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Validation for revision of the stage IIIA(T1N2) in the forthcoming ninth edition of the TNM classification for lung cancer

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Abstract

Objectives The 9th edition of the lung cancer tumor-node-metastasis (TNM) staging system downgrades certain non-small cell lung cancer (NSCLC) patients from stage IIIA (T1N2) to IIB(T1N2a). This study aimed to externally validate this stage adjustment.

Methods Consecutive resected stage IIB and IIIA (the 9th edition of lung cancer TNM staging manual) NSCLC patients were included. Stage IIB was divided into groups A, B, and C according to lymph node involvement. Group A, patients who having single-station N2 without N1 involvement; Group B, patients who having single-station N2 with N1 involvements; Group C, patients who having station N1 involvement or N0. The stage IIIA patients divided into Group D. Overall survival (OS) and disease-free survival (DFS) were compared using the Kaplan-Meier method, with propensity score matching (PSM) employed to mitigate potential biases. COX regression models were utilized to assess prognostic differences.

Results 224 stage IIB and 227 stage IIIA cases was included. There were 38, 66 and 120 patients in the Group A, B and C, respectively. Univariate COX analysis indicated comparable prognoses between the Group A and Group C patients, whereas Group B patients exhibited poorer outcomes. Upon combining the Group A and Group C patients, multivariate COX analysis demonstrated a significantly worse prognosis for Group B patients compared to those with Group A + C patients (OS, $P = 0.035$; DFS, $P = 0.021$). Further comparisons between Group B and Group D patients, following PSM analysis, indicated similar survivals (OS: $P = 0.390$; DFS: $P = 0.210$).

Conclusion In the 9th edition of the lung cancer TNM staging system, the prognosis of stage IIB N2a2 patients was worse than that of remaining stage IIB patients but comparable to that of stage IIIA patients. We proposed that stage IIB N2a2 patients should be maintained as stage IIIA.

†Tong Wu and Jingsheng Cai contributed equally to this work and share the first authorship.

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Keywords Non-small cell lung cancer, Stage IIB, Stage IIIA, Prognosis, The 9th edition of the lung cancer TNM staging system

Introduction

Lung cancer is the most malignant tumor with the highest incidence and mortality in the world [1]. Non-small cell lung cancer (NSCLC) constitutes approximately 85% of cases [2]. The lung cancer tumor-node-metastasis (TNM) staging manual, proposed by the International Association for the Study of Lung Cancer, serves as the cornerstone for the standardized treatment of patients with NSCLC [3, 4].

In 2024, the 9th edition of TNM staging manual for lung cancer [3] was released, maintaining the existing T staging without alterations. However, notable updates were made to N staging, introducing N2 subcategories (N2a: single-station N2 metastasis; N2b: multi-station N2 metastasis) [3]. Additionally, the M staging was further refined, with M1c now subdivided into M1c1 (multiple extra-thoracic metastases in one organ) and M1c2 (multiple extra-thoracic metastases in multiple organs) [3, 5]. From the TNM staging standpoint, T1N1, formerly assigned to stage IIB, has been reclassified to stage IIA. Conversely, T1N2, previously designated as stage IIIA, has been subdivided into T1N2a (stage IIB) and T1N2b (stage IIIA) [3].

The revisions introduced in the latest staging edition necessitate external validation to confirm their accuracy and generalizability. Within this manuscript, we direct our attention to a specific subgroup of patients transitioning from stage IIIA to IIB (T1N2a). Previous studies suggested that skip N2 metastasis is associated with improved survivals in N2 lung cancer [6–9]. Therefore, we further separated stage IIB patients into three subgroups: Group A, patients who having single-station N2 without N1 involvement; Group B, patients who having single-station N2 with N1 involvements; Group C, patients who having station N1 involvement or N0. In this study, we set out to investigate potential prognostic differences among stage IIB NSCLC patients and further externally validate the stage IIB classification in the 9th edition of lung cancer TNM staging manual.

Materials and methods

Study population

We systematically reviewed the clinical records of 7,931 patients diagnosed with pulmonary malignant tumors in our department between 1999 and 2018 (PKUPHTOI dataset). This well-managed dataset has been used before [10–13]. Inclusion criteria were as follows: (1) Diagnosis of NSCLC; (2) Underwent surgical resection; (3) stages IIB and IIIA (the 9th edition of lung cancer TNM staging manual). Exclusion criteria comprised: (1) Age < 18 years; (2) Presence of N3 disease; (3) Presence of M1 disease; (4) R1/R2 resection; (5) Su-blobar resection; (6) Non-systematic lymph node dissection; (7) Primary lung cancer; (8) Receipt of neoadjuvant therapy; (9) History of previous malignancies; (10) Unavailability of clinicopathological data. Finally, a total of 2051 eligible patients were enrolled, including 224 stage IIB patients and 227 stage IIIA patients. Figure 1 illustrates the patient selection process. Based on the lymph node metastasis status, the stage IIB patients were further divided into three categories: Group A, Group B, and Group C. The stage IIIA patients divided into Group D.

Surgical procedure

We included only patients who underwent radical surgical resection and systemic mediastinal lymph node dissection to ensure accurate N staging. The standard protocol of surgery was similar to the one previously described by Xu et.al [14]. Systemic lymphadenectomy was defined as mediastinal lymph node dissection of at least 3 stations, including station 7 (the subcarinal lymph node), from station 4 L, 5, 6, 7, 8 and 9 for the left-side NSCLCs and station 2R, 3 A, 4R, 7, 8 and 9 for the right-side NSCLCs. In addition, at least 6 lymph nodes were harvested. As for N1 station lymph nodes, in routine, the station 10, 11 and 12 were dissected intraoperatively. The station 13 and 14 lymph nodes were dissected by resident doctors from the excised specimen, but this procedure was not mandatory.

Follow-up

Routine follow-up strategies were conducted as previously reported [12]. Follow-up data were collected through medical record reviews, patient consultations, and telephonic interviews. Our center adheres to a rigorous postoperative follow-up protocol, involving assessments every three months during the initial two years post-surgery, biannually for the subsequent three to five years, and annually thereafter. Each follow-up includes physical examinations, serum tumor marker monitoring, and chest CT scans, with additional imaging performed as clinically indicated. The primary endpoints of this study were overall survival (OS) and disease-free survival (DFS). OS was defined as the period from the date of diagnosis to all-cause death or the date of last follow-up. DFS was defined as the period from the date of diagnosis to the date of disease recurrence, death or the last follow-up.

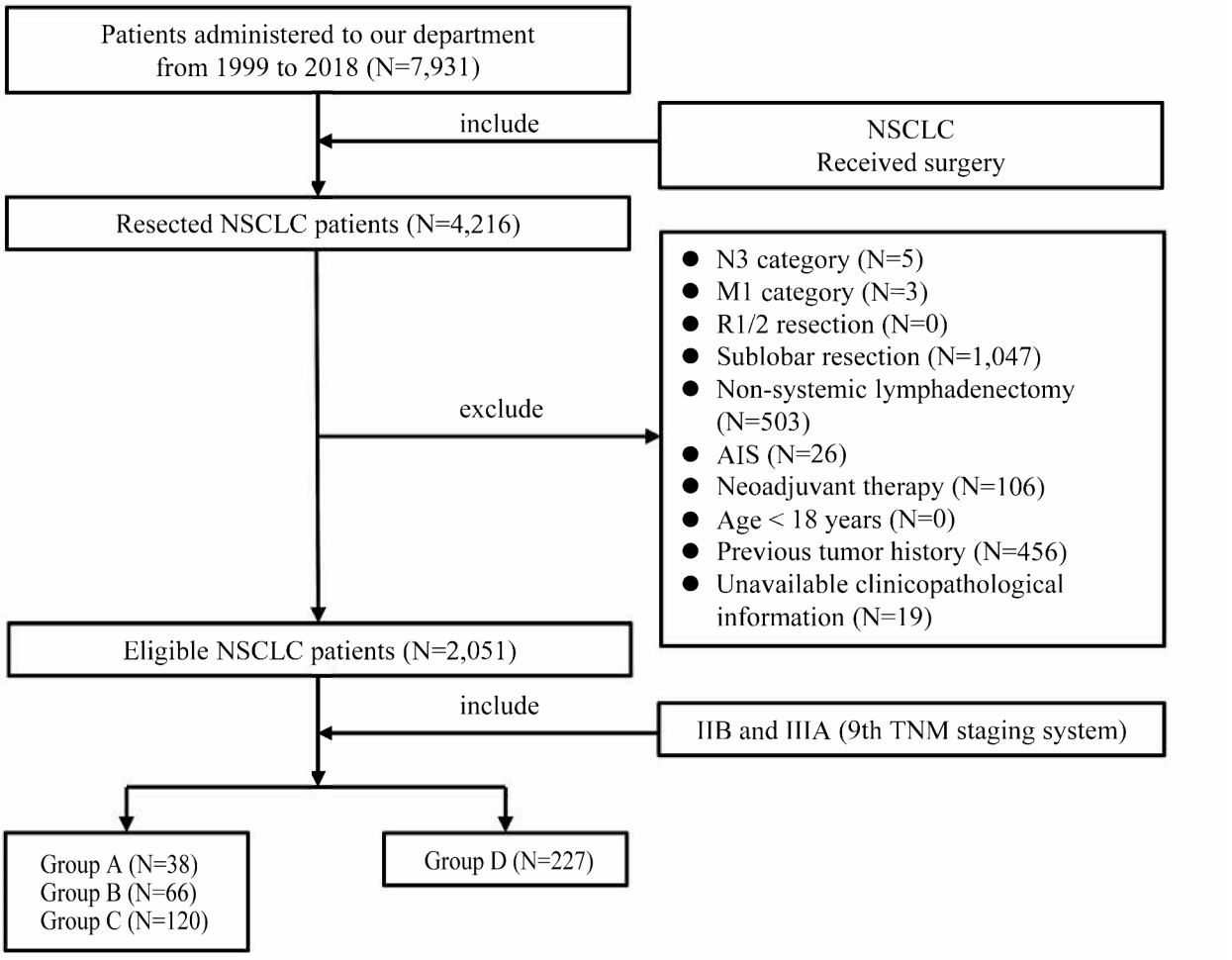


Fig. 1 The patient selection flow chart. NSCLC, non-small cell lung cancer; TNM, tumor-node-metastasis classification system; AIS, adenocarcinoma in situ

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics (version 27.0.1, IBM Corp, Armonk, NY, USA) and R version 4.3.1 (The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org). Categorical variables were presented as frequencies and percentages and compared using Pearson's chi-square test or Fisher's exact test. The Shapiro-Wilk test was utilized to assess whether data follows a normal distribution. Non-normally distributed continuous variables were described using medians and ranges and compared using the Mann-Whitney U test. Survival rates were assessed using the Kaplan-Meier method and the log-rank test. Bonferroni's adjustment was applied in comparisons involving multiple subgroups in the 1:1 analysis. To mitigate bias arising from disparate baseline characteristics, one-to-one propensity score matching (PSM) was performed utilizing the R package "MatchIt" (method = nearest, replace = FALSE). Univariate and multivariate Cox proportional hazards regression analysis (forced enter method) was employed to explore the prognostic factors, with hazard ratios (HR) and 95% confidence intervals (CI) serving as statistical indicators to ascertain independent prognostic factors. The proportional hazards assumption was checked using the Schoenfeld residuals. A two-tailed P value < 0.05 was considered statistically significant.

Results

Clinicopathological characteristics

Based on the aforementioned inclusion and exclusion criteria, a total of 2,051 eligible patients were identified, among which 224 were classified as stage IIB and 227 were classified as stage IIIA. There were 38 patients in Group A, 66 in Group B, and 120 in Group

C. The clinicopathological characteristics of the stage IIB patients are summarized in Table 1. The median age was 63 years (range: 32–86 years), with a predominance of male patients (72.8%). Patients in the Group B exhibited a higher incidence of adenocarcinoma histology ($P < 0.001$), VPI ($P = 0.02$), LVI ($P = 0.001$), and postoperative complications ($P = 0.007$) compared to the other two subgroups. Additionally, a higher proportion of patients in the Group B received postoperative adjuvant therapy ($P = 0.004$).

Patients in Group B and D were matched using PSM method, resulting in 66 well-matched pairs. The clinicopathological characteristics between Group B and Group D patients were well balanced after PSM (Table 2).

Prognosis analysis

Pairwise comparisons of survival among Groups A, B, and C using Kaplan-Meier and Bonferroni correction showed that Group B patients had the worst OS (5-years OS rate: 73.0% vs. 59.5% vs. 62.7%, $P = 0.078$, Fig. 2A; 5-years DFS rate: 65.5% vs. 35.5% vs. 56.6%, $P = 0.007$, Fig. 2B), while there was no difference in either OS or DFS between Group A and Group C patients (5-years OS rate: $P = 0.439$; 5-years DFS rate: $P = 0.398$). These results were further supported by univariate results (OS: Fig. 2C; DFS: Fig. 2D).

Based on the aforementioned findings, we further combined Group A and Group C into Group A + C, again compared with Group B, showing a significant difference in both DFS and OS between these two groups (5-year OS rate: 65.2% vs. 59.5%, $P = 0.03$, Fig. 3A; 5-year DFS rate: 58.8% vs. 35.5%, $P = 0.002$, Fig. 3B). The Cox analysis (Univariable: Table S1; Multivariable: Table S2) further confirmed that patients in the Group A + C had better prognosis than those in Group B (OS HR: 1.556, $P = 0.035$, Fig. 3C, Table S1; DFS HR: 1.626, $P = 0.021$; Fig. 3D, Table S2).

Prognostic comparisons between Group B and Group D patients

The survival outcomes of patients in the Group B and D were compared. Before PSM, there was no significant disparity in survivals between these two groups (OS: $P = 0.727$, Fig. 4A; DFS: $P = 0.482$, Fig. 4B). After PSM, the survival rates between the two groups remained statistically similar (5-year OS rate: 59.5% vs. 56.4%, $P = 0.390$, Fig. 4C; 5-year DFS: 35.5% vs. 46.2%, $P = 0.210$ Fig. 4D). Univariate Cox analysis further indicated no significant differences in OS and DFS between the two groups (OS:$P = 0.391$, Fig. 5A, Table S3; DFS:$P = 0.212$, Fig. 5B, Table S4).

Discussion

Our research team possesses a wealth of experience in the refinement of lung cancer TNM staging, having actively contributed to the advancement of previous iterations [13, 15–21]. We have previously observed variations in prognosis among NSCLC patients within the same TNM stage [16–19]. In this study, we aimed to assess prognostic differences among NSCLC patients in different stage IIB subgroups based on the 9th edition TNM staging criteria. Our findings revealed that the prognosis of stage IIB N2a2 (single-station N2 with N1 involvements) patients were significantly inferior to that of other stage IIB patients but comparable to that of stage IIIA patients. Consequently, we proposed that part of stage IIB (N2a2) patients should be maintained as stage IIIA. However, further validation is warranted to corroborate our conclusion.

As of now, there has been no research exploring and validating the rationality of downstaging certain patients, such as T1N2a patients, in the 9th edition TNM staging criteria. Our study specifically focuses on this patient subset and utilizes our center's well-maintained data to validate this new staging adjustment. Following rigorous statistical analyses including multivariate Cox analysis and PSM, our study innovatively proposed that patients with T1N2a1 diseases should indeed be down-staged to stage IIB, consistent with the 9th edition TNM staging criteria. However, patients with T1N2a2 diseases should remain classified as stage IIIA. Our research holds significant clinical implications, as accurate TNM staging constitutes the fundamental cornerstone for guiding subsequent patient management strategies. Our findings raise the possibility that certain NSCLC patients classified as stage IIB according to the 9th edition TNM staging criteria may be underestimated. The imprecise staging might ultimately have detrimental effects on their treatment and surveillance. For instance, in clinical practice, when physicians encounter patients with stage T1N2a2, they classify these patients as stage IIB. Relative to the previous classification as stage IIIA, clinicians might incline toward recommending less aggressive treatment modalities and less intensive surveillance strategies to these patients. However, such approaches may unfavorably impact the prognosis of these individuals.

In previous studies, several clinical series have reported the favorable prognosis of skip metastasis (N2a1) [6–9]. Therefore, it is necessary to further investigate the prognosis of patients with skip metastasis (N2a1) and sequential metastasis (N2a2) among those diagnosed with stage IIB (N2a). Our results were consistent with prior studies that the prognostic

Table 1 The baseline characteristics of the included stage IIB NSCLC patients

Characteristic	Group A (*n* = 38)	Group B (*n* = 66)	Group C (*n* = 120)	*P*
Sex				0.124
Male	26 (68.4%)	43 (65.2%)	94 (78.3%)	
Female	12 (31.6%)	23 (34.8%)	26 (21.7%)	
Age, years				0.103[a]
Median (range)	60.5 (37–86)	61 (37–81)	64.5 (32–80)	
Smoking				0.083
No	21(55.3%)	33(50.0%)	45(37.5%)	
Yes	17(44.7%)	33(50.0%)	75(62.5%)	
Family tumor history				0.110
Without	38 (100%)	60 (90.9%)	107 (89.2%)	
With	0 (0.0%)	6 (9.1%)	13 (10.8%)	
Preoperative comorbidity				0.239
Without	14 (36.8%)	23 (34.8%)	56 (46.7%)	
With	24 (63.2%)	43 (65.2%)	64 (53.3%)	
BMI				0.328[b]
< 18.5	1 (2.6%)	2 (3.0%)	5 (4.2%)	
18.5–24	13 (34.2%)	29 (43.9%)	62 (51.7%)	
>=24	24 (63.2%)	35 (53.0%)	53 (44.2%)	
ASA grade				0.573[b]
1	5 (13.2%)	13 (19.7%)	26 (21.7%)	
2	30 (78.9%)	52 (78.8%)	87 (72.5%)	
3	3 (7.9%)	1 (1.5%)	6 (5.0%)	
4	0 (0.0%)	0 (0.0%)	1 (0.8%)	
Surgical type				<0.001
Thoracoscope	32 (84.2%)	58 (87.9%)	73 (60.8%)	
Thoracotomy	6 (15.8%)	8 (12.1%)	47 (39.2%)	
Surgical extent				0.146[b]
Lobectomy	34 (89.5%)	60 (90.9%)	95 (79.2%)	
Bi-lobectomy	3 (7.9%)	5 (7.6%)	13 (10.8%)	
Pneumonectomy	1 (2.6%)	1 (1.5%)	12 (10.0%)	
Histology				<0.001
Adenocarcinoma	28 (73.7%)	54 (81.8%)	44 (36.7%)	
Squamous	9 (23.7%)	8 (12.1%)	64 (53.3%)	
Other	1 (2.6%)	4 (6.1%)	12 (10.0%)	
VPI				0.020
Without	30 (78.9%)	34 (51.5%)	77 (64.2%)	
With	8 (21.1%)	32 (48.5%)	43 (35.8%)	
LVI				0.001
Without	27 (71.1%)	36 (54.5%)	96 (80.0%)	
With	11 (28.9%)	30 (45.5%)	24 (20.0%)	
Postoperative complications				0.007[b]
Without	35 (92.1%)	60 (90.9%)	119 (99.2%)	
With	3 (7.9%)	6 (9.1%)	1 (0.8%)	
Adjuvant therapy				0.004
Not performed	17 (44.7%)	19 (28.8%)	65 (54.2%)	
Performed	21 (55.3%)	47 (71.2%)	55 (45.8%)	

a Kruskal-Wallis H test

b Fisher's exact test

Group A, patients who having single-station N2 without N1 involvement; Group B, patients who having single-station N2 with N1 involvements; Group C, patients who having station N1 involvement or N0.BMI, body mass index; ASA, American society of anesthesiologist physical status classification system; VPI, visceral pleural invasion; LVI, lympho-vascular invasion

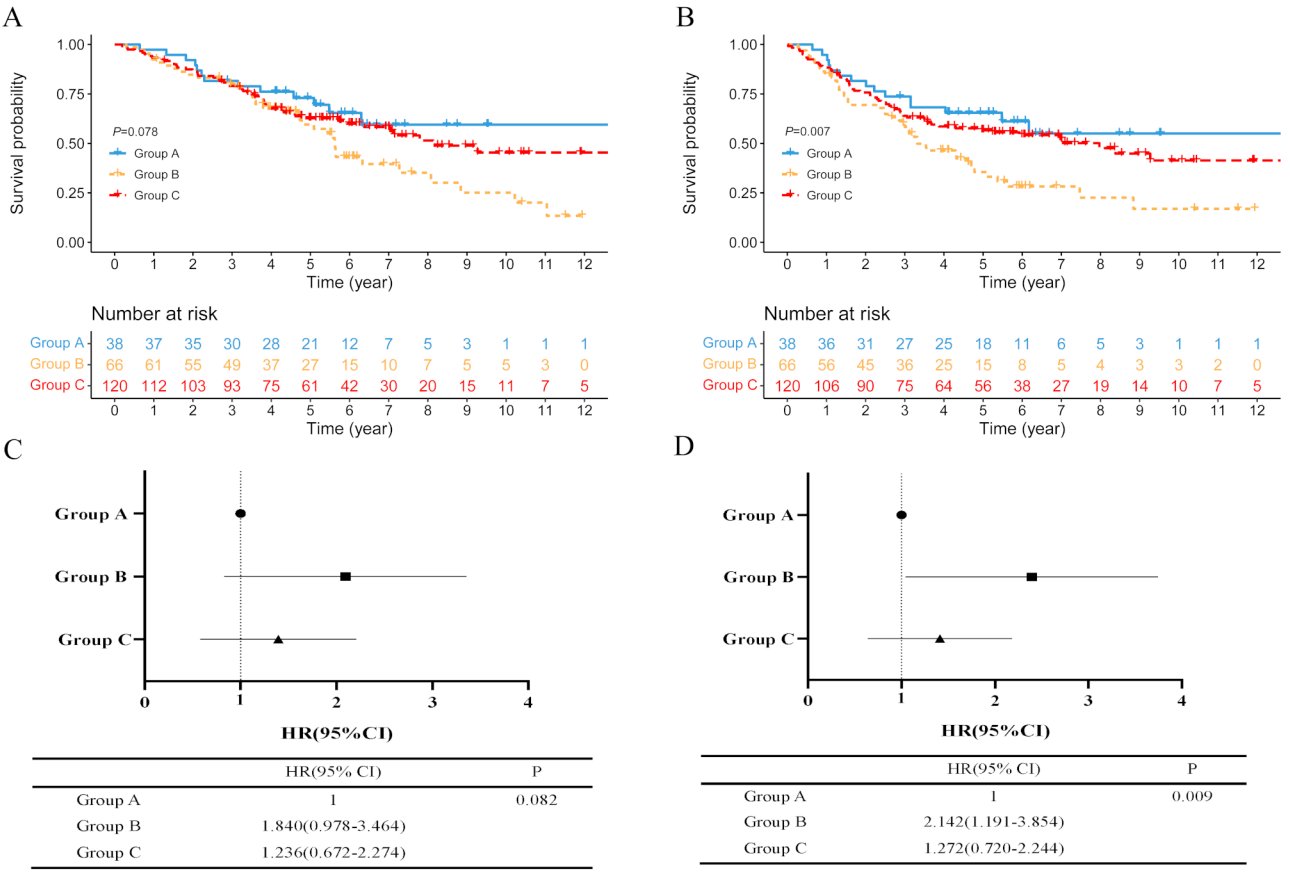
Table 2 The baseline characteristics of the Group B and D patients before and after PSM

Characteristic	Before PSM			After PSM		
	Group B (*n* = 66)	Group D (*n* = 227)	*P*	Group B (*n* = 66)	Group D (*n* = 66)	*P*
Sex			0.408			0.854
Male	43 (65.2%)	160 (70.5%)		43 (65.2%)	44 (66.7%)	
Female	23 (34.8%)	67 (29.5%)		23 (34.8%)	22 (33.3%)	
Age, years			0.401[a]			0.577[a]
Median (range)	61 (37–81)	61 (34–81)		61 (37–81)	62 (34–81)	
Smoking			0.240			0.862
No	33 (50.0%)	95 (41.9%)		33 (50.0%)	32 (48.5%)	
Yes	33 (50.0%)	132 (58.1%)		33 (50.0%)	34 (51.5%)	
Family tumor history			0.581			0.753
Without	60 (90.9%)	213 (93.8%)		60 (90.9%)	61 (92.4%)	
With	6 (9.1%)	14 (6.2%)		6 (9.1%)	5 (7.6%)	
Preoperative comorbidity			0.204			0.157
Without	23 (34.8%)	99 (43.6%)		23 (34.8%)	31 (47.0%)	
With	43 (65.2%)	128 (56.4%)		43 (65.2%)	35 (53.0%)	
BMI			0.406			0.501[b]
< 18.5	2 (3.0%)	11 (4.8%)		2 (3.0%)	4 (6.1%)	
18.5–24	29 (43.9%)	116 (51.1%)		29 (43.9%)	33 (50.0%)	
>=24	35 (53.0%)	100 (44.1%)		35 (53.0%)	29 (43.9%)	
ASA grade			0.605			0.306[b]
1	13 (19.7%)	47 (20.7%)		13 (19.7%)	13 (19.7%)	
2	52 (78.8%)	171 (75.3%)		52 (78.8%)	48 (72.7%)	
3	1 (1.5%)	9 (4.0%)		1 (1.5%)	5 (7.6%)	
4	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Surgical type			0.005			1.000
Thoracoscope	58 (87.9%)	161 (70.9%)		58 (87.9%)	58 (87.9%)	
Thoracotomy	8 (12.1%)	66 (29.1%)		8 (12.1%)	8 (12.1%)	
Surgical extent			0.069			0.266[b]
Lobectomy	60 (90.9%)	192 (84.6%)		60 (90.9%)	60 (90.9%)	
Bi-lobectomy	5 (7.6%)	12 (5.3%)		5 (7.6%)	2 (3.0%)	
Pneumonectomy	1 (1.5%)	23 (10.1%)		1 (1.5%)	4 (6.1%)	
Histology			0.003			0.118[b]
Adenocarcinoma	54 (81.8%)	138 (60.8%)		54 (81.8%)	49 (74.2%)	
Squamous	8 (12.1%)	77 (33.9%)		8 (12.1%)	16 (24.2%)	
Other	4 (6.1%)	12 (5.3%)		4 (6.1%)	1 (1.5%)	
VPI			0.250			0.159
Without	34 (51.5%)	135 (59.5%)		34 (51.5%)	42 (63.6%)	
With	32 (48.5%)	92 (40.5%)		32 (48.5%)	24 (36.4%)	
LVI			0.694			0.164
Without	36 (54.5%)	130 (57.3%)		36 (54.5%)	28 (42.4%)	
With	30 (45.5%)	97 (42.7%)		30 (45.5%)	38 (57.6%)	
Postoperative complications			0.968			0.572
No	60 (90.9%)	206 (90.7%)		60 (90.9%)	58 (87.9%)	
Yes	6 (9.1%)	21 (9.3%)		6 (9.1%)	8 (12.1%)	
Adjuvant therapy			0.006			0.554
No	19 (28.8%)	109 (48.0%)		19 (28.8%)	16 (24.2%)	
Yes	47 (71.2%)	118 (52.0%)		47 (71.2%)	50 (75.8%)	

a Mann-Whitney U test

b Fisher's exact test

Group B, patients who having single-station N2 with N1 involvements; Group D, patients with stage IIIA; BMI, body mass index; ASA, American society of anesthesiologist physical status classification system; VPI, visceral pleural invasion; LVI, lympho-vascular invasion



	HR(95% CI)	P
Group A	1	0.082
Group B	1.840(0.978-3.464)	
Group C	1.236(0.672-2.274)	

	HR(95% CI)	P
Group A	1	0.009
Group B	2.142(1.191-3.854)	
Group C	1.272(0.720-2.244)	

Fig. 2 Kaplan–Meier estimates of survivals and univariate Cox analysis of stage IIB patients (Group A vs. Group B vs. Group C). (**A**) overall survival curves; (**B**) disease-free survival curves; (**C**) forest plot: univariate Cox analysis of overall survival; and (**D**) forest plot: univariate Cox analysis of disease-free survival. HR: hazard ratio; CI, confidence interval; Group A, patients who having single-station N2 without N1 involvement; Group B, patients who having single-station N2 with N1 involvements; Group C, patients who having station N1 involvement or N0

outcomes of N2a1 patients resembled those of other stage IIB patients, which underscored the legitimacy of downstaging such individuals from stage IIIA to stage IIB. For the observed phenomenon of better prognosis in N2a1 patients compared to poorer prognosis in N2a2 patients, our interpretations were as follows: (1) patients with N2a2 status typically harbored a greater tumor burden, a factor previously associated with poorer prognosis in existing literature [6, 9, 22]; (2) due to incomplete lymph node dissection or limitations in pathological diagnostic techniques, N2a2 patients may indeed present with multi-station N2 lymph node involvements. However, given our stringent inclusion criteria, which exclusively included patients undergoing systematic lymph node dissection, coupled with the esteemed reputation of our pathology department as one of the premier medical pathology centers in mainland China, the likelihood of this scenario is considered minimal; (3) the occurrence of skip metastasis (N2a1) is attributed to several factors. One of the main reasons is the anatomical connectivity within the lymphatic system [23, 24]. Abundant lymphatic vessels and networks beneath the pleura provide a direct pathway for tumor cells to bypass the intrapulmonary and hilar lymph nodes, draining directly into the ipsilateral mediastinal lymph nodes. In theory, without these direct pathways, tumors may only metastasize to the hilar lymph nodes, failing to extend to the mediastinal lymph nodes. Therefore, N2a1 and N1 patients might have similar prognosis.

Our study had several limitations that warrant consideration. Firstly, it was a single-center retrospective study, inherently susceptible to bias. Secondly, although this study utilized a large dataset spanning nearly 20 years, the stringent inclusion and exclusion criteria resulted in a relatively small sample size within the stage IIB subgroups. This is undoubtedly a significant limitation of our study, as it potentially limits the statistical power of our results. Therefore, our conclusions require further validation by additional studies. Future research with larger sample sizes across multiple centers is necessary to strengthen the findings.

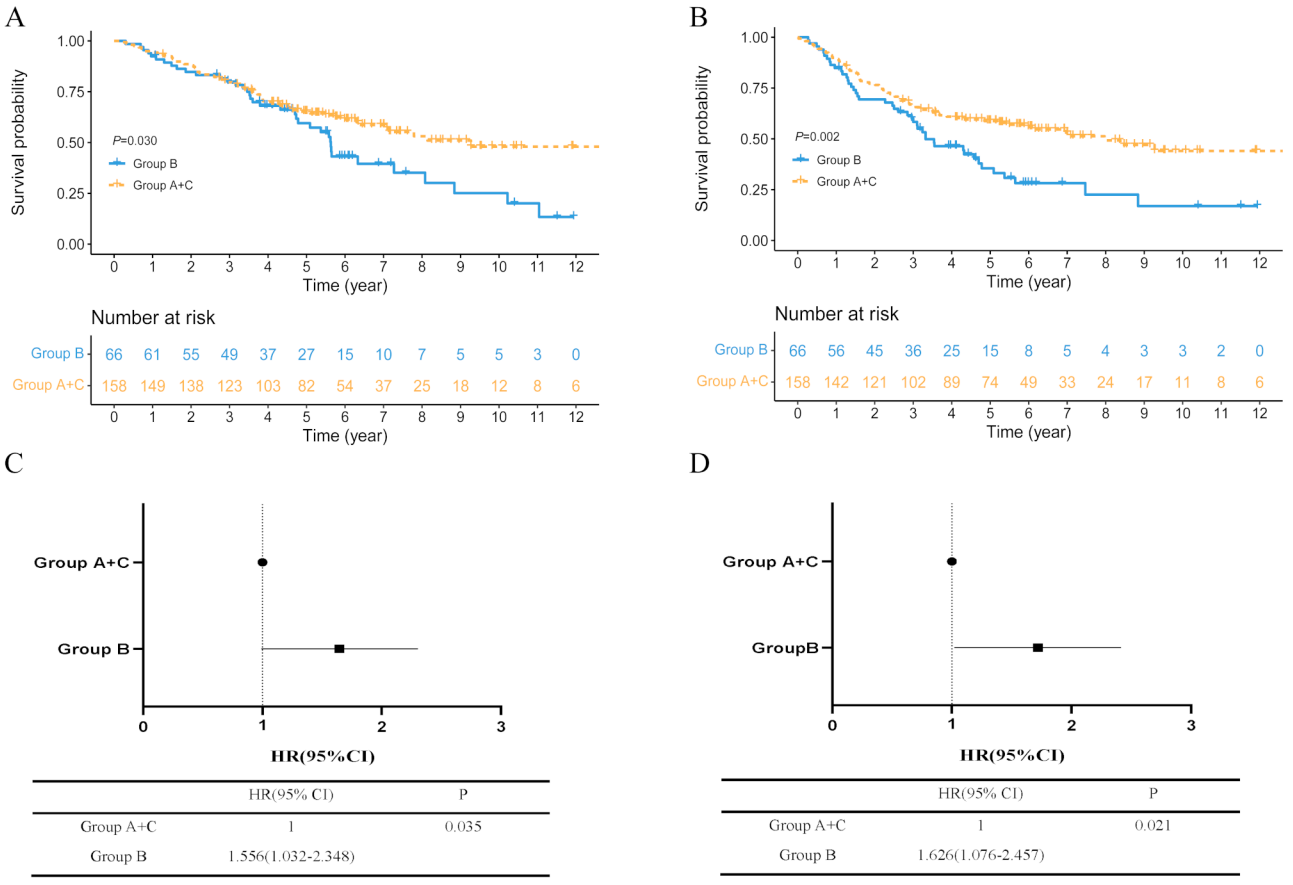


Fig. 3 Kaplan–Meier estimates of survivals and multivariate Cox analysis of stage IIB patients (Group A + C vs. Group B). Considering the similar prognosis between patients in the Group A and Group C, we combined these two groups into a single group: Group A + C. (**A**) overall survival curves; (**B**) disease-free survival curves; (**C**) forest plot: multivariate Cox analysis of overall survival; and (**D**) forest plot: multivariate Cox analysis of disease-free survival. HR: hazard ratio; CI, confidence interval; Group A, patients who having single-station N2 without N1 involvement; Group B, patients who having single-station N2 with N1 involvements; Group C, patients who having station N1 involvement or N0

Lastly, it remains uncertain whether the conclusions drawn from our exploration of pathological staging in this article are equally applicable to clinical staging. Our database lacks detailed records of clinical lymph node metastasis. Therefore, more detailed data are needed to validate our findings.

Conclusion

In conclusion, our study indicated that the prognosis of stage IIB (N2a2) patients was inferior to that of other stage IIB patients but comparable to that of stage IIIA patients. Thus, we propose to retain classification IIB (N2a2) in stage IIIA. However, our conclusions warranted further validations.

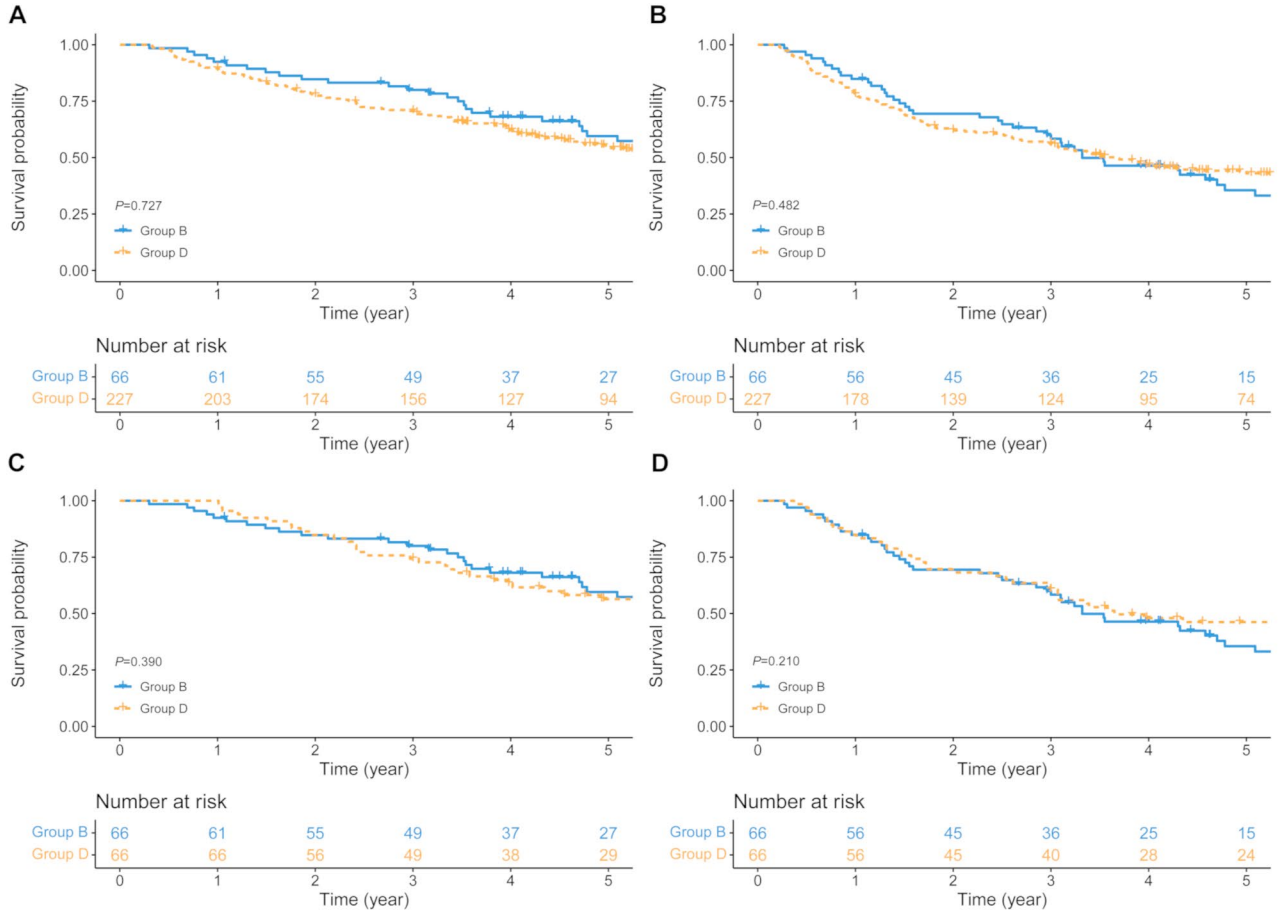


Fig. 4 Kaplan–Meier estimates of survivals differences between Group B and Group D patients both before PSM and after PSM. (**A**) overall survival before PSM; (**B**) disease-free survival before PSM; (**C**) overall survival after PSM; and (**D**) disease-free survival after PSM. PSM, propensity score matching; Group B, patients who having single-station N2 with N1 involvements; Group D: stage IIIA patients

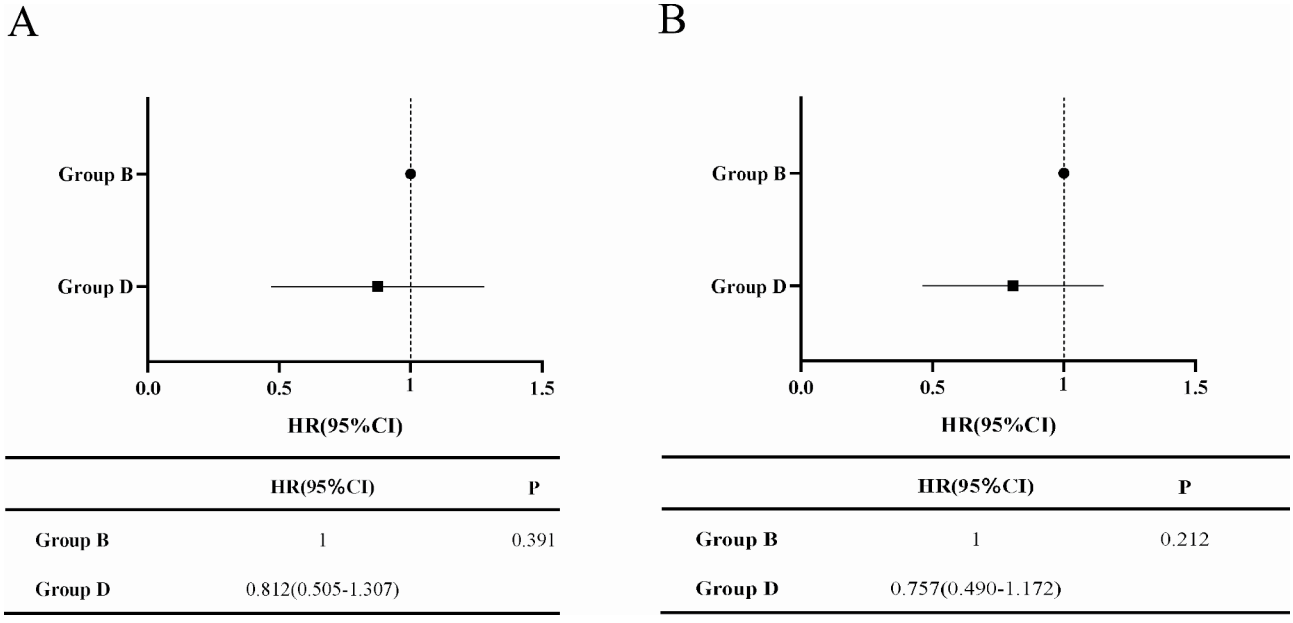


Fig. 5 Univariate Cox analysis of the Group B and Group D patients after PSM. (**A**) overall survival; (**B**) disease-free survival. PSM, propensity score matching; HR: hazard ratio; CI, confidence interval; Group B, patients who having single-station N2 with N1 involvements; Group D: stage IIIA patients

Abbreviations

ASA	American society of anesthesiologist physical status classification system;
BMI	Body mass index;
CI	Confidence interval
DFS	Disease-free survival
HR	Hazard ratio;
LVI	Lymphovascular invasion;
N2a1	Single-station N2 without N1 involvement;
N2a2	Single-station N2 with N1 involvement;
NSCLC	Non-small cell lung cancer
OS	Overall survival
PSM	Propensity score matching
TNM	Tumor node-metastasis
VPI	Visceral pleural invasion;

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13364-6.

Supplementary Material 1

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Data availability
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of Peking University People's Hospital. Given the anonymized patient data and retrospective design, written informed consent was not required for this study.

Consent for publication
This article was published with the unanimous consent of all the authors.

Competing interests
The authors declare no competing interests.

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References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians; 2024.
2. Nicholson AG, Tsao MS, Beasley MB, Borczuk AC, Brambilla E, Cooper WA, et al. The 2021 WHO classification of lung tumors: impact of advances since 2015. J Thorac Oncol. 2022;17(3):362–87.
3. Rami-Porta R, Nishimura KK, Giroux DJ, Detterbeck F, Cardillo G, Edwards JG et al. The International Association for the study of Lung Cancer Lung Cancer Staging Project: proposals for revision of the TNM stage groups in the forthcoming (ninth) edition of the tnm classification for lung cancer. J Thorac Oncol. 2024;19(7):1007–1027.
4. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM Stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol. 2016;11(1):39–51.
5. Fong KM, Rosenthal A, Giroux DJ, Nishimura KK, Erasmus J, Lievens Y et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the M descriptors in the forthcoming 9th edition of the TNM classification of lung cancer. J Thorac Oncol. 2024;19(5):786–802.
6. Taylor M, Soliman N, Paoletti E, King M, Crosbie PAJ, Granato F. Impact of skip mediastinal lymph node metastasis on outcomes after resection for primary lung cancer. Lung Cancer. 2023;184:107341.
7. Schlachtenberger G, Schallenberg S, Doerr F, Menghesha H, Gaisendrees C, Amorin A et al. Do skip-N2 metastases significantly impact overall survival and disease-free interval in N2 non-small-cell lung cancer patients? A multicentre analysis. Eur J Cardiothorac Surg. 2023;64(1).
8. Wang XX, Guo HX, Hu QT, Ying YQ, Chen BF. The impact of skip vs. non-skip N2 lymph node metastasis on the prognosis of Non-small-cell Lung Cancer: a systematic review and Meta-analysis. Front Surg. 2021;8.
9. Li X, Li XF, Fu XN, Liu LX, Liu Y, Zhao H, et al. Survival benefit of skip metastases in surgically resected N2 non-small cell lung cancer: a multicenter observational study of a large cohort of the Chinese patients. Ejso-Eur J Surg Onc. 2020;46(10):1874–81.
10. Cai JS, Li Y, Wang X. Is prior cancer history a hindrance for non-small cell lung cancer patients to participate in clinical trials? BMC Cancer. 2023;23(1):155.
11. Cai J-S, Yang F, Wang X. Occult lymph node metastasis is not a favorable factor for resected NSCLC patients. BMC Cancer. 2023;23(1).
12. Wang X, Cai J-S, Yang F. Investigation of the non-small cell lung cancer patients with uncertain resection: a population-based study. Lung Cancer. 2022;171:47–55.
13. Cai JS, Wang X, Yang F, Li Y, Qiu MT. Lymphovascular invasion: a non-sized T descriptor for stage IA non-small cell lung cancer. Thorac Cancer. 2022;13(17):2413–20.
14. Xu L, Su H, She Y, Dai C, Zhao M, Gao J, et al. Which N descriptor is more predictive of prognosis in resected non-small cell lung cancer: the number of involved nodal stations or the location-based pathological N stage? Chest. 2021;159(6):2458–69.
15. Huang BW, Wang WQ, Cai JS, Zhang SW. Investigations of the distant metastatic non-small cell lung cancer without local lymph node involvement: real world data from a large database. Clin Respir J. 2023;17(8):780–790.
16. Cai JS, Yang F, Wang X. Reconsidering the T category for the T3 non-small cell lung cancer with additional tumor nodules in the same lobe: a population-based study. Front Oncol. 2023;13:1043386.
17. Cai JS, Wang X. Investigation of early-stage non-small cell lung cancer patients with different T2 descriptors: real word data from a large database. Lung. 2023;201(4):415–423.
18. Cai J-S, Li Y, Yang F, Wang X. Investigation of the non-size-determined T4N0-2M0 non-small-cell lung cancer: what is the proper T category for the tumour with additional nodules in different lobes of ipsilateral lung? Eur J Cardiothorac Surg. 2023;64(1).
19. Cai JS, Yang F, Wang X. Is there a prognostic difference among T3N0-3M0 NSCLC patients with different T3 descriptors? Eur J Cardiothorac Surg. 2023;63(3):ezac558.

20. Cai JS, Lin QY, Dou XM. Is adjacent lobe invasion an T category upgrade factor for resected non-small cell lung cancer = 5 cm?</atz J Cancer Res Clin Oncol. 2023;149(5):1777–1784.
21. Cai JS, Dou XM. Non-small cell lung cancer surpassing the elastic layer should remain classified as pT2a. Semin Thorac Cardiovasc Surg; 2022.
22. Miyawaki T, Kenmotsu H, Doshita K, Kodama H, Nishioka N, Iida Y, et al. Clinical impact of tumour burden on the efficacy of PD-1/PD-L1 inhibitors plus chemotherapy in non-small-cell lung cancer. Cancer Med. 2023;12(2):1451–60.
23. Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the mediastinal nodes - an anatomic study on 260 adults. J Thorac Cardiov Sur. 1989;97(4):623–32.
24. Imai K, Minamiya Y, Saito H, Nakagawa T, Ito M, Ono T, et al. Detection of pleural lymph flow using indocyanine green fluorescence imaging in non-small cell lung cancer surgery: a preliminary study. Surg Today. 2013;43(3):249–54.

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