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Research Article

The prognostic role of markers of systemic inflammation in patients with metastatic lung cancer receiving immunotherapy: A comprehensive review of the literature

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Abstract

Lung carcinoma stands as a prevalent malignancy characterized by a distressingly elevated fatality rate. Immunotherapy, administered either as a monotherapy or together with chemotherapy, represents the primary therapeutic approach for the majority of individuals grappling with advanced non-small cell lung cancer. The influence of systemic inflammation in fostering cancer dissemination and progression is a well-documented phenomenon. This literature review examines contemporary indices and scoring systems, which have emerged as informative indicators of systemic inflammation in recent years. These indices and scores are valuable prognostic and predictive elements in assessing treatment response among patients with metastatic lung cancer undergoing immunotherapeutic treatment.

Keywords

markers of systemic inflammation, lung cancer, immunotherapy

Introduction

Lung cancer holds the unfortunate distinction of being the leading global cause of cancer-related mortality. In 2020, as per GLOBOCAN data, it accounted for a staggering 1,796,144 deaths, representing 18% of all cancer-related fatalities (Sung et al. 2021). Non-small cell lung cancer (NSCLC) constitutes the predominant histological subtype, making up approximately 85% of all cases, while small cell lung cancer (SCLC) accounts for the remaining cases. Lung cancer exhibits a formidable degree of aggressiveness, characterized by rapid growth and early metastatic spread, leading to diagnosis typically occurring at advanced stages (stage III/IV) for most patients (Flores et al. 2021). Despite substantial progress in pharmacotherapy for lung cancer, the 5-year survival rate for those with advanced or metastatic disease remains dishearteningly low, fluctuating at less than 5–10%, with regional variations (Sung et al. 2021).

Immunotherapy has emerged as the predominant treatment modality for NSCLC patients over the past decade, in line with recommendations from national and international treatment guidelines. In the majority of cases, patients with advanced and metastatic NSCLC currently

receive first-line immunotherapy either as a monotherapy or in conjunction with chemotherapy. The critical necessity of identifying clearly defined prognostic factors cannot be understated. These factors serve the crucial purpose of guiding treatment decisions individually and setting priorities for preventive and therapeutic strategies, especially in light of the escalating costs associated with treatment. The identification of prognostic factors that are readily accessible and cost-effective is of paramount importance in clinical practice.

Prognostic factors are closely linked to the disease outcome, with overall survival being the most commonly employed parameter for comparative analysis. These factors are measured before treatment initiation and significantly impact prognosis, independent of the treatment administered (Paesmans 2012). Traditional prognostic factors in the management of NSCLC patients include disease staging according to the TNM (Tumour, Node, Metastasis) classification, Eastern Cooperative Oncology Group (ECOG) performance status, gender, age, and histological subtype (Paesmans 2012). Numerous publications have substantiated the unfavorable prognosis associated with advanced disease stages, older age, compromised general health, male gender, and histological findings indicative of adenocarcinoma or large cell carcinoma (Paesmans 2012).

In recent decades, with the introduction of novel drug classes for advanced NSCLC treatment, such as targeted therapies and immunotherapies, researchers have been actively exploring new prognostic factors linked to poor survival. Markers of systemic inflammation have emerged as potential prognostic factors, with several of them integrated into total scores and indices for comprehensive assessment. This literature review endeavors to provide a succinct summary of the key systemic inflammation biomarkers with the potential to serve as prognostic indicators for immunotherapy treatment in patients grappling with metastatic NSCLC.

Materials and methods

In 2023, we undertook a bibliographic investigation to assess the indicators of systemic inflammation that have been explored as prospective prognostic determinants in managing lung carcinoma. Our study employed data from reputable sources, including PubMed and Google Scholar. It was conducted utilizing the following search terms: “markers of systemic inflammation,” “SII,” “ALI,” “Khorana score,” “lung cancer,” and “immunotherapy.” Our primary emphasis was on prognostic biomarkers that are straightforward to administer, facile to conduct, and suitable for integration into routine clinical practice.

The involvement of inflammation in the progression of lung cancer

Inflammation is linked to the initiation of tumor growth and the development of cancer, facilitating the proliferation, spread, and endurance of tumor cells through the activation of oncogenic signaling pathways. Tumor-promoting inflammation ensues when tumor cells induce the death of healthy cells, and this inflammation induced by tumors stands as a prominent hallmark of cancer (Hanahan and Weinberg 2011), as illustrated in Fig. 1.

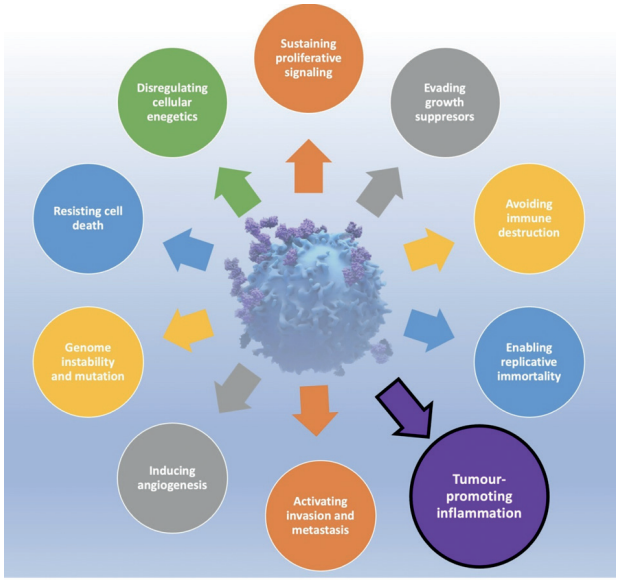

Figure 1. Biological Hallmarks of Cancer, Source: Adapted from Hallmarks of Cancer: The Next Generation, Hanahan D., Weinberg R.A. , Cell, Volume 144, ISSUE 5, P646-674, March 04, 2011, https://doi.org/10.1016/j.cell.2011.02.013.

The local immune response and the interplay between neoantigens, cytotoxic and regulatory T-cells, as well as suppressive factors, hold significant importance in the context of the inflammatory process (Herbst et al. 2018; Altorki et al. 2019; Isaksson et al. 2022). Conversely, in response to the activity occurring in and around tumor cells, the tumor microenvironment releases cytokines, proteins, and circulating immune cells that exert an influence on the systemic inflammatory process, as noted in reference (Diakos et al. 2014). The impact of inflammation induced by the invasive growth of tumors becomes more pronounced in advanced stages of cancer. This is in contrast to the early stages, where the tumor is typically surgically removed along with the surrounding tissue. In advanced stages, the tumor deposits persist as focal points of inflammation during systemic therapy or palliative care, as discussed in reference (Isaksson et al. 2022).

Markers of systemic Inflammation – the role of complete blood count parameters to inflammatory processes

Even prior to the introduction of immune checkpoint inhibitors into the lung cancer treatment landscape, certain

biomarkers associated with the systemic inflammatory response and malnutrition, assessed before the commencement of systemic therapy, were recognized as independent prognostic factors in various oncological conditions, including lung cancer.

The complete blood count (CBC) is a standard test conducted in all lung cancer patients before initiating systemic therapy. Specific CBC parameters, such as platelets, neutrophils, and lymphocytes, which serve as markers of systemic inflammatory response, play a pivotal role in the immune response against tumor cells. Platelets have been demonstrated to significantly influence metastasis by inducing epithelial-mesenchymal transition, increasing vascular permeability, affecting tumor angiogenesis, and shielding circulating tumor cells from natural killer (NK) cell activity (Erpenbeck and Schön 2010; Labelle et al. 2011; Placke et al. 2012). Other researchers have reported that neutrophils facilitate the adhesion and attachment of tumor cells to distant organ sites through the release of proteases and circulating growth factors like VEGF (Placke et al. 2012). Conversely, lymphocytes play a protective role in terms of anti-tumor defense, as they induce cytotoxic cell death and inhibit tumor cell proliferation and migration (Mantovani et al. 2008). A systematic review conducted by Caro et al. (Caro et al. 2001) in 2001 revealed that anemia is an independent adverse prognostic factor, especially in lung cancer patients, thus underscoring the well-established link between systemic inflammation and adverse prognostic outcomes, typically associated with malnutrition, hypoalbuminemia, weight loss, and other manifestations of cancer cachexia (Baracos et al. 2018).

Furthermore, various simple formulas have been developed using combinations of the aforementioned hematological parameters, including the neutrophil-to-lymphocyte ratio (NLR), derived NLR (dNLR) calculated as ANC/(WBC concentration – ANC), lymphocyteto-monocyte ratio (LMR), and platelet-to-lymphocyte ratio (PLR). These parameters have been subject to investigation as potential predictive factors (Proctor et al. 2012; Krenn-Pilko et al. 2014; Stotz et al. 2014; Gu et al. 2015; Mandaliya et al. 2019; Yilmaz and Yersal 2022).

Role of neutrophil-to-lymphocyte ratio (NLR) as a predictive and prognostic factor

The neutrophil-to-lymphocyte ratio (NLR) stands as one of the most extensively investigated prognostic indicators. Originating prior to the advent of immunotherapy as a therapeutic modality, NLR has demonstrated its utility in identifying unfavorable prognoses in patients with breast cancer, colorectal cancer, gastric cancer, hepatocellular carcinoma, and lung cancer (Limaye et al. 2013; Zhang et al. 2014; Gu et al. 2015; Hu et al. 2015; Petrova et al. 2020).

In Bulgaria, a multicenter retrospective study involving 119 patients delved into the predictive and prognostic role of the neutrophil-to-lymphocyte ratio in individuals with advanced non-small cell lung cancer (NSCLC) who underwent pembrolizumab immunotherapy as a secondline treatment (Petrova et al. 2020). The study findings revealed that patients with an NLR exceeding 5 exhibited a shorter progression-free survival when contrasted with those whose NLR was 5 or less. Furthermore, a multivariate analysis unveiled that the presence of bone metastases and an NLR exceeding 5 before the commencement of chemotherapy, along with a high platelet-to-lymphocyte ratio (PLR) before the initiation of chemotherapy, independently constituted adverse prognostic factors associated with a diminished progression-free survival (Petrova et al. 2020).

In another investigation conducted by Romano et al., the prognostic significance of NLR was corroborated in patients with NSCLC and elevated PD-L1 expression who were administered first-line pembrolizumab immunotherapy (Romano et al. 2023). The authors observed a notably reduced overall survival, particularly among patients with markedly elevated NLR exceeding 10, with a high mortality rate apparent in the initial months of immunotherapy (Romano et al. 2023).

New indices and scores for systemic inflammation, such as prognostic biomarkers in immunological treatment of advanced and metastatic NSCLC

Systemic immune inflammation index (SII)

The systemic immune inflammation index (SII) is a parameter that has garnered substantial attention as a prognostic marker for survival across various tumor types, including hepatocellular carcinoma, gastric cancer, germ cell tumors, prostate cancer, and lung cancer (Hu et al. 2014; Hong et al. 2015; Tong et al. 2017; Dan et al. 2018; Guo et al. 2018; Tomita et al. 2018; Yang et al. 2018; Bilgetekin and Basal 2020). SII is calculated based on the counts of lymphocytes, neutrophils, and platelets in peripheral blood using the following formula: SII = platelet count × neutrophil count / lymphocyte count (Hu et al. 2014).

An in-depth subgroup analysis, part of a meta-analysis conducted by Yang et al., encompassing 7,657 patients with diverse oncological conditions, concluded that an SII exceeding a predefined threshold reliably predicted poorer survival outcomes in patients with hepatocellular carcinoma, gastric cancer, esophageal squamous cell carcinoma, urinary neoplasms, small-cell lung cancer, and non-small cell lung cancer (Yang et al. 2018). Numerous clinical studies further affirm the practical utility of SII as a biological prognostic biomarker in the management of lung cancer (Hong et al. 2015; Tong et al. 2017; Dan et al. 2018; Guo et al. 2018; Tomita et al. 2018; Bilgetekin and Basal 2020). Specifically, in early stage lung cancer, a high preoperative SII level has been associated with increased rates of relapse and shorter time to relapse, signifying a more

aggressive disease phenotype among operable non-small cell lung cancer (NSCLC) patients (Tomita et al. 2018). In patients with advanced stage III NSCLC treated with chemo-radiotherapy, an elevated SII level has been linked to a decreased rate of objective response (Tong et al. 2017). Another study by Berardi et al. investigated the prognostic role of SII in patients with advanced and metastatic lung cancer who received first-line targeted therapy or chemotherapy (Berardi et al. 2019). Patients were stratified into two groups based on their SII: ≥ 1270 (Group A) and < 1270 (Group B). The authors discovered that patients with a lower baseline SII had longer progression-free survival and overall survival (Berardi et al. 2019).

Over recent years, a growing body of evidence has underscored the role of SII as a prognostic index in lung cancer patients, a trend supported by data from various meta-analyses conducted primarily in China, Japan, and the USA. One such systematic review and meta-analysis by Zhang et al. summarized results from 2,786 lung cancer patients across seven clinical studies (Zhang et al. 2019). The meta-analysis reported a median threshold of 640 (range 395.4–1600) for defining high SII in the included studies. The pooled hazard ratio (HR) for overall survival (OS) was 1.77 (95% CI: 1.54–2.00, p<0.001), indicating that patients with a high SII score experienced worse OS. Subgroup meta-analyses revealed the notable prognostic significance of SII in lung cancer, particularly in the multivariable model for NSCLC (HR: 1.97, 95% CI: 1.69–2.25, p<0.001; 5 studies, 1,746 patients) and small-cell lung cancer (HR: 1.38, 95% CI: 1.02–1.85, p<0.001; 1 study, 919 patients). Another meta-analysis by Wang et al. encompassing nine clinical studies and 2,441 patients similarly concluded that pre-treatment SII assessment may aid in prognosis and treatment strategy selection (Wang et al. 2019). Regrettably, this analysis did not incorporate studies assessing the prognostic role of SII in patients receiving immunotherapy (Wang et al. 2019).

A meta-analysis and systematic review by Hang et al., published in 2022, incorporated 8,877 patients with non-small cell lung cancer (NSCLC) and affirmed the role of SII as a promising prognostic biomarker for guiding appropriate NSCLC therapy (Hang et al. 2022).

The predictive value of SII for the effectiveness of nivolumab immunotherapy as a secondline or further-line treatment was explored by Liu et al. (Liu et al. 2019). Although the sample size was relatively small (n=44), the authors identified a correlation between SII, neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) levels before the initiation of immunotherapy and outcomes in terms of overall survival and progression-free survival. Lower SII, NLR, and PLR levels were associated with extended progression-free survival and overall survival (Liu et al. 2019).

In a retrospective study based on real-world data from two hospitals in China, the aim was to identify predictive clinical and hematological markers for the occurrence of immune-related adverse effects (Xu et al. 2022). The study found that patients with an SII of 780 or higher had a higher incidence of immune-related adverse effects, although the difference was not statistically significant (p=0.081). Nevertheless, it exhibited a certain predictive value for the occurrence of immune-related adverse effects (Xu et al. 2022).

An exploration of associations between various markers of systemic inflammation and outcomes in metastatic NSCLC patients receiving first-line immune checkpoint inhibitors yielded inconsistent evidence in a single-site retrospective study (Mahiat et al. 2023). The examined biomarkers/scores, including SII and the albumin-to-lymphocyte ratio (ALI), displayed a moderate prognostic role but were not predictive of the response to immune checkpoint inhibitor (ICI) therapy (Mahiat et al. 2023).

Lastly, a retrospective study tracked dynamic changes in markers of systemic inflammation and nutritional indices in patients with advanced NSCLC at Shanghai Pulmonary Hospital in China who underwent first-line combination therapy with a PD-1 inhibitor and chemotherapy (Fang et al. 2023). The studied inflammatory indices, including SII, were associated with overall survival and treatment response, with dynamic changes over time proving to be a superior predictor compared to baseline values before treatment initiation (Fang et al. 2023).

Advanced lung cancer inflammation index (ALI)

The Advanced Lung Cancer Inflammation Index (ALI) is another promising biomarker designed to predict the likelihood of a response to immune checkpoint inhibitors. ALI encompasses indicators of systemic inflammation within the host and reflects the influence of cancer-related cachexia. It comprises the following components: body mass index (BMI) measured in kg/m2, serum albumin levels in g/dL, and the neutrophil-to-lymphocyte ratio (NLR).

The role of ALI was examined in a retrospective study involving patients with stage IV lung cancer in Greece and Germany (Mountzios et al. 2021). This study encompassed 672 patients who received treatment with PD-L1 inhibitors either as monotherapy or in combination with chemotherapy, as well as a control cohort of 444 patients with stage IV non-small cell lung cancer (NSCLC) who were treated with platinum-based chemotherapy without subsequent targeted therapy or immunotherapy. The findings revealed that high ALI values (>18) were associated with extended overall survival (OS) in patients receiving monotherapy with immune checkpoint inhibitors but not in patients receiving a combination of immunotherapy and chemotherapy. The results were statistically significant, with a hazard ratio (HR) of 0.402 and p-value < 0.0001 in a sample of 460 patients receiving mono immunotherapy. In the cohort treated with chemo – immunotherapy, the HR was 0.624, with a p-value of 0.111 in a sample of 212 patients (Mountzios et al. 2021).

In conclusion, the authors noted that ALI serves as a robust prognostic and predictive biomarker for patients with advanced NSCLC who are treated with PD-L1

inhibitors alone but not when used in conjunction with chemotherapy. Its association with treatment outcomes appears to be more pronounced than that of other commonly used parameters, like NLR, PLL1 tumor proportion score, lung immune prognostic index, and EPSILoN scores. In patients with high expression of PD-L1≥50%, an ALI score exceeding 18 could aid in the selection of patients for whom chemotherapy is not necessary as an adjunct to immunotherapy (Mountzios et al. 2021).

Khorana score (KS)

The Khorana Score (KS) represents the initially validated algorithm designed for the risk stratification of cancer patients about their susceptibility to venous thromboembolism (VTE) (Khorana et al. 2008). Its utility has been substantiated through an extensive body of retrospective and prospective research. The Khorana Score is computed by summing five parameters, which include the primary tumor site (very high risk, such as pancreatic or gastric cancer, equating to 2 points; high risk, encompassing lung, gynecological, lymphoma, bladder, or testicular cancers, amounting to 1 point), prechemotherapy platelet count ≥ 350×10^9/L (1 point), prechemotherapy hemoglobin level <100 g/L or the usage of red blood cell growth factors (1 point), prechemotherapy leukocyte count >11×10^9/L (1 point), and a Body Mass Index ≥ 35 kg/m² (1 point) (Khorana et al. 2008). In addition to its predictive role in venous thromboembolism, the Khorana Score has also been linked to increased mortality among cancer patients.

A retrospective investigation carried out by Bjornhart et al. examined the potential of the Khorana Score as a biomarker for patients with non-small cell lung cancer (NSCLC) undergoing immunotherapy (Bjørnhart et al. 2019). The study involved data from 118 patients with advanced or metastatic NSCLC who received immunotherapy at an oncology center in Denmark from September 2015 to April 2018. The analysis focused on parameters like overall survival and progression-free survival. The findings revealed a significant correlation between the Khorana Score and overall survival, although no such correlation was observed with progression-free survival. Notably, a Khorana Score equal to or exceeding 3 emerged as a potential predictor of early mortality. However, the need for larger-scale retrospective studies is imperative to either confirm or refute this hypothesis (Bjørnhart et al. 2019).

Other prognostic markers and their role in the management of patients with metastatic NSCLC

In recent years, researchers have turned their attention to simultaneously investigating the impact of systemic inflammation and nutritional status on the treatment outcomes of individuals with metastatic non-small cell lung cancer (NSCLC). Numerous indices and scoring systems have been created and examined in this context, including the Prognostic Nutritional Index (PNI), Lung Immune Prognostic Index (LIPI), Lung Immuno-oncology Prognostic Score-3 (LIPS-3), Lung Immuno-oncology Prognostic Score-4 (LIPS-4), EPSILoN, Glasgow Prognostic Score (GPS), modified Glasgow Prognostic Score (mGPS), Holtzman Score, Scottish Inflammatory Prognostic Score (SIPS), Gustave Roussy Immune Score (GRIm), Royal Marsden Hospital Prognostic Score (RMH), Aarhus Composite Biomarker score (ACBS), and more. A retrospective analysis of data from a clinical site in Belgium compared most of these indices and scores, revealing a prognostic role but not a predictive one in patients with metastatic NSCLC who commenced first-line chemotherapy, immunotherapy, or a combination of both (Mahiat et al. 2023).

Conclusion

As immunotherapy gains greater prominence in managing metastatic NSCLC, the demand for effective prognostic and predictive biomarkers to gauge treatment response has become increasingly critical. Systemic inflammation is a pivotal feature in cancer, as it facilitates tumor progression and metastasis. Over the past few decades, numerous indices and scoring systems have emerged, considering the influence of systemic inflammation and a patient's nutritional status. These indices have predominantly demonstrated their prognostic value and, to a lesser extent, their predictive potential. Conducting comprehensive international prospective studies to ascertain the most suitable and practical indices and scores for assessing systemic inflammation in routine clinical practice is imperative. This, in turn, will aid in determining the most appropriate initial therapy for patients with advanced lung cancer.

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