Original Article

Circulomic variables predict pathologic staging preoperatively in treatment-naïve non-small cell lung cancer

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Background: Therapeutic decisions in non-small cell lung cancer (NSCLC) are stage-dependent, and, consequently, changes in an individual's stage carry potential for substantial alterations in management. Malignancy-related disturbances of the circulomic inflammatory environment may affect platelets quantitatively, ultimately leading to changes in tumor characteristics. Our objective was to identify circulomic characteristics associated with upstaging among chemotherapy-naïve patients with resected NSCLC and to assess the consequent impact on overall survival (OS).

Methods: A retrospective review of a prospectively maintained thoracic surgery database was performed, identifying chemotherapy-naïve patients who underwent resection of clinical stage I–III NSCLC between 1998 and 2021. Clinicopathologic characteristics were gathered; circulomic variables comprised of platelet and lymphocyte count from the last blood draw prior to resection. Platelet-to-lymphocyte ratio (PLR) was calculated. A multivariate model evaluated variables that might affect upstaging. Kaplan-Meier analysis was performed to assess OS.

Results: A total of 4,141 patients met inclusion criteria (median age: 67.0 years) among whom the sex distribution was fairly equal (2,189 female, 52.9%), and 1,016 (24.5%) individuals were upstaged. Patients with elevated PLR were found to have reduced risk of upstaging [odds ratio (OR): 0.757, 95% confidence interval (CI): 0.650–0.882]. Analyses revealed that median OS for patients who were upstaged was 80.0 months compared to 130.7 months among those who weren't upstaged (P<0.0001).

Conclusions: PLR appears to predict upstaging in treatment-naïve patients with resected NSCLC. In addition to clinicopathologic characteristics, circulomic variables may provide insight relating to pathologic staging prior to resection. These findings may guide patient counseling regarding survival probability, as well as referral patterns for adjuvant therapy.

Keywords: Staging; non-small cell lung cancer (NSCLC); circulomics; biomarkers

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Introduction

Current therapeutic strategies offered to patients with lung cancer are stage-dependent, emphasizing the importance of thorough and accurate clinical staging. In selecting patients for neoadjuvant therapy, an armamentarium of biomarkers may inform indicated treatment regimens; however, in patients who are managed with upfront surgery, adjuvant protocols often rely on pathologic stage and tumor

characteristics. Optimization of adjuvant therapy typically depends upon knowledge of both clinical and pathologic features, ultimately deferring to findings upon acquisition of tumor tissue for evaluation of the tumor microenvironment.

Despite advances in oncologic workup, clinical stage is not always concordant with pathological stage. Previous reports have suggested that stage discordance may occur between 14.3% (1) and 17.0% (2) of cases. These circumstances of stage incongruency between clinical and pathologic stages are of substantial consequence for patients, potentially changing their recommended plans of care as well as the prognoses with which they may have been provided.

Such instances of staging discordance may be consequent to issues that fall into two major categories. First, there may be errors in assessment due to limitations in clinical data, pathologic assays, radiologic strategies, or human judgment (3). Alternatively, pathologic upstaging may occur when patients have been appropriately staged clinically with subsequent disease progression during the interval prior to resection. A series of factors has been suggested to impact upstaging following resection, including surgical approach, extent of nodal harvest, or delay in surgical management (2).

Circulomic biomarkers have previously been shown to be associated with oncologic outcomes in lung cancer, specifically, circulating and infiltrating neutrophils, with previous authors showing poorer outcomes in patients with elevated neutrophil-to-lymphocyte ratio (NLR) (4-8) and tumor-infiltrating neutrophils (TIN) (9). Such observed relationships may be attributed to tumor-related inflammation, which, in turn, alters the host's immunologic milieu (6). As a corollary to the interest in circulomic evaluation, the platelet-to-lymphocyte ratio (PLR) has also been assessed, revealing that elevated PLR may be associated with poorer prognosis (10-15). Disturbance of the circulomic inflammasome from oncologic pressures may affect platelets in a quantitative manner, and ultimately lead to changes in tumor characteristics associated with disease overstaging or understaging.

Little is known regarding the association between systemic circulomic characteristics and disease progression leading to a change in disease stage, which may in turn result in substantial alterations in adjuvant management and prognostic discussions with patients. Thus, we sought to identify circulomic patterns, specifically relating to PLR, that may be associated with tumor upstaging following resection in patients who did not receive neoadjuvant systemic therapy. We aimed to elucidate such patterns in order to potentially raise attention to rigorous preoperative staging in such patients as well as to inform conversations surrounding oncologic outcomes, indications for adjuvant therapy, and postoperative surveillance plans. Additionally, we sought to assess the impact on survival outcomes associated with pathological upstaging among these patients. We hypothesized that we might find a PLR signature which would identify a subset of patients in whom risk of upstaging may be heightened, and in whom clinicians may adjust conversations to convey risks through patient-centered discussions. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-390/rc).

Highlight box

Key findings

- Patients with low platelet-to-lymphocyte ratio (PLR) should be counseled regarding potential adjuvant therapy.

What is known and what is new?

- A substantial portion of patients with non-small cell lung cancer (NSCLC) may be upstaged upon resection. Blood-based markers can inform the likelihood of upstaging patients with NSCLC.
- Elevated preoperative PLR is protective while low PLR increases risk of upstaging.

What is the implication, and what should change now?

- Pathologic upstaging may alter recommendations for multimodal therapy.

Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of University of Texas MD Anderson Cancer Center (Protocol No. 2023-0019). No informed consent was deemed necessary by our institutional review board given the retrospective nature of this work.

Patients were eligible for inclusion in this study if they underwent lung resection at MDACC between 1998 and 2021. Patients were included regardless of margin status, as this likely would not have impacted the incidence of upstaging. Patients were excluded if they received any neoadjuvant systemic therapy or radiotherapy. After identifying patients who met these inclusion criteria, clinicopathologic and operative characteristics were extracted from the departmental database.

Minimally invasive surgery (MIS) was defined as those

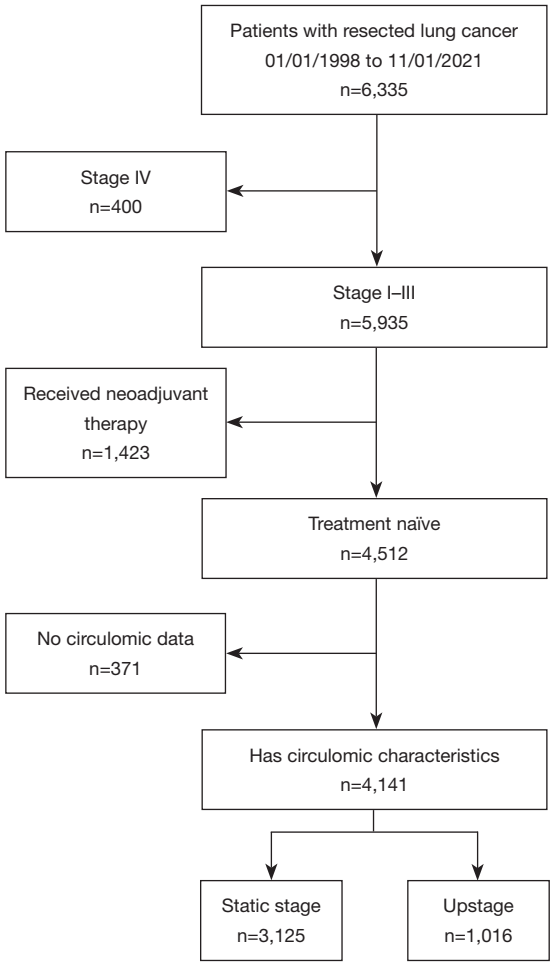

Figure 1 Consort diagram representing the patients included in this study.

resections performed via video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracic surgery (RATS). Circulomic variables including neutrophil, lymphocyte, and platelet count were obtained from the electronic health record, based on data from the peripheral blood draw closest to and prior to the date of resection. NLR and PLR were calculated based on previously published reports defining these biomarkers as correlates of the systemic inflammasome in thoracic oncology (4,5,12,16). Clinical and pathological stages were defined using the 8th edition of the American Joint Commission on Cancer (17) using available tumor characteristics from the electronic medical record. The pre-operative therapy strategy was based on clinical staging, expert thoracic surgeon opinion, and multidisciplinary discussions as appropriate. It is routine in our practice to perform positron emission tomography-computed tomography (PET-CT), brain magnetic resonance imaging (MRI), and histologic mediastinal nodal staging for clinical staging. Total nodal stations examined and number of lymph-nodes assessed were retrieved from our database. The primary outcome was the rate of pathologic upstaging, defined as an increase in stage following resection, compared to the stage defined clinically.

Statistical analysis

Categorical and continuous variables were evaluated individually using chi-squared tests, or parametric and non-parametric statistical tests, respectively. A multivariate model was built to investigate covariates that impacted the likelihood of being upstaged. Covariates were included in the model if univariate analysis revealed their associated value was below a threshold of 0.200. The model was then further narrowed using backward elimination using a P value threshold of 0.100. Collinearity amongst the included covariates was assessed using variance inflation factors. The analysis was corrected for surgical era. Kaplan-Meier analysis was performed to assess the survival difference between patients who were upstaged and those who were not. All statistical analyses were performed using GraphPad Prism (version 9.3.1 for Windows, GraphPad Software, San Diego, CA, USA) and R Studio (version 1.4.1717, PBC, Boston, MA, USA).

Results

Baseline characteristics

There were 4,141 patients who met inclusion criteria, among whom 24.5% (n=1,016) were upstaged following resection (*Figure 1*). The median age of the whole cohort was 67.0 years [interquartile range (IQR): 59.7–73.6], and the majority of patients were female (n=2,189, 52.9%). Prior or current smoking was quite common, with nearly three-quarters of the patients being smokers (n=3,090, 74.6%). Clinical staging most commonly reflected early disease, with stage cI and II accounting for 2,917 (70.4%) and 995 (24.0%) patients, respectively). The most frequent histopathology was adenocarcinoma (n=2,458, 59.4%), followed by squamous carcinoma (n=953, 23.0%). Tumors were most often moderately differentiated (n=1,832, 44.2%), followed by those that were poorly differentiated (n=1,089, 26.3%) (*Table 1*).

Table 1 Clinicopathologic and operative characteristics of the included cohort

Characteristics	Total cohort	Static stage	Pathologic upstage	P value
Included patients	4,141 (100.0)	3,125 (75.5)	1,016 (24.5)	
Age, years	67.0 [59.7–73.6]	67.0 [59.7–73.5]	66.9 [59.7–73.7]	0.744
Female sex	2,189 (52.9)	1,691 (54.1)	518 (51.0)	0.005
Smoking exposure	3,090 (74.6)	2,307 (73.8)	783 (77.1)	0.039
Clinical stage				<0.001
I	2,917 (70.4)	2,142 (68.5)	775 (76.3)	
II	995 (24.0)	761 (24.4)	234 (23.0)	
III	229 (5.5)	222 (7.1)	7 (0.7)	
Receipt of mediastinoscopy	390 (9.4)	277 (8.9)	113 (11.1)	0.032
NLR	2.34 [1.72–3.26]	2.35 [1.73–3.26]	2.33 [1.70–3.28]	0.930
PLR	134 [103–180]	135 [104–180]	131 [100–179]	0.132
Histopathology				0.090
Adenocarcinoma	2,458 (59.4)	1,828 (58.5)	630 (62.0)	
Squamous carcinoma	953 (23.0)	742 (23.7)	211 (20.8)	
Other	730 (17.6)	555 (17.8)	175 (17.2)	
Extent of resection				<0.001
Wedge	271 (6.5)	231 (7.4)	40 (3.9)	
Segmentectomy	323 (7.8)	280 (9.0)	43 (4.2)	
Lobectomy	2,622 (63.3)	1,963 (62.8)	659 (64.9)	
Extra-lobar or other	925 (22.3)	651 (20.8)	274 (27.0)	
Receipt of MIS	1,364 (32.9)	1,097 (35.1)	267 (26.3)	<0.001
Tumor size (cm)	2.60 [1.80–4.00]	2.50 [1.70–3.60]	3.20 [2.20–4.50]	<0.001
LVI	819 (19.8)	458 (14.7)	361 (35.5)	<0.001
NVI	83 (2.0)	38 (1.2)	45 (4.4)	<0.001
Nodal stations examined	4 [2–5]	4 [2–5]	4 [3–5]	0.004
Lymph-nodes examined	11 [5–17]	10 [4–16]	13 [7–19]	<0.001
Differentiation				<0.001
Well	918 (22.2)	777 (24.9)	141 (13.9)	
Moderate	1,832 (44.2)	1,351 (43.2)	481 (47.3)	
Poor	1,089 (26.3)	774 (24.8)	315 (31.0)	
Undifferentiated	7 (0.2)	4 (0.1)	3 (0.3)	
Not reported	248 (6.0)	188 (6.0)	60 (5.9)	

Dara are presented as n (%) or median [IQR]. NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MIS, minimally invasive surgery; LVI, lymphovascular invasion; NVI, neurovascular invasion; IQR, interquartile range.

Table 2 Logistical regression model investigating clinicopathologic and circulomic variables that impact upstaging in chemotherapy naïve patients with resectable non-small cell cancer

Variables	Univariable		Multivariable	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
PLR (> median)	0.854 (0.741–0.984)	0.029	0.757 (0.650–0.882)	<0.001
Ever smoker	1.192 (1.009–1.408)	0.039	1.202 (0.999–1.446)	0.051
Tumor size (increasing)	1.178 (1.140–1.218)	<0.001	1.154 (1.113–1.197)	<0.001
Extent of resection				
Wedge resection	Reference		Reference	
Segmentectomy	0.887 (0.557–1.141)	0.612	0.900 (0.559–1.450)	0.665
Lobectomy	1.939 (1.370–2.743)	<0.001	1.606 (1.117–2.310)	0.011
Other	2.431 (1.689–3.498)	<0.001	1.875 (1.250–2.813)	0.002
Receipt of minimally invasive surgery	0.659 (0.563–0.772)	<0.001	0.810 (0.675–0.972)	0.023
Histopathology				
Adenocarcinoma	Reference		Reference	
Squamous cell carcinoma	0.825 (0.691–0.968)	0.034	0.616 (0.506–0.751)	<0.001
Other	0.915 (0.755–1.109)	0.365	0.866 (0.700–1.070)	0.182
LVI	3.209 (2.729–3.775)	<0.001	2.909 (2.449–3.454)	<0.001
NVI	3.765 (2.430–5.833)	<0.001	2.955 (1.851–4.719)	<0.001

CI, confidence interval; PLR, platelet to lymphocyte ratio; LVI, lymphovascular invasion; NVI, neurovascular invasion.

Prior to resection, histologic mediastinal staging was performed in 1,071 (25.9%). This staging was achieved via mediastinoscopy in 9.4% (n=390) and endobronchial ultrasonography (EBUS) in 17.4% (n=721). It is important to note that 3,070 (74.1%) patients did not undergo any invasive mediastinal nodal staging procedures prior to resection, which certainly has implications for the accuracy of preoperative clinical staging. Pulmonary resections were performed via MIS in 32.9% of cases (n=1,364). The most frequent extent of resection was lobectomy (n=2,622, 70.8%), with 594 (14.3%) patients undergoing sublobar resection, 114 (3.1%) undergoing bilobectomy, and 70 (1.9%) undergoing pneumonectomy. The median tumor size resected was 2.60 cm (IQR: 1.80–4.00 cm). Lymphovascular invasion (LVI) was present on final surgical specimens in 19.8% (n=819) cases, while neurovascular invasion (NVI) was identified in 83 (20%) cases.

Predictors of pathologic upstaging

Univariate analysis revealed that patients who were upstaged following resection were more likely to be male, to have a smoking history, and to have earlier clinical stages of disease compared to patients who were not upstaged (*Table 1*). Interestingly, patients who underwent mediastinoscopy were more frequently upstaged, suggesting perhaps clinical factors or uncaptured nuances that led the clinicians to seek a more rigorous form of invasive mediastinal staging compared to EBUS or noninvasive mediastinal staging. We also found that the use of open surgery compared to minimally invasive techniques was more frequently associated with upstaging, again suggesting the potential presence of surgical gestalt for identifying theoretically more aggressive or advanced tumors. Larger-sized cancers, those which were found to have adenocarcinoma histopathology, and those which required extended resections (greater than lobe) were also found to be upstaged more commonly. The median number of stations assessed in both cohorts was 4 (IQR not upstaged: 2–5, IQR upstaged: 3–5, P=0.004). The median number of assessed lymph-nodes in patients who were not upstaged was 10 (IQR: 4–16) compared to 13 (IQR: 7–19, P<0.001) in those who were upstaged. Lastly, tumors that were moderately or poorly differentiated, or

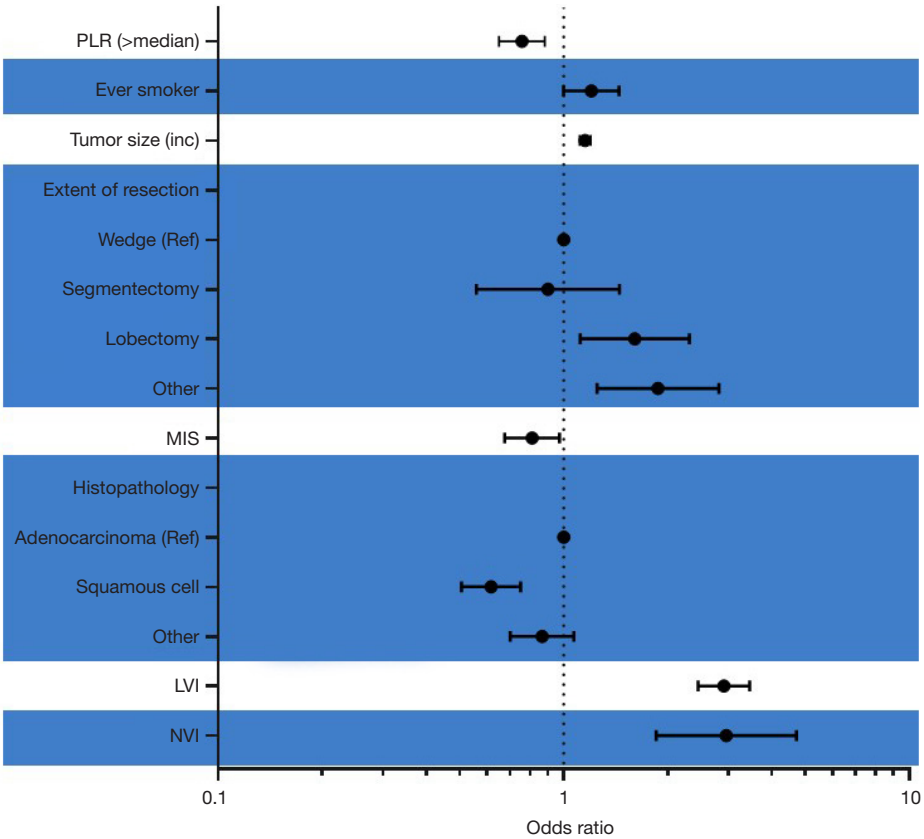

Figure 2 Forest plot representing binomial Logistical Regression model investigating clinicopathologic and circulomic variables that impact upstaging in chemotherapy naïve patients with resectable non-small cell cancer. PLR, platelet to lymphocyte ratio; inc, increasing; Ref, reference; MIS, receipt of minimally invasive surgery; LVI, lymphovascular invasion; NVI, neurovascular invasion.

those with positive LVI or NVI were also more likely to be upstaged, which may emphasize the fact that upstaging can be consequent to disease progression of more aggressive tumors—not just inadequate clinical staging.

Multivariate analysis revealed that elevated PLR was associated with lower likelihood of upstaging [odds ratio (OR): 0.757, 95% confidence interval (CI): 0.650–0.882]. Risk factors for upstaging included increasing tumor size (OR: 1.154, 95% CI: 1.113–1.197), requiring a lobectomy or non-sublobar resection (OR: 1.606, 95% CI: 1.117–2.310 and OR: 1.875, 95% CI: 1.250–2.813, respectively), presence of LVI or NVI (OR: 2.909, 95% CI: 2.449–3.454, and OR: 2.955, 95% CI: 1.851–4.719, respectively). In addition to elevated PLR, protective factors comprised of squamous histology (OR: 0.616, 95% CI: 0.506–0.751), and receipt of MIS (OR: 0.810, 95% CI: 0.675–0.972) (*Table 2*, *Figure 2*).

Survival analysis

Kaplan-Meier analysis showed that median overall survival (OS) was 80.0 (95% CI: 69.5–88.8) months for patients who were upstaged following resection, which was significantly lower (P<0.0001) than in patients who had the same clinical and pathological stage, who obtained a median OS of 130.7 (95% CI: 123.9–141.4) months (*Figure 3*).

Discussion

While a plethora of clinical, pathologic, and operative characteristics may inform the likelihood of patients being upstaged following resection for lung cancer, we have shown that circulomic variables prove useful in increasing the accuracy of this prediction. Specifically, we have demonstrated that elevated PLR may correlate with less aggressive tumors, or a robust inflammatory response

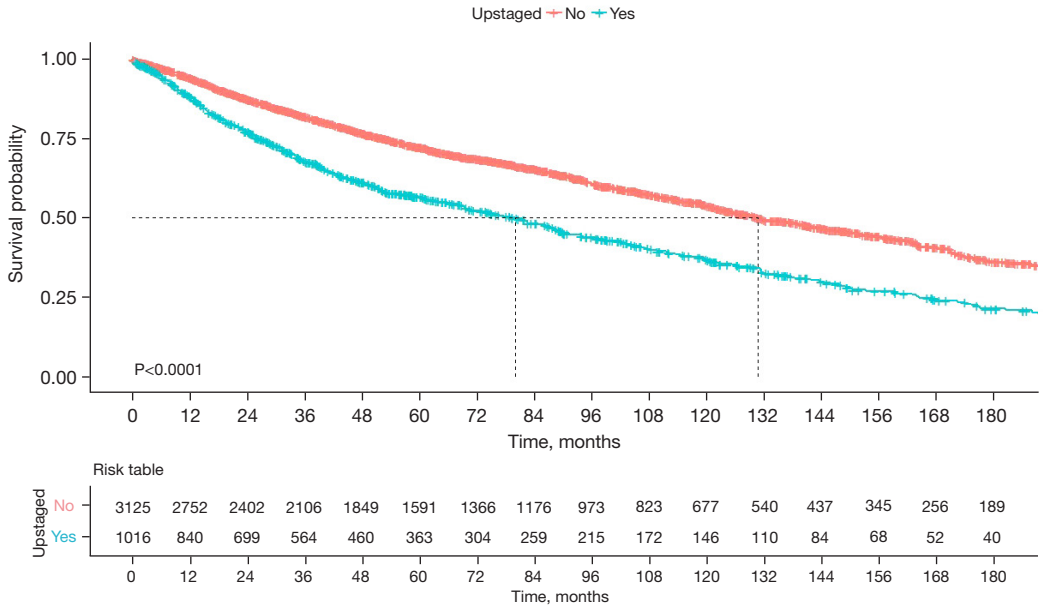

Figure 3 Kaplan-Meier analysis assessing the survival difference between patients who were upstaged following resection of non-small cell lung cancer, and those who were not.

to oncogenesis, corresponding to a lower likelihood of upstaging in patients who did not receive any neoadjuvant systemic therapy. As such, circulomic markers may be used in the pre-operative period to augment decisions regarding staging workup, as well as to guide patient-centered discussions regarding expectations as they relate to potential future recommendations for adjuvant therapy and ultimate prognosis.

In previous work, PLR has been investigated as a predictor of oncologic outcome, having been associated with worsened OS in patients with non-small cell lung cancer (NSCLC) (5). However, a large meta-analysis reported that elevated PLR had minimal effect on progression free survival (13). The role of platelets in carcinogenesis continues to be explored, with potential mechanisms surrounding angiogenesis and the cytokine secretory status of platelets. Platelets have previously been found to influence immune cell migration and cytokine expression via platelet-derived S1P18. This mechanism may contribute to our findings. Multiple analyses investigating the role of PLR as a biomarker in patients with NSCLC managed with immune checkpoint blockade have shown a lower response to therapy in patients with elevated PLR (10,11,15,18). As PLR is believed to correlate with perioperative inflammation, it is possible that an elevated PLR in therapy-naïve patients signifies an inflammatory response to the oncogenic process, limiting its progression.

Importantly, in addition to non-modifiable factors, certain precautions may be utilized in order to ensure appropriate pathological staging, such as meeting a standard of surgical quality of care. Surgical approach can impact rates of upstaging, with rates of nodal upstaging being higher in patients managed via thoracotomy or RATS compared to VATS (19,20); however, this may also be attributed to patient selection bias, founded on surgeon experience and consequent clinical decision making (21-23). A future strategy that merits investigation might be to select patients with advanced features characterizing aggressive disease to undergo anatomical resection. This may permit the appropriate evaluation of regional lymph nodes which may also be associated with higher rates of upstaging as reported by Bott and colleagues in a study where median nodes harvested were 10.9 in upstaged patients compared to 8.2 in patients with stage-concordant disease (2). Ultimately, systematic lymph node assessment in MIS (and all curative-intent resection) should be utilized to ensure adequate lymphadenectomy (24).

Pre-operative work-up may also impact the likelihood of pathologic upstaging, including more extensive or more rigorous mediastinal lymph node evaluation. Patients

may undergo mediastinoscopy, Chamberlain procedures, EBUS, endoscopic ultrasound guided, or thoracoscopic biopsies (25). These approaches may be associated with disease-specific factors, center-specific guidelines, available resources, or clinical gestalt regarding which patients may benefit from a more advanced pre-operative workup. In addition to molecular assessment and pathologic characteristics (26), an advanced models may improve prognostication of patients with resectable NSCLC, and may augment staging systems in the future (27).

In the modern era, the accuracy of clinical staging can have significant repercussions on clinical trial eligibility. As the number of clinical trials in lung cancer available for all stages of disease continues to increase (28), investigating both adjuvant and neoadjuvant therapies, appropriate staging paradigms remains paramount. As such, complimenting the current staging system with circulomic (29) and genomic (30) characteristics, or high may further stratify patients for future clinical trials, permitting the correlation of outcomes with patient-specific immunologic milieus.

Certain limitations associated with our study must be acknowledged. First, the length of the study's timeline necessitated the stratification by surgical era within the multivariate models to correct for changes in surgical approach. While controlling for surgical era, there may remain confounders that are associated with the year of resection. Furthermore, the time to resection was difficult to assess in this large cohort due to the absence of recorded biopsy dates for many patients. Additionally, the mechanistic nature of the association between PLR and disease progression remains to be explored. Circulomic characteristics may also correlate with tumor characteristics such as LVI or PNI, and further research is warranted to evaluate this association. Lastly, the presence of circulome modifying diseases, such as hematologic or infectious disorders, were not captured in this study, but could potentially have confounded our results.

Factors that may help inform patients most at risk of having an increase in stage following resection include circulomic characteristics such as decreased PLR, increased tumor size, receipt of thoracotomy, non-squamous-cell histopathology, and lymphovascular or NVI. Ultimately, once patients have been upstaged, multidisciplinary discussion should be employed as an important clinical tool, to strategize a robust adjuvant management (31), and to facilitate timely management of the upstaged pathology (32).

Conclusions

Patients with NSCLC who are managed with upfront surgery should be evaluated for blood marker disturbances such as elevated or decreased PLR, in order to augment patient-centered discussions surrounding the possible need for adjuvant therapy.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-390/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-390/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-390/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-390/coif). RR serves as an unpaid editorial board member of *Journal of Thoracic Disease* from April 2023 to March 2025. MBA serves as an unpaid editorial board member of *Journal of Thoracic Disease* from August 2021 to July 2024. ND and ME are supported by the Mason Family Philanthropic Research Fund. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of University of Texas MD Anderson Cancer Center (Protocol No. 2023-0019). No informed consent was deemed necessary by our institutional review board given the retrospective nature of this work.

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