Monaldi Archives for Chest Disease

eISSN 2532-5264 https://www.monaldi-archives.org/

Monaldi Arch Chest Dis 2025 [Online ahead of print]

To cite this Article:
Tsopa P, Syrigos N, Kosmas C, Kouvela M. **Inflammation markers in lung cancer: prognostic and predictive value.** *Monaldi Arch Chest Dis* doi: 10.4081/monaldi.2025.3580

Inflammation markers in lung cancer: prognostic and predictive value

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Contributions: each author has played a substantial role in the development of this review. All authors reviewed and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: no conflict of interest exists for any of the authors in relation to the research presented in this paper.

Ethics approval and consent to participate: Institutional Review Board approval was not required for this study, as only de-identified compliant data were used in the analysis. This review includes synthesizing existing published research and does not involve collecting new data from human participants or animals.

Informed consent: not applicable.

Patient consent for publication: not applicable.

Availability of data and materials: all data generated or analyzed during this study are included in this published article.

Funding: none.

Abstract

Lung cancer is a complex and heterogeneous disease with significant morbidity and mortality worldwide. Over the years, several inflammation markers have been studied, such as molecules, cells, genes, *etc*., that are implicated in the extremely complex interactions taking place in the inflammatory process implicated in cancer development.

This narrative review aims to present the most commonly studied inflammation markers in lung cancer, including C-reactive protein, tumor necrosis factor family members, and prostaglandin E synthase enzyme 3, as well as the significant number of scores and indexes that have been developed to improve the prognostic and predictive potential for non-small cell lung cancer and small cell lung cancer patients of different stages and treatment approaches. Scores and indexes originating from a combination of variables used in everyday clinical practice are emphasized due to their simplicity and cost-effectiveness. Studies addressing the prognostic and predictive value of the most important and recently studied markers, indexes, and scores in lung cancer are summarized, revealing their potential as indicators of overall survival, therapeutic response, and tumor immune characteristics. Limitations in utilizing inflammation markers as predictive biomarkers are discussed, including assay standardization, the complexity of the inflammatory response, confounding factors, and the dynamic nature of marker assessment. The progress of biotechnology, along with the combination of routine clinical practice insights, could result in the development of inflammation markers with improved prognostic and predictive value guiding treatment decisions for lung cancer patients in the context of precision medicine.

Key words: lung cancer, inflammation, prognostic, predictive, marker.

Introduction

Lung cancer is a global health challenge, ranking at the top of the cancer list in terms of fatality rate and accounting for a staggering 18% of all cancer-related deaths worldwide, as reported by GLOBOCAN 2022 [1]. Non Small Cell Lung Cancer (NSCLC) constitutes more than 85% of all lung cancer cases, whileSmall Cell Lung Cancer (SCLC) accounts for approximately14% of lung cancers [2,3].

Tumor inflammation is now considered an enabling characteristic of carcinogenesis. It plays a vital role for the acquisition of core hallmark capabilitiesin the development of cancer [4]. Chronic inflammation in particular plays a significant role in the immunosuppression and malignant progression of cancer [5]. The tumor microenvironment, which includes inflammatory cells and mediators, plays a crucial role in lung cancer development and progression. Circulating immune-cells such as neutrophils, as well as the mediators of systemic inflammation CRP and acute-phase proteins represent among others, the complex interaction between local and systemic inflammation and contribute to tumor progression with the components of the adaptive, humoral, and innate immune systems [6].

Interleukins (IL) and tumor necrosis factor-alpha (TNF-α) are examples of cytokines that play crucial roles in inflammation-related processes. They are involved in the activation of signaling pathways, which promote the occurrence, development, and metastasis of lung cancer [7]. Matrix metalloproteinases (MMPs) contribute to the degradation of extracellular matrix components and are involved in cancer invasion and metastasis. Reactive oxygen species (ROS) also play a role in lung cancer-associated inflammation by causing oxidative stress and damage to DNA, proteins, and lipids. In lung cancer, ROS production is often increased, leading to chronic oxidative stress, inflammation, and genomic instability [5].

Prostaglandins are lipid mediators up regulated in various inflammatory conditions, including lung cancer. Prostaglandins can modulate immune responses and promote inflammation through their effects on vascular permeability, immune cell function, and inflammatory gene expression. The enzyme cyclooxygenase-2 (COX-2) is involved in the production of prostaglandins and is often over expressed in lung cancer [8].

Inflammatory markers can reflect the state of systemic inflammation and provide insight into the aggressiveness of the disease. The field of prognostic and predictive markers in lung cancer is constantly evolving. Ongoing research is focused on identifying new markers that can improve patient outcomes and guide treatment decisions. Given the biotechnological advances, strategies of optimizing cancer treatment aim towards precision medicine with the identification of complex and unique biologic features associated with carcinogenesis [9]. On the other hand there is a growing interest in utilizing readily available and cost-effective markers that are routinely measured in day-to-day clinical practice [10].

This narrative review aims to describe inflammation markers and explore their potential prognostic and predictive value in the context of lung cancer. By comprehensively examining the existing literature, we can gain insights into the role of inflammation markers and their implications for clinical practice, ultimately paving the way for more targeted and personalized treatment approaches for lung cancer patients.

Inflammation markers

Inflammatory markers have been validated in a vast number of studies as useful indexes for the prediction and prognosis in lung cancer patients. In recent years the concept of precision cancer medicine is evolving. There is growing interest for the use of key genes driving carcinogenesis as prognostic and predictive indicators in cancer patients. Gao et alinvestigated the potential prognostic value of Prostaglandin E synthase enzyme3 (PTGES3) and its association with tumor immune infiltration in lung adenocarcinoma (LUAD). They found that the oncogene PTGES3 mRNA, as well as the protein PTGES3 they were significantly elevated in LUAD compared to normal lung tissues. High PTGES3 expression was an independent factor for overall survival (OS) and could be a potential prognostic indicator in lung cancer [11].

Shao et al in 2022 highlighted the association of lipid metabolism genes with the occurrence and progression of LUAD, suggesting the role of hematopoietic prostaglandin D synthase (HPGDS) as prognostic marker within the lipid metabolism pathway [12].

Liu et al in a study conducted at People's Hospital of Pengzhou aimed to analyze the expression levels of interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) in NSCLC patients and their correlation with cancer pain occurrence and prognosis. The analysis revealed that, among others, the levels of IL-1, IL-6, and TNF-α were independent risk factors for poor prognosis. In addition, the combined use of IL-1, IL-6, and TNF-α exhibited higher sensitivity and specificity in predicting poor prognosis compared to individual markers alone [13].

Concerning the predictive value of inflammation markers, Huang et al established a TNF scoring system and investigated the potential of tumor necrosis factor (TNF)-related genes (TNFRGs) in predicting outcomes in LUAD. A high TNF score was associated with unfavorable OS and immunotherapy responses [14].

In a study by Wang et al studied the expression of programmed cell death protein 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) and Cyclooxygenase-2 (COX2). A correlation between Prostaglandin-endoperoxide synthase 2 (PTGS2), (aliases of COX-2) and PD-1/PD-L1 was identified. Through various computational methods a novel signature consisting of 7 genes (among them PTGS2), was developed to classify hot and cold tumor subtypes and predict the treatment response of PD-1/PD-L1 inhibitors in NSCLC [15].

Liu et al described that a36-gene MMP signature showed enrichment in Kirsten rat sarcoma virus mutations (KRAS) in patients with stage I lung adenocarcinoma. The study concluded that high MMP-gene signature is a potential predictive and prognostic biomarker to stratify those patients [16].

Hu et al studied the circulating cytokine chemokine profile in NSCLC receiving immune checkpoint inhibitors (ICIs). Among others IL-6, IL-8, CXCL10, CCR1 and TNF associated with poor progression-free survival (PFS). A posttreatment elevation of CXCL10 CCL2 IL-13 was also associated with poor OS [17].

The research conducted by Kim and colleagues explored the role of Reactive oxygen species modulator-1 (Romo1), a protein that is involved in regulating reactive oxygen species(ROS) levels. This protein has been linked with influencing the invasiveness and proliferation of cancer cells via sustained inflammation. Their investigation showed that Romo1 promotes the lymphatic spread of NSCLC by persistently influencing inflammation and oxidative stress through ROS/VEGF signaling pathways. The correlation between increased Romo1 and lymphatic metastasis was identified as a significant cause for the poor survival rates in NSCLC [18].

A study with 192 NSCLC patients described that high CRP levels were associated with worse survival and poor response to chemotherapy, particularly in LUAD cases [19]. In addition in a study by Kuusisalo et al. CRP levels correlated with improved survival outcomes in NSCLC patients. Further, in patients undergoing ICI treatment, a combination of low CRP and high PD-L1 was associated with better progression-free survival [20]. According to a study involving 157 newly diagnosed SCLC patients, those with normal CRP levels exhibited a significantly longer median OS compared to those with high CRP levels. The study concluded that elevated CRP levels are an independent prognostic factor for poor survival in SCLC patients [21].

Higher serum procalcitonin (PCT) levels are associated with poor Performance Status (PS) and shorter OS in NSCLC [22]. Pre treatment PCT levels have a significant negative correlation with prognosis in SCLC patients [23] (Table 1).

On the other hand investigators have been trying to capture the complex inflammatory processes in lung cancer patients and mirror them into reproducible results that are used in every day clinical practice [24]. Numerous indexes and scores have been developed for such purposes with the combination of several inflammatory markers as well as other evaluations in lung cancer patients. The inflammation markers often included in the inflammation scores indexes are Albumin, CRP, Neutrophil count, Lymphocyte count, Thrombocyte count and Hemoglobin [25].

Inflammatory markers with prognostic/predictive value in NSCLC

Banna et al in a review evaluated the role of Full Blood Count (FBC) Elements included prognostic/predictive scores for patients with advanced NSCLC treated withcheckpoint inhibitors (ICI). The widely used Neutrophil to lymphocyte ratio (NLR) was included in more complex inflammation scores, such as the Lung Immune Prognostic Index (LIPI). This index is one of the most studied prognostic scores in pretreated advanced NSCLC (aNSCLC) and it is considered a validated prognostic tool. Moreover it is described that the Lung-Immune-Prognostic Score (LIPS) has prognostic value in untreated high-PD-L1 aNSCLC patients. In this review it is also mentioned that prognostic scores involving Eastern Cooperative Oncology Group Performance Status Scale EGOG PS (LIPS-3, LIPS-4) could help the prognostic and predictive stratification of aNSCLC patients [24].

In a retrospective study of 1431 patients with stage I lung adenocarcinoma patients who underwent complete surgical resection (lobectomy, pneumonectomy), higher NLR, Systemic Inflammation Response Index (SIRI) and Systemic Inflammation Index (SII) were all identified as independent prognostic factors for worse cancer-specific survival (CSS) and disease-free survival (DFS) [26] (Table 2).

Zhang et al in a review article focused on the potential of albumin-related inflammatory markers in predicting the prognosis of NSCLC. The review indicated that inflammation plays a crucial role in NSCLC development and influences the response to treatment. Numerous albumin-related inflammatory markers have shown prognostic value, including CRP to Albumin ratio (CAR), Glasgow prognostic score(GPS), modified Glasgow Prognostic Score(mGPS), high-sensitivity modified Glasgow Prognostic Score(Hs-mGPS), and adjusted Glasgow prognostic score(a-GPS). In the same review it is underlined that other markers such as Prognostic Nutritional Index(PNI), Advanced Lung cancer Inflammation index (ALI), Combination of albumin concentration and neutrophil-to-lymphocyte ratio(COA-NLR), Neutrophil – Lymphocyte - D-dimer - Albumin score (NLDA), Albumin and Neutrophil combined Prognostic Grade(ANPG), and Hemoglobin – Albumin - Lymphocyte - Platelet Score (HALP) have been also used in studies as prognostic/predictive indexes in NSCLC patients [27] (Tables 3 and 4).

In a registered based study of 6210 Danish lung Cancer patients that included 5320 patients with NSCLC, Aarhus Composite Biomarker Score (ACBS) significantly improved the prediction of OS with a hazard ratio (HR) of 2.24 (95%CI: 1.97–2.54). Similarly, the NLR also demonstrated strong prognostic value with an HR of 1.58 (95%CI: 1.47–1.69) for OS

[10]. Pre-treatment elevated levels of NLR as well as SII, CRP and PLR were associated with poor response and shorter PFS in patients treated with ICIs in a prospective study of 29 stage IV NSCLC patients receiving single agent PD-1 checkpoint-inhibitor in second line [28]. SII was also independently associated with Major Pathological Response MPR (the presence of 10% or fewer viable tumor cells in the primary tumor) [29].

Xie et al in a prospective multicenter study included 1843 patients with stage I to stage IV NSCLC patients and 16 systemic inflammation biomarkers were identified and evaluated. Among these 16 systemic inflammation biomarkers, Inflammatory Burden Index (IBI) was the biomarker that presented the best predictive accuracy for prognostic assessment in NSCLC and was independently associated with OS [30] (Table 4).

In a retrospective study of 352 patients with metastatic NSCLC 13 Inflammatory Scores based on biomarkers of systemic inflammation/nutritional status have been evaluated (Lung Immune Prognostic Index (LIPI), modified Lung Immune Prognostic Index (mLIPI), Scottish Inflammatory Prognostic Score (SIPS), Advanced Lung cancer Inflammation index (ALI), EPSILoN score, Prognostic Nutritional Index (PNI), SII, Gustave Roussy Immune Score (GRIm), Royal Marsden Hospital Prognostic Score (RMH), Lung Immuno-oncology Prognostic Score 3 (LIPS-3), Lung Immuno-oncology Prognostic Score 4 (LIPS-4), Holtzman Score, GPS). The patients included in the study received treatment with first-line therapy that consisted of ICIs in monotherapy or ICIs in combination with chemotherapy or chemotherapy alone. The study concluded that biomarkers/scores were moderately associated with OS and PFS and therefore the authors underlined the prognostic but not the predictive value of these inflammatory scores in metastatic NSCLC, due to the lack of association of the results with a specific treatment [31] (Tables 4 and 5).

In a retrospective study of 672 patients with stage IV NSCLC, treated with programmed death ligand 1 (PD-L1) inhibitors alone or in combination with chemotherapy, high ALI values were significantly associated with longer OS for patients receiving ICI monotherapy but not for those receiving chemo-immunotherapy. ALI had a stronger predictive effect than other widely used parameters (NLR, LIPI, EPSILoN scores). ALI was proved to be not only prognostic but predictive for patients with advanced NSCLC treated with PD-L1 inhibitors as monotherapy [32].

Inflammatory markers with prognostic/predictive value in SCLC

Winther et al in the previously mentioned registered based study that included 890 patients with small cell lung cancer (SCLC) found that NLR, mGPS, The Combined NLR and Glasgow Prognostic Score (CNG) were equally superior in improving the prognostication of OS [10].

In a systematic review of 33 articles, including 7762 SCLC patients, NLR was significantly associated with inferior OS [33].

In a retrospective study of 299 patients with limited-stage small-cell lung cancer (LS-SCLC) patients with elevated NLR or Platelet-to-Lymphocyte ratio (PLR) value presented worse than the patients with lower NLR [34]. In another retrospective study of 451 SCLC patients mGPS, CRP/ALB, Albumin to Globulin Ratio (AGR), PNI and ALI were the strongest predictors of OS [35].

Liu et al in a retrospective real world study of 612 patients diagnosed with SCLC, demonstrated that baseline C-reactive protein/albumin ratio, neutrophil/lymphocyte ratio among other findings were independent prognostic factors for both OS and PFS in SCLC [36]. In a prospective cohort population involving 53 extensive-stage small-cell lung cancer (ES-SCLC) patients that received platinum based chemotherapy plus etoposide and atezolizumab, PLR was the only independent prognostic factors for OS among ES-SCLC [37]. Moreover, Lymphocyte-to-C-reactive protein Ratio (LCR), SIRI, and Hemoglobin-to-Red cell distribution width Ratio(HRR) were independent prognostic parameters that predicted survival in a retrospective study of 162 extensive stage SCLC patients. In detail, LCR and SIRI were independent prognosticators for both PFS and OS and HRR was an independent prognostic factor only for OS [38].

In another retrospective study that included 55 patients who received first-line atezolizumab with etoposide plus platin regimen for ES-SCLC, NLR and PLR were significant prognostic indicators. In addition, the study demonstrated that PLR was an independent significant predictive factor for the response to atezolizumab plus chemotherapy [39].

Discussion and Conclusions

Inflammation markers have emerged as potential predictive and prognostic indicators in lung cancer, offering valuable insights into disease progression, therapeutic responses, and overall patient outcomes. The studies addressed in this narrative review shed light on the significance of various inflammation markers in assessing the prognostic and predictive values in all forms of lung cancer. The evaluation of interleukins, TNFRGs, and lipid metabolism-related genes provides valuable insights into the complex interplay between inflammation, tumor microenvironment, and therapeutic responses. The identification of these markers offers opportunities for personalized treatment approaches, facilitating the development of targeted therapies and improved patient outcomes in lung cancer. Further research is warranted to validate and expand upon these findings, ultimately leading to the translation of inflammation markers into clinical practice for enhanced prognostic assessment and treatment decision-making in lung cancer patients. Inflammatory-related genes in

NSCLC datasets have been studied recently in order to create a prognosis prediction model for distinguishing NSCLC patients with high risk for unfavorable prognostic outcome and establish prognostic and clinical therapeutic response biomarkers for NSCLC [40].

Utilizing inflammation biomarkers in lung cancer poses several challenges and limitations. Firstly, there is a need for standardized assay methods to ensure consistent and reliable measurement of inflammation markers [41]. Secondly, considering the complexity of the inflammatory response, relying on individual markers may not capture the full picture, necessitating the use of multiple markers or a panel approach [42]. However, determining the optimal combination and establishing standardized cutoff values is challenging. Additionally, the influence of co morbidities and unrelated systemic inflammation on inflammation markers must be considered to avoid confounding effects [43]. Timing of marker assessment is also crucial, as inflammation markers can change dynamically throughout the disease course. Longitudinal assessments may provide more accurate predictive information. Finally, while inflammation markers offer valuable insights, they should be considered alongside other established prognostic factors for comprehensive risk stratification in lung cancer.

To enhance prognostic prediction and optimize treatment strategies, there is a growing interest in utilizing readily available and cost-effective markers that are routinely measured in day-to-day clinical practice. These everyday tests offer a practical and accessible approach for clinicians to evaluate the prognosis and immune microenvironment of NSCLC, enabling the identification of high-risk patients and the allocation of healthcare resources more efficiently. In a review published at the BMC Lung Cancer Journal in 2023 Luo et al introduced the concept of Low Order Features LOFs (routine blood tests) and High Order Features HOFs (more complex features derived and calculated by LOFs e.g. scores and indexes).The authors conducted a comprehensive investigation of existing literature to assess their potential in predicting prognosis in NSCLC. The study also emphasized the need for establishing a sustainable expansion system for HOF research and proposes rules for their nomenclature. While the clinical significance and interpretability of most HOFs remain uncertain, integrating risk values derived from these markers with existing staging information has the potential to optimize prognostic efficiency in lung cancer. Further research and exploration are needed to fully understand the impact and calculation processes of each HOF, as well as to enhance the clinical application of these markers [44].

It is crucial to recognize that prognostic markers should not be used in isolation but rather as part of a comprehensive clinical assessment. The incorporation of these markers into existing prognostic models could distinguish those lung cancer patients that might benefit from a different treatment approach and may provide a more accurate and comprehensive approach to predicting outcomes in lung cancer patients [10].

Studies have shown the potential of inflammation markers in predicting oncological outcomes, risk assessment, and treatment response. To fully leverage the potential of inflammation markers in precision medicine for lung cancer it is crucial to integrate these markers with other clinical and molecular information. This includes genetic profiling, gene expression patterns, immunohistochemistry, cytokine profiles, proteomics, metabolomics, and microbiome analysis, among others.

However, further research and validation are necessary to fully integrate inflammation markers into the framework of precision medicine for lung cancer. By combining multiple data sources regarding inflammatory markers (routine clinical practice markers as well as more experimental laboratory ones) clinicians and researchers can improve the prognostic and predictive value of inflammation markers in lung cancer, resulting in predicting oncological outcomes as well as risk assessment and treatment response aiming to tailor treatment strategies accordingly for the benefit of lung cancer patients.

In conclusion, connecting inflammation markers with precision medicine in lung cancer holds great promise for improving risk stratification, prognosis assessment, and personalized treatment approaches.

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Table 1. Inflammation markers in lung cancer.

Name	Category	Assessment	References
PTGES3:Prostaglandin E Synthase Enzyme3 **HPGDS**: Hematopoietic Prostaglandin D Synthase	Lipid mediators	Poor prognosis (tumor growth, immune suppression, angiogenesis)	[11], [12]
IL: Interleukins e.g. IL-1, IL-6, IL-8	Pro-inflammatory cytokines immune response	Poor prognosis (tumor growth, angiogenesis, metastasis) Predictive	[11],[13], [17]
TNF-α: Tumor Necrosis Factor – alpha	Pro-inflammatory cytokine	Poor prediction (resistance to therapy)	[13],[14], [17]
COX-2: Cyclooxygenase-2	Prostaglandin synthesis	Poor prediction (resistance to therapy) Poor prognosis (increased inflammation, tumor progression) Prediction of hot/cold tumor	[15]
MMPS: Matrix Metalloproteinases e.g. MMP-9	Tissue remodeling	Poor prognosis (metastasis, invasion)	[16]
CXCL: Chemokines e.g.CXCL1, CXCL2, CCL5,CXCL9	Cell signaling immune cell recruitment	Poor prognosis (angiogenesis, immune cell infiltration) Predictive value	[17]
Romo1:Reactive Oxygen Species Modulator-1	Induces mitochondrial production of reactive oxygen species (ROS)	Poor prognosis	[18]
CRP: C-reactive Protein	Systemic inflammation	Poor prognosis Predictive value	[19], [20], [21]
PCT: Procalcitonin	Systemic inflammation	Poor prognosis Predictive value	[22], [23]

Table 2. Inflammation scores based on peripheral blood cells count.

Name	Assessment of Score	References
LMR: Lymphocyte to Monocyte ratio	Lymphocyte /Monocyte	[10], [24]
MLR: Monocyte to Lymphocyte ratio	Monocyte / Lymphocyte ratio	[24]
NLR: Neutrophil to Lymphocyte ratio	Neutrophil / Lymphocyte ratio	[10], [24], [25], [26]
NP: Neutrophil–Platelet Score	Neutrophil × Platelet score	[30]
PLR: platelet-to-lymphocyte ratio	Platelet / Lymphocyte	[10], [24], [25]
SII: Systemic Inflammation Index	Platelet count x NLR	[10], [26]
SIRI: Systemic Inflammation Response Index	Neutrophil count × Monocyte count/ Lymphocyte count	[26]

Table 3. Inflammation markers and scores based on albumin, CRP, and globulin.

Name	Assessment of Score	References
AGR: Albumin to Globulin Ratio	Albumin/Globulin	[35], [36]
a-GPS: adjusted Glasgow Prognostic Score	adjusted GPS (a-GPS) USING lower cut-off values in patients undergoing resection for primary lung cancer	[27]
CAR:CRP to Albumin Ratio	CRP to Albumin ratio	[27], [30], [36]
GPS: Glasgow Prognostic Score	C-reactive protein 10 mg/L and albumin 35 g/L: 0 score C-reactive protein 10 mg/L or albumin < 35 g/L: 1 score C-reactive protein > 10 mg/L and albumin < 35 g/L: 2 score	[25], [27]
Hs-mGPS: High-sensitivity modified Glasgow Prognostic Score	CRP 0.3 mg/dL: 0 CRP >0.3 mg/dL and albumin 3.5 mg/dL: 1 CRP >0.3 mg/dL and albumin <3.5 mg/dL: 2	[27]
mGPS:modified Glasgow Prognostic Score	CRP 8 mg/L and albumin 35 g/L=score 0; if one of the test results were abnormal=score 1; if both test results were abnormal=score 2	[10], [27]

Table 4. Inflammation scores based on peripheral blood, albumin, CRP, hemoglobin.

Name	Assessment of Score	References
ACBS: Aarhus Composite Biomarker Score	If Albumin, CRP, Neutrophil count, Lymphocyte count, Hemoglobin normal range:0 If Neutrophils high or Lymphocytes low or any other of the other mentioned biomarkers abnormal range:1 If two biomarkers were abnormal:2 if more than two biomarkers were abnormal:3	[25]
ANPG: Albumin and Neutrophil Combined Prognostic Grade	elevated Albumin and low Neutrophil: 1 low Albumin and low Neutrophil: 2 elevated Albumin and elevated Neutrophil: 2 low Albumin and elevated Neutrophil: 3	[27]
CALLY: C-reactive protein-Albumin-Lymphocyte Index	Albumin × Lymphocyte /CRP	[30]
CNG: The Combined NLR and Glasgow Prognostic Score	Albumin high, CRP low, NLR >2: 0 one abnormal test results:1 two abnormal test results:2 three abnormal test results:3	[10], [25]
COA-NLR: Combination of Albumin concentration and Neutrophil-to-Lymphocyte Ratio	Albumin (35 g/L) and NLR <2.5 : 0 Albumin (35 g/L) and NLR 2.5:1 Albumin (<35 g/L) and NLR <2.5:1 Albumin (<35 g/L) and NLR 2.5: 2	[27]
HALP: The Hemoglobin, Albumin, Lymphocyte and Platelet score	Hemoglobin×Albumin×Lymphocytes/Platelet count	[10]
IBI: Inflammatory Burden Index	C-reactive protein × Neutrophil /Lymphocyte	[30]
LA: Lymphocyte–Albumin Score	Lymphocyte × Albumin	[30]
LCR: Lymphocyte-to-C-reactive protein Ratio	Lymphocyte count/C-reactive protein	[30], [36]
LCS: Lymphocyte C-reactive protein Score	Lymphocyte 1 × 10^9/L and C-reactive protein 3 mg/L: 0 score; Lymphocyte 1 × 10^9/L or C-reactive protein 3 mg/L: 1 score; Lymphocyte < 1 × 10^9/L and C-reactive protein > 3 mg/L: 2 score	[30]
NAR: Neutrophil-to-Albumin ratio	Neutrophil /Albumin	[30]
NC: Neutrophil-C-reactive protein score	Neutrophil × C-reactive protein	[30]
NLDA: Neutrophil, Lymphocyte, D-dimer Albumin score	Neutrophil count/Lymphocyte count × D-dimer count/Albumin	[27]
PAR: Platelet-to-Albumin ratio	Platelet /Albumin	[30]
PC: Platelet-C-reactive protein Score	Platelet × C-reactive protein	[30]
PNI: Prognostic Nutritional Index	[10 × serum albumin (g/L)] + [0.005 × lymphocyte count]	[31]
SIPS: Scottish Inflammatory Prognostic Score	Albumin < 35 g/L: 1 point Neutrophil count > 7.5 × 109/L: 1 point Score 0: good; 1: intermediate; 2: poor	[31]

Table 5. Inflammation scores involving ECOG PS, LDH, NLR, dNLR albumin, patient history data.

Name	Assessment of Score	References
ALI: Advanced Lung cancer Inflammation index	Body mass index x Albumin /NLR	[31], [32]
EPSILoN	ECOG PS 2: 1 point, Smoking < 43 pack-years: 1 point, Liver metastases: 1 point, LDH > 400 mg/dL: 1 point, NLR > 4: 1 point Total points: 0: good; 1–2: intermediate; 3–5: poor	[31]
GRIm: Gustave Roussy Immune Score	LDH > ULN: 1 point Albumin < 35 g/L: 1 point NLR > 6: 1 point 0–1: low risk; 2–3: high risk	[31]
Holtzman Score	Age 65 years: 1 point, Female sex: 1 point, Never-smoker: 1 point, Adenocarcinoma: 1 point,dNLR 3: 1 point Total points: 0–2: favorable; 3–5: poor	[31]
LIPI: Lung Immune Prognostic Index	dNLR> 3: 1 point LDH > ULN: 1 point Total points: 0: good; 1: intermediate; 2: poor	[24], [31]
LIPS-3: Lung Immuno-oncology Prognostic Score 3	ECOG PS 2: 1 point, Pretreatment steroids: 1 point, NLR 4: 1 point Total points: 0: favorable; 1–2: intermediate; 3: poor	[24], [31]
LIPS-4: Lung Immuno-oncology Prognostic Score 4	ECOG PS 2: 1 point, Pretreatment steroids: 1 point, NLR 4: 1 point, LDH 252 U/L: 1 point Total points: 0: favorable; 1–2: intermediate; 3–4: poor	[24], [31]
mLIPI: modified Lung Immune Prognostic Index	ECOG PS = 1 or 2: 1 point, NLR > 3: 1 point, LDH > 1.5 × ULN: 1 point Total points: 0: good; 1: intermediate; 2: poor; 3: very poor	[31]
RMH: Royal Marsden Hospital prognostic score	LDH within normal range: 0 vs. > upper limit of normal (ULN): +1 , Albumin level (3.5g/dL: 0 vs. < 3.5g/dL: +1), and number of metastatic sites (< three sites: 0 vs. three sites: +1 LDH > ULN: 1 point Albumin > 35 g/L: 1 point Site of metastasis > 2: 1 point Total points: 0–1: low risk; 2–3: high risk	[31]

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; dNLR, derived Neutrophil to Lymphocyte ratio = neutrophil count/ (white blood cell count—neutrophil count); NLR, neutrophil to lymphocyte ratio; ULN, upper limit of normal.