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Research Progress of Systemic Immune Inflammatory Index in Prostate Cancer

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Abstract

Prostate cancer has gradually risen to become the second most common cancer threatening men's health, and prostate-specific antigen (PSA), as the main screening indicator for prostate cancer, has the defects of low specificity and insufficient diagnostic efficacy. As a novel inflammatory index based on neutrophil, lymphocyte and platelet counts, the systemic immune-inflammation index (SII) has recently become a more powerful biomarker for predicting the occurrence and progression of various malignancies. SII reflects the systemic inflammatory response of prostate cancer patients in a more balanced manner, and has higher predictive value than neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). High SII values are often associated with cancer progression and poor prognosis. This article reviews the research progress of SII in prostate cancer, in order to provide guidance for clinical practice.

Keywords

Prostate Cancer, Systemic Immune Inflammatory Index, Prostate-Specific Antigen

1. Introduction

Prostate cancer primarily occurs in elderly males and is one of the most common malignancies among men [1]. The challenge of enhancing the detection rates of prostate cancer in individuals with PSA levels ranging from 4 to 10 ng/mL warrants further investigation [2]. Numerous expert consensus statements suggest that a PSA level above 4 ng/mL is typically classified as a positive result, while values between 4 and 10 ng/mL are referred to as the "gray zone," necessitating further evaluation [3]. Various inflammation-based indicators, such as the neutrophil-to-

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lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and lymphocyte-C-reactive protein ratio (LCR), have been identified as potential predictors for certain cancers [4]. However, their predictive value for prostate cancer remains limited. The systemic immune-inflammation index (SII), a novel inflammatory marker derived from neutrophil, lymphocyte, and platelet counts, is considered to possess greater predictive value in assessing inflammation-related diseases compared to other inflammatory markers [5]. Future research should further explore the diagnostic efficacy of combining "gray zone" PSA values with SII in determining prostate cancer positivity rates, thereby enhancing clinical decision-making and improving the accuracy and effectiveness of prostate cancer screening.

2. Overview of SII and Its Mechanisms

The systemic immune inflammatory index (SII), calculated as the product of neutrophils and platelets divided by lymphocyte count, plays an important role in the assessment of inflammatory response and immune status [6]. Studies have shown that inflammation is closely related to the onset, development, and prognosis of cancer. Neutrophils, lymphocytes, platelets, interleukin, and tumor necrosis factor run through the whole process of tumor cell proliferation and metastasis [7], so the association between systemic inflammatory index and prostate cancer deserves further investigation. Some studies have shown that SII more evenly reflects the systemic inflammatory response of prostate cancer patients and has higher predictive value than PLR and NLR. Recently, it has emerged as a more powerful biomarker for predicting the occurrence and progression of various malignancies [8]. Clinical studies have shown that SII is closely related to the prognosis of various cancers such as lung cancer, liver cancer, gastric cancer, and colorectal cancer [9]-[11]. High SII values are often associated with cancer progression and poor prognosis [12]. In addition, SII can also be used as an indicator of early cancer screening [13], which can be used as an adjunct to other imaging and biological detection methods.

3. PSA Level "Gray Area" and Its Challenges

PSA is secreted by prostate epithelial cells and has organ specificity. Its concentration is positively correlated with the occurrence of prostate cancer [14]. PSA in the range of 4 to 10 ng/mL is defined as a "gray area", and according to the consensus at home and abroad, imaging should be combined with imaging to assist in diagnosis, and ultrasound-guided prostate biopsy is recommended to be minimized as much as possible [3]. Studies have shown that only about 4% of patients with PSA levels < 20 ng/mL are diagnosed with PCa after needle biopsy. The diagnostic efficacy of PSA varies greatly at different PSA levels [15]. Secondly, the expression of PSA is often affected by the following factors: since PSA is an organ-specific antigen rather than a tumor-specific antigen, its expression level is positively correlated with the volume of benign prostatic hyperplasia, and the higher the stage of most prostate cancers, the higher the PSA, the higher the degree of

acute infection, the positive correlation with age, and other non-malignant diseases; Maneuvers such as indwelling urinary catheter and prostate massage may result in varying degrees of elevation [16], while the use of 5a-reductase inhibitors decreases PSA [17]. Different factors can cause PSA to leak into the lymphatic system and then into the bloodstream. Therefore, the use of PSA alone to diagnose PCa may lead to missed or misdiagnosed diagnoses.

4. Research Progress of SII in Prostate Cancer

4.1. Overview of Prostate Cancer

According to the latest data from the World Health Organization, prostate cancer has jumped to one of the top cancers in the world for cancer incidence and mortality among men [18]. At present, the diagnosis of prostate cancer is based on PSA > 4 ng/mL, combined with prostate magnetic resonance, prostate needle biopsy, and postoperative pathology [19]. Chinese expert studies have shown that patients with significantly abnormally elevated PSA can be diagnosed with prostate cancer by Pet-CT without puncture, and patients without systemic metastasis can directly undergo radical prostatectomy. This will avoid related surgical complications such as infection, pain, etc., after prostate puncture [20]. At present, the treatment of prostate cancer is still based on radical surgery [21], so early diagnosis of the prostate will be of great value for the recovery of the disease.

4.2. Inflammatory Factors Contribute to the Development and Progression of Prostate Cancer

4.2.1. PLR or NLR

Studies have shown that PLR has the effect of influencing the growth and progression of cancer in the systemic circulation [22]. Platelets promote vascular growth and enhance tumor cell aggregation through the release of VEGF, which further promotes tumorigenesis and progression [23]. Platelets can not only enhance tumor growth and progression, but also respond to T cell-mediated immune responses in antibody circulation [24]. Tumor cells elevate platelet counts and cause activation by affecting the levels of various thrombocytopenic factors and platelet agonists [25]. There are two types of lymphocytes present in the systemic circulation, including T cells, which destroy cancer cells and viral host cells, and B cells, which produce antibodies. As the most important immune cells in the body, lymphocytes mainly induce target cell division and apoptosis, and exert anti-tumor effects [26]. Rulando *et al.* demonstrated that high NLR was associated with higher GS and higher rates of progression [27]. As the most important cancer-related systemic inflammatory factor, NLR has been proven to predict PCa and Gleason score escalation (GSU) in men undergoing prostate biopsy [28]. Baylan *et al.* believe that for patients with high NLR and PLR values, radical treatment options such as surgery or radiotherapy should be preferred [29].

4.2.2. Diagnostic Relationship between SII and Prostate Cancer

Hu *et al.* were the first to propose and use the systemic immune inflammation

(SII) index, and through a retrospective analysis, it was concluded that a high SII value is a strong prognostic indicator of poor prognosis in patients with hepatocellular carcinoma [30]. The diagnostic value of SII for prostate cancer lies in the fact that it may provide a more objective measurement by capturing the complex interplay between host inflammation and immune response. Due to the influence of long-term inflammatory factors in chronic prostatitis, DNA damage is triggered, cell proliferation is promoted, and the apoptosis mechanism of cells is destroyed, which leads to the occurrence of cancer [31]. A high SII may correspond to an increased inflammatory response, which in turn increases the risk of prostate cancer. PSA is an important indicator of prostate cancer screening, but it is difficult to diagnose in the "gray area" of 4 - 10 ng/mL. A study of 148 patients with PSA in the "gray area" found a significant positive correlation between SII and PSA levels [13]. In addition, patients with high SII have a higher rate of positive prostate biopsy. This suggests that SII may be used as an adjunct indicator to help improve the diagnostic positivity rate of PSA in gray zone prostate cancer.

4.2.3. Prognostic Relationship between SII and Prostate Cancer

In the direction of PCa, SII was first applied to it in 2016 and is considered to be an important marker for predicting the prognosis of metastatic castration-resistant prostate cancer (mCRPC) [32]. In 2017, SII was first reported to be associated with the prognosis of a variety of solid tumors, including prostate cancer [33]. Massive neutrophil expansion in the tumor microenvironment and systemic circulation is associated with poor prognosis in cancer patients [12]. Neutrophils, while activating endothelial hyperplasia in vascular and parenchymal cells, increase the adhesion of tumor cells in the systemic circulation and lead to distant metastasis. The increase in platelets inhibits the cytolytic function of lymphocytes, activated T cells, and natural killer cells, thereby inhibiting tumor clearance by the immune system. Platelets protect circulating tumor cells (CTCs) from destruction by the immune system [34]. Platelets and endothelial cell adhesion proteins may facilitate spread by increasing tumor cell efflux. An increase in tumor-infiltrating lymphocytes (TILs) is associated with immunotherapy response and prognosis in cancer patients [35]. Many studies have found that SII is closely related to the clinical features and prognosis of prostate cancer. A study of 297 prostate cancer patients found that patients with prostate cancer with a higher SII had higher Gleason scores and a higher probability of metastasis of their cancer [28]. A meta-analysis of 8083 prostate cancer patients by Zhang *et al.* showed that in the PCa population, higher SII was significantly associated with poor overall survival (OS) and worse progression-free survival (PFS), while high SII was not significantly associated with T stage, lymph node metastasis, age, and Gleason score [36]. This conclusion is the same as that of the Chinese scholar Meng [37]. However, a meta-analysis of 7986 prostate cancer patients by Qi *et al.* showed that high SII was associated with advanced tumor stage of PCa (OR = 2.19. 95% CI: 1.11 - 4.33, P = 0.024), presence of lymph node involvement (OR = 2.72, 95% CI: 1.96 - 3.76, P < 0.001), Gleason score (OR = 1.27, 95% CI: 1.13 - 1.44, P < 0.001) [38]. SII and T

stage, lymph node metastasis, and Gleason score remain controversial. An analysis of 291 pathologically confirmed prostate cancer patients after radical prostate cancer resection (RP) showed that high SII (HR, 4.521; 95% CI: 2.262 - 9.037, P < 0.001) and high NLR (HR, 4.787; 95% CI: 2.339 - 9.798, P < 0.001) were significant predictors of biochemical recurrence (BCR) after RP and were significantly associated with adverse clinicopathologic outcomes [39]. One study of 61 patients with mCRPC confirmed that SII was a strong independent prognostic indicator for predicting survival in patients with mCRPC treated with 177Lu-PSMA-617 [40]. One study of 519 patients with mCRPC treated with radium dichloride ($[^{223}Ra]RaCl_2$) showed that a high SII predicts worse OS [41]. Zapala *et al.* showed that SII can be used as a potential auxiliary marker to predict the survival of RP patients with non-metastatic prostate cancer, and suggested that the combination of CAPRA-S score and Charlson comorbidity index has higher value [42]. In summary, the studies concluded that SII may be an important indicator for predicting the prognosis of prostate cancer.

5. Comparative Analysis of SII with Other Prostate Cancer Biomarkers

After PSA was used as a diagnostic criterion for prostate cancer, many PCa biomarkers have been developed one after another, such as the prostate health index (PHI) and the emergence of PCA3 (prostate cancer antigen 3) new prostate cancer biomarkers, which provide new tools for the diagnosis of prostate cancer [43]. PHI, an algorithm based on PSA and its subtypes ([−2] proPSA and fPSA), has been found to have higher diagnostic efficacy than PSA and fPSA in distinguishing PCa with and without PCa and PCa with Gleason score ≥ 7 [44]. However, PCA3 is a prostate-specific, non-coding RNA, and its levels in the urine of PCa patients are significantly increased [45]. The Prognostic Nutrient Index (PNI) is calculated using albumin levels that reflect nutritional status and lymphocyte counts that reflect immune status and can be used to show nutritional and immune status associated with survival and prognosis for many cancers [46]. Ellez *et al.* showed that cancer-specific survival (CSS) was significantly better in patients with high PNI (median: 65.60, 95% CI: 39.36 - 91.83) than in patients with low PNI (median: 34.93, 95% CI: 21.52 - 48.34) (P = 0.016) [47]. Sonmez *et al.* included 508 patients with PSA < 10 ng/mL and PI-RADS ≥ 3 who underwent transfusion prostate biopsies, and the results showed that SII plus PI-RADS score appeared to be an important diagnostic marker in patients with high-grade PCa neuropathological grade (ISUP grade 3 - 5). These values are higher compared to patients with benign pathology and patients with lower ISUP scores [48]. However, compared with these novel markers, SII has shown unique advantages as an indicator reflecting the state of immune inflammation, which can not only predict the occurrence of prostate cancer, but also predict the clinical diagnosis and prognosis of the disease. Due to the high cost of these experiments, they cannot be widely used in primary hospitals, which means that they cannot be used as a test for routine screening for PCa.

6. Prospect

Early diagnosis of PCa is the main influencing factor affecting the treatment effect and quality of life of PCa. SII reflects the immune inflammatory status of the body and plays a key role in the development and progression of tumors, such as affecting the efficacy of immunotherapy. Therefore, SII may be used in individualized treatment decisions for prostate cancer, such as predicting the efficacy of immunotherapy and guiding the selection of treatment regimens. Although more studies are needed to verify its application value in prostate cancer, SII, as a novel biomarker, has great research potential and future application prospects. At present, many scholars have done a lot of research work on the early diagnosis of prostate cancer, but there is no direct use of SII combined with PSA for early prediction of prostate cancer and reduction of prostate needle biopsy. As an emerging biomarker, SII is still in the early stage of prostate cancer research, and there are many problems that need to be solved, such as its combination application with other biomarkers, and its role in the individualized treatment of prostate. With the deepening of research and the advancement of technology, the author believes that SII will play a greater role in the diagnosis and treatment of prostate cancer and bring new breakthroughs to the diagnosis and treatment of prostate cancer.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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