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Predictive Value of the Lung Immune Prognostic Index for Immune Checkpoint Inhibitor Therapy Outcomes in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis

Wenquan Lu and Jingjing Su

Department of Oncology, Yuyao People's Hospital, Yuyao, Zhejiang, China

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ABSTRACT

Non-Small Cell Lung Cancer (NSCLC) patients undergoing Immune Checkpoint Inhibitors (ICIs) therapy exhibit diverse clinical outcomes. The Lung Immune Prognostic Index (LIPI) may emerge as a potential prognostic marker. This study systematically reviews and meta-analyzes the prognostic value of LIPI in predicting the clinical efficacy of ICIs therapy for NSCLC patients. A thorough literature review was performed using the Cochrane Library, Web of Science, PubMed, and Embase, following PRISMA guidelines. Studies assessing LIPI's predictive value in NSCLC patients treated with ICIs were included. Effect sizes were aggregated utilizing a fixed-effects model. The studies featured in the review were appraised using the Newcastle-Ottawa Scale for quality assessment. Eight studies were incorporated into the meta-analysis, encompassing various treatment lines and ICIs. No substantial heterogeneity was detected across the studies. The meta-analysis revealed that the low-risk group exhibited significantly extended overall survival (OS) (HR=3.18, 95%CI: 2.78~3.59 and progression-free survival (PFS) (HR=1.60, 95%CI: 1.4~61.74, underscoring the predictive significance of LIPI for NSCLC patients treated with ICI therapy. No significant publication bias was detected. LIPI demonstrates potential as a prognostic marker for NSCLC patients receiving ICI therapy, contributing to the development of therapeutic strategies. Further prospective researches are required to investigate its relationship with factors such as tumor mutational burden, PD-L1 and PD-1.

Keywords: Immune checkpoint inhibitors; Lung immune prognostic index; Meta-analysis; Non-small cell lung cancer

INTRODUCTION

Non-small cell lung cancer (NSCLC) continues to be among the one of the most challenging types of cancer, with a significant global mortality rate. One of the promising breakthroughs in its treatment is the application of immune checkpoint inhibitors (ICIs).[1] ICIs, which reinvigorate the immune response against tumor cells, have revolutionized the NSCLC treatment landscape. Their efficacy, in terms of durable responses and survival benefits, has been firmly established, and their utility extends from monotherapy to integration into combined therapeutic regimens.[2]

A key area of current oncology research is the

Corresponding Author: Jingjing Su, MM;
Department of Oncology, Yuyao People's Hospital, Yuyao, Zhejiang, China. Tel/Fax: (86 0574) 6262 9999, Email: luwenquanlu@163.com

discovery and validation of biomarkers that can accurately predict how patients will respond to ICIs. Identifying these biomarkers is crucial for personalizing treatment plans and improving health status. Programmed Death Ligand-1 (PD-L1) is an example that has been extensively studied and used as a biomarker for NSCLC patients in ICI clinical trials.[3] It is noteworthy, however, that not all patients who exhibit positive PD-L1 expression experience advantages from ICIs. This discrepancy highlights the intricate dynamics between tumor cells and the immune system, revealing the complexity of their interactions.[4] This stark observation underscores the need to discover and validate additional biomarkers, to facilitate precise patient stratification, optimize the therapeutic index of ICIs, and mitigate the risks of unnecessary treatments.

Considering the complex cycle inherent in immune checkpoint pathways, peripheral blood has emerged as a rich, accessible source of biofluids and cellular parameters possibly associated with the response to immunotherapy. Mounting evidence has accentuated the instrumental role of inflammation in the oncogenic process.[5] The body's inflammatory reactions, seen as a facilitator of immune resistance mechanisms in patients with cancer, have been linked to the promotion of tumor cell proliferation, dissemination, and the activation of signaling pathways involved in carcinogenic .[6] Several novel biomarkers have been explored to assess the inflammatory conditions across multiple cancers, such as NSCLC. Highlighted examples include the Neutrophil-to-Lymphocyte Ratio (NLR), derived Neutrophil-to-Lymphocyte Ratio (dNLR), and the Platelet-to-Lymphocyte Ratio (PLR). In this context, the Lung Immune Prognostic Index (LIPI), developed based on dNLR>3 and lactate dehydrogenase (LDH) levels above normal levels, has emerged as a promising tool. The LIPI assigns patients to low, intermediate, and high-risk tiers depending on these risk factors, providing clinicians with a valuable resource for optimizing treatment strategies.[7]

Previous studies have investigated the prognostic implications of LIPI across a range of solid tumors, including melanoma, gastric cancer, and NSCLC, all under the umbrella of immunotherapy.[8,9] The research findings, however, have been fraught with discrepancies, leading to uncertainty regarding the utility of LIPI. To reconcile these inconsistencies, and to thoroughly comprehend LIPI's prognostic value, we perform an analytical review and meta-synthesis. We aim to deliver robust research-supported conclusions. Additionally, we seek to shed new light on the value of LIPI as a reliable gauge for forecasting survival and relapse risk in NSCLC subjects undergoing ICI treatment.

MATERIALS AND METHODS

Search Protocol

Our systematic review followed the PRISMA guidelines.[10] We executed a query dated December 1, 2024, across four major electronic resources-PubMed, Embase, Web of Science, and Cochrane Library-without temporal restrictions. The PubMed search strategy included the following terms: ((("LIPI"[Title/Abstract]) OR ("Lung Immune Prognostic Index"[Title/Abstract])) AND ((("Non-Small Cell Lung Cancer"[Title/Abstract]) OR ("NSCLC"[Title/Abstract])) AND ((((((("Immune Checkpoint Inhibitors"[MeSH Terms]) OR ("Immune Checkpoint Inhibitors"[Title/Abstract])) OR ("Nivolumab"[Title/Abstract])) OR ("Pembrolizumab"[Title/Abstract])) OR ("Atezolizumab"[Title/Abstract])) OR ("Durvalumab"[Title/Abstract]))).

The search strategy for Embase included the following terms: 'immune checkpoint inhibitor'/exp OR 'immune checkpoint inhibitor' OR ('immune checkpoint inhibitors': ab,ti OR nivolumab:ab,ti OR pembrolizumab:ab,ti OR atezolizumab:ab,ti OR durvalumab:ab,ti) AND ('lung immune prognostic index':ab,ti OR lipi:ab,ti) AND ('non-small cell lung cancer':ab,ti OR nsclc:ab,ti).

The Web of Science search strategy included the following terms: ((TS="LIPI") OR (TS="Lung Immune Prognostic Index")) AND ((TS="Non-Small Cell Lung Cancer") OR (TS="NSCLC")) AND ((TS="Immune Checkpoint Inhibitors") OR (TS="CTLA-4") OR (TS="PD-1") OR (TS="PD-L1") OR (TS="ICIs") OR (TS="Nivolumab") OR (TS="Pembrolizumab") OR (TS="Atezolizumab") OR (TS="Durvalumab")).

The Cochrane Library search strategy included the following terms: (MeSH descriptor: [Immune Checkpoint Inhibitors] this term only OR "immune checkpoint inhibitor": ti,ab OR nivolumab:ti,ab OR pembrolizumab:ti,ab OR atezolizumab:ti,ab OR durvalumab:ti,ab) AND ("LIPI":ti,ab OR "Lung Immune Prognostic Index":ti,ab) AND ("Non-Small Cell Lung Cancer":ti,ab OR "NSCLC":ti,ab).

Inclusion Criteria

The review process required studies fulfilling the follwing specific standards: 1) This analysis involves subjects with pathologically confirmed NSCLC who have undergone therapy with ICIs such as nivolumab, pembrolizumab, atezolizumab, or durvalumab. 2) The research should be a clinical trial, prospective cohort study, or retrospective study that evaluates the predictive value of the LIPI 3) The study must include valid pre-treatment levels of both dNLR and LDH, and LIPI grouping should be clearly defined. LIPI categorizes cases into three risk classifications depending on LDH levels exceeding the maximum normal range and dNLR>3: minimal risk, moderate risk, and elevated risk. 4) The research needs to investigate the correlation between LIPI levels and OS and PFS. 5) The study must provide adequate information to determine hazard ratios (HR) and 95% confidence intervals (CI).

Studies were omitted for the reasons detailed below: 1) Duplicate articles 2) Incomplete analytical data or inconsistent outcome measures 3) Insufficient original data or poor methodological quality.

Data Extraction

According to the study objectives and inclusion/exclusion criteria, two scholars will separately analyze the relevant studies and gather pertinent information. The initial stage involves screening titles and abstracts. Following this preliminary review, the full texts of the studies will be evaluated to determine their final inclusion. In case of discrepancies between the two researchers, an additional researcher will be engaged, a consensus will be reached through discussion. The following information will be gathered: authorship, publication year, treatment line, ICIs, LIPI cut-off value, predictive indicators, and outcome indicators.

Evaluation of Quality

The research articles incorporated into our meta-analysis will be rigorously evaluated by two separate evaluators using the Newcastle-Ottawa Scale (NOS).[11] The NOS is an extensively accepted tool intended to evaluate research quality across nine specific criteria, organized into three domains: selection, comparability, and outcome. This framework helps identify possible biases within the research. Each study will recieve a numerical score from 0 to 9, reflecting its quality level. The scoring is as follows: studies rated 0 to 3 are deemed of low quality, those scoring 4 to 6 are categorized as average quality, and studies rated 7 to 9 are considered excellent quality.

Statistical Analyses

To assess heterogeneity across studies, we utilized chi-square statistics and measured variability using the I^2 value. An I^2 statistic of 0% indicates no heterogeneity, while values grater than 50% suggest significant heterogeneity. A sensitivity analysis was conducted to examine the reliability of our results and to identify any potential influence of single studies on the aggregate effect size. This evaluation included systematically excluding each study and recalculating the overall effect size to determine whether the point estimates remained within the 95% confidence interval of the original pooled effect. Publication distortions were evaluated employing funnel plot symmetry and Egger's test. To address potential publication bias affecting the impact estimates, hypothetical unpublished negative studies were assumed when the funnel plot showed asymmetry. A significance threshold of $p<0.05$ was used for all statistical analyses. Data analysis was conducted with Stata version 17 (StataCorp, College Station, TX, USA).

RESULTS

Search Outcomes and Study Selection

The initial search across digital databases identified 332 potentially relevant publications. After removing duplicates and applying stringent eligibility standards through a careful review of titles and abstracts, 20 pertinent studies were identified. Of these, 12 were excluded from further analysis. Ultimately, eight articles met the inclusion criteria.[12-19] The results of document review process are illustrated in Figure 1.

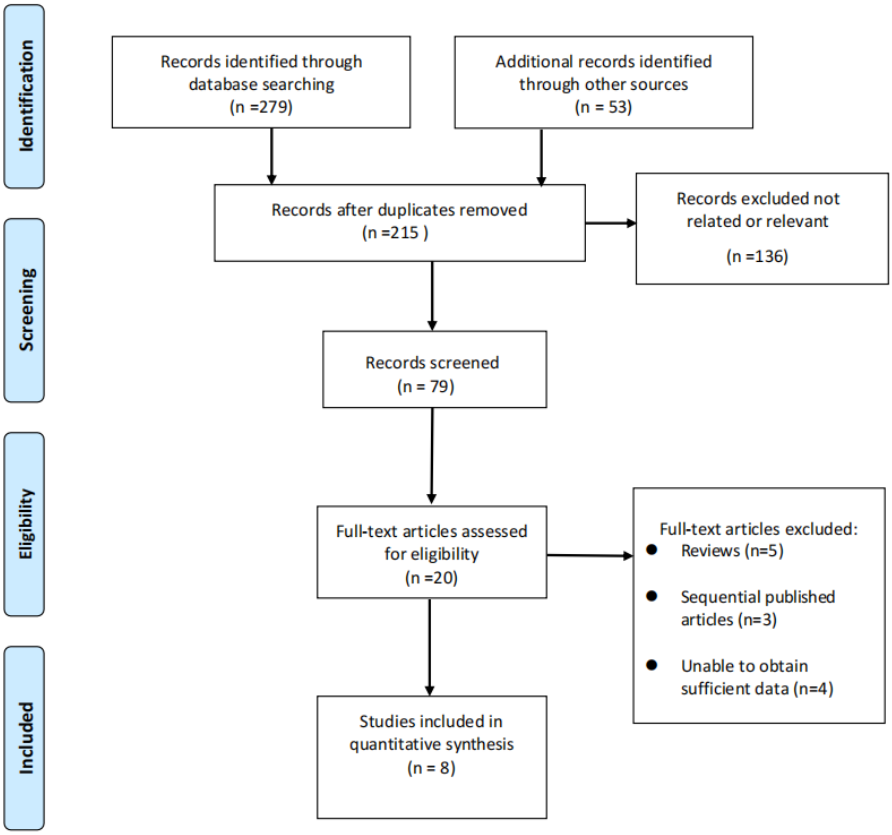

Figure 1. Selection process of included studies

Research Features

The meta-analysis included a diverse array of studies, both retrospective and prospective, conducted between 2018 and 2021. Sample sizes ranged from a modest 109 in Mazzaschi et al.'s study to as large as 3,987 in the study by Kazandjian et al. Various treatment lines were examined across the studies, including first-line, second-line, third-line, and unspecified lines. The studies also investigated a variety of ICIs including nivolumab, pembrolizumab, atezolizumab, durvalumab, and durvalumab-ipilimumab, with some studies not specifying the ICI used. The LIPI was a common predictive indicator across all studies, with a cut-off value defined by dNLR ≥3 or >3 and LDH levels higher than the normal maximum. Outcome indicators across the studies included PFS and OS. In summary, the included studies provided a broad and varied perspective on the application of ICIs for treating NSCLC, with a particular focus on the prognostic value of LIPI (Table 1).

Results of Quality Assessment

Using the New Castle-Ottawa Scale, we evaluated the methodology of each study. In general, one study received a 7 out of 10, three received an 8 out of 10, and four received a 9 out of 10. There was no evidence of allocation concealment, and none of the studies employed blinding methods. Additionally, no signs of funding bias were present in any of the studies. Furthermore, the studies did not show baseline discrepancies, early termination effects, or data deficiencies. Table 2 summarizes the risk of bias.

Table 1. Features of studies incorporated into the meta-analysis

Author	Year	Study Type	Sample Size	Treatment Line	Immune Checkpoint Inhibitors	Predictive Indicator	Lung Immune Prognostic Index (LIPI) Cut-off Value	Outcome Indicator
Mezquita et al	2018	Retrospective	466	Second Line or Later	Nivolumab, Pembrolizumab, Atezolizumab, Durvalumab, Durvalumab-ipilimumab	LIPI	dNLR≥3, LDH>Upper Limit of Normal	DCR, PFS, OS
Kazandjian et al	2019	Prospective	3987	Not Specified	Not Specified	LIPI	dNLR≥3, LDH>Upper Limit of Normal	PFS, OS
Hopkins et al	2021	Prospective	766	First Line	Atezolizumab	LIPI	dNLR>3, LDH>Upper Limit of Normal	PFS, OS
Ruiz-Bañobre et al	2019	Retrospective	188	Second Line or Later	Nivolumab	LIPI	dNLR>3, LDH>Upper Limit of Normal	DCR, PFS, OS
Sorich et al	2019	Prospective	1489	Not Specified	Atezolizumab	LIPI	dNLR≥3, LDH>Upper Limit of Normal	PFS, OS
Hopkins et al	2020	Prospective	1548	Not Specified	Atezolizumab	LIPI	dNLR≥3, LDH>Upper Limit of Normal	OS
Mazzaschi et al	2020	Prospective	109	First Line, Second Line, Third Line	Nivolumab, Pembrolizumab, Atezolizumab	LIPI	dNLR≥3, LDH>Upper Limit of Normal	PFS, OS
Wang et al	2020	Retrospective	330	First Line, Second Line, Third Line	Not Specified	LIPI	dNLR>3, LDH>Upper Limit of Normal	PFS, OS

DCR: Disease Control Rate; PFS: Progression-Free Survival; OS: Overall Survival

Table 2. The quality assessment according to NOS of each cohort study

study	selection				comparability	outcome			Total score
	Representativ-eness of the exposed cohort	Selection of the non -exposed cohort	Ascertainment of exposure	Demonstration that outcome	Comparability of cohorts	Assessment of outcome	Was follow-up long enough	Adequacy of follow up of cohorts	
Mezquita et al	★	★	★	★	★★	★	★	★	9
Kazandjian et al		★	★	★	★★	★	★	★	8
Hopkins et al	★	★	★	★	★★	★	★	★	9
Ruiz-Bañobre et al	★	★	★	★	★★	★		★	8
Sorich et al	★		★	★	★	★	★	★	7
Hopkins et al	★	★	★	★	★	★	★	★	8
Mazzaschi et al	★	★	★	★	★★	★	★	★	9
Wang et al	★	★	★	★	★★	★	★	★	9

NOS: New Castle-Ottawa Scale

Association of LIPI with Progression-free Survival (PFS)

A systematic review was performed to evaluate the combined effect sizes for PFS from eight studies included in this review. The assessment showed no substantial heterogeneity among these studies (p=0.864, I^2=0.0%), allowing for applying a fixed-effects strategy. The evidences indicated the low-risk group had a significantly extended PFS (HR=1.60, 95%CI: 1.46~1.74, p<0.00001), indicating a statistically significant difference. These findings are presented in Figure 2.

Impact of LIPI on Overall Survival (OS)

We also performed a meta-analysis to review influence of LIPI on OS across the eight studies included in this review. While some heterogeneity was present (p=0.068, I^2=42.3%), it was not sufficient to necessitate a random-effects model, so a fixed-effects strategy was applied. The analysis revealed a significant relation of LIPI and OS in NSCLC patients on ICI therapy. Specifically, the low-risk group showed a markedly better OS (HR=3.18, 95% CI: 2.78–3.59, p<0.00001). These findings are depicted in Figure 3.

Publication Bias

Funnel plots showed no evidence of bias in publication, displayed symmetry (Figure 4). Additionally, Egger's linear regression analysis did not reveal significant publication distortion across various factors (p>0.05 for all), supporting the robustness of the meta-analysis results.

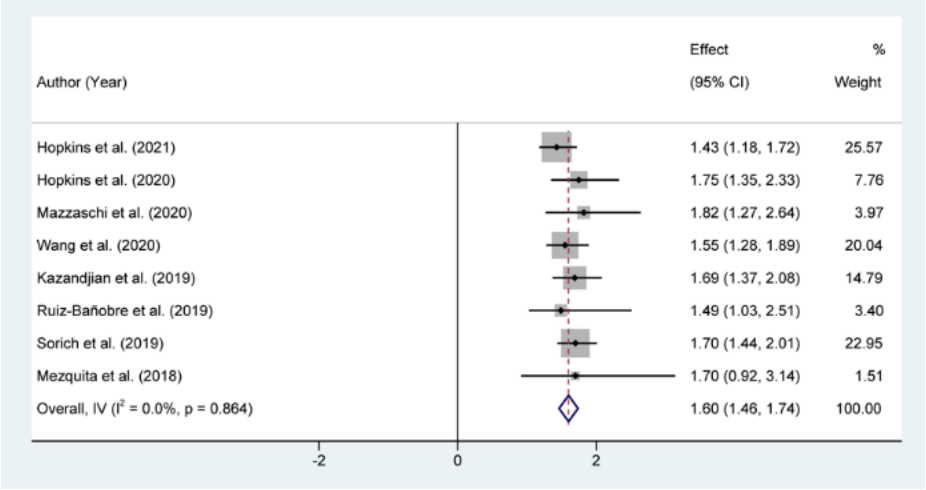

Figure 2. Forest plot of the association between Lung Immune Prognostic Index score and progression-free survival.

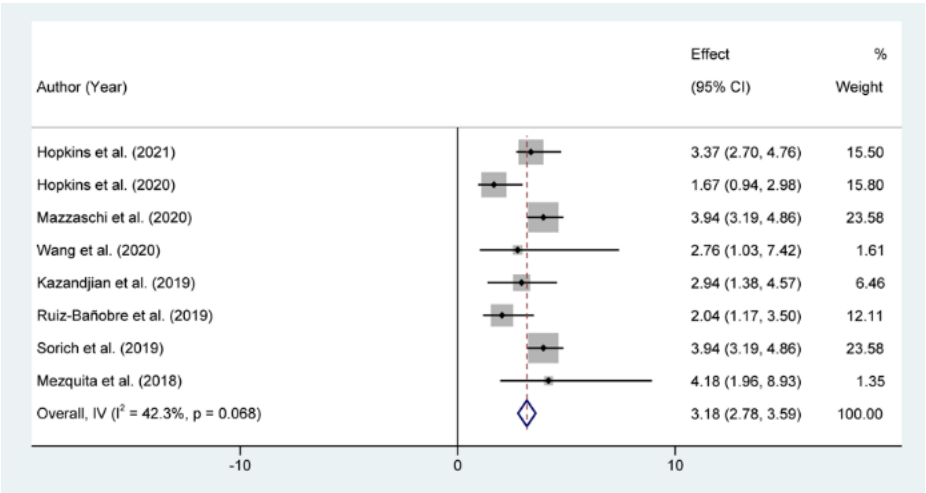

Figure 3. Forest plot of the association between Lung Immune Prognostic Index score and overall survival.

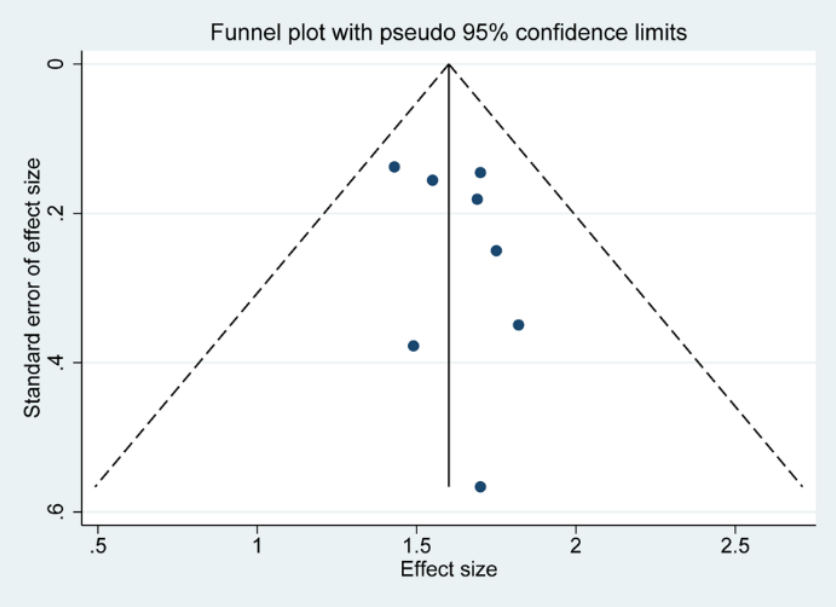

Figure 4. Funnel plot for publication bias in all included studies.

DISCUSSION

The forecasting ability of the LIPI in sensing the effectiveness of ICIs for NSCLC patients continues to provoke debate. Given the limitations in sample sizes and the variability of results across previous studies, this comprehensive review and quantitative synthesis have clarified predictive role of LIPI in NSCLC patients receiving immunotherapy. Specifically, the analysis has demonstrated significant associations between LIPI and both PFS and OS.[16]. The meta-analysis of the combined effect sizes for PFS from eight studies showed no significant heterogeneity (p=0.864, I^2=0.0%). This lack of heterogeneity allowed for applying a fixed-effects strategy for the review. The results showed that patients classified as low-risk by LIPI had a notably longer PFS (HR=1.60, 95%CI: 1.46~1.74, p<0.00001). These findings underscore the potential of LIPI as a reliable tool for predicting PFS in NSCLC patients undergoing ICI therapy. Similarly, the examination of the relationship between LIPI and OS across these studies yielded comparable results. Although some heterogeneity was present (p=0.068, I^2=42.3%), it was not sufficiently pronounced to necessitate a random-effects strategy, thus a fixed-effects strategy was applied. The low-risk group, as identified by LIPI, demonstrated a significantly better OS (HR=3.18, 95%CI: 2.78~3.59, p<0.00001). This suggests that LIPI could be a valuable prognostic marker for OS in NSCLC patients undergoing ICI treatment.

The aggressiveness of malignant tumors is influenced not only by the inherent characteristics of the cancer cells, but also by the tumor's microenvironment. Early research has established inflammation as a significant feature of cancer, with inflammatory responses playing a crucial role in driving tumor initiation and advancement. In solid malignant tumors, inflammation can drive immune cell infiltration, stimulate angiogenesis, and promote fibroblast proliferation.[20,21] Conversely, inflammation also facilitates immune tolerance, which can enhance tumor growth, metastasis, and activate oncogenic signaling pathways in cancer patients.[22]

The derived neutrophil-to-lymphocyte ratio (dNLR), calculated from neutrophil and lymphocyte counts, is a key factor in tumor-associated inflammation and immunity, and it contributes to tumor progression.[23,24] Neutrophils produce vascular endothelial growth factor (VEGF), a key driver of blood vessel formation in tumors and a potent inhibitor of both natural and acquired anti-cancer immune mechanisms.[25] Moreover, proteases released by neutrophils can break down inflammatory signaling molecules, alter the structure of the extracellular matrix, and hyperactivate the PI3K pathway within tumor cells, thereby promoting unchecked tumor expansion.[26,27] Additionally, T cells

that produce Interleukin (IL)-17 can release CXC chemokines that recruit neutrophils, with IL-17a being associated with resistance to immune checkpoint inhibitors.[28] Thus, elevated levels of dNLR may indicate detrimental inflammation and contribute to resistance to immune checkpoint blockade.

Conversely, peripheral blood lymphocyte count is considered a predictor of prognosis in multiple cancers. Lymphocytes are crucial for tumor-related immunity, possessing the potential to inhibit tumor development through their anti-tumor immunological functions. They participate in inducing cell death and generating signaling molecules, aiding in the inhibition of tumor cell growth and spread by triggering immune reactions against malignancies.[29]

Lactate dehydrogenase (LDH), an enzyme present throughout major organs in the human body, catalyzes the conversion of lactate to pyruvate and vice versa. It is commonly used as a biomarker for tumor burden, cellular damage, and necrosis. Elevated levels of LDH have been associated with poor prognosis in various cancers. For example, a retrospective study involving 238 melanoma patients found that those treated with pembrolizumab experienced a significant reduction in LDH levels six weeks after treatment. In contrast, increased LDH levels were observed in patients whose disease progressed.[30]

High LDH levels result from increased tumor glycolysis and necrosis induced by hypoxia. Tumors with elevated glycolytic activity, whether under aerobic or anaerobic conditions, often suffer from glucose deficiency and acidic environments, which can negatively affect immune cell function. Additionally, hypoxia or the overexpression of hypoxia-inducible factors in such tumors can impair anti-tumor immunity. Hypoxia also activates Hypoxia-Inducible Factor-1 (HIF-1), the main controller of angiogenesis, leading to increased VEGF expression. VEGF promotes angiogenesis by stimulating endothelial cell proliferation and survival, resulting in numerous malformed and dysfunctional blood vessels within the tumor. These aberrant vessels can disrupt the anti-cancer immune response and reduce the effectiveness of ICIs.[31,32] Hence, LDH levels can significantly impact the efficacy of ICIs.

This research establishes the significance of the LIPI for predicting treatment efficacy in NSCLC patients undergoing ICIs therapy. However, its limitations include small sample sizes and variability in previous study results, suggesting potential unaccounted factors impacting ICIs efficacy. While correlations between LIPI and survival rates was found, the complex interplay of inflammation and other factors like derived neutrophil-to-lymphocyte ratio and LDH levels, which also influence tumor progression and therapy response, is not fully understood. Additional researche is necessary to verify these outcomes and examine further possible prognostic factors.

LIPI could function as a prognostic tool for NSCLC patients undergoing ICI therapy, thereby assisting in the formulation of targeted treatment strategies. Future prospective research should focus on examining the relationship between LIPI and key factors such as PD-1, PD-L1, and tumor mutational burden (TMB). Investigating how these factors interact could provide insights into their roles in tumor progression and their impact on treatment response.

STATEMENT OF ETHICS

Not applicable

FUNDING

Not applicable

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Not applicable

DATA AVAILABILITY

Upon reasonable request from the corresponding author.

AI ASSISTANCE DISCLOSURE

Not applicable.

REFERENCES

1. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. Nature 2018;553(7689):446-54.

2. Song R, Liu F, Ping Y, Zhang Y, Wang L. Potential non-invasive biomarkers in tumor immune checkpoint inhibitor therapy: response and prognosis prediction. Biomark Res. 2023;11(1):57.
3. Büttner R, Gosney JR, Skov BG, Adam J, Motoi N, Bloom KJ, et al. Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol 2017;35(34):3867-76.
4. Zhang S, Bai X, Shan F. The progress and confusion of anti-PD1/PD-L1 immunotherapy for patients with advanced non-small cell lung cancer. Int Immunopharmacol. 2020; 80:106247.
5. Yang T, Hao L, Yang X, Luo C, Wang G, Lin Cai C, et al. Prognostic value of derived neutrophil-to-lymphocyte ratio (dNLR) in patients with non-small cell lung cancer receiving immune checkpoint inhibitors: a meta-analysis. Bmj Open. 2021;11(9):e049123.
6. Zhang N, Jiang J, Tang S, Sun G. Predictive value of neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in non-small cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. Int Immunopharmacol. 2020;85:106677.
7. Hopkins AM, Kichenadasse G, McKinnon RA, Rowland A, Sorich MJ. Baseline tumor size and survival outcomes in lung cancer patients treated with immune checkpoint inhibitors. Semin Oncol. 2019;46(4-5): 380-4.
8. Minami S, Ihara S, Komuta K. Pretreatment Lung Immune Prognostic Index Is a Prognostic Marker of Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor. World J Oncol. 2019;10(1):35-45.
9. Benitez JC, Recondo G, Rassy E, Mezquita L. The LIPI score and inflammatory biomarkers for selection of patients with solid tumors treated with checkpoint inhibitors. Q J Nucl Med Mol Im. 2020;64(2):162-74.
10. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj-Brit Med J. 2021;372: n71.
11. Scheidt S, Vavken P, Jacobs C, Koob S, Cucchi D, Kaup E, et al. Systematic Reviews and Meta-analyses. Z Orthop Unfallchir. 2019;157(4):392-9.
12. Hopkins AM, Kichenadasse G, Abuhelwa AY, McKinnon RA, Rowland A, Sorich MJ. Value of the Lung Immune Prognostic Index in Patients with Non-Small Cell Lung Cancer Initiating First-Line Atezolizumab Combination Therapy: Subgroup Analysis of the IMPOWER150 Trial. Cancers 2021;13(5).
13. Hopkins AM, Wagner J, Kichenadasse G, Modi N, Rowland A, Sorich MJ. Patient-reported outcomes as a prognostic marker of survival in patients with advanced nonsmall cell lung cancer treated with immunotherapy. Int J Cancer. 2020;147(11):3085-9.
14. Kazandjian D, Gong Y, Keegan P, Pazdur R, Blumenthal GM. Prognostic Value of the Lung Immune Prognostic Index for Patients Treated for Metastatic Non-Small Cell Lung Cancer. Jama Oncol. 2019; 5(10):1481-5.
15. Mazzaschi G, Minari R, Zecca A, Cavazzoni A, Ferri V, Mori C, et al. Soluble PD-L1 and Circulating CD8+PD-1+ and NK Cells Enclose a Prognostic and Predictive Immune Effector Score in Immunotherapy Treated NSCLC patients. Lung Cancer. 2020;148(5):1-11.
16. Mezquita L, Auclin E, Ferrara R, Charrier M, Remon J, Planchard D, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. Jama Oncol. 2018;4(3):351-7.
17. Ruiz-Banobre J, Areses-Manrique MC, Mosquera-Martinez J. Evaluation of the lung immune prognostic index in advanced non-small cell lung cancer patients under nivolumab monotherapy. Transl Lung Cancer R. 2019;8(6):1078-85.
18. Sorich MJ, Rowland A, Karapetis CS, Hopkins AM. Evaluation of the Lung Immune Prognostic Index for Prediction of Survival and Response in Patients Treated With Atezolizumab for NSCLC: Pooled Analysis of Clinical Trials. J Thorac Oncol. 2019;14(8):1440-6.
19. Wang W, Huang Z, Yu Z, et al. Prognostic Value of the Lung Immune Prognostic Index May Differ in Patients Treated With Immune Checkpoint Inhibitor Monotherapy or Combined With Chemotherapy for Non-small Cell Lung Cancer. Front Oncol. 2020;10(4):572853.
20. Chen Q, Yang LX, Li XD, Yin D, Shi SM, Chen EB, et al. The elevated preoperative neutrophil-to-lymphocyte ratio predicts poor prognosis in intrahepatic cholangiocarcinoma patients undergoing hepatectomy. Tumour Biol 2015;36(7):5283-9.
21. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature. 2008;454(7203):436-44.
22. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144(5):646-74.
23. Cho Y, Kim JW, Yoon HI, Lee CG, Keum KC, Lee IJ. The Prognostic Significance of Neutrophil-to-Lymphocyte Ratio in Head and Neck Cancer Patients Treated with Radiotherapy. J Clin Med. 2018;7(12).
24. Mezquita L, Preeshagul I, Auclin E. Predicting immunotherapy outcomes under therapy in patients with advanced NSCLC using dNLR and its early dynamics. Eur

J Cancer. 2021;151(8):211-20.
25. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer. 2016;16(7):431-46.
26. Colloca GA, Venturino A, Guarneri D. Second-generation inflammation-related scores are more effective than systemic inflammation ratios in predicting prognosis of patients with unresectable or metastatic pancreatic cancer receiving cytotoxic chemotherapy. Med Oncol. 2018;35(12):158.
27. Colloca GA, Venturino A, Guarneri D. Retrospective analysis by site of primary tumor of patients with unresectable locally-advanced or metastatic pancreatic adenocarcinoma receiving chemotherapy. Clin Exp Metastas. 2019;36(6): 519-25.
28. Faget J, Groeneveld S, Boivin G, et al. Neutrophils and Snail Orchestrate the Establishment of a Pro-tumor Microenvironment in Lung Cancer. Cell Rep. 2017;21(11):3190-3204.
29. Chen XF, Qian J, Pei D. Prognostic value of perioperative leukocyte count in resectable gastric cancer. World J Gastroentero. 2016;22(9):2818-27.
30. Heppt MV, Heinzerling L, Kähler KC, Forschner A, Kirchberger MC, Loquai C, et al. Prognostic factors and outcomes in metastatic uveal melanoma treated with programmed cell death-1 or combined PD-1/cytotoxic T-lymphocyte antigen-4 inhibition. Eur J Cancer. 2017;82(14):56-65.
31. Schaaf MB, Garg AD, Agostinis P. Defining the role of the tumor vasculature in antitumor immunity and immunotherapy. Cell Death Dis. 2018;9(2):115.
32. Missiaen R, Mazzone M, Bergers G. The reciprocal function and regulation of tumor vessels and immune cells offers new therapeutic opportunities in cancer. Semin Cancer Biol. 2018;52(Pt 2):107-16.