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Dose-Response Impact of Micropapillary Burden on Survival and Its Clinical Interaction with Surgical Extent in Lung Adenocarcinoma: A Propensity Score-Matched Competing Risks Analysis

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Abstract

Background

Micropapillary (MP) components denote aggressive behavior in lung adenocarcinoma, but whether MP grading modifies the survival benefit of lobectomy versus sublobar resection remains undefined.

Methods

We retrospectively analyzed 497 patients with micropapillary lung adenocarcinoma undergoing surgical resection. MP components were graded as < 5%, 5–20%, 20–40%, and > 40%. Overall survival (OS) and recurrence-free survival (RFS) were evaluated using Kaplan-Meier analysis, log-rank tests, and Cox regression. Propensity score matching (PSM), interaction tests, competing risks analysis (Fine-Gray model), and nomogram construction were additionally performed.

Results

Higher MP grades correlated significantly with worse OS and RFS (both P < 0.001). Multivariate analysis identified MP > 40% as the strongest predictor of mortality (HR 8.60, 95% CI 4.58–16.13, P < 0.001) and recurrence (HR 2.04, 95% CI 1.10–3.79, P = 0.024). Sublobar resection independently predicted inferior OS (HR 2.45, 95% CI 1.59–3.78, P < 0.001) and RFS (HR 2.38, 95% CI 1.59–3.57, P < 0.001), persisting after PSM (n = 410; OS: HR 2.95, 95% CI 1.75–4.98; RFS: HR 2.61, 95% CI 1.65–4.13; both P < 0.001). No MP grade–surgical approach interaction was observed (OS: P = 0.910; RFS: P = 0.564). MP > 40%, sublobar resection, and spread through air spaces (STAS) were the most critical prognostic factors. Competing risk analysis confirmed sublobar resection increased recurrence incidence (SHR 2.15, P < 0.001).

Conclusions

MP grading and surgical extent independently affect prognosis without interaction. MP > 40% defines a high-risk subgroup requiring aggressive adjuvant therapy. Sublobar resection should be avoided regardless of MP burden; lobectomy remains the preferred strategy when feasible.

Introduction

Lung cancer continues to be the primary cause of cancer-related mortality globally, resulting in about 1.8 million deaths each year [1]. While targeted therapies and immunotherapy have advanced, surgical resection remains the fundamental approach for curative treatment of early-stage non-small cell lung cancer (NSCLC), encompassing a spectrum from limited segmental or wedge resection to standard lobectomy [2]. Nevertheless, the prognosis of individuals with lung adenocarcinoma exhibits significant

variability, influenced by factors such as tumor stage, histologic subtype, and high-risk pathologic characteristics.

The micropapillary (MP) component in lung adenocarcinoma, characterized by small clusters of malignant cells floating in the alveolar lumen without a central fibrovascular core, is associated with aggressive tumor behavior, including lymphovascular invasion, lymph node metastasis, and distant dissemination [3, 4]. This distinct morphology contributes to higher rates of pleural invasion, postoperative recurrence, and is recognized as an independent adverse prognostic factor in the 2021 WHO Thoracic Tumor Classification [5–7, 8]. Despite the acknowledged prognostic significance of MP, there is no consensus on the optimal quantitative threshold for risk stratification. Various studies have proposed thresholds like 5%, 20%, and 40% to define high-risk MP, with some even considering any detectable MP as indicative of poor prognosis. This lack of standardized thresholds has resulted in inconsistencies in clinical decision-making [9, 10]. The optimal extent of surgical resection for lung adenocarcinoma is a contentious issue. While lobectomy with lymph node dissection has been the conventional approach [11], recent trials such as JCOG0802 and CALGB 140503 have shown that lung segmental resection can achieve comparable survival outcomes for peripheral stage IA NSCLC [12, 13].However, a key question remains: does the presence and proportion of high-risk histologic features alter the relative effectiveness of sublobar resection compared to lobectomy?

In this study, we employed a thorough multimodal analytical framework, incorporating traditional survival analysis, Cox regression-based analysis of variance, propensity score matching, competing risk modeling, and column-line diagram development, to unravel the prognostic interactions between MP proportions and surgical extent. Moreover, we recommend integrating risk-stratification-based assessment of MP thresholds into personalized surgical decision-making processes.

Materials and Methods

Study Population and Data Source

This retrospective cohort study comprised 497 patients diagnosed with lung adenocarcinoma containing a micropapillary component who underwent radical surgical resection at our institution between January 2018 and December 2023. Patients were confirmed pathologically. Inclusion criteria encompassed complete surgical resection (R0) without residual tumor, evaluation of micropapillary component percentage, comprehensive follow-up data on survival and recurrence, and absence of preoperative chemotherapy or radiotherapy. Exclusion criteria involved incomplete resection (R1/R2), absence of essential pathologic data, presence of other malignancies, and follow-up duration < 6 months. The institutional review board granted approval for this retrospective analysis and waived the requirement for informed consent.

Variables and Endpoint Definitions

The micropapillary component was quantified as a percentage of the total tumor area and categorized into four grades: grade 1 (< 5%), grade 2 (5–20%), grade 3 (20–40%), and grade 4 (> 40%). Lung visceral pleural invasion (VPI), spread through air spaces (STAS), perineural invasion (PNI), and lymphovascular invasion (LVI) were documented. Pathological staging was conducted following the 8th edition of the AJCC TNM staging system.

Surgical approach: The choice of surgical approach is made by the surgeon, taking into account tumor characteristics, patient lung function, and comorbidities. Lobectomy is defined as the resection of the affected lung lobe, accompanied by dissection of the hilar and mediastinal lymph nodes. Sublobar resections encompass both segmental and wedge resections. The covariates analyzed included age (both continuous and categorical variables: ≤60, 61–70, and > 70 years), sex, smoking history, tumor size (cm), T stage (T1, T2, T3, T4), N stage (N0, N1, N2), and CEA level.

The primary endpoints were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the duration from surgery to death from any cause, with patients who were alive at the last follow-up censored. RFS was defined as the interval from surgery to disease recurrence or death from any cause, with patients who remained recurrence-free at the last follow-up censored.

Statistical Analysis

Statistical analysis involved expressing continuous variables as median (interquartile range) and comparing them using the Kruskal-Wallis test. Categorical variables were assessed using either the chi-square test or Fisher's exact test. Survival curves were generated using the Kaplan-Meier method and compared with the log-rank test. Additionally, univariate and multivariate Cox proportional hazards regression analyses were conducted.

Propensity Score Matching (PSM)

To ascertain the causal impact of surgical methods while mitigating indication bias, we conducted nearest neighbor propensity score matching in a 1:1 ratio with a caliper set at 0.2 times the standard deviation of the logit of the propensity score. Propensity scores were computed through logistic regression incorporating baseline characteristics (age, sex, smoking status, tumor dimensions, T-stage, N-stage, CEA levels, VPI, STAS, LVI). We evaluated balance using the standardized mean difference (SMD), deeming |SMD|<0.10 as acceptable. Subsequent survival analysis post-matching entailed Kaplan-Meier analyses, log-rank tests, and Cox regression.

Interaction and Effect Modification Analysis

Likelihood ratio tests were employed to evaluate multiplicative interactions by contrasting nested Cox models with and without an interaction term (micropapillary grading × surgical approach). Additive interactions were measured on a risk ratio scale utilizing relative excess risk (RERI), attributable

proportion (AP), and synergy index (S) [14]. Effect modification was examined through stratified Cox regression within individual surgical modality subgroups.

Competing Risks Analysis

A Fine-Gray subdistribution risk model was fitted using an inverse probability censored weighted (IPCW) approximation. Separate estimates of subdistribution risk ratios were calculated for recurrent and nonrecurrent deaths, considering covariates such as micropapillary grading, surgical approach, demographic characteristics, staging, and pathologic features. Cumulative incidence functions (CIF) were graphed based on micropapillary classification and surgical approach.

Prognostic Model.

Column line plots were generated using multivariate Cox regression coefficients to predict patient survival post-surgery. Internal validation was conducted through 500 Bootstrap resamplings (500 iterations), categorizing patients into low, intermediate, and high-risk groups based on risk score tertiles. Model discrimination was assessed using the Harrell concordance index (C-index). The analyses were carried out utilizing R 4.3 software (packages: survival, cmprsk, glmnet, MatchIt). All statistical tests were two-sided, with statistical significance set at $P < 0.05$.

Results

Baseline Characteristics

The study cohort's baseline characteristics comprised 497 patients with a median age of 64.0 years, consisting of 228 (45.9%) males and 269 (54.1%) females. Micropapillary grading was as follows: <5% (n = 297, 59.8%), 5–20% (n = 134, 27.0%), 20–40% (n = 38, 7.6%), and > 40% (n = 28, 5.6%). Surgical procedures were distributed as lobectomy (n = 291, 58.6%), segmental resection (n = 118, 23.7%), and wedge resection (n = 88, 17.7%). Table 1 displays the baseline characteristics. Patients with higher micropapillary (MP) grades exhibited larger tumors, advanced T and N stages, and increased rates of positive vascular invasion (VPI), spread through air spaces (STAS), and lymph node involvement. Sublobar resection was more prevalent in the < 5% MP group (44.4%) compared to the > 40% MP group (17.9%).

Table 1
Baseline Characteristics by Micropapillary Grade

Characteristic, n (%)	Total (n = 497)	MP < 5% (n = 297)	MP 5–20% (n = 134)	MP 20–40% (n = 38)	MP > 40% (n = 28)
Age (years)					
Age < 60	175 (35.2%)	102 (34.3%)	51 (38.1%)	14 (36.8%)	8 (28.6%)
Age 60–70	200 (40.2%)	119 (40.1%)	52 (38.8%)	16 (42.1%)	13 (46.4%)
Age > = 70	122 (24.5%)	76 (25.6%)	31 (23.1%)	8 (21.1%)	7 (25.0%)
Tumor location					
Left	227 (45.7%)	131 (44.1%)	66 (49.3%)	16 (42.1%)	14 (50.0%)
Right	270 (54.3%)	166 (55.9%)	68 (50.7%)	22 (57.9%)	14 (50.0%)
Tumor size group					
≤ 1cm	60 (12.1%)	42 (14.1%)	13 (9.7%)	4 (10.5%)	1 (3.6%)
1-2cm	309 (62.2%)	197 (66.3%)	78 (58.2%)	19 (50.0%)	15 (53.6%)
2-3cm	91 (18.3%)	41 (13.8%)	35 (26.1%)	9 (23.7%)	6 (21.4%)
> 3cm	37 (7.4%)	17 (5.7%)	8 (6.0%)	6 (15.8%)	6 (21.4%)
T stage					
T1	460 (92.6%)	280 (94.3%)	126 (94.0%)	32 (84.2%)	22 (78.6%)
T2	23 (4.6%)	10 (3.4%)	5 (3.7%)	3 (7.9%)	5 (17.9%)
T3	8 (1.6%)	3 (1.0%)	2 (1.5%)	2 (5.3%)	1 (3.6%)
T4	6 (1.2%)	4 (1.3%)	1 (0.7%)	1 (2.6%)	0 (0.0%)
N stage					
N0	403 (81.1%)	244 (82.2%)	110 (82.1%)	27 (71.1%)	22 (78.6%)
N1	31 (6.2%)	20 (6.7%)	8 (6.0%)	1 (2.6%)	2 (7.1%)
N2	63 (12.7%)	33 (11.1%)	16 (11.9%)	10 (26.3%)	4 (14.3%)
Surgical					
Lobectomy	291 (58.6%)	165 (55.6%)	82 (61.2%)	21 (55.3%)	23 (82.1%)
Segmentectomy	118 (23.7%)	77 (25.9%)	28 (20.9%)	13 (34.2%)	0 (0.0%)
Wedge resection	88 (17.7%)	55 (18.5%)	24 (17.9%)	4 (10.5%)	5 (17.9%)
Sublobar resection	206 (41.4%)	132 (44.4%)	52 (38.8%)	17 (44.7%)	5 (17.9%)

Characteristic, n (%)	Total (n = 497)	MP < 5% (n = 297)	MP 5–20% (n = 134)	MP 20–40% (n = 38)	MP > 40% (n = 28)
LN stations, median [IQR]	6.0 [4.0–7.0]	5.0 [4.0–7.0]	6.0 [4.0–8.0]	6.0 [5.0–7.0]	7.5 [6.0–9.0]
LN count, median [IQR]	11.0 [6.0–17.0]	11.0 [5.0–16.0]	11.5 [7.0–16.0]	12.0 [7.5–17.8]	17.0 [10.8–22.5]
Gender	228 (45.9%)	141 (47.5%)	59 (44.0%)	14 (36.8%)	14 (50.0%)
Smoking	68 (13.7%)	42 (14.1%)	14 (10.4%)	10 (26.3%)	2 (7.1%)
CEA	102 (20.5%)	47 (15.8%)	35 (26.1%)	10 (26.3%)	10 (35.7%)
VPI	82 (16.5%)	40 (13.5%)	28 (20.9%)	9 (23.7%)	5 (17.9%)
STAS	109 (21.9%)	57 (19.2%)	34 (25.4%)	14 (36.8%)	4 (14.3%)
Perineural invasion	14 (2.8%)	10 (3.4%)	2 (1.5%)	1 (2.6%)	1 (3.6%)
Vascular invasion	82 (16.5%)	38 (12.8%)	27 (20.1%)	10 (26.3%)	7 (25.0%)
Lymph node positive	96 (19.3%)	42 (14.1%)	29 (21.6%)	14 (36.8%)	11 (39.3%)

Survival Outcomes

Kaplan-Meier analysis indicated a significant association between MP classification and both overall survival (OS) and recurrence-free survival (RFS) ($P < 0.0001$; RFS: $P = 0.00071$), displaying a notable dose-response relationship. The 3-year OS probabilities were 0.921 for the MP < 5% group, 0.874 for the MP 5–20% group, 0.816 for the MP 20–40% group, and 0.693 for the MP > 40% group; the corresponding 3-year RFS probabilities were 0.871, 0.812, 0.738, and 0.612. The survival curves exhibited a gradual downward shift and significant separation with increasing MP percentage, with the most pronounced decline observed in the MP > 40% group.

Statistically significant differences were observed in overall survival (OS) and recurrence-free survival (RFS) among the three surgical modalities (OS: $P = 0.0097$; RFS: $P = 0.00052$). Optimal survival curve was demonstrated by lobectomy, while segmental lung resection and wedge resection exhibited a less favorable prognosis. A significant discrepancy in OS ($P = 0.0056$) and an even more pronounced difference in RFS ($P = 0.00087$) were noted when comparing lobectomy with sublobar resection. The survival curves for lobectomy and sublobar resection began to diverge early in the follow-up period and maintained a consistent gap, indicating the persistent survival advantage of lobectomy. Importantly, the separation between the groups was more prominent for RFS than for OS, suggesting a stronger impact of the surgical approach on recurrence risk than on mortality risk.

Cox Regression

Univariate and multivariate Cox regression analyses were conducted on clinicopathologic variables to adjust for confounding factors (Tables 2 and 3, Fig. 2). The findings indicated that the MP component emerged as a robust independent predictor of OS and RFS. Having an MP > 40% represented the highest risk factor for mortality (HR 8.60, 95% CI 4.58–16.13, P < 0.001), elevating the risk of death by about 7.6 times compared to an MP < 5%. Moreover, an MP ranging from 20% to 40% independently amplified the risk of death (HR 2.78, 95% CI 1.46–5.29, P = 0.002). Even an MP between 5% and 20% exhibited statistical significance (HR 1.67, 95% CI 1.02–2.73, P = 0.041), indicating that even a modest MP component was linked to a poorer prognosis. Regarding recurrence-free survival (RFS), only patients with micropapillary (MP) component > 40% exhibited significant independent predictive value (hazard ratio [HR] 2.04, 95% confidence interval [CI] 1.10–3.79, P = 0.024), while those with MP 5–20% (HR 1.14, P = 0.585) and MP 20–40% (HR 1.15, P = 0.631) did not demonstrate statistical significance. Sublobar resection consistently emerged as a common independent adverse prognostic factor for overall survival (OS) and RFS. Following adjustment for all covariates, sublobar resection was associated with a higher risk of mortality (HR 2.45, 95% CI 1.59–3.78, P < 0.001) and recurrence (HR 2.38, 95% CI 1.59–3.57, P < 0.001). The risk ratios for both outcomes were similar (2.45 vs. 2.38) with precise estimates and robust findings, as indicated by narrow confidence intervals and P values < 0.001, underscoring the consistent and reliable nature of the effect estimate, irrespective of the outcome definition.

Age, gender, smoking history, CEA level, tumor size, N stage, vascular invasion, nerve invasion, and lymph node positivity did not achieve statistical significance in the multivariate model (all P > 0.05), indicating that the prognostic impact of these factors might be overshadowed by the explanatory capacity of robust predictors like the MP component and surgical approach.

Subgroup analysis

To assess the consistency of adverse effects post sublobar resection across various clinical subgroups, we performed segmented Cox regression analyses considering age, gender, smoking history, CEA level, N stage, and MP grading (Fig. 2-D). A significant finding emerged from the subgroup analysis based on MP classification: the adverse impact of sublobar resection was most notable in the MP < 5% subset (OS: HR = 3.53, 95%CI: 1.79–6.97, P < 0.001; RFS: HR = 2.4, 95%CI: 1.38–4.19, P = 0.002). In contrast, within the MP ≥ 5% category, this impact was markedly reduced (OS: HR = 1.14, 95%CI: 0.68–1.91, P = 0.618; RFS: HR = 1.56, 95%CI: 0.95–2.55, P = 0.078). These findings strongly suggest the importance of tailoring surgical interventions for patients with exceptionally low MP levels.In contrast, individuals with elevated MP levels may not benefit sufficiently from merely expanding the surgical scope to offset the negative prognosis linked to MP. Therefore, a combination of alternative therapeutic strategies may be required. Significantly, the results of this subgroup analysis fully support the finding that the surgical intervention had the greatest effect in the MP < 5% group in the interaction analysis, establishing a strong body of evidence.

Table 2
Univariate Cox Proportional Hazards Regression Analysis

Variable	OS		RFS	
	HR	P_value	HR	P_value
Age	1.02(0.99–1.04)	0.152	1.03(1.01–1.05)	0.001
Gender	0.83(0.56–1.22)	0.341	0.93(0.66–1.32)	0.705
Smoking	1.37(0.82–2.27)	0.23	1.55(0.99–2.43)	0.057
CEA	1.83(1.20–2.79)	0.005	1.89(1.28–2.78)	0.001
Tumor size	1.29(1.05–1.58)	0.014	1.65(1.39–1.96)	< 0.001
T0	REF		REF	
T2	1.00(0.41–2.46)	0.996	2.61(1.22–5.61)	0.014
T3	4.98(2.03–12.25)	< 0.001	2.76(1.13–6.76)	0.026
T4	3.12(0.99–9.86)	0.052	9.26(2.88–29.73)	< 0.001
N1	1.43(0.69–2.94)	0.332	0.74(0.38–1.46)	0.387
N2	2.07(1.31–3.27)	0.002	1.65(1.04–2.61)	0.033
MP <5	REF		REF	
MP 5–20%	1.11(0.72–1.70)	0.633	1.06(0.70–1.61)	0.774
MP 20–40%	2.65(1.53–4.61)	< 0.001	1.65(1.03–2.64)	0.036
MP > 40%	4.72(2.80–7.98)	< 0.001	2.21(1.32–3.69)	0.003
Sublobar resection	1.72(1.17–2.54)	0.006	1.81(1.27–2.58)	0.001
VPI	1.48(0.92–2.36)	0.106	2.41(1.52–3.83)	< 0.001
STAS	1.67(1.08–2.58)	0.021	1.71(1.14–2.55)	0.009
Perineural invasion	1.25(0.40–3.94)	0.703	2.14(1.04–4.37)	0.038
Vascular invasion	1.54(0.97–2.45)	0.07	1.98(1.32–2.97)	< 0.001
LN positive	2.06(1.36–3.11)	< 0.001	1.8(1.21–2.66)	0.003

Table 3
Multivariate Cox Proportional Hazards Regression Analysis

Variable	OS		RFS	
	HR (95% CI)	P_value	HR (95% CI)	P_value
Age	1.0 (0.98–1.03)	0.836	1.02 (1.00-1.04)	0.098
Gender	0.78 (0.51–1.19)	0.246	1.01 (0.70–1.47)	0.941
Smoking	1.11 (0.62–1.98)	0.724	1.03 (0.62–1.74)	0.898
CEA	1.28 (0.79–2.08)	0.321	1.39 (0.86–2.26)	0.184
Tumor size	0.9 (0.62–1.32)	0.595	1.29 (0.87–1.93)	0.209
T0	REF			
T2	0.71 (0.22–2.31)	0.572	1.13 (0.36–3.49)	0.833
T3	4.14 (1.07–16.03)	0.039	1.0 (0.25–4.03)	0.995
T4	9.08 (1.58–52.29)	0.014	2.65 (0.38–18.68)	0.328
N1	2.09 (0.97–4.51)	0.06	1.1 (0.54–2.24)	0.79
N2	1.47 (0.78–2.76)	0.233	0.88 (0.50–1.56)	0.668
MP <5	REF			
MP 5–20%	1.67 (1.02–2.73)	0.041	1.14 (0.71–1.85)	0.585
MP 20–40%	2.78 (1.46–5.29)	0.002	1.15 (0.65–2.05)	0.631
MP > 40%	8.6 (4.58–16.13)	< 0.001	2.04 (1.10–3.79)	0.024
Sublobar resection	2.45 (1.59–3.78)	< 0.001	2.38 (1.59–3.57)	< 0.001
VPI	1.23 (0.72–2.08)	0.446	1.85 (1.07–3.22)	0.028
STAS	1.84 (1.15–2.92)	0.01	1.62 (1.05–2.49)	0.029
Perineural invasion	0.87 (0.25–3.02)	0.828	2.12 (0.94–4.76)	0.069
Vascular invasion	0.97 (0.57–1.65)	0.92	1.2 (0.74–1.95)	0.456
LN positive	1.5 (0.86–2.61)	0.152	1.34 (0.79–2.27)	0.284

Propensity Score-Matched Analysis

To mitigate confounding in the selection of surgical procedures, we performed propensity score matching (PSM) using a 1:1 nearest-neighbor matching strategy with a caliper set at 0.2 × SD (logit PS). The standardized mean difference of all covariates in the matched cohort, comprising 410 patients (205 who underwent lobectomy and 205 who underwent sublobar resection), was below 0.10, indicating

satisfactory balance in covariates. Subsequent to matching, sublobar resection continued to exhibit significantly poorer overall survival (OS) (HR 2.95, 95% CI 1.75–4.98, P < 0.001) and recurrence-free survival (RFS) (HR 2.61, 95% CI 1.65–4.13, P < 0.001) compared to lobectomy (Table 4). The survival curves remained distinctly separate after matching, suggesting that the survival disadvantage associated with sublobar resection is unlikely due to selection bias or unmeasured confounders but may genuinely reflect oncological differences between anatomical and limited resections.

Table 4
Results of multifactor Cox regression analysis in the PSM matched cohort

Variable	**OS(HR, 95%CI)**	**P**	**RFS(HR, 95%CI)**	**P**
Sublobar lobectomy	2.95(1.75–4.98)	< 0.001	2.61(1.65–4.13)	< 0.001
Age	1.01(0.98–1.03)	0.548	1.02(1.00–1.05)	0.042
Male	0.65(0.39–1.08)	0.096	1.05(0.69–1.60)	0.806
CEA	1.69(0.97–2.93)	0.063	1.89(1.16–3.08)	0.010
Tumor size	0.86(0.58–1.28)	0.469	1.60(1.05–2.43)	0.027
MP 5–20%	1.69(0.96–2.98)	0.070	1.25(0.75–2.09)	0.394
MP20–40%	2.52(1.13–5.62)	0.024	1.45(0.76–2.77)	0.261
MP > 40%	11.62(5.59–24.16)	< 0.001	3.59(1.85–6.94)	< 0.001
N1	2.84(1.24–6.51)	0.014	1.15(0.54–2.42)	0.717
N2	1.73(0.83–3.59)	0.143	0.57(0.24–1.35)	0.199

Analysis of the interaction between MP components and surgical approach

To explore the potential moderating effect of the MP component on the influence of the surgical approach on survival outcomes, we incorporated an interaction term between MP and sublobar resection into a multifactorial Cox model. The analysis indicated that the interaction term did not hold statistical significance for overall survival (OS) (HR = 0.97, 95% CI: 0.55–1.71, P = 0.910) and recurrence-free survival (RFS) (HR = 1.17, 95% CI: 0.69–1.99, P = 0.564), suggesting that the MP content did not significantly alter the relative risk linked with sublobar resection. Despite the lack of a significant interaction, we performed subgroup analyses based on MP content to further clarify the impact of surgery across varying MP levels. In the subgroup with MP < 5%, sublobar resection was linked to a notably higher risk of mortality (OS: HR = 2.45, 95% CI: 1.42–4.22, P = 0.001; RFS: HR = 1.98, 95% CI: 1.23–3.19, P = 0.005), a trend consistent in the 5%-20% MP category (OS: HR = 2.03, 95% CI: 1.05–3.91, P = 0.034; RFS: HR = 2.94, 95% CI: 1.48–5.86, P = 0.002). However, in the 20%-40% MP group, the hazard ratio for sublobar resection decreased to 0.53 (95% CI: 0.19–1.46, P = 0.219), displaying a reversed pattern, albeit with broad confidence intervals and no statistical significance. In the MP > 40% group, the HR was 1.11 (95% CI: 0.33–3.80, P = 0.863), once again failing to achieve statistical significance.

The apparent contradiction can be clarified by the following mechanism: in patients with high microsatellite instability (MSI) content (> 20%), the significant adverse prognostic impact of the MSI component itself may mask differences between surgical approaches. Conversely, in patients with low MSI content (≤ 20%), the effect of the MSI component is relatively weak, underscoring the importance of the extent of surgery as a critical prognostic factor. This inference was visually supported by the Kaplan-Meier (KM) curves: among individuals with high MSI levels, the overall survival (OS) patterns following lobectomy and sublobar resection closely mirrored each other (P = 0.63, Fig. 4C); whereas in the low MSI group, a marked discrepancy was observed between the two patterns (P < 0.001, Fig. 4D).

Competitive risk analysis

The Fine-Gray competing risk model was utilized to separately estimate the cumulative incidence function (CIF) of recurrence and death without recurrence, considering them as competing events. Figure 5 depicts a significant distinction among various MP content groups in terms of MP grading (Fig. 5, E1), with the MP > 40% group showing the highest cumulative incidence of recurrence, reaching nearly 50% at 3 years, markedly exceeding the MP < 5% group at around 25%. Regarding the surgical approach (Fig. 5, E2), the sublobar resection group exhibited a notably higher recurrence CIF compared to the lobectomy group, while the death CIF showed minimal variation between the two groups. This indicates that sublobar resection predominantly impacts prognosis by increasing the risk of local recurrence, whereas the risk of death is more influenced by tumor biology. The results of the competing risks analysis are consistent with those of the Kaplan-Meier analysis, providing further validation of the robustness of the findings.

prognostic model

The prognostic model, derived from multifactorial Cox regression analysis, integrated independent prognostic factors including MP components, surgical modalities, STAS, and T stage into a nomogram. This nomogram was utilized to forecast the overall postoperative survival probability in MP patients. By translating the regression coefficients of each variable into a user-friendly visual scoring system, the nomogram assigns a score scale to each variable. The total score is calculated by summing the scores of all variables, facilitating the determination of the corresponding survival probability through a table lookup. The discrimination of the model was evaluated using Harrell's consistency index (C-index). The OS C-index of the multifactorial Cox model stood at 0.756, while the RFS C-index was 0.722, indicating a moderate to good discriminatory capacity of the model.The C-index of the PSM cohort was 0.71 for OS and 0.67 for RFS, consistent with the entire cohort. The column-line diagram model integrated key variables including MP component, surgical approach, STAS, and T stage to offer personalized prognostic predictions for clinical decision-making. Each patient's risk score was computed using the multifactorial Cox model, leading to categorization into low-risk (n = 166), intermediate-risk (n = 165), and high-risk (n = 166) groups via the three-quartile method. Significant differences in OS (P < 0.001) and RFS (P < 0.001) were observed among the three groups (Fig. 5E3-4). The 3-year OS rates were 96.3% for the low-risk group, 88.1% for the intermediate-risk group, and only 65.2% for the high-risk group,

demonstrating the efficacy of this risk stratification system in distinguishing patients with varying prognoses. A calibration curve was utilized to evaluate the predictive accuracy of the column-line graph model. The calibration curve depicted in Fig. 6 illustrated that the predicted probabilities closely aligned with the actual observed probabilities in both the OS and RFS calibration curves, indicating excellent model calibration.

Discussion

The micropapillary (MP) component is a well-established high-risk pathological characteristic in lung adenocarcinoma [15, 16]. Pyo et al. [17] demonstrated a significant association between the MP component and increased rates of lymphovascular invasion, as well as inferior overall survival (OS) and disease-free survival (DFS). Wang et al.'s meta-analysis [18] further validated that the presence of the MP component and MP-predominant phenotypes were indicative of unfavorable postoperative survival outcomes. A recent study by Miyahara et al. [19] revealed that the MP component substantially elevated the risks of postoperative recurrence and mortality. This investigation systematically explores the independent and combined impacts of micropapillary component content and surgical approach on postoperative survival.The key findings were as follows: (1) The content of the MP component independently predicted OS and RFS, with patients having MP > 40% facing a 7.60 times higher risk of death compared to those with MP < 5% (HR 8.60), showing a significant dose-response relationship; (2) Sublobar resection was also an independent adverse prognostic factor for OS (HR = 2.45, 95% CI 1.59–3.78, P < 0.001), with a more pronounced impact post PSM matching (HR = 2.95, 95% CI 1.75–4.98, P < 0.001); (3) While the interaction test between the MP component and surgical approach was non-significant (P = 0.910), further analysis revealed a significant difference in surgical approaches for patients with low MP (< 5%), whereas for those with high MP (> 20%), the adverse impact of the MP component obscured the distinction between surgical modalities; (4) The column-line diagram model, developed based on key prognostic factors, exhibited moderate discriminative capacity (C-index = 0.72), enabling personalized prognostic forecasting for clinical applications.

In recent years, the JCOG0802 and CALGB 140503 randomized controlled trials (RCTs) have significantly influenced the clinical management of early-stage NSCLC by establishing sublobar resection as a viable standard option for specific patient populations [20, 21]. However, these trials did not consider high-risk pathologic characteristics such as micropapillary (MP) and airway spread (STAS) in their stratification or exclusion criteria, prompting concerns about the safety of this approach in such scenarios. Our present study revealed a hazard ratio (HR) of 2.45 (95% CI 1.59–3.78, P < 0.001) for overall survival (OS) in the entire cohort with sublobar resection and 2.95 (95% CI 1.75–4.98, P < 0.001) following propensity score matching (PSM), indicating a significant and consistent adverse prognostic effect.Consistent with a 2025 meta-analysis by Khairullah et al., these results indicate that sublobar resection is associated with poorer overall survival (OS), recurrence-free survival (RFS), and higher rates of recurrence and mortality, especially in patients with high-risk characteristics like vascular invasion (VPI) and STAS [22, 23]. In essence, although sublobar resection is a feasible choice for the majority of early-stage NSCLC cases,

individuals with high-risk pathological features should deliberate carefully before opting for this surgical strategy.

The study's key clinical finding was the correlation between micropapillary (MP) component and the surgical approach. Despite the non-significant result of the interaction test (P = 0.910), further analysis revealed a notable trend: sublobar resection exhibited the most unfavorable prognosis in the MP < 5% subgroup (OS HR = 2.45, P < 0.001); conversely, the difference in surgical approach was insignificant in the MP > 40% subgroup (HR = 1.11, P = 0.863). This observation does not diminish the risk of sublobar resection in high MP patients; instead, it indicates that the highly aggressive nature of high MP itself strongly influences the prognosis, making it challenging for localized surgical intervention to offer additional benefits. For patients with MP < 5%, our findings strongly advocate for prioritizing lobectomy. The overall survival hazard ratio for sublobar resection in this subgroup reached 2.45 (P = 0.001) and 3.20 (P < 0.001) in the propensity score matching analysis, indicating that around two-thirds of the elevated mortality risk could be linked to an insufficient surgical strategy. These patients exhibited relatively indolent tumor characteristics, underscoring the critical role of surgical adequacy in determining prognosis. Warth et al. [24] reported a more pronounced prognostic distinction between lobectomy and sublobar resection in lung adenocarcinomas lacking invasive pathological features. Hence, for early-stage lung adenocarcinomas with a micropapillary component < 5% and tumor diameter > 1 cm, lobectomy should be the preferred treatment. Notably, in cases with a low micropapillary component (≤ 20%), a significant survival advantage favored lobectomy over sublobar resection (P < 0.001), suggesting a considerable survival benefit with lobectomy. Conversely, in patients with a high micropapillary component (> 20%), the survival curves nearly converged (P = 0.21), indicating that opting for a more extensive surgical intervention did not yield a substantial improvement in prognosis. Competing risk analysis revealed that the 3-year cumulative incidence of recurrence (CIF) was close to 50% in the MP > 40% group, significantly surpassing that in the MP < 5% group (approximately 25%). The disparity between the mortality CIF groups was even more pronounced, indicating that MP not only heightens the recurrence risk but also diminishes survival post-recurrence. Concerning the surgical approach, the sublobar resection cohort exhibited a notably higher recurrence CIF, while the variance in death CIF was minor, implying that this procedure primarily escalates the risk of local recurrence due to inadequate resection scope, residual tumor, or airway spread (STAS), rather than directly impacting overall mortality [25]. This finding aligns with prior research, demonstrating a substantially elevated recurrence risk in STAS-positive patients undergoing sublobar resection, underscoring the critical importance of surgical extent adequacy for tumors manifesting aggressive pathological characteristics [23].

Tumors with a micropapillary (MP) component demonstrate high invasiveness, as micropapillary cell clusters acquire the capacity to spread systemically through mechanisms like anti-apoptotic and anchorage-independent growth [26]. The expanded local surgical scope presents challenges in eradicating potential micrometastatic foci, consistent with Kamiya et al.'s findings indicating significantly lower long-term survival rates in MP-positive patients compared to MP-negative individuals [27]. Therefore, systemic interventions such as adjuvant chemotherapy and targeted therapy may play a

crucial role in improving the prognosis of patients with substantial MP content, rather than solely focusing on widening the local surgical intervention. Furthermore, a recurrence risk prediction model customized for small-focal lung adenocarcinomas by Bains et al. demonstrated that invasive pathological features including the MP component, spread through air spaces (STAS), and solid component are vital predictors of recurrence risk following sublobar resection [28].

In this investigation, we developed a predictive column chart encompassing essential parameters including MP components, surgical approach, STAS, T stage, etc., capable of individually forecasting the likelihood of survival at 3 and 5 years post-surgery. The OS model exhibited a C-index of 0.72, with the calibration curve demonstrating favorable concordance between predicted and observed values. In contrast to prevailing models, this novel framework integrates both pathological aggressiveness markers and treatment-related variables, offering utility in preoperative surgical decision-making and postoperative risk assessment. This model enables precise responses to critical clinical inquiries, such as the 3-year survival probability following lobectomy in high MP patients and the survival impact on individuals with low MP opting for sublobar resection, facilitating informed decision-making collaboration between clinicians and patients. External validation is imperative to enhance the model's accuracy.

Limitations

Several limitations need to be acknowledged. Firstly, the retrospective single-center design introduced inherent selection and information biases. Secondly, the small sample size of the MP > 40% group (n = 28) restricted the statistical power of the subgroup analysis. Thirdly, the absence of cause-of-death-specific data necessitated the use of proxies to define competing events. Lastly, the prognostic model lacked external validation, and its generalizability requires further confirmation. Subsequent prospective, multicenter studies are warranted to validate these results and investigate the optimal comprehensive treatment approach for high-risk MP patients.

Conclusion

This study examined the individual and combined impacts of micropapillary (MP) components and surgical methods on prognosis. The findings revealed that MP exceeding 40% represented the most potent adverse prognostic determinant (HR 8.60) exhibiting a dose-response correlation. Additionally, sublobar resection emerged as an autonomous risk factor (HR 2.45), displaying a heightened impact post PSM (HR 2.95). Subgroup analysis indicated a preference for lobectomy in individuals with minimal MP (< 5%), while patients with substantial MP (> 20%) necessitated systemic adjuvant therapy, thereby furnishing novel insights for tailored surgical decision-making in early-stage lung adenocarcinoma.

Abbreviations

MP

micropapillary
OS
overall survival
RFS
recurrence-free survival
PSM
propensity score matching
HR
hazard ratio
CI
confidence interval
SHR
subdistribution hazard ratio
CIF
cumulative incidence function
VPI
visceral pleural invasion
STAS
spread through air spaces
PNI
perineural invasion
LVI
lymphovascular invasion
CEA
carcinoembryonic antigen
LN
lymph node
NSCLC
non-small cell lung cancer
RCT
randomized controlled trial
RERI
relative excess risk due to interaction
AP
attributable proportion
S
synergy index
SMD
standardized mean difference
IPCW

inverse probability of censoring weighting.

Declarations

Reporting Checklist

The authors have completed the STROBE-MR reporting checklist.

Conflicts of Interest:

The authors have no relevant financial or non-financial interests to disclose.

Ethical Statement

This study was approved by the Ethics Committee of Jiaxing First Hospital (Zhejiang, China), (Ethics No. 2026-LY-014).

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Author Contribution

All authors contributed to the study conception and design. Liang Zhou: writing-original draft preparation, writing-review and editing, Conceptualization, methodology, Resources; Niu Niu Junjie Zhao: Formal analysis and investigation, writing-original draft preparation, writing-review and editing; Niu Niu Weibo Qi: writing-original draft preparation, writing-review and editing; Haitao Liu Fan Yang: writing-original draft preparation, writing-review and editing, Supervision; Weibo Qi: Funding acquisition, Supervision, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability:

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Figures

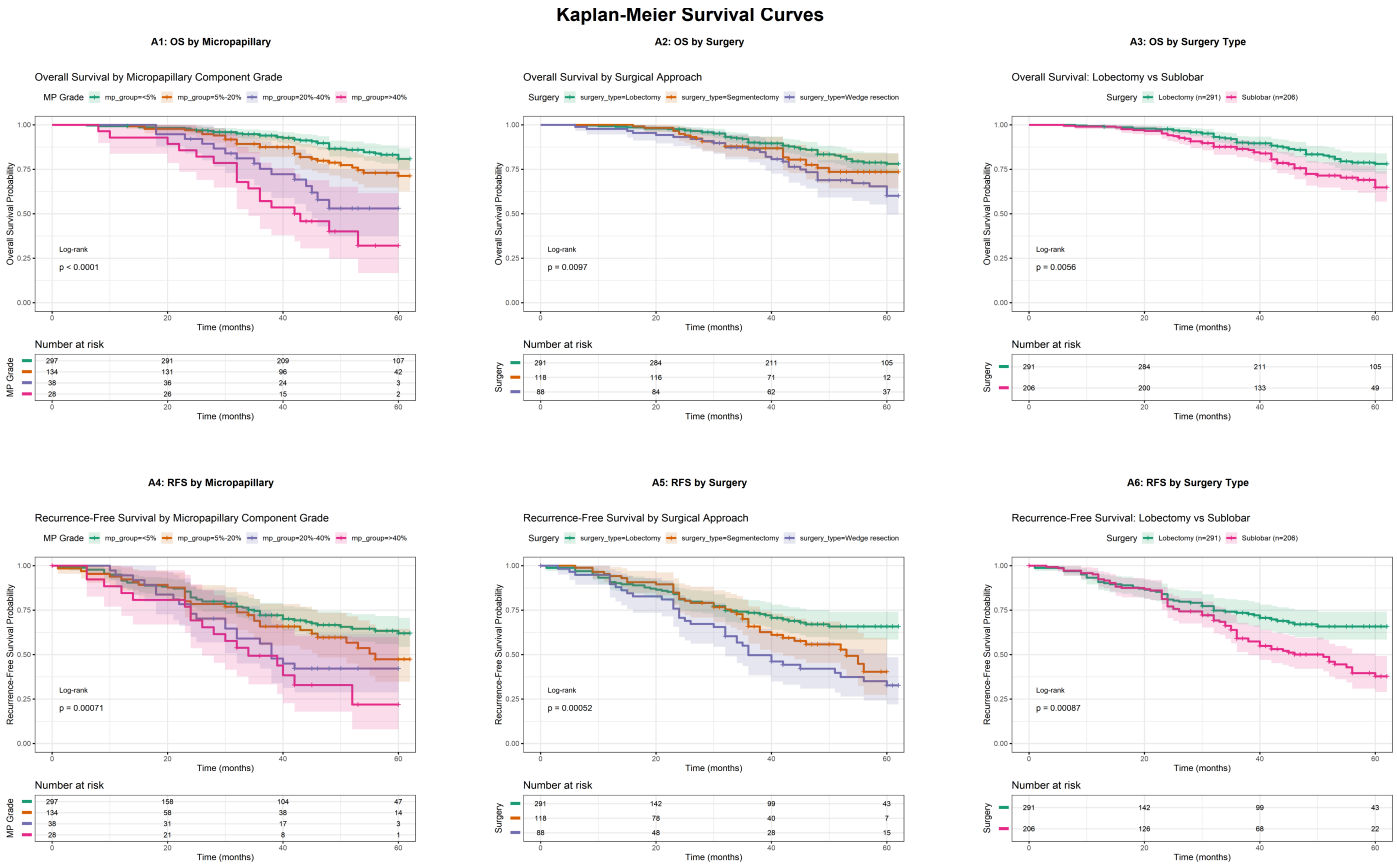


Figure 1

Kaplan-Meier survival curves. A1-A3 are overall survival (OS), A4-A6 are recurrence-free survival (RFS); the left column is graded by MP component, the middle column by type of surgery (lobectomy/segmental resection/wedge resection), and the right column by surgical modality (lobectomy/sublung lobectomy). Shaded areas are 95% confidence intervals, and the risk table below lists the number of survivors at each time point. p-values are derived from log-rank trend tests or comparisons of two groups.

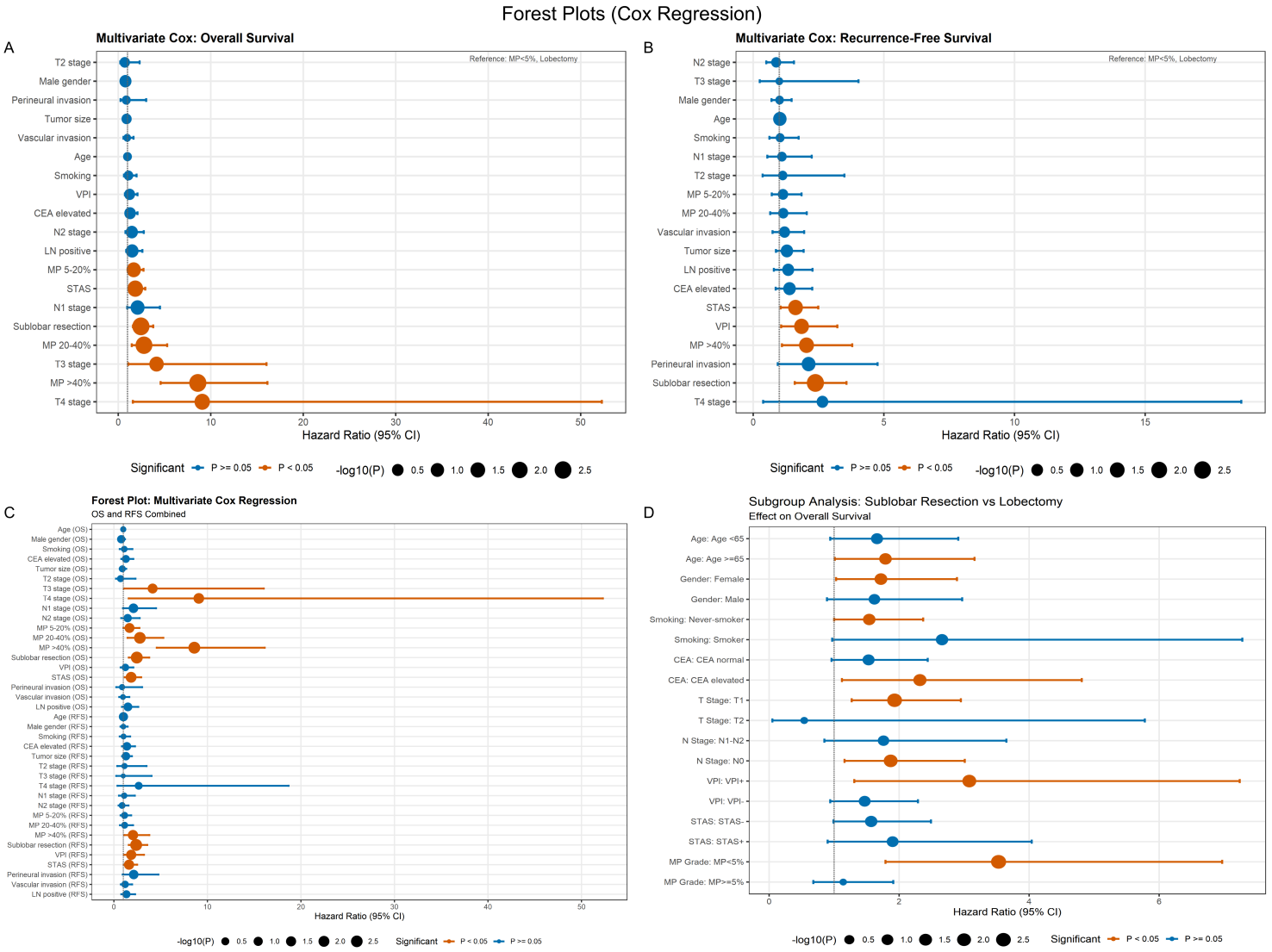


Figure 2

Cox regression forest plot panels. A: OS multifactorial Cox regression forest plot, sorted by HR value; B: RFS multifactorial Cox regression forest plot; C: OS and RFS combined forest plot; D: subgroup analysis forest plot. Orange/purple dots represent P<0.05 and blue dots represent P>=0.05. Dot size is proportional to the degree of statistical significance. The dashed line is the reference line for HR=1.

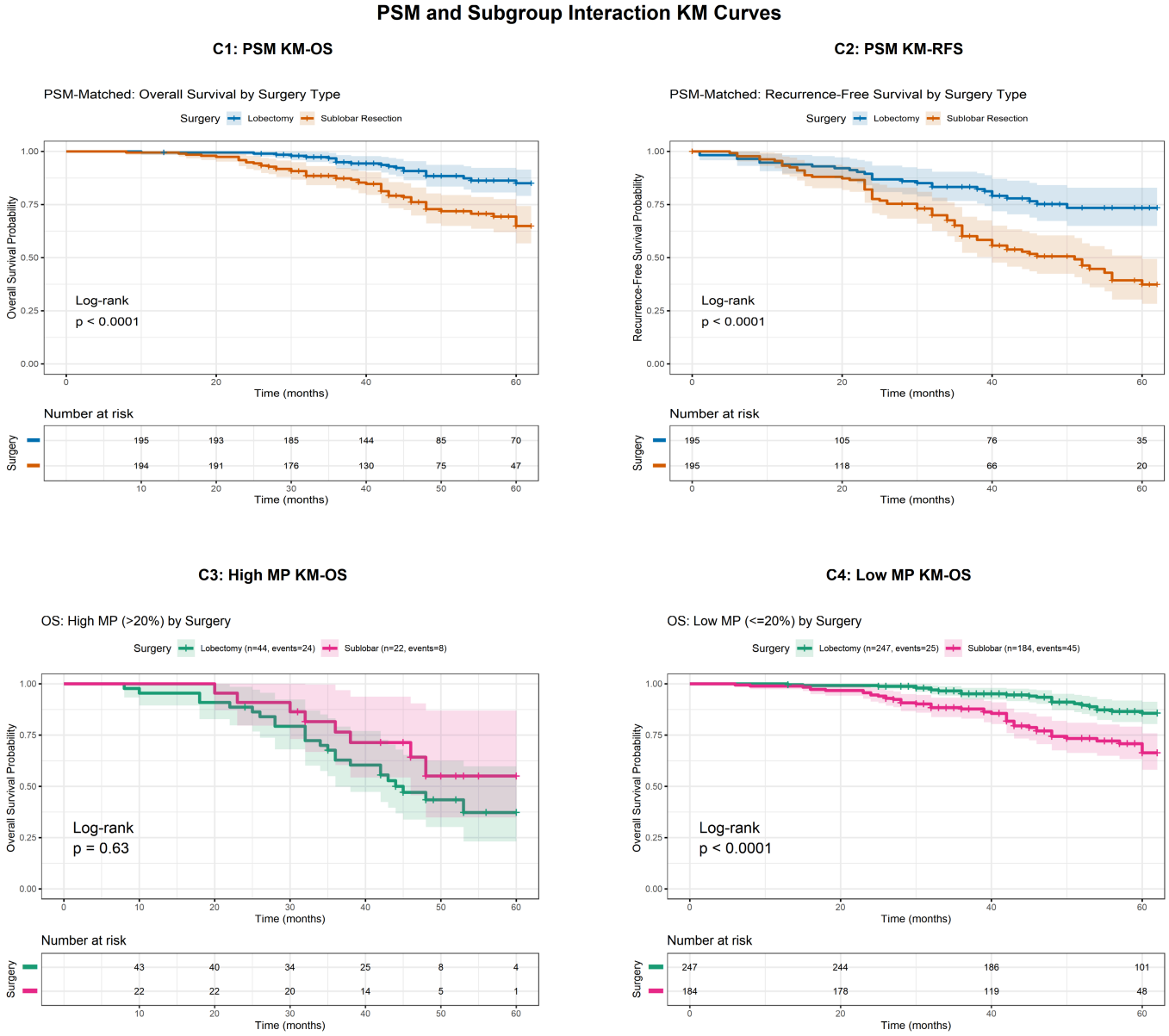


Figure 3

PSM matching analysis with interaction KM curves. C1: OS curve of lobectomy versus sublobar resection after PSM matching (p<0.001); C2: RFS curve after PSM matching (p<0.001); C3: OS curve of lobectomy versus sublobar resection in high MP (>20%) population (p=0.63);C4: low MP (≤20%) OS curves for lobectomy versus sublobar resection in the population (P<0.001). Shaded areas are 95% confidence intervals.

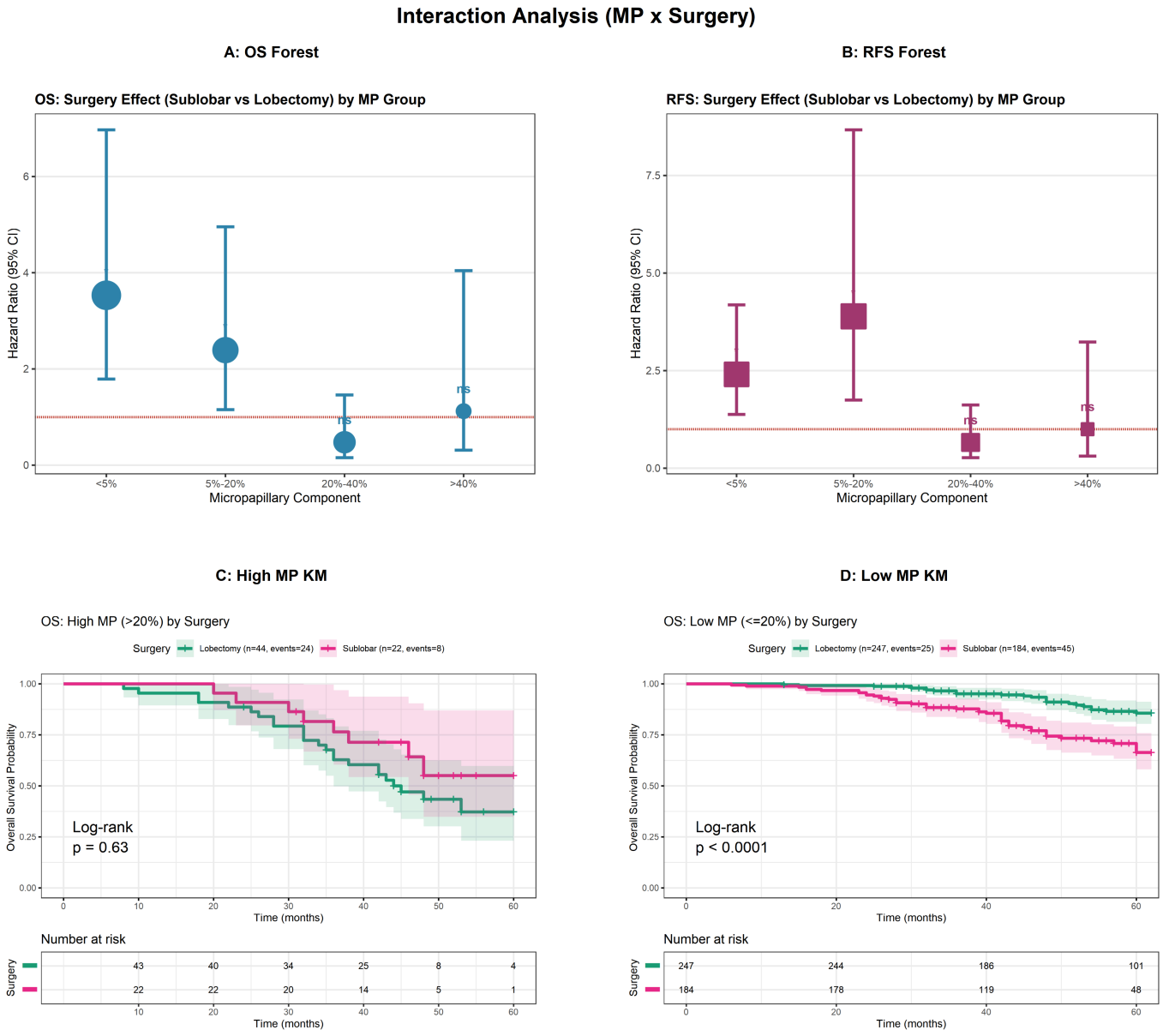


Figure 4

Interaction analysis. A: Forest plot of OS stratified by MP showing HR of sublobar resection vs lobectomy in each MP group; B: Forest plot of RFS stratified by MP; C: OS KM curve by surgical modality in the high MP (>20%) population (p=0.2105); D: OS KM curve by surgical modality in the low MP (≤20%) population (p< 0.001). * indicates P<0.05 and ns indicates no statistical significance. Shaded areas are 95% confidence intervals.

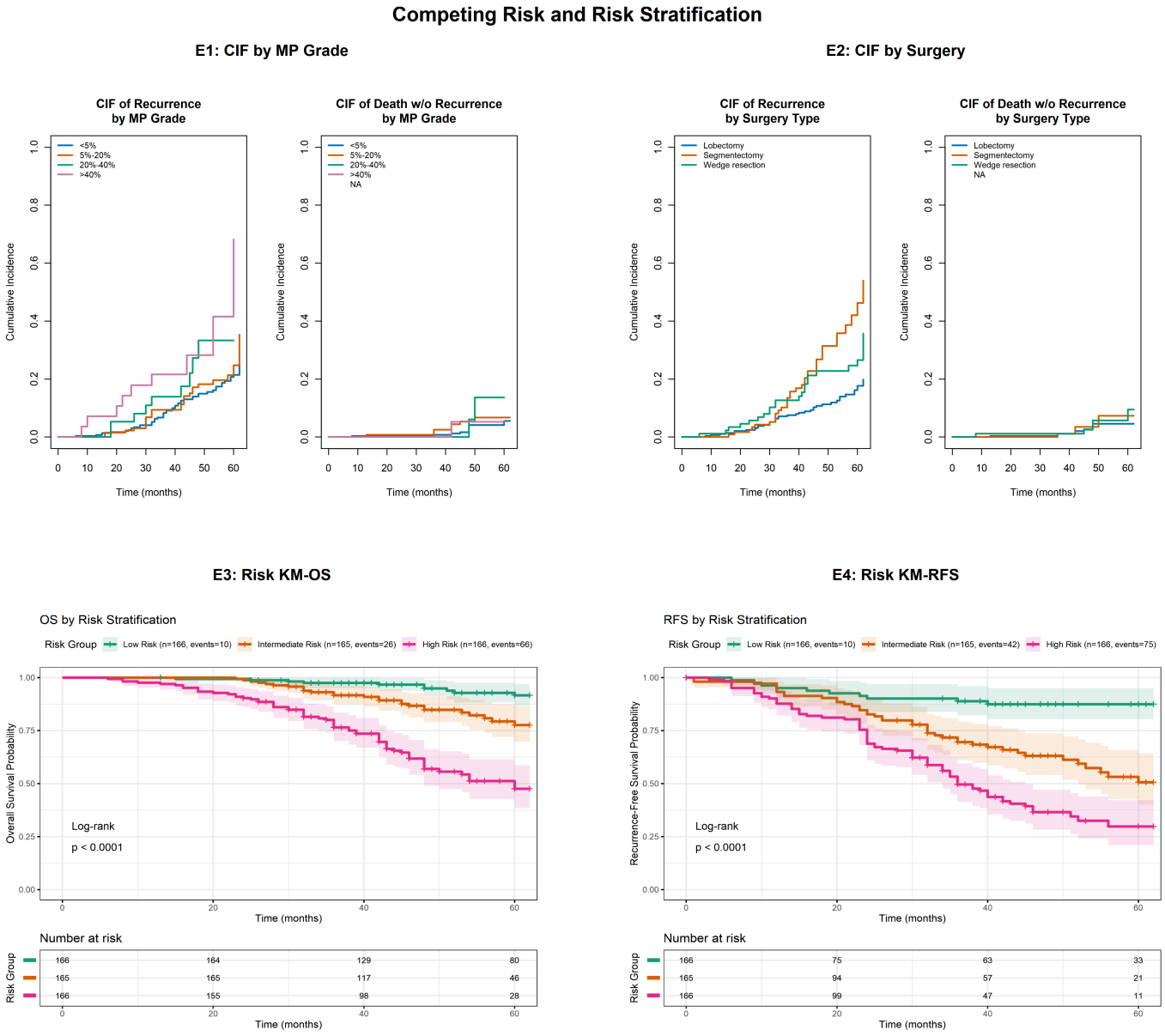


Figure 5

Cumulative incidence function (CIF) curves for competitive risk analysis. E1 is graded by MP component, E2 is grouped by surgical procedure, and different color curves represent different groups.

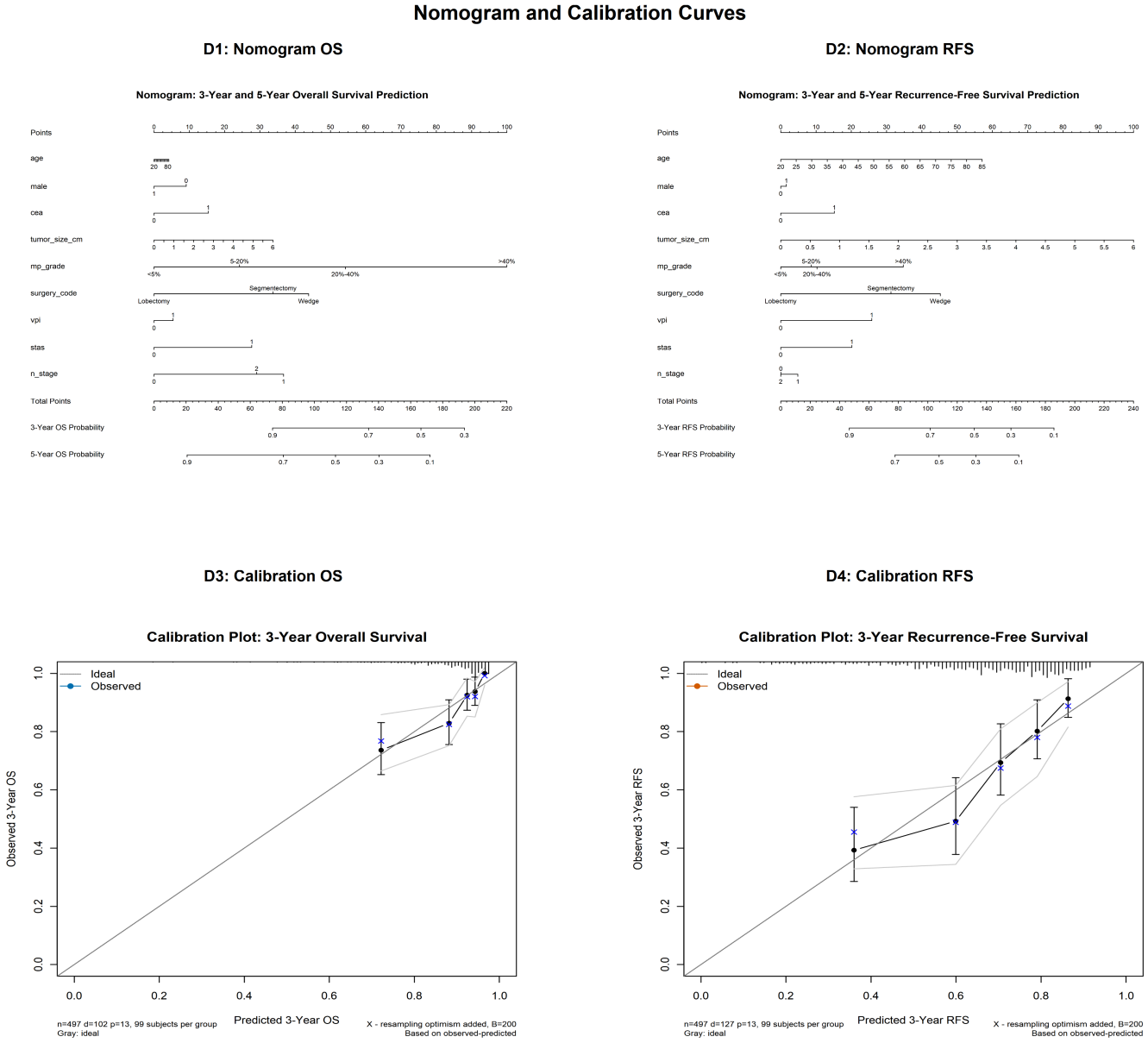


Figure 6

Prognostic nomogram (D1-2) and calibration curve (D3-4).