Research Square

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Immune ratios from complete blood count can predict outcomes for lung cancer surgery: a retrospective cohort of open surgery data

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Abstract

Background

Lung cancer surgery represents a significant form of tissue trauma that triggers a complex inflammatory response involving both the innate and adaptive immune systems. Complete blood count (CBC) is one of the routine laboratory tests evaluated in lung cancer surgery. This study was designed to assess the potential impact of surgery on immune response by analyzing simple immunological markers and their ratios, all derived from routinely performed preoperative and postoperative CBC tests.

Methods

399 patients who underwent lung resection via thoracotomy for primary lung cancer at a single center between 2010 and 2017 were retrospectively were included in the statistical analysis. To evaluate the immunological markers used in this study, leukocyte, neutrophil, lymphocyte, and monocyte values from the CBC from both preoperative and postoperative tests, and their ratios were compared. To standardize the assessment of the immunological response to surgical stress in lung cancer patients, nine different ratios were defined. To evaluate the effectiveness of these immunological markers, patients were grouped under nine different parameters and subjected to statistical analysis.

Results

Elevated Pre N/Leu and Pre N/Lym values, calculated solely from preoperative measurements, were found to be significantly associated with poor prognosis. Higher Post N/Lym value, based on postoperative measurements, was also linked to poor prognosis. Lower values of the Post N/Pre N ratio, the inflammatory immune response change ratio, and the neutrophil dominance change ratio were each found to be indicators of unfavorable prognosis.

Conclusion

Laboratory values routinely observed in daily practice could serve as useful predictive tools for clinicians and could offer insight into patient prognosis.

Introduction

Lung cancer surgery is a major procedure associated with potentially high morbidity and mortality. It represents a significant form of tissue trauma that triggers a complex inflammatory response involving both the innate and adaptive immune systems. The postoperative immune response is regulated by a balance between proinflammatory immune cell activity—mediated by humoral factors such as cytokines and the complement system—and local as well as systemic immunosuppressive mechanisms (1). Although preoperative evaluation of a patient's suitability for lung resection typically involves routine laboratory tests, pulmonary function tests, and cardiopulmonary reserve assessments, in clinical practice, the same surgical procedure may affect each patient's physiological condition differently.

In oncological pathologies, immunological factors and the impact of immunity on cancer survival have gained significant prominence in the current literature (2). Surgical trauma is considered a major factor influencing the immune response (3). In gastrointestinal surgery, parameters such as the serum albumin-to-monocyte ratio provide objective criteria assessing a patient's physical condition and nutritional status (4). However, in lung cancer surgery, there is no established objective laboratory parameter that effectively reflects or predicts the impact of surgery on immunity and the patient's overall functional status.

Complete blood count (CBC) is one of the routine laboratory tests evaluated both before and after lung cancer surgery. The CBC includes simple immunological markers such as leukocyte, neutrophil, lymphocyte, and monocyte counts and percentages. Changes in these immunological markers observed during follow-up may provide insight into the effects of surgical trauma on the immune system. This study was designed to assess the potential impact of surgery on immune response by analyzing simple immunological markers and their ratios, all derived from routinely performed preoperative and postoperative CBC tests. Additionally, the study aims to evaluate the association between this immune response and postoperative morbidity and survival outcomes.

Methods

This study was designed as a retrospective observational cohort study conducted at a single tertiary thoracic surgery center. A total of 458 patients who underwent open anatomical lung resection due to primary non-small cell lung carcinoma at a single center between 2010 and 2017 were retrospectively evaluated using hospital records, discharge summaries, operative notes, laboratory findings, and pathological reports. The aim was to include only the thoracotomy cases performed with conventional methods (posterior approaches, no muscle sparing or intercostal nerve protection etc.) to evaluate the maximum effect of surgical trauma on immunity. There were not any standardized enchanced recovery after surgery (ERAS) protocols during the selected period. Sixteen patients who underwent surgery via sternotomy (excluded for standardization), 36 patients with a history of recurrent lung resection or concomitant surgery for malignancies in other organs, and 7 patients with incomplete medical records were excluded from the study. Ultimately, 399 patients who underwent open anatomical lung resection via thoracotomy for primary lung carcinoma, with no prior oncological history, were included in the statistical analysis.

Routine laboratory tests for preoperative evaluation were conducted no more than 14 days prior to surgery, while postoperative blood tests were assessed within postoperative day 1key . To evaluate the immunological markers used in this study, leukocyte, neutrophil, lymphocyte, and monocyte values from the CBC were recorded in units of $10^3/\mu L$ from both preoperative and postoperative tests, and their ratios were compared. Lung cancer staging was performed according to the 8th edition of the TNM classification by the International Association for the Study of Lung Cancer (IASLC). Without applying a specific scoring system, postoperative adverse events such as pneumonia or atrial fibrillation were classified as morbidity, regardless of their severity. All patients were routinely monitored in the intensive

care unit (ICU) for at least one day postoperatively. Discharge to home was carried out after the removal of the chest drains.

To standardize the assessment of the immunological response to surgical stress in lung cancer patients, nine different ratios were defined. These ratios are as follows:

Preoperative Neutrophil/Leukocyte Ratio (Pre N/Leu): The patient's preoperative neutrophil percentage (innate + adaptive immunity),

Postoperative Neutrophil/Leukocyte Ratio (Post N/Leu): The patient's postoperative neutrophil percentage (innate + adaptive immunity),

Preoperative Neutrophil/Lymphocyte Ratio (Pre N/Lym): Preoperative dominance of neutrophils (innate + adaptive immunity),

Postoperative Neutrophil/Lymphocyte Ratio (Post N/Lym): Postoperative dominance of neutrophils (innate + adaptive immunity),

Postoperative/Preoperative Neutrophil Ratio (Post N/Pre N): Early-phase change in acute inflammatory response (innate immunity),

Postoperative/Preoperative Lymphocyte Ratio (Post Lym/Pre Lym): Early-phase change in the acute cellular immune response (humoral + cellular immunity),

Postoperative/Preoperative Monocyte Ratio (Post Mono/Pre Mono): Early-phase change in monocytes, reflecting acute inflammatory response apart from neutrophils (innate immunity),

Postoperative/Preoperative Neutrophil/Leukocyte Ratio (Inflammatory response change ratio): Change in inflammatory immune response in the early postoperative phase (innate + adaptive immunity),

Postoperative/Preoperative Neutrophil/Lymphocyte Ratio (Neutrophil dominance change ratio): Early postoperative change in neutrophil dominance, indicating the strength of the acute inflammatory response (innate + adaptive immunity).

To evaluate the effectiveness of these immunological markers, patients were grouped under nine different parameters and subjected to statistical analysis:

T Parameter in TNM Staging:
a. Group 1: Patients with T1 or T2 lesions
b. Group 2: Patients with T3 or T4 lesions

Overall TNM Stage:
a. Group 1: Stage IA, IB, IIA, IIB
b. Group 2: Stage IIIA, IIIB

Extent of Lung Resection:
a. Group 1: Anatomical resections smaller than pneumonectomy
b. Group 2: Pneumonectomy

Histological Subtype of Lung Cancer:
a. Group 1: Adenocarcinoma
b. Group 2: Squamous cell carcinoma
c. Group 3: Other carcinomas

Postoperative Length of Hospital Stay:
a. Group 1: 0–8 days
b. Group 2: 9 days or longer

Length of ICU Stay:
a. Group 1: 1 day
b. Group 2: More than 1 day

Hospital Readmission:
a. Group 1: Readmitted
b. Group 2: Not readmitted

Postoperative Morbidity:
a. Group 1: Morbidity present
b. Group 2: No morbidity

5-Year Survival Completion:
a. Group 1: Survived for five years
b. Group 2: Did not survive five years

Patients' demographic characteristics, including age and sex, were evaluated across the defined groups. To assess the validity of the nine immunological evaluation ratios outlined above, a statistical analysis was conducted. Receiver Operating Characteristic (ROC) analysis was used to determine cut-off values for each ratio, and group comparisons were performed using the chi-square test.

Statistical Analysis

The normality of data distribution was assessed using the Shapiro-Wilk test. Descriptive statistics for continuous variables were presented as mean ± standard deviation for normally distributed data, and as median (minimum–maximum) for non-normally distributed data. Categorical variables were summarized as frequency and percentage (n (%)). All variables collected from patients were analyzed. To assess relationships between dependent and independent variables, the Kruskal-Wallis test was used for comparing more than two independent groups when data did not follow a normal distribution, and the Mann-Whitney U test was used for comparisons between two independent groups. For comparisons

between categorical variables, Pearson’s chi-square test, Yates’ correction, and Fisher’s exact test were employed where appropriate. ROC (Receiver Operating Characteristic) analysis was performed to determine cut-off values of the variables. All statistical analyses were conducted using IBM SPSS version 21. A p-value of <0.05 was considered statistically significant.

Results

General Distributions

The mean age of the 399 patients included in the study was 62.09 ± 9.01 years. The distribution of patients across different groups is presented in Table 1.

Table 1
Distribution of Patients by Demographic Characteristics

Gender	Patient count	Percentage (%)
Female	58	14.5
Male	341	85.5
5-Year Survival		
Alive	240	60.2
Exitus	159	39.8
Surgical Procedure		
Less than pneumonectomy	321	80.5
Pneumonectomy	78	19.5
Tumor Histology		
Adenocarcinoma	135	33.8
Squamous cell carcinoma	177	44.4
Other	87	21.8
T Parameter		
Group 1 (T1 + T2)	244	61.2
Group 2 (T3 + T4)	155	38.8
TNM Stage		
Group 1 (Stage I–IIB)	286	71.7
Group 2 (Stage III)	113	28.3
ICU Length of Stay		
1 day	365	91.5
More than 1 day	34	8.5
Postoperative Hospital Stay		
0–8 days	226	56.6
≥ 9 days	173	43.4
Hospital Readmission		

Gender	Patient count	Percentage (%)
Yes	60	15.0
No	339	85.0
Postoperative Morbidity		
Present	104	26.1
Absent	295	73.9

Statistically significant differences were found between the gender variable and several other parameters, including cell type, T parameter, overall stage, and postoperative morbidity. Adenocarcinoma was more frequent in female patients (56.9%, $p < 0.001$). T1–T2 lesions were more common among women (75.9%, $p = 0.019$), as was Stage I–II disease (84.5%, $p = 0.029$). Postoperative morbidity was significantly lower in female patients (12.1%, $p = 0.014$).

Patients who survived five years ($p = 0.001$), those who underwent pneumonectomy compared to smaller resections ($p = 0.043$), and those categorized under “other carcinomas” in terms of histological subtype ($p = 0.01$) were found to be significantly younger. In contrast, patients who were readmitted to the hospital were generally older ($p = 0.001$).

ROC and Chi-Square Analysis of Parameters

Group analyses were given in Table 2. Only statistically significant results are listed.

T Parameter in TNM Staging

Table 2

a. ROC and Chi-Square Analysis According to T Parameter (TNM Staging) ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Pre N/Leu	0.674 (0.619–0.729)	0.65	$p < 0.001$	70.9	42.6
Pre N/Lym	0.690 (0.636–0.743)	2.60	$p < 0.001$	68.0	36.8
Post N/Lym	0.565 (0.506–0.624)	14.75	0.028	79.1	64.5
Post N/Pre N	0.604 (0.547–0.660)	2.36	$p < 0.001$	67.6	47.7
Inflammatory response change ratio	0.663 (0.608–0.718)	1.27	$p < 0.001$	78.3	52.3
Neutrophil dominance change ratio	0.573 (0.515–0.631)	4.04	0.014	57.0	40.0

Chi-Square Test – T Stage

Marker	Group (T1–2) n (%)	Group (T3–4) n (%)	*p*-value
Pre N/Leu ≤ 0.65	173 (70.9%)	66 (42.6%)	$p < 0.001$
Pre N/Leu > 0.65	71 (29.1%)	89 (57.4%)	
Pre N/Lym ≤ 2.60	166 (68.0%)	57 (36.8%)	$p < 0.001$
Pre N/Lym > 2.60	78 (32.0%)	98 (63.2%)	
Post N/Lym ≤ 14.75	193 (79.1%)	100 (64.9%)	0.002
Post N/Lym > 14.75	51 (20.9%)	54 (35.1%)	
Post N/Pre N ≤ 2.36	79 (32.4%)	79 (51.0%)	$p < 0.001$
Post N/Pre N > 2.36	165 (67.6%)	76 (49.0%)	
Inflammatory ratio ≤ 1.27	50 (20.6%)	70 (45.2%)	$p < 0.001$
Inflammatory ratio > 1.27	193 (79.4%)	85 (54.8%)	
Neutrophil ratio ≤ 4.04	105 (43.0%)	93 (60.4%)	0.001
Neutrophil ratio > 4.04	139 (57.0%)	61 (39.6%)	

Pre N/Leu, Pre N/Lym, and Post N/Lym ratios increased with higher T stages, whereas the Post N/Pre N, inflammatory immune response change ratio, and neutrophil dominance change ratio decreased as T stage advanced. The cut-off values were determined as follows: Pre N/Leu: 0.65, Pre N/Lym: 2.60, Post

N/Lym: 14.75, Post N/Pre N: 2.36, inflammatory immune response change ratio: 1.27, and neutrophil dominance change ratio: 4.04 (Table 2a).

TNM Stage

Table 2
b. ROC and Chi-Square Analysis According to TNM Stage ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Pre N/Leu	0.641 (0.579–0.702)	0.62	$p < 0.001$	56.6	33.6
Pre N/Lym	0.651 (0.591–0.710)	2.38	$p < 0.001$	53.8	29.2
Post N/Pre N	0.584 (0.522–0.646)	2.18	0.009	70.6	56.6
Inflammatory response change ratio	0.641 (0.580–0.703)	1.30	$p < 0.001$	69.6	44.2
Neutrophil dominance change ratio	0.598 (0.535–0.660)	4.35	0.002	51.4	31.0

Chi-Square Test – TNM Stage

Marker	Group I–IIB n (%)	Group III n (%)	*p*-value
Pre N/Leu ≤ 0.62	143 (50.2%)	34 (30.1%)	$p < 0.001$
Pre N/Leu > 0.62	142 (49.8%)	79 (69.9%)	
Pre N/Lym ≤ 2.38	154 (53.8%)	33 (29.5%)	$p < 0.001$
Pre N/Lym > 2.38	132 (46.2%)	79 (70.5%)	
Post N/Pre N ≤ 2.18	84 (29.4%)	49 (43.4%)	0.008
Post N/Pre N > 2.18	202 (70.6%)	64 (56.6%)	
Inflammatory ratio ≤ 1.30	87 (30.5%)	63 (55.8%)	$p < 0.001$
Inflammatory ratio > 1.30	198 (69.5%)	50 (44.2%)	
Neutrophil ratio ≤ 4.35	139 (48.8%)	77 (68.1%)	$p < 0.001$
Neutrophil ratio > 4.35	146 (51.2%)	36 (31.9%)	

Pre N/Leu and Pre N/Lym ratios increased with advancing stage. The cut-off values were determined as follows: Pre N/Leu: 0.62, Pre N/Lym: 2.38, Post N/Pre N: 2.18, inflammatory immune response change ratio: 1.30, and neutrophil dominance change ratio: 4.35 (Table 2b).

Extent of Lung Resection

Table 2
c. ROC and Chi-Square Analysis According to Extent of Lung Resection ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Neutrophil dominance change ratio	0.573 (0.503–0.643)	4.89	0.046	40.8	26.9

Chi-Square Test – Lung Resection Extent

Marker	Pneumonectomy n (%)	Pneumonectomy n (%)	*p*-value
Neutrophil ratio ≤ 4.89	190 (59.4%)	56 (72.7%)	0.042
Neutrophil ratio > 4.89	130 (40.6%)	21 (27.3%)	

The neutrophil dominance change ratio was found to be lower in pneumonectomy cases. The cut-off value for the neutrophil dominance change ratio was determined as 4.89 (Table 2c).

Tumor Histology

Table 2
d. ROC and Chi-Square Analysis According to Tumor Histology ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Post N/Pre N	0.583 (0.524–0.642)	2.64	0.006	59.3	42.8
Neutrophil dominance change ratio	0.569 (0.509–0.629)	4.08	0.024	60.7	44.3

Chi-Square Test – Tumor Histological Subtype

Marker	Adenocarcinoma n (%)	Squamous Cell Carcinoma n (%)	Other Carcinomas n (%)	*p*-value
Post N/Pre N ≤ 2.64	55 (40.7%)	106 (59.9%)	45 (51.7%)	0.004
Post N/Pre N > 2.64	80 (59.3%)	71 (40.1%)	42 (48.3%)	
Neutrophil ratio ≤ 4.08	53 (39.3%)	102 (58.0%)	45 (51.7%)	0.005
Neutrophil ratio > 4.08	82 (60.7%)	74 (42.0%)	42 (48.3%)	

Post N/Pre N ratio was observed to be lower in squamous cell carcinomas and higher in adenocarcinomas. Similarly, the neutrophil dominance change ratio was lower in squamous cell carcinomas and higher in adenocarcinomas. The cut-off value for the Post N/Pre N ratio was determined as 2.64, and for the neutrophil dominance change ratio as 4.08 (Table 2d).

Postoperative hospital stay

Table 2
e. ROC and Chi-Square Analysis According to Postoperative Hospital Stay ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Post Mono/Pre Mono	0.563 (0.507–0.620)	1.62	0.030	77.4	66.5

Chi-Square Test – Postoperative Length of Stay

Marker	0–8 Days n (%)	≥ 9 Days n (%)	*p*-value
Post Mono/Pre Mono ≤ 1.62	175 (77.4%)	115 (66.5%)	0.015
Post Mono/Pre Mono > 1.62	51 (22.6%)	58 (33.5%)	

Post Mono/Pre Mono ratio was found to be higher in patients with longer stays. The cut-off value for the Post Mono/Pre Mono ratio was determined as 1.62 (Table 2e).

ICU stay duration

Table 2
f. ROC and Chi-Square Analysis According to ICU Stay Duration ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Pre N/Leu	0.643 (0.543–0.744)	0.65	0.006	62.7	35.3
Pre N/Lym	0.652 (0.555–0.748)	2.49	0.003	55.3	29.4
Inflammatory response change ratio	0.618 (0.521–0.715)	1.33	0.023	57.5	32.4

Chi-Square Test – ICU Stay Length

Marker	1 Day n (%)	> 1 Day n (%)	*p*-value
Pre N/Leu ≤ 0.65	227 (62.2%)	12 (35.3%)	0.004
Pre N/Leu > 0.65	138 (37.8%)	22 (64.7%)	
Pre N/Lym ≤ 2.49	201 (55.1%)	10 (29.4%)	0.007
Pre N/Lym > 2.49	164 (44.9%)	24 (70.6%)	
Inflammatory ratio ≤ 1.33	155 (42.6%)	23 (67.6%)	0.009
Inflammatory ratio > 1.33	209 (57.4%)	11 (32.4%)	

Pre N/Leu and Pre N/Lym ratios were found to be higher in patients with prolonged ICU stays, whereas the inflammatory immune response change ratio was lower in these patients. The cut-off values were determined as follows: Pre N/Leu: 0.65, Pre N/Lym: 2.49, and inflammatory immune response change ratio: 1.33 (Table 2f).

Hospital Readmission

No statistically significant difference was found between rehospitalization and the immune response ratios identified in the study.

Postoperative Morbidity

Table 2
g. ROC and Chi-Square Analysis According to Postoperative Morbidity ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Pre N/Leu	0.576 (0.512–0.641)	0.66	0.020	43.3	28.5
Pre N/Lym	0.594 (0.530–0.659)	2.46	0.004	60.6	42.7
Inflammatory response change ratio	0.570 (0.505–0.634)	1.34	0.034	60.6	46.4

Chi-Square Test – Postoperative Morbidity

Marker	Morbidity Present n (%)	Morbidity Absent n (%)	*p*-value
Pre N/Leu ≤ 0.66	56 (53.8%)	199 (67.7%)	0.011
Pre N/Leu > 0.66	48 (46.2%)	95 (32.3%)	
Pre N/Lym ≤ 2.46	41 (39.4%)	169 (57.3%)	0.002
Pre N/Lym > 2.46	63 (60.6%)	126 (42.7%)	
Inflammatory ratio ≤ 1.34	60 (57.7%)	130 (44.1%)	0.017
Inflammatory ratio > 1.34	44 (42.3%)	165 (55.9%)	

Pre N/Leu and Pre N/Lym ratios were found to be higher in patients who developed postoperative morbidity, while the inflammatory immune response change ratio was lower in these patients. The cut-off values were determined as follows: Pre N/Leu: 0.66, Pre N/Lym: 2.46, and inflammatory immune response change ratio: 1.34 (Table 2g).

5-year Survival

Table 2
h. ROC and Chi-Square Analysis According to 5-year Survival ROC Analysis

Marker	AUC (95% CI)	Cut-off	*p*-value	Sensitivity (%)	Specificity (%)
Pre N/Leu	0.607 (0.551–0.664)	0.63	$p < 0.001$	56.6	38.3
Pre N/Lym	0.624 (0.569–0.680)	2.30	$p < 0.001$	70.4	48.3
Post N/Lym	0.558 (0.500–0.616)	14.63	0.050	33.3	22.5
Post N/Pre N	0.592 (0.536–0.648)	3.02	0.002	74.8	57.9
Inflammatory response change ratio	0.585 (0.529–0.642)	1.34	0.004	59.1	44.2

Chi-Square Test – 5-year Survival Status

Marker	Survived n (%)	Exitus n (%)	*p*-value
Pre N/Leu ≤ 0.63	135 (57.0%)	68 (42.8%)	0.006
Pre N/Leu > 0.63	102 (43.0%)	91 (57.2%)	
Pre N/Lym ≤ 2.30	124 (51.7%)	47 (29.6%)	< 0.001
Pre N/Lym > 2.30	116 (48.3%)	112 (70.4%)	
Post N/Lym ≤ 14.63	185 (77.4%)	106 (66.7%)	0.018
Post N/Lym > 14.63	54 (22.6%)	53 (33.3%)	
Post N/Pre N ≤ 3.02	139 (57.9%)	119 (74.8%)	0.001
Post N/Pre N > 3.02	101 (42.1%)	40 (25.2%)	
Inflammatory ratio ≤ 1.34	102 (42.5%)	88 (55.3%)	0.012
Inflammatory ratio > 1.34	138 (57.5%)	71 (44.7%)	

Pre N/Leu, Pre N/Lym, and Post N/Lym ratios were found to be higher in patients who did not complete five-year survival, while the Post N/Pre N ratio and the inflammatory immune response change ratio were lower in these patients. The cut-off values were determined as follows: Pre N/Leu: 0.63, Pre N/Lym: 2.30, Post N/Pre N: 3.02, and inflammatory immune response change ratio: 1.34 (Table 2h).

Summary of Results

A summary of statistical analysis results for nine different ratios is given in Table 3.

Elevated Pre N/Leu and Pre N/Lym values, calculated solely from preoperative measurements, were found to be significantly associated with poor prognosis. Specifically, higher levels of these markers correlated with larger tumor size, advanced stage, the occurrence of postoperative morbidity, and failure to achieve five-year survival.

Likewise, a higher Post N/Lym value—based on postoperative measurements—was also linked to poor prognosis. This elevation was associated with both increased tumor size and incomplete five-year survival.

An elevated Post Mono/Pre Mono ratio, derived by comparing postoperative to preoperative values, was associated with prolonged postoperative hospital stay. In contrast, lower values of the Post N/Pre N ratio, the inflammatory immune response change ratio, and the neutrophil dominance change ratio were each found to be indicators of unfavorable prognosis. Specifically, a reduced Post N/Pre N ratio was associated with larger tumors, advanced stage, the presence of squamous cell carcinoma, and poor long-term survival. A decreased inflammatory immune response change ratio correlated with larger tumor size, advanced stage, extended ICU stay, and the development of postoperative morbidity.

Similarly, a lower neutrophil dominance change ratio was associated with larger tumors, advanced stage, undergoing pneumonectomy, and the presence of squamous cell carcinoma.

Table 3
Summary of Study Findings

Marker	General Cut-off in Study	Significant Associations	Interpretation
Pre N/Leu	> 0.66 (range: 0.62–0.66)	T stage, TNM stage, ICU stay, morbidity, survival	Higher values are associated with advanced T stage, higher TNM stage, prolonged ICU stay, presence of morbidity, and poor survival.
Post N/Leu	Not statistically significant	–	–
Pre N/Lym	> 2.60 (range: 2.30–2.60)	T stage, TNM stage, ICU stay, morbidity, survival	Higher values are associated with advanced T stage, higher TNM stage, prolonged ICU stay, presence of morbidity, and poor survival.
Post N/Lym	> 14.75 (range: 14.63–14.75)	T stage, survival	Higher values are associated with advanced T stage and poor survival.
Post N/Pre N	< 2.18 (range: 2.18–3.02)	T stage, TNM stage, histology, survival	Lower values are associated with advanced T stage, higher TNM stage, presence of squamous cell carcinoma, and poor survival.
Post Lym/Pre Lym	Not statistically significant	–	–
Post Mono/Pre Mono	> 1.62	Postoperative hospital stay	Higher values are associated with longer hospital stay.
Inflammatory immune response change ratio	< 1.27 (range: 1.27–1.34)	T stage, TNM stage, ICU stay, morbidity, survival	Lower values are associated with advanced T stage, higher TNM stage, prolonged ICU stay, presence of morbidity, and poor survival.
Neutrophil dominance change ratio	< 4.04 (range: 4.04–4.89)	T stage, TNM stage, extent of lung resection, histology	Lower values are associated with advanced T stage, higher TNM stage, pneumonectomy, and presence of squamous cell carcinoma.

Discussion

Recent studies in the literature demonstrate a strong association between systemic inflammation and cancer-related morbidity and survival (5–8). For instance, markers such as the Systemic Inflammatory Response Index (SIRI) are simple, cost-effective, accessible, and practical tools that can be used to

reflect both local and systemic inflammatory responses across various cancer types (9). Moreover, the postoperative immune response is also known to have a significant relationship with both morbidity and survival outcomes (10,11).

Based on the hypothesis that the postoperative immune response may serve as a critical prognostic factor, our study emphasized the comparison between postoperative and preoperative immune markers. In our formulas for evaluating immune response, we used preoperative and postoperative values of neutrophils, leukocytes, lymphocytes, and monocytes, as well as the ratios between these parameters. The prospective study by Erus et al.—which focused more specifically on cellular immunity—did not find significant differences in immune parameters such as CD4 levels when comparing pre- and postoperative values across minimally invasive surgical groups (12). They only observed an increase in leukocyte count on the first postoperative day across all patients (12).

When demographic characteristics were examined, it was observed that, across the entire study population, women represented a smaller proportion of patients. Among female patients, adenocarcinoma, smaller tumors, and early-stage disease were more frequently encountered. Similarly, postoperative morbidity rates were also lower in women. In older patients, pneumonectomy was performed less frequently, survival rates were lower, and hospital readmission rates were higher. These findings are consistent with other studies in the literature that assess demographic characteristics, suggesting that the study population is comparable to the general population (13).

In the current literature, as in our study, the SIRI (Systemic Inflammatory Response Index) formula—commonly used to assess immune response based on hemogram parameters—is defined as neutrophil × monocyte / lymphocyte (9). In our study, we chose not to include monocyte counts in most of the ratio calculations due to the lack of available Charlson Comorbidity Index data for the patients. Considering that monocytes are closely associated with chronic diseases, we excluded them from the composite ratios except for the Post Mono/Pre Mono ratio, which was analyzed independently. The only context in which a monocyte-related parameter showed statistical significance in our study was in the group of patients with prolonged postoperative hospital stays (more than 8 days), where the Post Mono/Pre Mono ratio was found to be significantly higher. Sayan et al.'s recent study including video-assisted thoracoscopic surgery (VATS) lung resection patients focused on the standardized markers in postoperative morbidity prediction and found them valuable even for the minimally invasive approach (14).

In lung cancer, it is well established that larger tumor size, advanced stage, and high-risk procedures such as pneumonectomy—which are associated with greater morbidity and mortality—are indicative of a poorer prognosis. In our study, the preoperative assessment ratios, specifically Pre N/Leu and Pre N/Lym, were found to be higher in patients with these unfavorable prognostic features compared to the overall study population. These findings suggest that these ratios may possess predictive value even in the preoperative setting. Similarly, in the study by Sarraf et al., an elevated preoperative neutrophil-to-lymphocyte ratio (NLR) was shown to be associated with poor prognosis (7).

When prolonged ICU stay and the development of postoperative morbidity were evaluated, it was observed that the Pre N/Leu and Pre N/Lym ratios were higher in patients with extended ICU stays and those who developed morbidity. These findings suggest that, in addition to cancer-related parameters such as disease stage, these ratios may also have predictive value for the postoperative course (15). When postoperative ratios were assessed independently, the only parameter found to be statistically significant in our study was the Post N/Lym ratio. This ratio was higher in patients with larger tumors and in those who did not achieve five-year survival. Similarly, in the study by Tsukioka et al., which included patients with centrally located T3–T4 lung tumors, elevated Post N/Lym levels were also associated with poor prognosis (16).

Three key ratios were utilized to evaluate the impact of surgery on the immune system: the inflammatory immune response change ratio (defined as the postoperative/preoperative neutrophil-to-leukocyte ratio), the neutrophil dominance change ratio (postoperative/preoperative neutrophil-to-lymphocyte ratio), and the Post N/Pre N ratio. These parameters were specifically designed to reflect the immunological effect of surgical trauma. Analysis revealed that lower values across all three ratios were significantly associated with poor prognosis. In particular, reduced levels were linked to larger tumor size and more advanced disease stage. The neutrophil dominance change ratio was found to be lower in patients who underwent pneumonectomy, while the inflammatory immune response change ratio was lower in those with prolonged intensive care unit (ICU) stays. Regarding tumor histology, both the Post N/Pre N ratio and the neutrophil dominance change ratio were higher in adenocarcinoma cases and lower in patients with squamous cell carcinoma.

In patients who did not achieve five-year survival following surgery, both the Post N/Pre N ratio and the inflammatory immune response change ratio were found to be lower. These findings suggest that these two ratios may have predictive value in assessing postoperative long-term survival.

Limitations

This study has certain limitations, primarily its retrospective, single-center design and the specific timeframe of the patient cohort (2010–2017). Over the past decade, perioperative management has evolved significantly, particularly with the widespread adoption of ERAS protocols and minimally invasive techniques such as VATS and robotic-assisted thoracoscopic surgery (RATS). To control for the highly variable immunological impacts of these different approaches, our study deliberately restricted the cohort exclusively to open anatomical resections via thoracotomy. This strict inclusion criterion ensured a uniform, standardized degree of major surgical tissue trauma across all patients, thereby eliminating the confounding variables that arise when comparing open and minimally invasive approaches. Furthermore, while the cohort predates some modern anesthetic and perioperative pathways, the fundamental biological and systemic inflammatory responses to severe surgical stress remain constant. Therefore, evaluating this specific, uniformly treated cohort provides a pure, highly reliable baseline for establishing the prognostic value of CBC-derived immune ratios in major thoracic surgery.

Conclusion

In lung cancer, there is a growing need for predictive markers beyond TNM staging, particularly due to the lack of objective parameters that evaluate the impact of surgery on patients. The aim of our study was to explore whether immunological parameters found within CBC tests—already used in daily clinical practice—could offer insight into patient prognosis.

The answers we seek regarding the evaluation of lung cancer stage, the immunological impact of surgery, and the extent to which patients' preoperative immune profiles are influenced by their disease—and how all of these factors affect the disease course—may lie in places we often overlook. By emphasizing that the ratios examined in our study are derived from laboratory values routinely observed in daily practice, we propose that these markers could serve as useful predictive tools for clinicians when interpreted from this perspective.

Abbreviations

CBC
Complete Blood Count
NLR
Neutrophil-to-Lymphocyte Ratio
ICU
Intensive Care Unit
TNM
Tumor, Node, Metastasis
ROC
Receiver Operating Characteristic
AUC
Area Under the Curve

Declarations

Ethics approval and consent to participate:

This study was approved by Haydarpasa Numune Ethics Committee, Istanbul, Turkey *(Approval No:* NHEAH-KAEK2023/134, *Date*: 17/7/2023
Written informed consent was obtained from all patients prior to the procedures, including consent for the use of their clinical data for research purposes.
The study was conducted in accordance with the principles of the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional data protection policies but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Interpretation of data: All authors
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