

Research Article

Inflammation and Prognosis: Research Progress on the Clinical Value of SII in NSCLC

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Abstract

Lung cancer is the malignant tumor with the highest incidence rate and mortality rate in China. The treatment options for Non-Small Cell Lung Cancer (NSCLC) include surgery, radio chemotherapy, immunotherapy, and targeted therapy. For patients with tumors, the selection of treatment strategies and prognostic evaluation are of critical importance; therefore, exploring reliable biomarkers holds significant clinical value. The Systemic Immune-Inflammation Index (SII), as a novel biomarker, comprehensively assesses the immune and inflammatory status of the tumor microenvironment by integrating peripheral blood inflammatory indicators, and is closely associated with disease progression and therapeutic response. This article provides a systematic review of the current research progress on the application of SII in the prognostic diagnosis of patients with NSCLC.

Keywords: Peripheral blood inflammatory markers; Prognostic value; SII; NSCLC

Introduction

With the advancement of globalization and population aging, the incidence rate and mortality rate of malignant tumors have risen sharply. Among them, lung cancer has the highest incidence rate of all malignant tumors (accounting for 11.6% of total cases) and is the

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leading cause of cancer-related deaths (accounting for 18.4% of all malignant tumor deaths) [1]. Statistical data show that lung cancer has the highest incidence rate (21.98%) and mortality rate (28.49%) among all cancers in China, and it is also the primary cause of cancer-related deaths in both men (31.66%) and women (23%) [2]. From a histological perspective, lung cancer is mainly classified into two major subtypes: small cell lung cancer and Non-Small Cell Lung Cancer (NSCLC). Among them, NSCLC accounts for approximately 85% of all lung cancer cases [3].

The Systemic Immune-Inflammation Index (SII), a novel inflammatory marker proposed by Hu et al. in 2014 [4], provides a more comprehensive assessment of the tumor immune microenvironment through the algorithm neutrophil × platelet/lymphocyte. Recent studies have shown that peripheral blood inflammatory indicators are associated with the prognosis of malignant tumors [5-9]. In particular, in NSCLC, SII, by integrating immune cells such as neutrophils, has significant prognostic predictive value [10].

Inflammation and Tumors

As early as the mid-19th century, Rudolf Virchow first proposed the theory of the association between inflammation and tumors [11], suggesting that chronic inflammation (such as ulcers or unhealed wounds) could induce malignant transformation. This pioneering concept laid a crucial foundation for subsequent research. In 1971, Folkman proposed the theory that "tumor growth depends on angiogenesis [12]." Although it did not directly focus on inflammation, angiogenesis constitutes an essential component of the inflammatory response. In 1986, Dvorak discovered that tumor cells exploit the inflammatory microenvironment to promote their own growth and survival [13]. In 2011, Hanahan and colleagues expanded the hallmark features of cancer from six to ten [14], revealing that inflammation drives cancer cell proliferation, invasion, and immune evasion through modulation of the tumor microenvironment [15]. In 2017, the Suarez-Carmona team extended the concept that "a tumor is a wound that never heals [16]," emphasizing that chronic inflammation is a defining feature of tumors. In 2022, Hanahan updated the hallmarks of cancer to fourteen, highlighting that inflammation drives tumor progression through epigenetic regulation and metabolic reprogramming [17].

Neutrophils and Malignant Tumors

Neutrophils are the most abundant type of leukocytes in peripheral blood and play a crucial role in the innate immune response. Studies have shown that neutrophils participate in the regulation of the tumor microenvironment by producing inflammatory mediators, thereby promoting tumor proliferation, angiogenesis, and metastasis, as well as facilitating tumor cell immune evasion [18-21]. Specifically, Huang et al. demonstrated that neutrophil-derived inflammatory factors enhance tumor growth and metastasis, whereas the study by Ozel and colleagues elucidated the molecular mechanism by which neutrophils promote tumor angiogenesis through the vascular endothelial growth factor (VEGF) signaling pathway [18,20].

Platelets and Malignant Tumors

Lymphocytes are a core component of the immune system and play a crucial role in the adaptive immune response. A reduction in the number of lymphocytes can impair the body's anti-tumor immune response, leading to the formation of a tumor-promoting microenvironment [22]. The Hiraoka team found that CD8⁺ T cells and CD4⁺ T cells synergistically inhibit cancer progression [23], and high levels of CD8⁺ T cells and CD4⁺ T cells are important indicators of a favorable prognosis in patients with non-small cell lung cancer (NSCLC). Scholars such as Guo [24] discovered that regulatory T cells are associated with a poor prognosis of lung adenocarcinoma. Teams led by Li et al. found that the number and subtypes of lymphocytes are closely related to the survival rate of cancer patients [25-27].

Platelets and Malignant Tumors

Platelets are important components of the circulatory system and play a crucial role in physiological and pathological processes such as hemostasis, thrombosis, inflammatory responses, and tumor metastasis. In 1865, Armand Trousseau first reported the association between platelet activation and malignant tumors [28]. Previous studies have shown that platelets promote tumor progression through multiple mechanisms: releasing factors to facilitate the proliferation and metastasis of malignant tumor cells [29,30]; enhancing vascular permeability to promote lymphatic metastasis [31]; and forming a "platelet shield" to protect tumor cells, assisting in their adhesion, extravasation, and metastatic colonization [32].

From the pioneering proposal that inflammation is associated with tumors to the confirmation that inflammation is a key hallmark of tumors, relevant studies have gradually uncovered the multidimensional role of inflammation in tumor initiation, progression, and metastasis. All existing studies indicate that inflammatory factors are closely related to tumors, and this association provides a new research direction for the early diagnosis and intervention of tumors.

Relationship Between SII and Prognosis in NSCLC Patients

Undergoing surgical treatment

Surgical treatment is the main curative method for patients with stage-I and some stage IIIA non-small cell lung cancer (NSCLC). The surgical approaches include sublobar resection, lobectomy, pneumonectomy, and sleeve lobectomy. Currently, the prognostic evaluation indicators include Overall Survival (OS), Disease-Free Survival (DFS), Recurrence-Free Survival (RFS), Event-Free Survival (EFS), Major Pathological Response (MPR), etc.

In terms of Overall Survival (OS) and Disease-Free Survival (DFS), Gao et al.^[33] were the first to confirm that a high Systemic Inflammatory Index (SII) (>395.4) was significantly associated with shorter OS. Subsequent studies by teams such as Taylor et al. further supported this conclusion [33-37], suggesting that a higher SII is associated with poorer OS and DFS. Specifically: Guo et al. used Receiver Operating Characteristic (ROC) curves and found that SII had better predictive efficacy for OS; Cox regression analysis by Ma et al. showed that SII was an independent risk factor for OS and Progression-Free Survival (PFS) ($P < 0.05$) [34,35]; Yan et al. observed that the 5-year DFS and OS rates in the low SII group (<402.37) were superior to those in the high SII group (49.7% vs. 34.9%; 54.3% vs.

38.2%) [37]. However, in a multivariate analysis, Tomita et al. found that there was no significant association between SII and 5-year survival rate ($P = 0.841$). In other aspects [38], Gao et al. discovered that the high SII group (>395.4) was more likely to present with advanced T stage ($P < 0.01$) and lymph node metastasis ($P < 0.05$) [33].

In conclusion, existing studies support the predictive value of the Systemic Inflammatory Index (SII) for the postoperative prognosis (Overall Survival/OS, Disease-Free Survival/DFS) of patients with non-small cell lung cancer (NSCLC), as it is significantly associated with tumor progression, metastasis risk, and survival outcomes. However, some studies have shown that the predictive value of SII is limited in multivariate analysis, suggesting that its clinical application requires comprehensive evaluation combined with other factors.

Non-Surgical Treatment

For patients with non-small cell lung cancer (NSCLC) who have early-stage inoperable disease, locally advanced disease (stage III), or advanced disease (stage IV), surgical resection of lesions provides limited clinical benefits. Therefore, radiotherapy or pharmacotherapy should be selected individually based on molecular characteristics and disease burden.

In clinical studies on chemoradiotherapy, Xu Ensong et al. found that the baseline SII level was significantly elevated in the group with poor treatment response [39]. Tong et al. confirmed that a high SII was associated with poorer OS, advanced T stage ($P < 0.001$), later clinical stage ($P = 0.019$), and lower treatment response rate ($P = 0.018$). For special populations [40], Zhang et al. reported that NSCLC patients with brain metastasis and a low SII (<480) had a better median PFS (11.5 vs. 9 months) and median OS (20 vs. 18 months) [41]. In clinical studies on immunotherapy, Xie Bin et al. all found that the SII level was significantly increased in patients with disease progression [42-44]. Specifically: Jin et al. confirmed that the low SII group (<531.26) had better PFS ($P < 0.05$); Liu et al. reported that patients with a low SII (≤ 603.5) had significantly prolonged PFS and OS ($P < 0.05$) [42,45]; Chen et al. found that a high SII (>792) was associated with poorer OS and PFS [46]. However, the teams of Zhang and Putuz did not confirm the predictive value of SII for treatment response and survival rate [47,48]. In clinical studies on targeted therapy, Gibson et al. found that patients with a high SII (≥ 1200) had significantly shorter PFS (15.6 vs. 10.8 months) and OS (30.4 vs. 20.1 months) (both $P < 0.001$) [49]. Multiple studies consistently confirmed that the SII level is associated with the prognostic efficacy of targeted therapy: Olmez et al. and Sebnem Yucel et al. used 934.7 and 640 as SII cut-off values, respectively, and both found that patients with a low SII had a better prognosis [50-52]; Deng et al. and Ju et al. further verified that a high SII is associated with poorer survival outcomes [53,54]; Xu Jing et al. confirmed that the pre-treatment SII has predictive value for PFS and OS [55].

In conclusion, the Systemic Inflammatory Index (SII) holds unique clinical value in the prognostic assessment of non-surgical NSCLC patients. Therefore, integrating SII into the whole-course management of non-surgical NSCLC patients is expected to improve clinical prognosis and provide potential evidence for their individualized treatment strategies. However, current studies have not yet established a standard cut-off value for SII, and the determination of cut-off values in some studies mostly relies on previous literature, lacking systematic validation research.

Neoadjuvant Therapy

Neoadjuvant therapy refers to systemic treatment administered before surgery, aiming to reduce tumor size and eliminate micrometastases [56]. Currently, neoadjuvant therapy mainly includes the following types: neoadjuvant immunotherapy, neoadjuvant chemotherapy, and neoadjuvant immunotherapy combined with chemotherapy. In the field of neoadjuvant immunotherapy research, Huai et al. found that although pre-treatment SII had limited predictive value for major pathological response (MPR) [57], a high SII was significantly associated with poorer overall survival (OS) and event-free survival (EFS) ($P < 0.05$). Ren Weidong et al. further confirmed that the pre-operative SII level in the non-MPR group was significantly higher than that in the MPR group ($P < 0.001$) [58], and the risk of non-MPR in patients with a high SII was 4.397 times that of patients with a low SII ($P < 0.001$). In the field of neoadjuvant chemotherapy research, a study by Lan et al. revealed that the SII level in the pathological complete response (pCR) group was lower than that in the non-pathological complete response group ($P < 0.01$) [59]. Logistic regression analysis confirmed that SII was a relevant factor influencing the efficacy of neoadjuvant chemotherapy ($P < 0.001$), and the receiver operating characteristic (ROC) curve showed that it had good predictive performance. However, a study by Xu et al. indicated that there was no significant correlation between SII and MPR ($P = 0.054$) [60].

In the field of neoadjuvant immunotherapy combined with chemotherapy research, Li et al. found that the SII of patients in the progressive disease (PD) group was significantly increased ($P = 0.019$), and a high SII was associated with poorer progression-free survival (PFS) [61]. Nevertheless, a multi-center study by Li et al. showed that post-treatment SII had higher predictive value for MPR than baseline SII [62].

The above studies indicate that the SII index has certain reference value in predicting the disease remission of NSCLC patients receiving neoadjuvant therapy, and is expected to provide new ideas for the optimization of neoadjuvant therapy regimens. However, current research on the correlation between the SII index and neoadjuvant targeted therapy remains relatively scarce. This field has broad exploration space and deserves focused attention and in-depth investigation in future studies.

Summary and Outlook

The occurrence and progression of tumors is a complex process, which is closely related to systemic immune function. As important indicators of the body's inflammatory and immune function, inflammatory markers exhibit observable changes during tumor progression. The expression level of SII (Systemic Inflammatory Index) can not only reflect the body's inflammatory status, but also provide auxiliary value for clinicians in evaluating preoperative tumor invasiveness, chemoradiotherapy sensitivity, and the efficacy of immunotherapy and targeted therapy in NSCLC (Non-Small Cell Lung Cancer).

However, SII still has limitations in clinical application. In current studies, there are significant differences in patient individuals and the treatment methods they receive, and no reference threshold or reference range for SII has been established yet. Based on these limitations, future studies should conduct multi-center, large-sample prospective cohort studies to establish standardized SII cut-off values, while designing randomized controlled trials to systematically evaluate the predictive value of SII in different treatment regimens. These

studies will help establish the clinical status of SII in the precise diagnosis and treatment of NSCLC, and promote its transformation from a research indicator to clinical application.

Data Sharing Statement

The data that support the results of this study are available from the corresponding author on reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Ethics Approval Statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Hohhot First Hospital (IRB2024323). All participants provided written informed consent prior to inclusion in the study.

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Disclosure of interest

The authors declare that they have no competing interests.

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