Progress of peripheral blood immunoinflammatory markers in oral squamous cell carcinoma

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***Abstract:** Oral squamous cell carcinoma (OSCC) is the most common form of head and neck squamous cell carcinoma (HNSCC), and its incidence has been on the rise worldwide in recent years. Although the prognosis is good in the early stage, it is mostly in the localized or advanced stage when diagnosed. Although the prognosis is good in early stage, it is mostly localized in advanced stage when diagnosed. Treatment is mostly surgical resection as the preferred method, but due to the presence of subclinical metastases, tumor cells can never be completely eliminated, and even after radical resection, patients are still at risk of tumor recurrence. Immune response and inflammatory response play an important role in tumor development and progression, and studies have shown that the number of certain inflammatory cells and their ratios in the peripheral blood are important prognostic factors for malignant tumors, such as platelets, neutrophils, lymphocytes, monocytes, and so on. In this paper, we present the results of the peripheral blood platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), systemic immune- inflammation index (SII), and the number of inflammatory cells in the peripheral blood. NLR, neutrophil-to-lymphocyte ratio (NLR), systemic immune- inflammation index (SII), and lymphocyte-to-monocyte ratio (LMR) in OSCC, with the aim of providing a more comprehensive reference for the comprehensive diagnosis and treatment of OSCC.*

***Keywords:** Oral squamous cell carcinoma; PLR; NLR; SII*

1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignant tumor that occurs in the oral cavity and is predominantly composed of squamous cells, which accounts for up to 50% of squamous cell carcinomas of the head and neck region and up to 90% of oral cancers, and OSCC has a high degree of malignancy and is highly hazardous [1,2]. OSCC has a strong local infiltrative nature, is prone to metastasis, and most patients are already in advanced stages when they are diagnosed [3]. Most of the patients are already in the middle and late stages when diagnosed [3] Globally, there are about 300,000 new cases of oral squamous carcinoma each year, of which 100,000 patients die [4].OSCC treatment is mostly based on surgical resection as the preferred method, but due to the presence of subclinical metastatic foci, the tumor cells can never be completely eliminated, and even after radical resection, the patients are still at the risk of tumor recurrence [5]. Studies have shown that recurrent tumor metastasis after surgery is considered to be a rather important factor affecting survival [6]. Therefore, early identification of indicators associated with poor prognosis in oral squamous carcinoma is essential for developing appropriate treatment and follow-up strategies. In recent years, as the role and mechanisms of inflammation in the development and progression of malignant tumors have been better understood, a number of peripheral blood inflammatory markers have been shown to correlate with the prognosis of malignant tumors. Like other cancer types, the inflammatory microenvironment is an important component of oral squamous carcinoma development and progression [7]. In this article, we present a review of the progress of several common inflammatory markers in peripheral blood in oral squamous carcinoma, aiming to provide a more comprehensive reference for the comprehensive diagnosis and treatment of oral squamous carcinoma.

2. Relationship between inflammation and malignant tumors

Inflammation plays an important role in tumorigenesis, progression and prognosis.In 1863, researchers discovered the phenomenon of lymphocyte infiltration in tumor tissues, and for the first time

suggested that inflammation was associated with tumors [8]. To this day, it has been found that 1/4 of all cancer diseases are closely related to inflammation [9]. Many solid tumors present infiltrating immune cells and release inflammatory cytokines into the surrounding tissues and bloodstream, leading to systemic inflammation [10]. Systemic inflammation and pro-inflammatory processes are associated with poor prognosis in cancer patients. The tumor microenvironment (TME) is involved in tumor progression. It has a complex composition consisting of different types of tumor cells and non-cellular components [11].The TME is enriched with immune and inflammatory cells, including macrophages, T cells, B cells, dendritic cells (DCs), and neutrophils, which directly or indirectly interact with the cancer cells through a variety of mediators such as cytokines and chemokines [12].

2.1 Tumor-associated neutrophils (TANs)

An increasing number of studies have shown that neutrophils are part of the immune response to tumors, and initially, they were thought to have an antiproliferative role against tumor cells. Neutrophils are an important part of the inflammatory microenvironment and are at the forefront of the body's defense response, but their numerous means of protection for the body can be exploited by cancer cells as carriers of tumor metastasis [13]. However, a few years later, studies have reported the opposite result, that neutrophils have a pro-cancer role in tumor development. There has been substantial evidence of the dual nature of the inflammatory immune system in preventing or promoting tumor growth and metastasis [14-16]. During tumorigenesis, progression, and metastasis, TANs play a role in a variety of ways. Due to the plasticity and heterogeneity of neutrophils, TANs exhibit both anti-tumor and pro-tumor activities.

2.2 Tumor-infiltrating lymphocyte (TIL)

TIL is a heterogeneous group of predominantly lymphoid immune cells present in tumors and their mesenchyme, including T cells, B cells, dendritic cells, and natural killer cells (natural killer cells, NK cells), etc. TME releases chemokines that recruit peripheral blood lymphocytes to the tumor site, eliminating cancer cells by targeting tumor antigens and membrane ligands [17]. A relative decrease in peripheral blood lymphocyte counts may imply a decrease in TIL counts.TIL has been shown to be a more accurate predictor of 5-year overall survival in patients with oral squamous carcinoma in combination with TLS [18].NISHA et al. showed that invasive tumor frontal TIL-derived MLL2 was an independent prognostic factor for DFS in patients with early-stage oral squamous carcinoma [19]. However, TIL is more difficult to obtain because of the need for pathologic specimens and the small amount of specimens punctured, and its assessment is not representative of the assessment of TIL. In addition, there is a certain degree of inherent error in the assessment of TIL counts, which makes it difficult to generalize in clinical practice [20]. Overall the more readily available peripheral blood lymphocyte counts correlate with TIL and may be used as an alternative to TIL in assessing the prognosis of patients with oral squamous carcinoma.

2.3 Platelet (PLT)

In the 1860s, French physicians described that in the early stages of a tumor, local tumors can induce thrombosis at distant sites, and thrombosis is one of the prominent features of tumors [21]. Platelets and tumors can interact with each other, and this interaction facilitates tumorigenesis and metastasis. Cancer cells can directly activate platelets or indirectly induce platelet activation by releasing platelet-activating mediator adenosine diphosphate (ADP) [22], high mobility group box 1 protein (HMGB1) [23], or by expressing various types of tissue factors that lead to thrombin generation. platelet activation. Activated platelets, in turn, promote tumor progression through various mechanisms. Platelets originate from bone marrow megakaryocytes and are involved in a variety of important pathophysiological processes, such as hemostasis, cellular inflammatory response, nonspecific immunity, and tumor invasion and proliferation. Platelets not only promote angiogenesis, but also promote tumor cell expansion by interfering with the recognition of tumor cells by the immune system and establishing a physical barrier to phagocytosis [24], while tumor growth further activates platelets, thus creating a vicious expansion cycle.

2.4 Tumor-associated macrophage (TAM)

Tumor-associated macrophages (TAMs) are the most abundant immune cells in TME and are considered to be the drivers of inflammation, playing an important role as a bridge between chronic inflammatory mediator response and tumorigenesis and development, and participating in the

proliferation, invasion, and metastasis of tumor cells by mediating angiogenesis and establishing an immunosuppressive microenvironment [25]. TAM secretes growth factors such as epidermal growth factor (EGF),vascular endothelial growth factor(VEGF)[26], and platelet-derived growth factor (PDGF), as well as components such as CXCL and CCL family chemokines and matrix-degrading enzymes [27]. VEGF-C is expressed by M2-type TAM and promotes the production of nodular lymphatic vessels [28]. The key step in invasion and metastasis is the destruction of the basal membrane by proteases, and TAMs assist in the malignant behavior of tumor cells by secreting active substances such as matrix proteins, matrix remodeling enzymes, proteases, cathepsins, and chemokines to digest and remodel the normal tissue interstitium [29-30].

3. Peripheral blood immunoinflammatory markers in oral squamous carcinoma

In recent years, several reports have indicated that tumor recurrence and metastasis and body inflammation are associated with immune imbalance, which guided us to seek for an indicator such as simultaneously reflecting inflammation and immune status to assess OSCC recurrence and metastasis. Calcitonin and C-reactive protein (CRP) and calcitonin are known to be traditional indicators of inflammation, but calcitonin levels vary significantly during the day and calcitonin has a concentration-dependent biphasic half-life. In addition, calcitonin can be rapidly degraded by serum protease [31], and these limit calcitonin application. Inflammation affects tumor growth differently; acute inflammation inhibits tumor growth, while chronic inflammation promotes tumor growth. Among the etiologies of malignant neoplasia, chronic inflammation has been identified as the main cause of about 20% of malignant neoplasia cases [32].Although CRP is an egg self that reflects the acute response of the body, it has been shown that CRP levels also reflect the body's early defense system [33]. The potential predictive value of CRP in OSCC lymph node metastasis has been demonstrated in a prospective study of 40 OSCC patients [34]. This calls for a large number of prospective studies to further understand the potential value of CRP in assessing OSCC progression as well as the mechanisms.

NLR, PLR, LMR and SII, as recognized common indicators of systemic immune-inflammatory response, are closely related to the anti-tumor effects of the body and cancer prognosis [35-37], and they have been clinically demonstrated to be associated with a wide range of neoplastic diseases [38].NLR, PLR, LMR and SII can be used as indicators of trophic status and inflammation associated with tumor growth, invasion and increased angiogenesis that can be used to assess tumor progression and immune status [39]. Studies have amply demonstrated that inflammation is closely related to OSCC, and in terms of NLR, PLR, and LMR, Charles et al [40] conducted a study on 145 patients with squamous cell carcinoma of the head and neck, and found that NLR can be used as a prognostic factor, whereas an NLR of greater than 5 implies a shorter survival period. In addition, NLR can be used to identify those patients who are at risk of recurrence, and NLR, PLR, and LMR biomarkers can also be used for the follow-up of patients with OSCC [41].Perisanidis et al [42], on the other hand, analyzed the relationship between NLR and other markers and preoperative chemotherapy in 97 patients with locally invasive OSCC, and observed that NLR was an independent marker of poor prognosis.Park et al [43] found that low LMR, high NLR, and PLR were associated with highly diseased lesions in a study of 69 cases of OSCC patients, with low LMR and high NLR correlating with the size of the tumor, and elevated PLR correlating with lymph node involvement. Other scholars have found that high preoperative NLR and PLR were associated with poor survival in studies of paranasal sinus carcinoma [44].In 2014, Hu et al [45] developed a systemic immunoinflammatory index, named SII (SII=neutrophils (N) × platelets (P)/lymphocytes (L)), to predict the prognosis of patients after radical resection for hepatocellular carcinoma. Several studies have shown that SII is a reliable and accurate independent prognostic indicator for patients with all types of tumors [46-49].Eda [50] et al. have demonstrated that SII can be used as a prognostic indicator for early OSCC. Moreover, these inflammatory markers are derived from blood cell analysis, the results are easy to obtain, inexpensive, and the data are more stable and independent of the operator's clinical experience, which has great potential in predicting the efficacy of therapeutic agents, the diagnosis of malignant tumors, and the prognosis of patients.

4. Conclusions

In conclusion, the current study demonstrates the value of peripheral blood PLR, NLR, SII, and LMR in OSCC. Hematology has many advantages in the epidemiological study of OSCC, such as reliable detection method, economy, and good reproducibility, etc. The combined application of inflammatory markers, such as PLR, NLR, SII, and LMR, with other indexes can provide more references for the

comprehensive diagnosis and treatment of OSCC. However, there are fewer related studies at present, and the conclusions of the existing studies are somewhat controversial. Therefore, multicenter studies with larger sample sizes are needed to evaluate their effectiveness as prognostic predictors for patients with OSCC, and it is hoped that, with the development and depth of the studies, peripheral blood markers can become independent indicators in preoperative examinations in the future, which will provide more guidance for the comprehensive diagnosis and treatment of OSCC.

Acknowledgements

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