda et al. demonstrated for the first time in a prospective study that the serum sTREM-1 level in patients with acute pancreatitis (AP) was significantly increased (63 ± 11 pg/mL) and was correlated with the Ranson score and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score. The incidence rates of early (within 7 days after the onset) organ dysfunction in AP patients with serum sTREM-1 levels < 40 pg/mL and > 40 pg/mL were 17% and 83%, respectively, with a sensitivity and specificity both of 83% [27]. Lu et al. found in a multivariate Logistic regression analysis that a sTREM-1 level > 285.6 pg/mL in the fine-needle aspiration fluid during endoscopic ultrasonography was an independent predictor for infectious necrosis in AP, with a sensitivity of 94.4%, a specificity of 91.7%, and an area under the curve (AUC) of 0.972, which was helpful for quickly and accurately diagnosing secondary infections in necrotic tissues of patients with severe acute pancreatitis (SAP) [28]. In 2020, Zhen Pin et al. found that the sTREM-1 level was positively correlated with the severity of secondary pulmonary infections in SAP, with a sensitivity of 84.5%, a specificity of 81%, and an AUC of 0.879. Among the single-index detections, the diagnostic value of sTREM-1 was the highest, and combined with other serum inflammatory cytokines (procalcitonin [PCT], tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6]), the value of diagnosing secondary pulmonary infections in SAP could be significantly improved [29]. In 2021, Zeng et al. found that the cut-off value of serum sTREM-1 for predicting the prognosis of SAP patients was 128.325 ng/mL, with an AUC of 0.883, which could be used as an important reference indicator for judging the prognosis of SAP [30]. In the same year, Long Jiangchao et al. found that sTREM-1 could be used to predict the risk of peripancreatic infection in SAP, with a sensitivity of 69.2%, a specificity of 88.2%, and an AUC of 0.828, and its predictive value was better than that of the traditional indicators PCT and C-reactive protein (CRP) [31]. In general, sTREM-1 may have potentially important value in the diagnosis of AP complicated with infections, prognosis judgment, and treatment guidance, but further studies are still needed to verify it.

8. Soluble Urokinase Plasminogen Activator Receptor (suPAR)

suPAR is a soluble protein that exists in blood, urine, cerebrospinal fluid, etc. It plays an important role in the body's inflammatory response, immune regulation, and fibrinolytic system. suPAR binds to cell surface receptors and activates multiple signal transduction pathways, affecting processes such as cell proliferation, migration, apoptosis, and

inflammatory responses. It is widely used in clinical studies to assess the prognosis and disease progression risk of inflammatory diseases. Lipinski et al. found that the sensitivity of suPAR concentration in predicting SAP was 90%, the specificity was 94.6%, and the AUC was 0.966. As the suPAR concentration increased, the severity and mortality of AP patients also increased [32]. In addition, the AUC of suPAR in predicting fatal AP was 0.894, while that of the systemic inflammatory response syndrome (SIRS) was 0.65. Therefore, suPAR could predict the prognosis of SAP better than SIRS [33]. Nikkola et al. measured the suPAR concentration in patients with acute alcohol-induced pancreatitis (AAP) and found that its sensitivity and specificity in predicting non-mild AAP were 79% and 78%, respectively, and the AUC was 0.81, which was higher than that of commonly used laboratory markers (CRP, hematocrit [HCT], and serum creatinine [sCr]) [34]. Their subsequent study pointed out that a suPAR level ≥ 3.4 mg/mL measured after the first recovery from AAP could be used as an independent risk factor to predict an increased 10-year mortality rate of patients, which could be used to identify patients at the highest risk after AAP so that preventive health care actions could be focused on [35]. Long et al. found that serum suPAR had relatively high value in predicting pancreatic necrosis (with a sensitivity of 52%, a specificity of 96%, and an AUC of 0.7), peripancreatic infection (with a sensitivity of 80%, a specificity of 85%, and an AUC of 0.833), and multiple organ failure (MOF) (with a sensitivity of 72.4%, a specificity of 76.2%, and an AUC of 0.782). Moreover, the level of suPAR in ascites was positively correlated with that in serum, suggesting that the levels of suPAR in serum and ascites could be used as predictive indicators for the risk of severe complications in SAP patients [36]. Recently, some studies have pointed out that suPAR had good value in predicting the increase in in-hospital mortality of SAP patients, with an AUC of 0.806. Numerically, its predictive value was not inferior to that of the Ranson score, APACHE II score, Sequential Organ Failure Assessment (SOFA) score, and CRP [37]. To sum up, existing studies suggest that suPAR can be obtained in the early stage of AP and can be used as a potential biomarker for the disease severity, inflammatory response, and in-hospital mortality of SAP patients.

9. Soluble fms-like Tyrosine Kinase-1 (sFlt-1)

sFlt-1 is one of the induced receptors of vascular endothelial growth factor. It is a membrane-bound tyrosine kinase receptor, mainly derived from vascular endothelial cells, smooth muscle cells, and peripheral monocytes, etc. As an anti-angiogenic factor, the physiological functions of sFlt-1 include not only anti-angiogenesis but also anti-edema and anti-inflammation. It can be used as a marker for endothelial dysfunction under acute inflammatory response conditions and has been proven to be a potentially effective factor for predicting the severity of AP. In 2016, Dumnicka et al. found that serum sFlt-1 was positively correlated with the Bedside Index for Severity in Acute Pancreatitis (BISAP) score and the length of hospital stay. In the early stage of AP, sFlt-1 could predict organ failure, especially renal failure. When the serum sFlt-1 > 139 pg/mL, it indicated the aggravation of AP, with a sensitivity of 94%, a specificity of 63%, and an AUC of 0.836 [38]. In recent years, some studies have also pointed out that the serum sFlt-1 level in AP patients was higher than that in the normal control group, and that in SAP patients was higher than that in non-SAP patients. After treatment, the serum sFlt-1 levels of all AP patients gradually decreased. The sFlt-1 level at admission in AP patients with poor prognosis was significantly higher than that in patients with good prognosis. The sensitivity of the serum sFlt-1 level at admission in predicting poor prognosis in AP patients was 81.8%, the specificity was 72.4%, and the AUC was 0.728, indicating a certain predictive value [39]. The serum sFlt-1 level in AP patients can effectively predict the severity of AP, but its impact on prognosis still needs more studies to clarify.

10. Soluble CD14 Subtype (sCD14-ST)

sCD14-ST, also known as Presepsin, is the N-terminal fragment of CD14. It is a protein produced by monocytes and macrophages. When bacteria enter the human body, they bind to monocytes/macrophages, and the binding receptor is CD14. There are two types of CD14, membrane-bound CD14 and soluble CD14. Presepsin is a glycoprotein fragment and is an acute-phase reaction marker, playing an important role in the processes of inflammation and infection. Clinically, Presepsin can be used as an auxiliary diagnostic indicator for infectious diseases, with the characteristics of being rapid and sensitive. It can rise rapidly in the early stage of infection, which is helpful for early detection of the occurrence of infections in AP patients. In a prospective study, Rotar et al. found that in patients with acute necrotizing pancreatitis (ANP) without infection but with signs of SIRS, the Presepsin concentration increased to 332 pg/mL, which was only 78% higher than that in normal people. It increased to 677 pg/mL in cases of local infection, 988 pg/mL in cases of sepsis, and 2668 pg/mL in cases of severe sepsis, indicating that Presepsin was a sensitive and specific marker for early pancreatic infection in ANP patients. In addition, PCT, interleukin-6 (IL-6), and CRP had only slight and insignificant changes until local infection in the early stage of infection, while the Presepsin level doubled. The AUC value of Presepsin in predicting various infectious complications (including infectious necrosis, bacteremia, infectious ascites, and various infections) was 0.956, which was significantly higher than that of PCT, IL-6, and CRP [40]. Long Jiangchao et al. also found that Presepsin had a relatively high value in predicting SAP complicated with peripancreatic infection, with a sensitivity of 78.8%, a specificity of 92.1%, and an AUC of 0.894, and its predictive value was better than that of the traditional indicators PCT and CRP [31]. A multicenter cohort study found that the Presepsin levels on the 3rd, 5th, and 7th days were independent predictors for the 28-day mortality rate of AP patients, with AUCs of 0.781, 0.846, and 0.843, respectively, suggesting that Presepsin could be used as an indicator for dynamically predicting the 28-day mortality rate of AP patients [41]. In 2023, Hao Lei et al. found that the sensitivity of serum Presepsin in predicting the risk of renal injury in AP patients was 76.5%, the specificity was 66.3%, and the AUC was 0.752. High expression of serum Presepsin was an independent risk factor for renal injury in AP patients [42]. Currently, the accumulation of high-quality clinical evidence for Presepsin is insufficient, and further clinical studies are still needed.

11. Conclusion

In recent years, many scholars have conducted in-depth research on various serological infection markers in patients with acute pancreatitis (AP). By detecting patients' blood samples, they aim to evaluate the degree of infection and the severity of the inflammatory response. Although commonly used serological infection markers in clinical practice, such as C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6), play important roles in the diagnosis and treatment of AP, they still have deficiencies in predicting the disease severity. For example, they cannot directly assess tissue damage and functional impairment, lack comprehensive prediction of the severity and prognosis of AP, are affected by many factors such as age, gender, comorbidities, and medication use, are prone to misjudgment and uncertainty, may show falsely elevated values in some mild cases, and may be insensitive in some severe cases, leading to delayed diagnosis and treatment. New infection markers have potential value and broad application prospects in the management of AP. Ideal serological markers for predicting the severity of AP should be detectable in the early stage of AP onset, possess high sensitivity and specificity, be rapid, convenient, economical, and practical, accurately reflect the actual severity of patients' conditions, and have good repeatability and stability. Combinations of different serum markers may improve the accuracy of prediction. It should be noted that these markers are still in the research stage and require further clinical verification and application promotion. On the one hand, with the improvement and refinement of detection techniques, the detection accuracy and sensitivity of these markers will be further enhanced. On the other hand, analysis models for infection markers based on technologies such as artificial intelligence are also constantly being optimized and developed, which will provide better support for clinical applications. The above markers are expected to play increasingly important roles in the future and provide better protection for the health of AP patients.

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