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NOVEL BIOLOGICAL MARKERS OF ACUTE KIDNEY INJURY IN SEPSIS

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Abstract: Sepsis is a problem faced by every ICU medical staff, and its concurrent acute kidney injury is an even more difficult challenge. So far, there are still many deficiencies in its early diagnosis. How to detect and intervene early has become an academic issue. hot issues in research circles. With the in-depth early research on acute kidney injury caused by sepsis in recent years, several markers of septic acute kidney injury have gradually come into people's field of vision. This article summarizes these new markers based on new advances in academic circles in recent years.
Keywords: Sepsis; Acute kidney injury; Biological markers; Neutrophil gelatinase-associated apolipoprotein; Renal injury factor

1 CURRENT STATUS OF SA-AKI DIAGNOSIS

Sepsis is a life-threatening condition caused by a dysregulated host response to infection Organ dysfunction syndrome, which develops rapidly and has high morbidity and mortality Mortality rates remain high [1]. If the condition is severe or treatment is not timely, it is easy to Septic shock develops, leading to multiple organ failure. in sepsis During the development process, the kidney is one of the most commonly affected organs and is often associated with Sepsis-associated acute kidney injury (SA-AKI) occurs. According to statistics, SA-AKI accounts for more than 50% of clinical acute kidney injury (AKI), and when After AKI secondary to sepsis, the mortality rate of patients is as high as 70%, and AKI is Sepsis is one of the most common and serious complications [2]. One item in our country The results of a national multi-center study show that in 2013, there were approximately 2.9 million people in the country When a person suffers from AKI and is hospitalized for treatment, the total medical cost is approximately 13 billion US dollars, accounting for 10% of my country's total medical expenses [3], and the mortality rate is 12.4%. The in-hospital mortality rate of patients with septic AKI is as high as that of patients with simple AKI. 6 times (about 70%). This article aims to summarize various new biomarkers The predictive and diagnostic value of substances for SA-AKI and the early diagnosis of SA-AKI Provide new ideas.
According to the 2012 Kidney Disease Improving Global Outcomes Organization (KDIGO) New definition of AKI: When the patient's serum creatinine (SCr) level rises >0.3 mg/dl (26.5 μmol/L) within 48 hours, the SCr level rises to 1.5 times the baseline value within 7 days, or AKI can be diagnosed when the hourly urine output is <0.5 ml/kg and lasts for 6 to 12 hours [4]. The current clinical diagnosis of AKI mainly relies on indicators such as urine output, SCr, serum urea nitrogen (BUN), the presence of cast urine, high sodium excretion index, urea excretion index, and hypotonic urine. Among them, SCr and urine output are important diagnostic core indicators. However, glomerular filtration rate (GFR), which truly represents kidney function, does not can be accurately reflected by SCr levels alone because renal tubular creatinine secretion and other nonrenal factors such as muscle mass, liver function, and nonrenal gastrointestinal excretion Outcomes are also closely related [5]. SCr is generally considered to be a cause of kidney damage Late markers [6], but they have certain shortcomings in diagnosing the occurrence of AKI. trapping, lack of diagnostic accuracy for structural kidney injury, and Patients with structural kidney injury cannot provide information such as cause, prognosis, and treatment response. Related information[7]. For example, in the ICU with sepsis, hypotension, urinary Sediment testing revealed that patients with granular cast urine had structural kidney disease. Injury and poor prognosis require close attention and active treatment. But SCr There are no similar features, and in diseases with non-structural kidney damage, such as decompensated congestive heart failure who are receiving diuretics, patients, start taking renin-angiotensin-aldosterone system (RAAS) inhibitors preparations for patients with diabetic nephropathy and those with long-term high blood pressure who initiate intensive blood pressure control. Patients with blood pressure have elevated SCr levels. in these patients Among them, increased SCr levels are not associated with poor prognosis [8]. Therefore, for the sake of early to diagnose the occurrence of AKI at an early stage, and look for other methods that can be used for early diagnosis of AKI. Metrics are extremely important.

2 NEW SA-AKI MARKERS

For new markers of SA-AKI, currently common ones include neutrophil gelatinase-associated apolipoprotein (NGAL), kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP), cystatin C (Cys C), tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP 7), etc. The following will analyze and introduce some of the biological markers that play an important role in the pathophysiological process of septic AKI.

2.1 NGAL

NGAL is an emerging biological marker of kidney injury in recent years. It has a molecular weight of 25 kDa and is a secreted glycoprotein. It was first discovered by Kjeldsen et al. when studying neutrophils. That In various pathologies such as inflammation, infection, poisoning, ischemia, AKI and tumor transformation, state and expressed in kidney, liver, and epithelial cells. NGAL Exists as a 25 kDa monomer and a 45 kDa homodimer, and as The heterodimeric form of 135 kDa binds to gelatinase [9]. in small kidneys In tube epithelial cells, the main forms of NGAL production are the monomeric form and a heterodimeric form to some extent, while the homodimeric form is neutral Granulocyte-specific form [10]. In recent years, studies have confirmed that NGAL is involved in It is related to the body's immune response, lipid metabolism, repair of kidney damage, and cell differentiation. transformation and apoptosis, inflammatory response, embryonic development, and oxidative stress [11]. NGAL is mainly produced in the distal tubule and collecting duct, and in the normal proximal tubule Low expression in epithelium. When proximal tubule epithelial cells are damaged, serum NGAL (pNGAL) and urine NGAL (uNGAL) levels showed an increasing trend. In cases of ischemia-reperfusion injury, severe infection, surgical trauma and other factors In AKI, the expression levels of pNGAL and uNGAL are significantly increased [12]. because Therefore, NGAL has become the focus of research on renal injury markers in recent years. Head Previously, there have been a number of large-scale clinical studies on NGAL as an AKI biologic. The value of markers was evaluated, and both showed that NGAL is an early stage of AKI. The diagnostic indicators have high diagnostic accuracy. In recent years, it has gradually begun Try to use NGAL to judge the need for continuous renal replacement therapy (CRRT) Timing and discovery of septic AKI patients using uNGAL It is feasible and can be used as an indicator to guide the initiation of CRRT [13]. In addition, there are research Studies have found that NGAL levels may be related to patient prognosis. in SA-AKI pNGAL levels were significantly elevated in patients, and their levels increased with severe sepsis The degree of The level of pNGAL in the group was much higher than that in the survival group; suggesting that pNGAL is important for early stage It is of great significance to diagnose AKI and evaluate the prognosis of patients with sepsis [14]. However, NGAL also has disadvantages, such as the specificity of pNGAL is not high enough; NGAL is also expressed in other diseases besides renal injury, such as infection, inflammation, tumor, hypertension and other disease states, pNGAL levels will also be increased. Abnormality occurs. Rampoldi et al.[15] observed that pNGAL levels increased in systemic inflammation. It is elevated in patients with acute response syndrome, severe sepsis and septic shock, and should be used with caution as a diagnostic tool for AKI in ICU patients with septic shock. of markers. Study results on the accuracy of pNGAL in diagnosing AKI The results show that pNGAL >150 ng/ml is effective in patients with AKI suspected of sepsis. The sensitivity is 96%, but the specificity is only 51% [16]. Comparable to pNGAL Compared with uNGAL, it is more useful for predicting SA-AKI because in the absence of AKI uNGAL levels are not elevated in patients with sepsis. It can be seen that uNGAL It is more suitable to become a marker for diagnosis and monitoring of SA-AKI patients.

At present, NGAL is one of the more maturely studied new markers. However, the relationship between its expression in serum and urine and renal injury needs further exploration. At present, its practicality and feasibility in clinical practice are still It needs to be explored through further experiments.

2.2 TIMP-2 and IGFBP7

TIMP-2 and IGFBP7 are two emerging AKI markers. Their predictive role in AKI has attracted widespread academic attention, but their role in predicting patient prognosis is still poorly understood.

TIMP-2 and IGFBP7 are both cell cycle arrest biomarkers has been shown to be a good predictor of AKI and has been FDA approves risk for AKI in critically ill patients Evaluate. Among them, TIMP-2 is a 21 kDa protein that belongs to the metal Protease tissue inhibitor family, endogenous source of metalloproteinase activity sexual inhibitory factor. IGFBP7 is a 29 kDa secreted protein that binds and inhibits signaling through the insulin-like growth factor (IGF)-1 receptor. transfer[17]. Relevant studies have shown that in the early stages of kidney injury, the damage The renal tubular epithelial cells enter a brief cell cycle arrest in the G1 phase. stagnation. Under the action of the cell's own protective mechanism, in order to avoid damage-induced Cells that cause death or senescence cannot continue to divide before the damage is repaired. As markers of cell cycle arrest, IGFBP7 and TIMP-2 will Sends a signal that the renal tubular epithelial cells have been damaged and stop Stop splitting[18]. They usually take an autocrine or paracrine form, from Spread from damaged parts, serving as a "warning" because it occurs over a relatively long time Early, thereby having the opportunity to detect damage early and improve prognosis [19]. in AKI The role of IGFBP7 in surgical patients under the influence of different mechanisms. Better than TIMP-2, which is more effective in diagnosing SA-AKI patients Good[18]. Studies have shown that the product of the two can affect AKI II. The changes in the patient's kidneys are reflected within 12 hours of the appearance of stage 1 and stage 3, and earlier than SCr level [20]. Research finds that developing AKI stages 2 and 3 In patients, the urine [TIMP-2] × [IGFBP7] concentration usually occurs on the same day. It will increase, and may have a characteristic rise and fall as the condition changes.

[TIMP-2] × [IGFBP7] also has a certain degree in SA-AKI Predictive value. One study found that linking infection and sepsis A powerful marker procalcitonin (PCT) and [TIMP-2] × Joint analysis of the results of [IGFBP7] (critical values are 0.5 and 0.3 respectively) can stratify the risk of AKI development within 48 hours. The risk of developing AKI increased 26-fold when the patient was combined with positive A positive record is also significantly associated with mortality within 7 days [18]. After that, there were Multiple studies and analyzes have proven that [TIMP-2] × [IGFBP7] can accurately predict SA-AKI, but it was also found that although the product of the two has a higher sensitivity sex, but the negative predictive value is low [21]. Currently, both are used in the early diagnosis of AKI The role of judgment has been widely and profoundly recognized, but it still has certain shortcomings, such as the inability to

differentiate between transient and persistent AKI, and only predictability The patient's condition changes within 24 hours, and it is easy to lose the opportunity for diagnosis. No relevant effects were found in measuring patient prognosis. Thus, in In clinical use, it needs to be supplemented by other examination results and can only be used as a Determined reference [22].

2.3 KIM-1

KIM-1 is a new kidney injury marker. Its role in diabetic nephropathy and chronic kidney disease has been widely understood, and its role in SA-AKI has gradually attracted academic attention. It has been proven to have a strong ability to detect early and predict the development of disease, but it still has certain shortcomings in the detection of disease and injury severity.

KIM-1 is a transmembrane glycoprotein of renal proximal tubule epithelial cells. The extracellular region contains mucin domains and Ig-like domains. generally Under this condition, it is difficult for testers to detect KIM-1 in healthy kidneys. because Normal kidney tissue rarely expresses KIM-1, but it is expressed in AKI caused by ischemia, hypoxia, poisoning, infection, or some tubulointerstitial and polycystic kidney diseases. The expression level of KIM-1 is significantly increased [23]. At this time, the dedifferentiated proximal small The expression level of KIM-1 is significantly upregulated in duct cells, and it is released into the small Intraluminal, KIM-1 levels increased significantly in urine. Likewise, when the kidneys are near KIM-1 can also be detected in the blood when the terminal tubules are damaged. KIM-1 Mainly expressed in differentiated proximal renal tubular epithelial cells. proximal renal tubule Epithelial cells can regenerate after injury, especially in the S3 outer medullary region. During the time of injury, KIM-1 levels in urine and kidney tissue increased over a short period of time. Significantly increased and related to the degree of renal damage. Since KIM-1 in animals It has shown strong feasibility in experiments and clinical trials, and researchers It is considered to be a potential early biomarker, and some studies Studies have shown that it is involved in the damage and healing process of the kidney, so it is considered It is a relatively reliable factor for predicting prognosis [24]. Compared to serum KIM-1 (SKIM-1), people's research on urinary KIM-1 (UKIM-1) is more Go deeper. FDA and European Medicines Agency select UKIM-1 as a drug biomarkers of physical nephropathy [25]. Zhang et al. [26] found that the KIM-1 levels in serum and urine of patients with SA-AKI were higher than those without. Sepsis patients with AKI, and KIM-1 in serum and urine can be detected in Prediction of septic AKI within 72 hours. But because KIM -1 not only reflects The damage situation of AKI has also increased during the repair and regeneration process. Therefore, whether it is KIM-1 in serum or urine, it is serious for AKI. There is no obvious predictive value in the judgment of patient prognosis and severity. Breaking also has certain limitations.

3 CONCLUSION

In summary, there is an urgent need for more specific and practical clinical There is currently no search for strong markers to improve the early diagnosis of SA-AKI. Find a method that can completely replace conventional indicators (such as serum creatinine or urine amount) of biomarkers. And relative to biomarkers alone, in Early combined detection of biomarkers is an important factor in predicting AKI in patients with sepsis. Finally, it is highly sensitive and special to judge the severity and grasp the changes of the condition as soon as possible. A good detection strategy for the opposite sex, thereby providing early clinical treatment plans for guidance. With the advancement of science and technology, more and more suitable for clinical application SA-AKI diagnostic and prognostic markers are expected to be developed and applied clinically, providing a stronger basis for early diagnosis and early treatment of SA-AKI.

COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

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