ORIGINAL ARTICLE

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Predictive Value of the Royal Marsden Hospital Score in Second-line Immunotherapy for Metastatic NSCLC

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ABSTRACT

Objective: Although immune checkpoint inhibitors have transformed routine oncology practice in the treatment of advanced non-small cell lung cancer (NSCLC), the identification of reliable predictive biomarkers, particularly in the second-line setting, remains an unmet clinical need. In this context, where programmed death-ligand 1 (PD-L1) expression alone is often inadequate, the Royal Marsden Hospital (RMH) score, which integrates objective laboratory and imaging data, has emerged as a potential prognostic tool for various cancer types. This study aims to evaluate the predictive value of the RMH score in patients with advanced NSCLC receiving second-line nivolumab and to investigate its role in stratifying patients based on treatment efficacy and survival outcomes.

Material and Methods: This retrospective study explores the association between the RMH score, assessed prior to immunotherapy initiation, and survival outcomes in metastatic NSCLC patients. Fifty patients who received second-line nivolumab between 2010 and 2023 were included. The RMH score was categorized into low-risk (0-1) and high-risk (2-3) groups based on baseline serum albumin levels, lactate dehydrogenase levels, and metastatic burden. Patients with conditions affecting these biomarkers were excluded. All assessments were conducted before the initiation of nivolumab.

Results: The RMH score was a significant predictor of survival in metastatic NSCLC patients receiving second-line nivolumab. High-risk patients had a median overall survival (OS) of 4 months, while those in the low-risk group had a median OS of 15 months [hazard ratio (HR)=3.1, p=0.003]; and a median progression-free survival (PFS) of 3 months versus a median PFS of 8 months in the low-risk group (HR=2.4, p=0.008). In multivariate analysis, the RMH score remained the significantly independent predictor of OS, while PD-L1 expression showed no significant impact.

Conclusion: Our study highlights the RMH score, based on radiological and laboratory parameters, as a predictive marker for survival in metastatic NSCLC patients treated with second-line nivolumab.

Keywords: Immune checkpoint inhibitors; RMH score; mNSCLC; systemic inflammation; NLR

INTRODUCTION

Recent advancements in oncology, particularly in the use of immune checkpoint inhibitors (ICIs), have introduced significant innovations in the treatment of advanced non-small cell lung cancer (NSCLC). However, despite their potential, predicting patient responses to these therapies remains a substantial challenge, especially in second-line treatments.[1] There is a critical need for reliable prognostic and predictive biomarkers. While a variety of complex biomarkers have been identified, programmed death-ligand 1 (PD-L1) remains the only validated biomarker currently employed in clinical practice.[2] This highlights a gap in the availability of biomarkers that can be readily integrated into clinical care.

The Royal Marsden Hospital (RMH) score is a validated prognostic model initially developed to assess patient outcomes in early-phase clinical trials. Unlike other scoring systems that incorporate subjective clinical parameters, the RMH score consists solely of objective laboratory and radiologic criteria, making it a reproducible and clinically relevant tool. This model includes two laboratory-based

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markers-elevated lactate dehydrogenase (LDH) and low serum albumin- along with the presence of metastases in the liver or other visceral organs. Since its introduction, the RMH score has been extensively validated across multiple tumor types, including lung, pancreatic, and head and neck cancers, demonstrating its prognostic value in various treatment settings. The results of a study by Arkenau et al.[3], involving 19 phase I clinical trials, demonstrated a significant association between a low RMH score and improved overall survival (OS). Similarly, Garrido-Laguna et al.[4] reported that patients with lower RMH scores (0-1) had significantly longer median OS compared to those with higher scores (2-3).[3-7]

More recently, retrospective analyses of NSCLC patients receiving ICIs have indicated that the RMH score may serve as both a prognostic and predictive biomarker, particularly in patients treated with atezolizumab in the first-line setting.[8] In contrast to prior studies, the present work specifically evaluates the RMH score in NSCLC patients treated with second-line nivolumab following chemotherapy failure, an underrepresented yet clinically relevant subgroup in the current literature.

Given the increasing recognition of systemic inflammation and metabolic dysregulation in shaping the tumor microenvironment and modulating the response to immunotherapy, the RMH score offers a unique and easily accessible method for stratifying patients based on expected clinical outcomes. However, the prognostic and predictive value of this score in patients receiving PD-1 inhibitor-based immunotherapy following chemotherapy remains unclear.

This study aims to evaluate whether the RMH score can function as a predictive marker for clinical outcomes in patients with advanced NSCLC treated with nivolumab as a second-line therapy. We hypothesize that the RMH score may serve as a valuable predictor of both treatment efficacy and survival outcomes in this patient population.

MATERIAL AND METHODS

Research Design

This retrospective study investigated the association between the RMH score, assessed prior to the initiation of second-line immunotherapy, and survival outcomes in patients with metastatic NSCLC who had progressed after first-line systemic chemotherapy. The RMH score was categorized into risk groups based on criteria established in previous studies, with scores of 0-1 considered low risk and scores of 2-3 considered high risk.

Patients who had experienced disease progression following systemic chemotherapy and were treated with nivolumab between 2010 and 2023 were evaluated for eligibility in this study. A total of 50 adult patients with available baseline LDH, serum albumin levels, and measurable metastatic lesions prior to the initiation of nivolumab treatment were included in the analysis. The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Ethics Committee on March 24, 2025 (approval no: 2025-467, date: 24.03.2025). All procedures were conducted in accordance with institutional guidelines and relevant regulations. Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

Study Population and Data

The study included adult patients with histologically confirmed metastatic NSCLC who were negative for estimated glomerular filtration rate mutations, *ALK* rearrangements, and ROS1 translocations. Serum albumin, LDH, and complete blood count were analyzed using peripheral venous blood samples collected from patients within 15 days prior to the initiation of nivolumab immunotherapy. Patients with conditions that could potentially alter these laboratory parameters, such as active infectious diseases, were excluded from the study to prevent bias in study outcomes (Figure 1).

Clinical, radiologic, and laboratory evaluations, including the assessment of serum albumin, LDH levels, and the determination of metastatic sites, were conducted prior to the first dose of nivolumab.

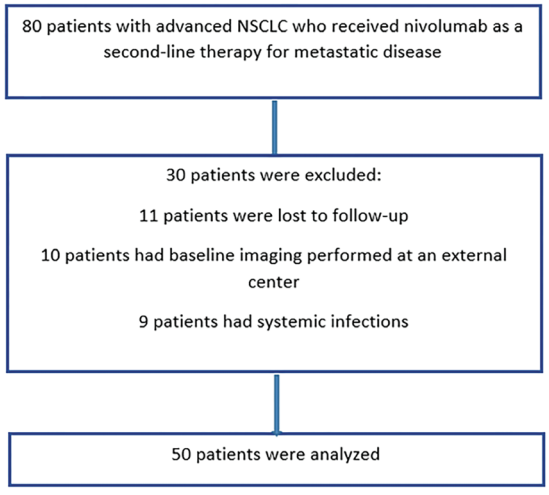

FIGURE 1: Screening excluded patients with factors affecting RMH score or insufficient imaging.

RMH: Royal Marsden Hospital; NSCLC: Non-small cell lung cancer

Evaluation of the RMH Score

Baseline radiological evaluations and laboratory tests were conducted within 30 days prior to the commencement of nivolumab treatment. The RMH score was calculated using three objective clinical parameters. These included serum albumin concentration (categorized as <3.5 g/dL or ≥3.5 g/dL) and LDH levels relative to the upper limit of normal (normal vs. elevated). The extent of metastatic disease was assessed based on the number of involved anatomical sites (≥3 vs. ≤2), not the presence or absence of visceral involvement.

Evaluation and Statistical Analyses

Patients' radiological responses were evaluated based on the RECIST 1.1 guidelines. The dataset was processed using SPSS version 27, with patient survival curves generated via the Kaplan-Meier estimator to assess survival likelihoods over time. To determine independent factors influencing OS and PFS, Cox proportional hazards models were utilized to examine the relationship between clinical variables and survival outcomes. A p-value of less than 0.05 was considered indicative of statistical significance.

Findings

Study Population Characteristics

A total of fifty patients who were diagnosed with metastatic NSCLC between 2010 and 2023 and who did not fulfill any of the exclusion criteria that had been predefined as part of the study design were retrospectively included in this analysis. The demographic and baseline clinical characteristics of these patients are presented in Table 1. Following their initial diagnosis, all patients were treated with first-line systemic chemotherapy as part of the standard treatment protocol. Upon radiologically confirmed disease progression, each patient subsequently received second-line immunotherapy with nivolumab.

Prognosis and Survival Rates

Tables 2 and 3 summarize the key findings from the analyses of OS and PFS outcomes. The univariate analysis indicated a significant link between the RMH score and OS (p=0.003). In contrast, no statistically meaningful associations were found for neutrophil-to-lymphocyte ratio (NLR) or PD-L1 expression,

TABLE 1: Distribution of clinical and demographic characteristics among patients.

		Royal Marsden Hospital (RMH)		
Patient cohort	**All patients (50)**	**Low RMH (26)**	**High RMH (24)**	**p**
Age group n (%)				
<65 years	21 (42)	14 (45)	7 (37)	0.56
≥65 years	29 (58)	17 (55)	12 (63)	
Gender n (%)				
Male	45 (90)	27 (87)	18 (95)	0.60
Female	5 (10)	4 (13)	1 (5)	
Baseline ECOG status				
0-1	31 (62)	23 (74)	8 (42)	0.02
≥2	19 (38)	8 (26)	11 (58)	
Tumoral PD-L1 status n (%)				
<1%	24 (48)	13 (42)	11 (58)	0.22
1-49%	15 (30)	12 (39)	3 (16)	
≥50%	11 (22)	6 (19)	5 (26)	
Tumor histology n (%)				
Adenocarcinoma	25 (50)	15 (48)	10 (53)	0.77
Squamous-cell carcinoma	25 (50)	16 (52)	9 (47)	
Distribution of disease n (%)				
Bone only	11 (22)	8 (26)	3 (16)	0.001
Visceral disease only	18 (36)	17 (55)	1 (5)	
Multiple sites	21 (42)	6 (19)	15 (79)	

ECOG: Eastern Cooperative Oncology Group; PD-L1: Programmed death-ligand 1.

TABLE 2: Risk factors for overall survival based on univariate and multivariate Cox proportional hazards models.

Clinical variable	n %	Median OS (months)	Univariate analyses			Multivariate analyses		
			HR	95% CI	p	HR	95% CI	p
Age								
<65 years	21 (42)	13	1					
≥65 years	29 (58)	14	0.8	(0.4-1.6)	0.48			
Gender								
Male	45 (90)	13	1					
Female	5 (10)	15	1.4	(0.5-3.8)	0.45			
ECOG								
0-1	31 (62)	15	1					
≥2	19 (38)	10	1.6	(0.8-3.3)	0.18			
PD-L1								
<1%	24 (48)	13	1					
≥1%	26 (52)	15	0.7	(0.3-1.4)	0.28	0.5	(0.3-2)	0.7
Tumor histology								
Adenocarcinoma	25 (50)	12	1					
Squamous-cell carcinoma	25 (50)	15	0.9	(0.5-1.9)	0.82			
NLR								
<Median (3.7)	25 (50)	15	1					
≥Median (3.7)	25 (50)	9	1.6	(0.8-3.3)	0.17	1.5	(0.7-3)	0.3
RMH score								
Low risk	31 (62)	15	1					
High risk	19 (38)	4	3.1	(1.5-6.6)	0.003	2.6	(1.2-6)	0.02

RMH: Royal Marsden Hospital; OS: Overall survival; PD-L1: Programmed death-ligand 1; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

TABLE 3: Cox proportional hazards univariate analysis for PFS.

Characteristics	n %	Survival (months) mPFS	Univariate models		
			HR	95% CI	p
Age					
<65 years	21 (42)	4.4	1		
≥65 years	29 (58)	3.8	0.9	(0.5-1.7)	0.77
Gender					
Male	45 (90)	4	1		
Female	5 (10)	3	1.3	(0.5-3.3)	0.59
ECOG					
0-1	31 (62)	3.7	1		
≥2	19 (38)	3.8	1	(0.6-2)	0.85
PD-L1					
<1%	24 (48)	3	1		
≥1%	26 (52)	4	0.8	(0.4-1.4)	0.37
Tumor histology					
Adenocarcinoma	25 (50)	3	1		
Squamous-cell carcinoma	25 (50)	3	1	(0.5-1.9)	0.99

TABLE 3: Continued.

Characteristics	n %	Survival (months) mPFS	Univariate models		
			HR	95% CI	p
NLR					
<Median (3.7)	25 (50)	8	1		
≥Median (3.7)	25 (50)	3	1.5	(0.8-2.8)	0.19
RMH score					
Low risk	31 (62)	8	1		
High risk	19 (38)	3	2.4	(1.3-4.7)	0.008

RMH: Royal Marsden Hospital; PFS: Progression-free survival; PD-L1: Programmed death-ligand 1; ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil-to-lymphocyte ratio; HR: Hazard ratio; CI: Confidence interval.

with p-values of 0.17 and 0.28, respectively. Nonetheless, considering their possible clinical implications, both NLR and PD-L1 were incorporated into the multivariate analysis alongside the RMH score. In this model, the RMH score stood out as the only variable independently associated with OS (Table 2). Regarding PFS, univariate analysis similarly revealed a significant relationship between the RMH score and progression-free outcomes (p=0.008) (Table 3).

Median OS was notably shorter in patients with elevated RMH scores, reaching only 4 months, compared to 15 months observed in those with lower scores [hazard ratio (HR): 3.1, 95% confidence interval (CI): 1.5-6.6; p=0.002]. Kaplan-Meier plots illustrating these differences are presented in Figures 2 and 3.

An examination of PD-L1 expression showed no substantial effect on PFS or OS as demonstrated in Figures 4 and 5.

A similar pattern was observed for median PFS, with high RMH score patients exhibiting a median of 3 months compared to a median of 8 months in the low RMH score group (HR: 2.4, 95% CI: 1.3-4.7; p=0.008). These survival distributions are also visually summarized in Figures 2 and 3.

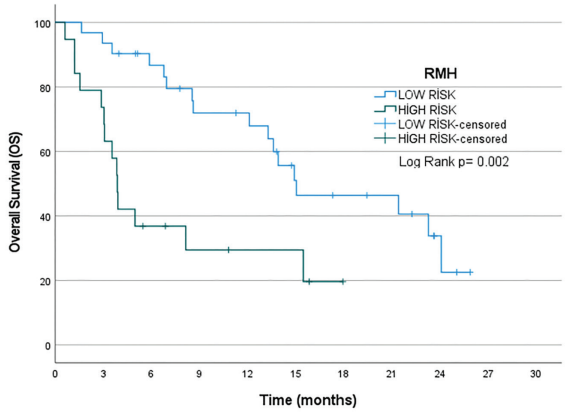

FIGURE 2: Overall survival Kaplan-Meier curves stratified by RMH score before initiation of nivolumab therapy.

RMH: Royal Marsden Hospital

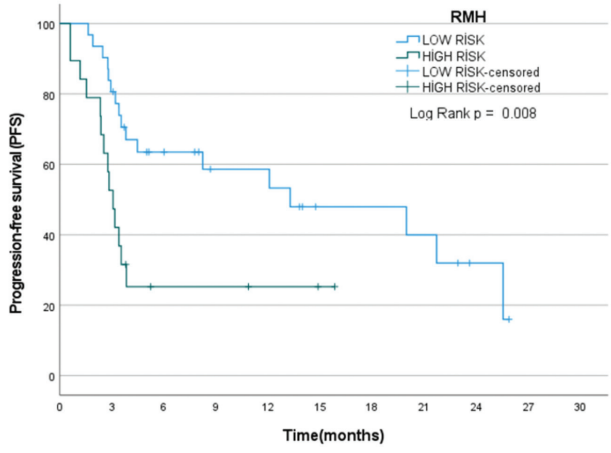

FIGURE 3: Progression-free survival curves stratified by baseline RMH score in patients treated with nivolumab.

RMH: Royal Marsden Hospital

DISCUSSION

In this study, we investigated the predictive value of the RMH score in patients with metastatic NSCLC who received second-line nivolumab therapy following disease progression after chemotherapy. The findings revealed a significant correlation between the RMH score and both OS and PFS, indicating its potential role as a predictive biomarker for treatment efficacy. Comprising objective laboratory and radiological parameters, the RMH score was identified as an independent predictor of survival outcomes, regardless of PD-L1 expression status.

Similarly, multiple clinical investigations have reported a correlation between systemic inflammatory biomarkers and

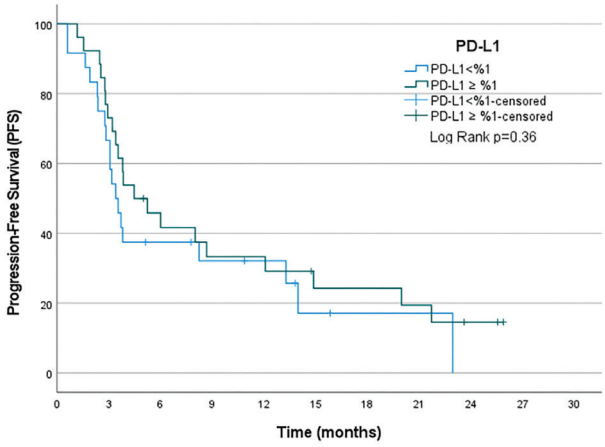

FIGURE 4: Kaplan-Meier analysis of PFS based on baseline PD-L1 expression before initiating nivolumab therapy.

PFS: Progression-free survival; PD-L1: Programmed death-ligand 1

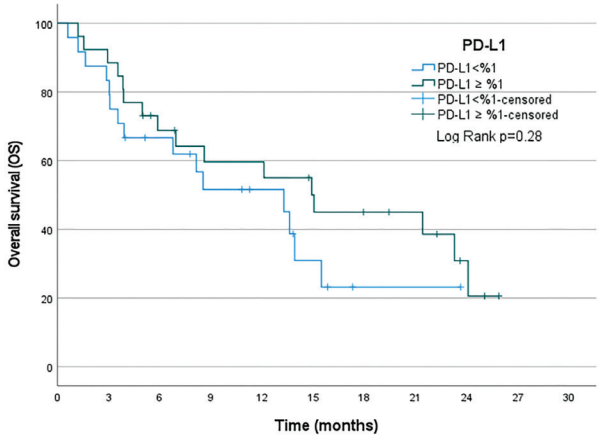

FIGURE 5: Survival curves (Kaplan-Meier) for overall survival according to baseline PD-L1 expression before nivolumab initiation.

PD-L1: Programmed death-ligand 1

reduced responsiveness to immunotherapy.[9,10] In our study, we utilized the RMH score, a recently defined and validated metric that integrates radiological and laboratory parameters. Notably, to the best of our knowledge, this is the first study to demonstrate an association between this composite score and survival outcomes specifically in metastatic NSCLC patients, all of whom had previously received chemotherapy and were uniformly treated with nivolumab as second-line therapy.

The RMH score has been previously validated in various cancer types and is known to correlate with poor outcomes in patients with high scores. In particular, elevated LDH, low serum albumin, and the presence of metastases in visceral organs are all indicative of increased systemic inflammation and tumor burden, which may contribute to immune resistance.[3,11,12] In our study, we observed that patients with high RMH scores (2 to 3) had significantly shorter OS and PFS compared to those with low scores (0 to 1). These findings support the hypothesis that systemic inflammation and poor nutritional status are associated with worse outcomes in patients treated with ICIs.

Consistent with the existing literature, elevated LDH and low albumin levels are widely recognized as markers of poor prognosis in cancer patients, and their role in predicting immunotherapy response has been increasingly acknowledged. LDH elevation reflects not only tumor burden and aggressiveness, but also hypoxia-induced immunosuppression.[13] Hypoalbuminemia has been shown to predict poor OS and diminished response to immunotherapy; for instance, in NSCLC patients treated with ICIs, low pretreatment albumin and early albumin decline were independently associated with worse outcomes.[14] The presence of ≥3 metastatic sites, particularly in visceral organs such as the liver, correlates with systemic immunosuppression and T-cell exclusion within the tumor microenvironment. Liver metastases are a negative predictor of ICI efficacy and are associated with immunosuppressive macrophage infiltration and reduced circulating $CD8^+$ T-cells.[15] These mechanisms together may explain the poor outcomes observed in patients with high RMH scores.[13,16-18]

A review of the literature demonstrates that the RMH score possesses prognostic value across various cancer types, including NSCLC, colorectal cancer, and sarcoma.[12,19,20] In a study, the predictive role of the RMH score in a heterogeneous cancer population was confirmed, supporting its broad applicability in clinical trials involving multiple malignancies.[21] Similarly, in another phase I study, the utility of this score was validated in a Far Eastern patient population.[22] Consistent with these findings, our analysis also demonstrated a strong association between a high RMH score and poorer OS and PFS. Notably, to our knowledge, this is among the first studies to specifically evaluate the prognostic significance of the RMH score in the setting of second-line nivolumab immunotherapy in patients with metastatic NSCLC.

Unlike other biomarkers, which may not always be readily available or easy to interpret, the RMH score is derived from widely accessible clinical data, making it a promising tool for routine clinical practice. Moreover, as an objective, reproducible model, the RMH score has the potential to complement existing biomarkers like PD-L1 in guiding treatment decisions for patients with metastatic NSCLC.

Numerous publications have examined the association between neutrophil-to-lymphocyte ratio and clinical outcomes in patients undergoing immunotherapy. For

instance, Mandaliya et al.[23] reported that elevated baseline NLR, measured prior to initiating ICIs in metastatic NSCLC patients, was linked to reduced OS, a finding they attributed to systemic inflammation reflected in peripheral blood parameters.[24] Similarly, Alessi et al.[25] identified low pre-treatment NLR values as significantly correlated with longer OS and PFS in NSCLC patients receiving pembrolizumab as a first-line treatment. Supporting this, Valero and colleagues also found that baseline NLR served as a meaningful prognostic factor in patients undergoing immunotherapy.9 In another study, Hwang et al.[26] described an inverse relationship between initial NLR levels and therapeutic response to immunotherapy. Consistent with these findings, Anpalakhan et al.[27] demonstrated that patients (NSCLC cases included) with lower baseline NLR exhibited more favorable clinical outcomes following immunotherapy.

Contrary to previous studies that identified baseline NLR as a prognostic marker for survival in NSCLC patients undergoing immunotherapy, our analysis did not find a statistically significant association. This discrepancy may be due to the limited sample size, which likely reduced the statistical power to detect subtle differences. However, the RMH score, constructed from both laboratory and imaging-based indicators, demonstrated a significant association with survival outcomes in this patient cohort, independent of PD-L1 status, when assessed prior to initiating second-line nivolumab therapy in patients who had progressed after chemotherapy.

Study Limitations

While our study provides strong evidence for the predictive value of the RMH score, it is not without limitations. Its retrospective design and the relatively small sample size inherent to single-center real-world datasets reduce the statistical power and generalizability of the findings. Therefore, our results should be interpreted with caution and validated in larger, prospective multicenter studies. Nivolumab was initiated as second-line or later therapy in all patients, in accordance with national reimbursement constraints that allowed access at the earliest eligible point.

Furthermore, the heterogeneity of the patient population, including varying levels of PD-L1 expression and prior chemotherapy regimens, may have influenced the results. However, the RMH score's predictive value was observed even when adjusted for these factors, suggesting its robustness as a prognostic tool. Additionally, further validation in larger, prospective cohorts is necessary to confirm its utility in routine clinical practice.

Future research should also explore the potential of combining the RMH score with other biomarkers, such as the NLR or other immune-related indices, to enhance its predictive accuracy. The integration of multiple factors reflecting both tumor burden and immune status may offer a more comprehensive approach to patient stratification and treatment optimization in metastatic NSCLC. Moreover, longitudinal studies assessing changes in the RMH score over the course of treatment could provide insights into how this model evolves with therapy and help identify patients who could benefit from early or aggressive interventions.

CONCLUSION

In conclusion, the RMH score appears to be a promising prognostic tool for predicting survival outcomes in metastatic NSCLC patients undergoing second-line nivolumab therapy. By incorporating objective clinical parameters, the model offers a simple and reproducible method for identifying patients at higher risk of poor treatment response. These findings support further investigation into the RMH score's clinical application, with the potential to improve patient stratification and guide more personalized treatment approaches in NSCLC.

Ethics

Ethics Committee Approval: The study protocol was reviewed and approved by the Gazi University Faculty of Medicine Ethics Committee on March 24, 2025 (approval no: 2025-467, date: 24.03.2025).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.A., N.R.C., A.Ö., N.Ö., O.Y., Concept: V.A., N.R.C., A.Ö., N.Ö., O.Y., Design: V.A., A.Ö., N.Ö., O.Y., Data Collection or Processing: V.A., N.R.C., O.Y., Analysis or Interpretation: V.A., O.Y., Literature Search: V.A., N.R.C., A.Ö., N.Ö., O.Y., Writing: V.A., N.R.C., A.Ö., N.Ö., O.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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