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Survival analysis and prognostic factors of diffuse bilateral intrapulmonary metastases in patients with non-small cell lung cancer

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Abstract

The study aimed to develop a nomogram utilizing the surveillance, epidemiology, and end results (SEER) database to predict the survival probability of diffuse bilateral intrapulmonary metastases (DBIM) in patients with non-small cell lung cancer (NSCLC). Clinical data from 2010 to 2020 were retrieved from the SEER database. Independent prognostic factors influencing overall survival (OS) were identified through univariate and multivariate Cox proportional hazards regression analyses conducted on the training cohort. Subsequently, a nomogram was constructed and its performance was assessed using concordance index (C-index), calibration curves, receiver operating characteristic (ROC) curves and area under the curve (AUC) results. Propensity score matching was employed to reduce variability in subgroup analysis comparing patients who received chemotherapy alone versus chemoradiotherapy. A total of 2075 patients were included in this study, wherein race, sex, marital status, age, household income, AJCC N stage, AJCC M stage, tumor size, total number of in situ/malignant tumors, bone metastasis, brain metastasis (BM), liver metastasis, surgery, and chemotherapy were independent prognostic factors. The nomogram demonstrated excellent performance, as evidenced by the high C-indexes, AUC results, and calibration curves. Subgroup analysis revealed potential benefits for women, patients with combined BM, and high-income individuals who received chemotherapy in conjunction with local radiotherapy. However, no significant impact on the 0.5-year survival rate was observed. Notably, a reliable nomogram was successfully developed to estimate the probability of survival in patients with DBIM. Overall, our study highlights the potential benefit of adding radiotherapy to chemotherapy specifically for women, those with combined BM, and high-income individuals.

Abbreviations: AUC = area under the curve, BM = brain metastasis, C-index = concordance index, DBIM = diffuse bilateral intrapulmonary metastases, NSCLC = non-small cell lung cancer, OS = overall survival, ROC = receiver operating characteristic, SEER = the surveillance, epidemiology, and end results.

Keywords: diffuse bilateral intrapulmonary metastases, nomogram, NSCLC, prognosis, radiotherapy, the SEER database

1. Introduction

According to the Global Cancer Statistics 2020, lung cancer accounts for 18% of cancer-related deaths.[1] The lack of specific clinical manifestations in early-stage lung cancer often leads to delayed diagnosis.[2] By the time obvious symptoms such as hemoptysis, cachexia, intolerable pain, or superficial lymph node mass appear, it may already indicate an advanced stage of the disease. With increasing life expectancy and advancements in examination technology and public health awareness, there has been a growing detection of lung cancers,[3–5] among which multiple lung nodules are identified at the initial diagnosis.

According to the eighth edition of the American Joint Committee on Cancer Staging Manual, T4 stage is assigned when multiple ipsilateral lung tumor nodules are present, while M1 stage is assigned when contralateral lung tumor nodules are found. However, distinguishing between multiple primary lung cancers and intrapulmonary metastases poses a challenge in clinical practice. These 2 types of cancer differ significantly in terms of treatment modality and prognosis.[6] Multiple primary lung cancers refer to the simultaneous or consecutive occurrence of 2 or more primary lesions in different parts of the lungs, accounting for approximately 15% of all cases of lung cancer.[7,8] A retrospective study evaluating the prognosis after surgery for bilateral multiple primary lung cancer reported a 3-year survival rate of 94.4%.[9] On the other hand, when lung cancer metastasizes, a combination therapy involving chemotherapy, radiotherapy, and targeted therapy is typically recommended with a median survival

This retrospective study was based on an open database which permission to collect data could be obtained through an email request, and informed patient consent was not required.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

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time limited to only 12 months. The presence of multi-organ metastasis significantly restricts prognosis with an average survival period usually <6 months.[10] With the individualization of tumor treatment, the survival time of lung cancer combined with metastasis has significantly improved. Several studies have consistently demonstrated that targeted therapy can effectively enhance the survival time for end-stage lung cancer patients harboring genetic mutations, such as common EGFR and ROS1 mutations.[11,12] However, there is limited understanding regarding the epidemiology and characteristics of diffuse bilateral intrapulmonary metastases (DBIM), which is crucial for informing clinical decision-making. Therefore, our study aimed to establish and validate a prognostic nomogram specifically designed for patients with DBIM using data from the surveillance, epidemiology, and end results (SEER) database.

2. Methods

2.1. Patient

The SEERStat software (version 8.4.2; Surveillance Research Program, National Cancer Institute, Bethesda, MD) was utilized to filter and gather data from a representative patient population for our research study. Inclusion criteria required enrolled patients to meet the following conditions: TNM 7/CS v0204 + Schema recode = "Lung"; Year of diagnosis = "2010," "2011," "2012," "2013," "2014," "2015," "2016," "2017," "2018," "2019," "2020"; Laterality = "Bilateral, single primary"; SEER Combined Mets at DX-lung (2010+) = "Yes." According to the SEER Program Coding and Staging Manual 2023, Laterality = "Bilateral, single primary" is rarely used except for diffuse bilateral lung nodules. Exclusion criteria were as follows: unknown or 0 survival time; small cell lung cancer pathology type; incomplete data on relevant indicators of patients.

2.2. Research variables and end points

A total of 19 variables were included including: race, gender, marital status, age, household income, primary site, histologic type, AJCC T stage, AJCC N stage, AJCC M stage, tumor size, separate tumor nodules in the ipsilateral lung, total number of in situ/malignant tumors, bone metastasis, brain metastasis (BM), liver metastasis, surgery, chemotherapy, and radiotherapy. OS defined as the duration between date of diagnosis and date of death from any cause or last follow-up visit was considered as the endpoint for this research study.

2.3. Statistical analysis

2.3.1. Construction of the nomogram. Patients were randomly assigned in a 7:3 ratio to the training and validation cohorts. In the baseline information, categorical variables were expressed as numbers (n) and percentages (%). Chi-square or Fisher's exact tests were used to compare categorical variables between the 2 groups to determine between-group differences. We initially performed univariate Cox proportional hazards regression analysis to evaluate the association between each variable and overall survival (OS). Variables demonstrating statistically significant associations ($P < .05$) in the univariate analysis were subsequently included in the multivariate Cox proportional hazards regression model for further investigation. Hazard ratio (HR) and 95% confidence intervals (CI) were used as effect estimates. To enhance model stability, LASSO regression with 10-fold cross-validation was applied to screen potential predictors and determine the optimal regularization parameter (λ). The final predictive model was established using multivariate Cox proportional hazards regression analysis.

2.3.2. Validation of the nomogram. Discriminatory ability was assessed using concordance index (C-index), receiver operating characteristic (ROC) curves, and area under the curve (AUC) calculation. Calibration curves were used to

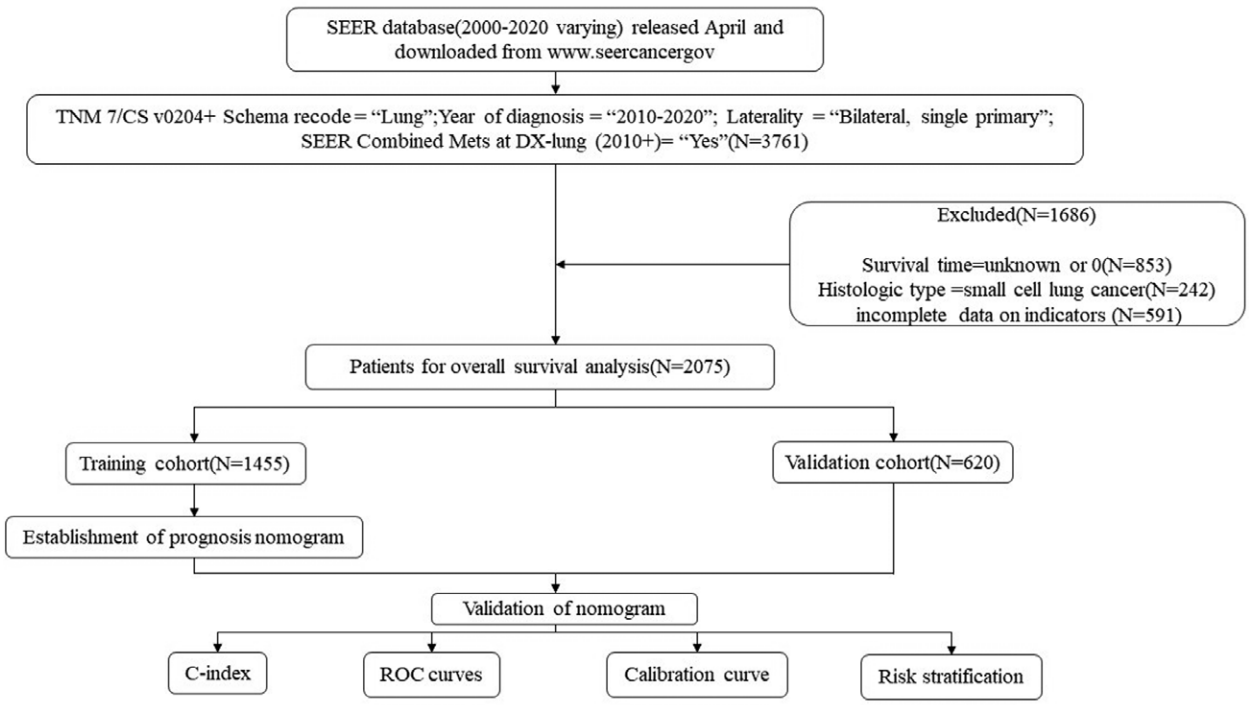

Figure 1. Flowchart of participant inclusion and exclusion.

evaluate the agreement between the predicted probabilities from the nomogram and observed probabilities. Each patient was assigned a risk score based on the nomogram model, with the median risk score used as a threshold for categorizing individuals into high-risk and low-risk groups. Kaplan–Meier survival plots were generated, and differences between groups were evaluated using log-rank tests. The flowchart in Figure 1 illustrates the patient screening process and study design.

2.3.3. Subgroup analysis to evaluate the prognosis of different treatment options. Patients treated with chemotherapy alone and chemoradiotherapy were paired using propensity score matching to reduce the bias between the 2 groups. The screened independent prognostic factors were used for subgroup analysis. Pairs of patients receiving chemoradiotherapy or chemotherapy-only were derived using 1:1 greedy nearest neighbor matching within PS score of 0.1. Kaplan–Meier survival curves were utilized to calculate survival rates in order to explore the prognosis in various populations, with the results presented in a forest plot. Differences between groups were evaluated using log-rank tests. Statistical significance was defined as $P < .05$ (2-sided). All statistical analyses were performed using R software (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). Specific R packages were employed as follows: the rms package (v6.7-1; Prof Frank E Harrell Jr, Department of Biostatistics, Vanderbilt University, Nashville) for nomogram construction; the pROC package (v1.18.4; Dr Xavier Robin, Institute of Computational Science, University of Zurich, Switzerland) for ROC curve analysis; and the survival package (v3.5-5; Dr Terry Therneau, Department of Health Sciences Research, Mayo Clinic, Rochester) for survival analyses.

2.4. Study design and reporting standards

This study was conducted in strict accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guidelines to ensure transparent development and validation of the prediction model.

3. Results

3.1. Clinical characteristics of participants

A total of 2075 patients, with a median survival time of 6 months, were included and randomly assigned at a ratio of 0.7 to either the training cohort (n = 1455) or the validation cohort (n = 620). No significant differences in clinical characteristics were observed between these 2 cohorts. Of the 2075 patients, the majority were White, 80.0%, with 9.8% Black. The patients were predominantly elderly, with 1412 (68%) older than 65 years, and the gender distribution was almost equal between men and women. Of the social attributes included, nearly half of the patients were married, and 48.6% had a mean household income in the range of $55,000 to $74,999. The primary site of the tumor was overwhelmingly unspecified as to which portion of the lung lobe it occurred in specifically, with adenocarcinoma being the most common type of pathology, and squamous carcinoma being the least common in this population (n = 299). According to the AJCC staging system, over half of the patients were diagnosed with T4 tumors at initial presentation, while at least 56% had N2 or N3 nodal involvement and 52.4% exhibited extrapulmonary organ metastases. The most common sites of extrapulmonary metastasis were bone followed by brain, whereas liver metastases were infrequent (15.8%). A total of 514 patients developed a second (or more) primary malignancy during the follow-up period. Regarding the choice of treatment regimen, over half of the patients opted for chemotherapy, with documented radiation therapy being administered to 29.4% of them, while surgical intervention was only performed on a small

Table 1

Demographics and clinicopathologic characteristics of the training and validation cohort.

Characteristics	Overall (n = 2075)	Training cohort (n = 1455)	Validation cohort (n = 620)	*P* value
Race (%)				.926
White	1659 (80.0)	1162 (79.9)	497 (80.2)	
Black	204 (9.8)	142 (9.8)	62 (10.0)	
Others	212 (10.2)	151 (10.4)	61 (9.8)	
Age (%)				.987
0–64 yr	663 (32.0)	464 (31.9)	199 (32.1)	
65–74 yr	688 (33.2)	484 (33.3)	204 (32.9)	
75 + yr	724 (34.8)	507 (34.8)	217 (35.0)	
Sex (%)				.441
Female	1019 (49.1)	706 (48.5)	313 (50.5)	
Male	1056 (50.9)	749 (51.5)	307 (49.5)	
Marital status (%)				.153
Married	1005 (48.4)	722 (49.6)	283 (45.6)	
Unmarried	415 (20.0)	277 (19.0)	138 (22.3)	
Divorced	655 (31.6)	456 (31.4)	199 (32.1)	
Income (%)				.94
$0–$54,999	365 (17.6)	254 (17.5)	111 (17.9)	
$55,000–$74,999	1009 (48.6)	711 (48.9)	298 (48.1)	
$75,000+	701 (33.8)	490 (33.7)	211 (34.0)	
Primary site (%)				.645
Lower lobe	22 (1.1)	17 (1.2)	5 (0.9)	
Main bronchus	173 (8.3)	122 (8.4)	51 (8.2)	
Overlapping lesion	124 (6.0)	80 (5.5)	44 (7.1)	
Upper lobe	25 (1.2)	18 (1.2)	7 (1.1)	
Lung, NOS	1731 (83.4)	1218 (83.7)	513 (82.7)	
Histology (%)				.299
Adenocarcinoma	1228 (59.2)	872 (59.9)	356 (57.4)	
SCC	299 (14.4)	213 (25.4)	86 (13.9)	
Others	548 (26.4)	370 (25.4)	178 (28.7)	
AJCC T (%)				.888
T1	55 (2.7)	38 (2.6)	17 (2.8)	
T2	102 (4.9)	76 (5.2)	26 (4.2)	
T3	539 (26.0)	380 (26.1)	159 (25.6)	
T4	1182 (57.0)	823 (56.6)	359 (57.9)	
TX	197 (9.4)	138 (9.5)	59 (9.5)	
AJCC N (%)				.387
N0	618 (29.8)	433 (29.8)	185 (29.9)	
N1	137 (6.6)	89 (6.1)	48 (7.7)	
N2	625 (30.1)	448 (30.8)	177 (28.5)	
N3	544 (26.2)	386 (26.5)	158 (25.5)	
NX	151 (7.3)	99 (6.8)	52 (8.4)	
AJCC M (%)				.357
M1a	987 (47.6)	682 (46.9)	305 (49.2)	
M1b/M1c	1088 (52.4)	773 (53.1)	315 (50.8)	
STNIL (%)				.211
None	328 (15.8)	240 (16.5)	88 (14.2)	
Yes	1747 (84.2)	1215 (83.5)	532 (85.8)	
Tumor size (%)				.556
0.1–3.0 cm	552 (26.6)	377 (25.9)	175 (28.3)	
3.1–5.0 cm	345 (16.6)	245 (16.8)	100 (16.1)	
5.1–7.0 cm	167 (8.0)	117 (8.0)	50 (8.1)	
More than 7 cm	106 (5.1)	81 (5.6)	25 (4.0)	
Unable to evaluate	905 (43.7)	635 (43.6)	270 (43.5)	
MTN (%)				.665
1	1538 (74.1)	1074 (73.8)	464 (74.8)	
More than one	537 (25.9)	381 (26.2)	156 (25.2)	
Bone metastasis (%)				.292
No	1437 (69.3)	997 (68.5)	440 (71.0)	
Yes	638 (30.7)	458 (31.5)	180 (29.0)	
Brain metastasis (%)				1
No	1640 (79.0)	1150 (79.0)	490 (79.0)	
Yes	435 (21.0)	305 (21.0)	130 (21.0)	
Liver metastasis (%)				1
No	1748 (84.2)	1226 (84.3)	522 (84.2)	
Yes	327 (15.8)	229 (15.7)	98 (15.8)	
Surgery (%)				.262
No	2002 (96.5)	1399 (96.2)	603 (97.3)	
Yes	73 (3.5)	56 (3.8)	17 (2.7)	
Chemotherapy (%)				.258
No/Unknown	973 (46.9)	670 (46.0)	303 (48.9)	
Yes	1102 (53.1)	785 (54.0)	317 (51.1)	
Radiation (%)				.936
No/Unknown	1465 (70.6)	1026 (70.5)	439 (70.8)	
Yes	610 (29.4)	429 (29.5)	181 (29.2)	

MTN = malignant tumors number, SCC = squamous cell carcinoma, STNIL = separate tumor nodules in the ipsilateral lung.

proportion (3.5%). The detailed distribution of patients can be observed in Table 1.

3.2. Independent prognostic factors

The univariate Cox regression analysis revealed significant correlations ($P < .05$) between survival and various factors including race, gender, marital status, age, household income, AJCC T stage, AJCC N stage, AJCC M stage, tumor size, total number of in situ/malignant tumors, bone metastasis, BM, liver metastasis, surgery, chemotherapy, and radiotherapy. The aforementioned variables were further subjected to multivariate Cox regression analysis resulting in the identification of 14 independent prognostic factors: race, gender, marital status, age, household income, AJCC N stage, AJCC M stage, tumor size, total number of in situ/malignant tumors, bone metastasis, BM, liver metastasis, surgery, and chemotherapy. The specific HR values along with their corresponding 95% CI are presented in Table 2.

3.3. Construction and validation of the nomogram

A predictive model was developed to estimate the survival probability of DBIM, utilizing the selected variables (Fig. 2). The risk score for each variable was computed using the nomogram, and their cumulative sum yielded the total risk score, enabling prediction of survival probabilities at 0.5-years, 1-year, and 2-years. The C-index for the predictive model was 0.702 (95% CI: 0.686–0.718) in the training cohort and 0.688 (95% CI: 0.663–0.713) in the validation cohort. Figure 3 illustrates the ROC curves of the nomogram for predicting survival probabilities at 0.5-, 1-, and 2-year intervals in both cohorts, with AUC values of 0.762 (95% CI: 0.737–0.788), 0.750 (95% CI: 0.723–0.777), and 0.757 (95% CI: 0.724–789) for the training cohort. For the validation cohort, the AUC values for 0.5, 1, and 2 years were 0.747 (95% CI: 0.709–0.785), 0.755 (95% CI: 0.715–0.794), and 0.770 (95% CI: 0.721–0.820), respectively. These findings indicated that our model exhibits excellent discriminatory ability. Figure 4 presents calibration curves depicting predicted versus actual survival probabilities at 0.5, 1, and 2 years for the training and validation cohorts, demonstrating strong concordance between predicted and observed OS.

3.4. Hazard stratification based on the nomogram

The risk scores of all patients in the training cohort were calculated, and the median (risk score 453) was used as the intercept value. Patients with a risk score ≥453 were classified into the high-risk group, while those with a risk score <453 were classified into the low-risk group. The survival rates at 0.5, 1, and 2 years for the high-risk group in the training cohort were 35%, 16%, and 6%, respectively. In contrast, for the low-risk group, these rates were significantly higher at 73%, 52%, and 29%, respectively (Fig. 5A). In the validation cohort, similar trends were observed with survival rates of 35%, 19%, and 5% at years of follow-up for high-risk patients compared to rates of 73%, 54%, and 29% for low-risk patients (Fig. 5B).

3.5. Prognostic value of radiotherapy

After performing 1:1 nearest neighbor matching, a total of 219 pairs of patients were included in the subgroup analysis, comparing those who received chemoradiotherapy with those who received chemotherapy alone. The study findings revealed no significant difference in the 0.5-year survival rate between the 2 groups within the entire population (chemoradiotherapy group: 58%, 95% CI: 51%–64%; chemotherapy group: 58%, 95% CI: 52%–65%). Notable statistically significant differences in survival rates were observed when analyzing specific subgroups

Table 2

Univariate and multivariate Cox proportional hazards analysis in the training cohort.

	Univariate analysis		Multivariate analysis	
Characteristics	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Race				
White	Reference		Reference	
Black	1.04 (0.86–1.25)	.680	1.14 (0.94–1.37)	.181
Others	0.75 (0.62–0.90)	.002	0.69 (0.56–0.84)	<.001
Age				
0–64 yr	Reference		Reference	
65–74 yr	1.09 (0.94–1.24)	.234	1.15 (0.99–1.32)	.058
75 + yr	1.36 (1.18–1.55)	<.001	1.59 (1.36–1.84)	<.001
Sex				
Female	Reference		Reference	
Male	1.47 (1.32–1.65)	<.001	1.43 (1.26–1.60)	<.001
Marital status				
Married	Reference		Reference	
Unmarried	1.21 (1.04–1.40)	.011	1.24 (1.05–1.44)	.007
Divorced	1.17 (1.03–1.32)	.013	1.12 (0.97–1.27)	.096
Income				
$0–$54,999	Reference		Reference	
$55,000–$74,999	0.75 (0.64–0.86)	<.001	0.77 (0.66–0.90)	<.001
$75,000+	0.69 (0.86–0.80)	<.001	0.72 (0.61–0.84)	<.001
Primary site				
Lower lobe	Reference			
Main bronchus	0.75 (0.43–1.28)	.291		
Overlapping lesion	0.74 (0.41–1.28)	.284		
Upper lobe	0.94 (0.46–1.88)	.863		
Lung, NOS	0.93 (0.56–1.55)	.796		
Histology				
Adenocarcinoma	Reference			
SCC	1.12 (0.96–1.31)	.143		
Others	1.12 (0.98–1.28)	.074		
AJCC T				
T1	Reference		Reference	
T2	1.78 (1.14–2.76)	.010	1.54 (0.97–2.46)	.066
T3	1.66 (1.12–2.43)	.010	1.27 (1.31–1.77)	.249
T4	1.59 (1.09–2.32)	.016	1.31 (0.88–1.94)	.182
TX	1.74 (1.14–2.62)	.009	1.20 (0.78–1.85)	.412
AJCC N				
N0	Reference		Reference	
N1	1.42 (1.11–1.80)	.005	1.27 (0.98–1.62)	.062
N2	1.61 (1.39–1.86)	<.001	1.52 (1.30–1.76)	<.001
N3	1.61 (1.38–1.86)	<.001	1.50 (1.27–1.76)	<.001
NX	1.53 (1.20–1.94)	<.001	1.52 (1.19–1.94)	<.001
AJCC M				
M1a	Reference		Reference	
M1b/M1c	1.81 (1.61–2.02)	<.001	1.41 (1.21–1.66)	<.001
STNIL				
None	Reference			
Yes	0.99 (0.85–1.15)	.911		
Tumor size				
0.1–3.0 cm	Reference		Reference	
3.1–5.0 cm	1.25 (1.05–1.48)	.012	1.17 (0.98–1.40)	.073
5.1–7.0 cm	1.91 (1.53–2.37)	<.001	1.76 (1.41–2.21)	<.001
More than 7 cm	1.92 (1.49–2.47)	<.001	1.44 (1.11–1.88)	.005
Unable to evaluate	1.43 (1.24–1.63)	<.001	1.36 (1.18–1.57)	<.001
MTN				
1	Reference		Reference	
More than one	0.79 (0.69–0.89)	<.001	0.76 (0.67–0.87)	<.001
Bone metastasis				
No	Reference		Reference	
Yes	1.46 (1.29–1.64)	<.001	1.18 (1.02–1.37)	.026
Brain metastasis				
No	Reference		Reference	
Yes	1.54 (1.34–1.76)	<.001	1.28 (1.09–1.51)	.002
Liver metastasis				
No	Reference		Reference	
Yes	1.78 (1.53–2.05)	<.001	1.37 (1.16–1.61)	<.001
Surgery				
No	Reference		Reference	
Yes	0.43 (0.31–0.59)	<.001	0.59 (0.42–0.81)	<.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.63 (0.57–0.71)	<.001	0.55 (0.49–0.62)	<.001
Radiation				
No/unknown	Reference		Reference	
Yes	1.21 (1.07–1.36)	.002	0.93 (0.81–1.06)	.303

CI = confidence interval, HR = hazard ratio, MTN = malignant tumors number, SCC = squamous cell carcinoma, STNIL = separate tumor nodules in the ipsilateral lung.

based on gender (female), family income ($75,000+), and presence of BM. Among female patients, the chemoradiotherapy group exhibited a higher 0.5-year survival rate compared to the chemotherapy group (70%, 95% CI: 61%–80% vs 62%, 95% CI: 53%–73%). Similarly, patients with a family income $75,000+ showed improved outcomes with chemoradiotherapy compared to chemotherapy alone (66%, 95% CI: 55%–78% vs 56%, 95% CI: 45%–70%). Furthermore, individuals diagnosed with BM demonstrated significantly better results when treated with chemoradiotherapy than those receiving only chemotherapy (71%, 95% CI: 60%–85%) versus (47%, 95% CI: 35%–63%), respectively (Fig. 6). Addition of radiotherapy to chemotherapy may enhance the short-term survival rate at 6 months for patients belonging to these aforementioned populations.

4. Discussion

With the widespread adoption of low-dose chest CT screening for lung cancer, there has been a gradual increase in the detection rate of early-stage lung cancer, accompanied by a relative decrease in the incidence of advanced lung cancer.[13,14] However, the prognosis for metastatic lung cancer remains unfavorable. The current TNM staging system has limited ability to predict survival probability in end-stage lung cancer. Previous studies have constructed prognostic analysis of lung cancer with bone metastasis, lung cancer with BM, and lung cancer with liver metastasis.[15–18] Since the survival rate of DBIM is extremely low at the time of initial diagnosis, it is challenging to construct a prognostic model from a single research center, and there is no relevant prediction model to evaluate the prognosis of this specific population. Therefore, we conducted an analysis using data from the SEER database to identify independent risk factors influencing prognosis and developed a nomogram capable of predicting survival probabilities at 0.5, 1, and 2 years individually. Our study revealed that physiological characteristics (race, gender, age), social factors (marital status, household income), tumor staging characteristics (N stage, M stage, tumor size), presence of other primary malignancies, distant metastases (bone, brain, liver) and treatment options (surgery, chemotherapy) were associated with prognosis.

Consistent with the majority of previous studies, advanced age and male gender have been identified as unfavorable prognostic factors for lung cancer survival. In our study cohort, 68% of patients were aged over 65 years old. The diminished physiological reserve associated with aging contributes to reduced treatment tolerance, while treatment-related toxicities continue to escalate.[19] Hsu CL et al reported a relatively low utilization rate of systemic therapy in elderly patients with advanced lung cancer, with only 40.9% of individuals aged 70 to 79 receiving chemotherapy and even fewer patients above the age of 80 undergoing chemotherapy (12.3%).[20] This phenomenon can also be observed in patients with stage III lung cancer.[21] Notably, older patients exhibit a lower frequency of EGFR and KRAS mutations compared to their younger counterparts, resulting in limited availability of targeted therapies.[22] Furthermore, DNA damage accumulates with advancing age,[23] while DNA repair capacity declines[24]; these phenomena are more pronounced in males. Consequently, men experience significantly higher mortality risks than women (HR 1.43, 95% CI: 1.26–1.60), primarily due to higher smoking rates and greater sensitivity to tobacco carcinogens.[25] Regarding the effect of race on the prognosis of BDIM, we observed worse outcomes among African Americans

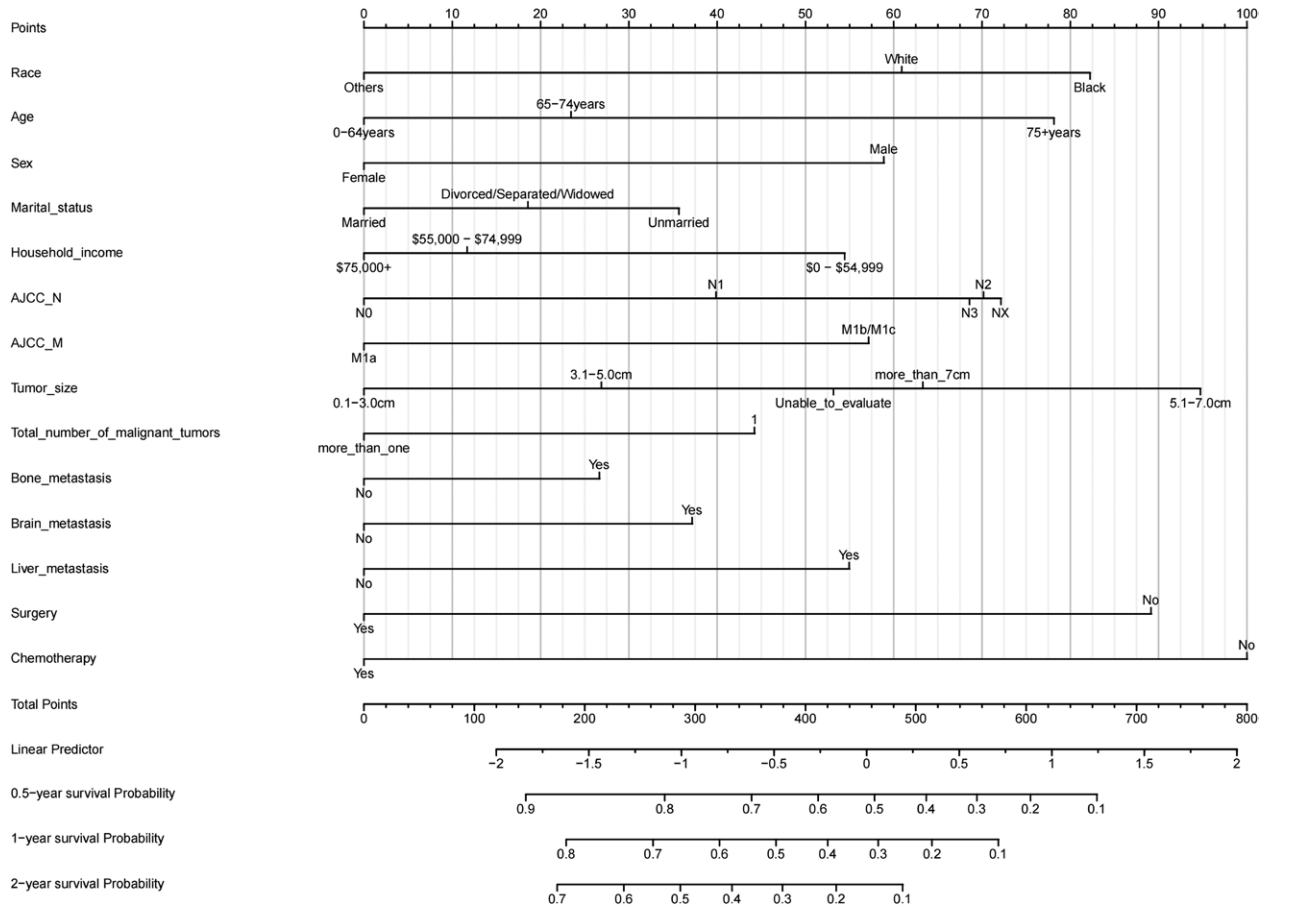

Figure 2. Nomograms for predicting 0.5, 1, and 2-yr OS. OS = overall survival.

compared to other racial groups. A study conducted by Gu Y et al explored the metastasis patterns of lung cancer in different races, and found that the probability of multiple metastasis was higher in Black people,[19] which may be attributed to racial genetic differences or income.

Since the introduction of the biopsychosocial model, an increasing number of scholars have been focusing on factors beyond the disease itself. Consequently, we investigated the impact of familial support on survival and found that being married and having a higher income are advantageous factors for individuals with DBIM. Given that metastatic non-small cell lung cancer (NSCLC) is incurable, it places a significant burden on patients. Although emerging antitumor drugs can improve prognosis, their healthcare costs have also escalated. A cross-sectional study concluded that despite competition among oncology drugs, prices for NSCLC treatments varied to some extent between 2015 and 2020.[26] Moreover, elderly patients commonly experience treatment-related toxicities such as myelosuppression and cardiotoxicity, leading to prolonged hospitalization and increased expenses; this financial burden is further exacerbated in patients with metastatic lung cancer. A Korean study examining the economic burden of NSCLC with BM demonstrated that these patients had longer hospital stays and more outpatient visits compared to stage IV patients without BM, resulting in a significant increase in medical costs (29%).[27] The cost associated with family care cannot be overlooked since terminally ill cancer patients often require assistance with daily activities; consequently, family members may need to resign from work or take leave to provide care which further amplifies the economic burden experienced by these families. Nearly 1 quarter of respondents identified caregiving expenses as a major financial strain.[28] DBIM imposes a significant burden on

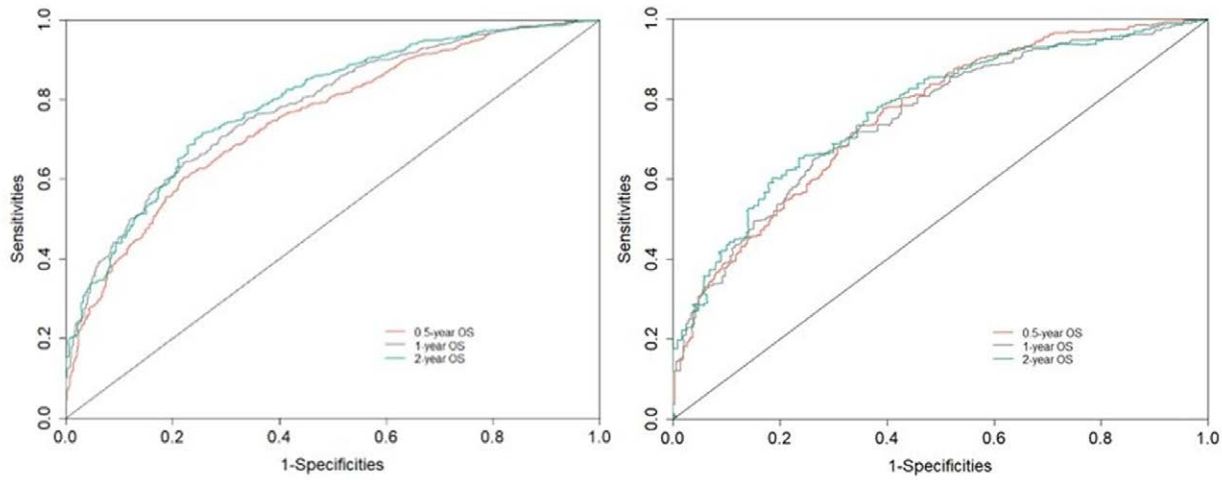

Figure 3. The time-dependent ROC curves of the nomogram predicting OS at (A) 0.5-yr and 1-yr and 2-yr in the training cohort, and at (B) 0.5-yr and 1-yr and 2-yr in the validation cohort. OS = overall survival, ROC = receiver operating characteristic.

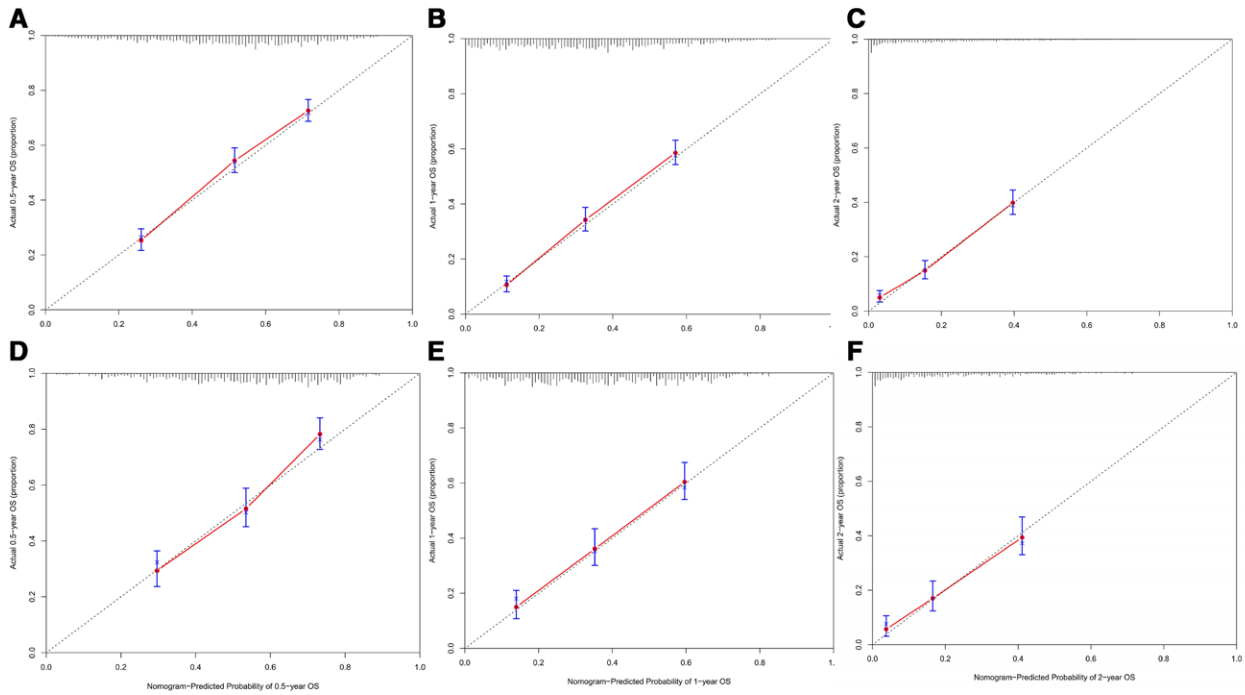

Figure 4. The calibration curves for predicting OS at (A) 0.5-yr and (B) 1-yr and (C) 2-yr in the training cohort, and at (D) 0.5-yr (E) 1-yr and (F) 2-yr in the validation cohort. OS = overall survival.

patients, both financially and in terms of mental health. A study reported that 44% of patients with advanced tumors experienced mental distress, including feelings of despair, fear, meaninglessness, and shame.[29] Additionally, another recent study revealed that 14% of patients with metastatic NSCLC developed depression, leading to a significant reduction in survival rate.[30] Notably, the partner not only serves as the primary caregiver but also plays a crucial role as a source of spiritual support. Spiritual well-being assists terminal tumor patients in combating depression and pain associated with their illness while enabling them to approach life optimistically. Kathrin Milbury et al conducted physical and psychological interventions on patients with metastatic NSCLC and their spouses, and the results showed that psychological interventions could relieve patients' sleep disorders and depression,[31] which corroborates the positive role of partner's spiritual support in advanced NSCLC patients. This study investigated the underexplored significance of familial support in patients with DBIM, a topic that has received limited attention in previous research studies.

Given the tendency for NSCLC cases with bilateral diffuse lung metastases to be overcategorized in the T stage, a majority of them were classified as T4 (1182, 57.0%). However, after conducting multivariate Cox regression analysis, the T stage did not show statistical significance. Therefore, we incorporated tumor size as an additional measure to better reflect the tumor burden. Our study revealed that higher N-stages and larger tumor sizes are associated with poorer prognosis in patients. Furthermore, we also investigated the prognostic impact of various patterns of extrapulmonary metastases. Consistent with previous studies, bone metastasis remains the most prevalent,[15] while liver metastasis is associated with the poorest prognosis.[18] Interestingly, we observed a more favorable prognosis during follow-up in cases where concurrent primary tumors from other sites were present. In many prognostic analyses of tumors, the combination of other primary tumors is often considered an exclusion criterion by most scholars. However, among patients with NSCLC combined with DBIM, the incidence of second-site primary tumors was remarkably high at 25.9%. Previous studies have confirmed mutations in TP53 and RB1 genes in metastatic lung cancer,[32,33] which are also known to be carcinogenic factors for various cancers. Therefore, it is imperative to include patients with concomitant primary tumors at other sites in our study. The improved prognosis of this population can be attributed to 2 key factors. Firstly, cancer patients typically undergo more comprehensive examinations and follow-up procedures compared to the general population, enabling a more accurate determination of metastasis from other sites. Consequently, early detection and intervention are possible in cases where a second primary tumor is present. Secondly, a study conducted in China revealed that the average and median time between lung cancer diagnosis and the emergence of a second primary tumor were 36.2 months and 10 months, respectively[34]; moreover, DBIM had a median survival time of only 6 months. This suggests that only patients who survive long enough have an opportunity to develop a second primary tumor.

Common treatment modalities for metastatic lung cancer include chemotherapy, radiation therapy, and surgery. Our study demonstrated that both chemotherapy and surgical treatment were positive prognostic factors for NSCLC combined with DBIM. The risk of death was reduced by approximately 45% in patients receiving chemotherapy compared to those who did not receive it, while the risk of death was reduced by about 41% in patients undergoing surgery compared to those who did not undergo it. Yang et al concluded that surgical treatment for cT1-2, N0-1, M1 or cT3, N0, M1 lung cancer had a correlation with survival time.[35] Additionally, surgery may improve the survival rate of lung cancer with extra thoracic metastasis; the 3-year survival rate can reach 16.9%.[36] However, there is a lack of large-scale real-world studies on the effect of surgery on stage IV lung cancer, and randomized controlled trials are needed to further explore the indications and prognosis of surgery. In our study, the risk ratio for radiotherapy was 0.93 (95%CI: 0.81–1.06), but there was no significant difference ($P = .303$). Systemic chemotherapy is the standard treatment for stage IV NSCLC, while radiotherapy serves as an effective modality to alleviate symptoms arising from local tumor growth (such as cough, hemoptysis, pain, dyspnea). In cases of multiple lesions, caution should be exercised when applying radiotherapy due to potential functional damage to irradiated organs. The toxicity associated with radiotherapy may not depend on the total number of lesions but rather on the dose delivered to the organ at risk. To mitigate this risk, it is crucial to protect critical volumes of organs from high-dose radiation exposure; typically, about 1/3 of the organ volume. Two randomized studies investigating metastatic NSCLC treated with systemic therapy combined with local radiotherapy demonstrated a significant improvement in progression-free survival at the expense of increased toxicity without any treatment-related deaths.[37,38] Ablation therapy remains an exploratory approach for metastatic NSCLC. NCT03721341 represents a randomized phase III trial evaluating stereotactic ablation radiotherapy in

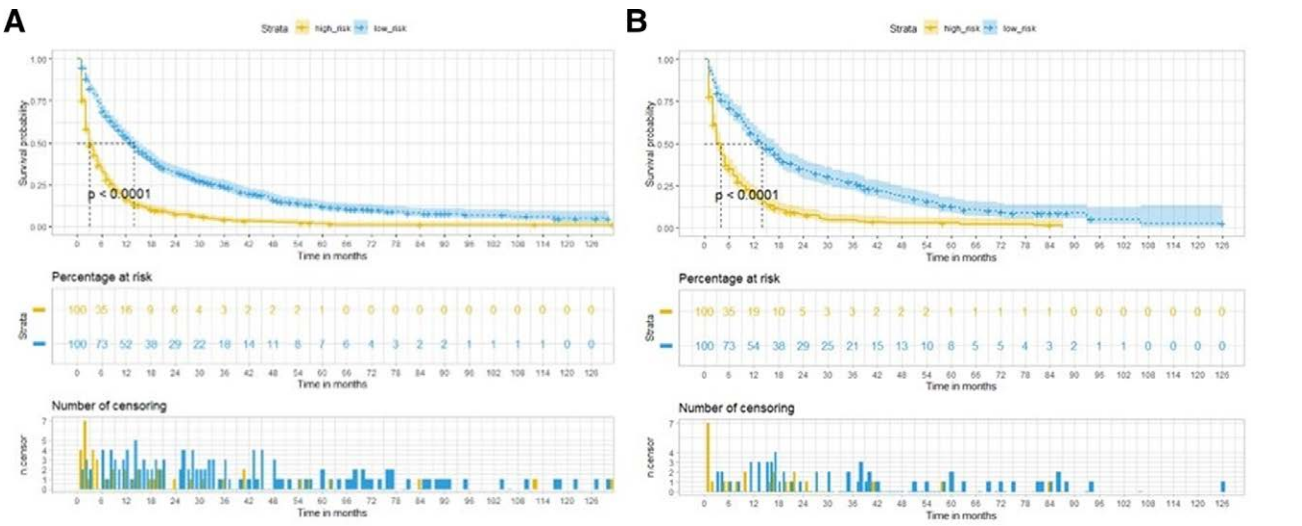

Figure 5. Kaplan–Meier curves for correlation with OS for the low and high- risk groups in the training cohort (A), internal validation cohort (B). OS = overall survival.

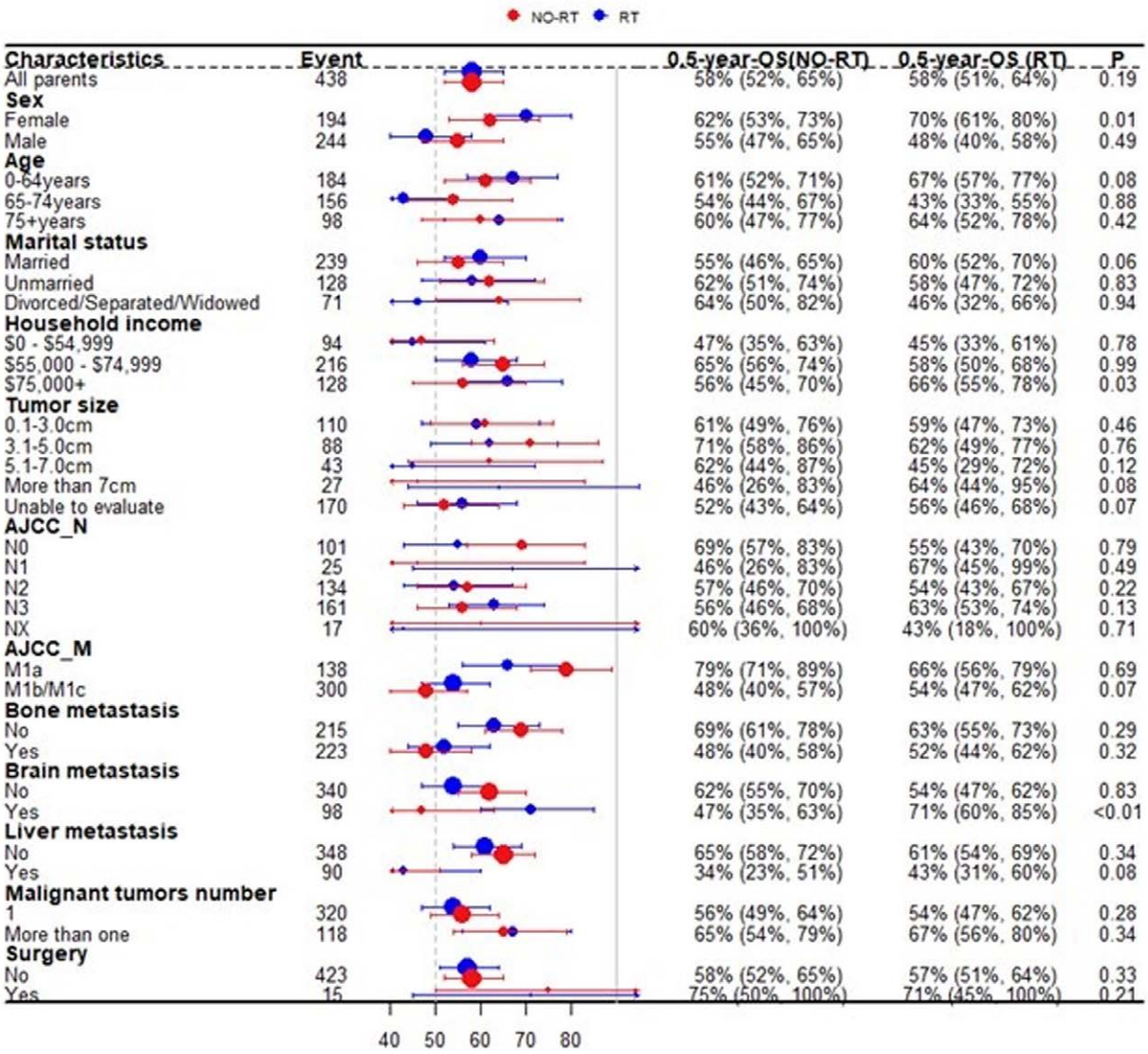

Figure 6. Subgroup analysis of differences in 0.5-yr-OS in the 2 treatment groups. OS = overall survival.

treating 4 to 10 metastatic tumors and is expected to provide robust evidence in future research endeavors. We believe that radiotherapy holds substantial potential in managing DBIM. A prior investigation into the survival outcomes of advanced lung cancer patients utilized median survival time as a metric for prognosis.[15] In this study, we also adopted median survival time to assess the survival prognosis of patients undergoing chemotherapy compared to those receiving chemoradiotherapy. Figure 4 demonstrates no significant difference in the 0.5-year survival probability between the 2 groups across all populations, with both groups having a similar rate of 58%, which is consistent with the findings of a previous retrospective study.[39] However, combining radiotherapy with chemotherapy may have a positive effect on survival in women, patients with family incomes over $75,000 and those diagnosed with BM. Videtic GMM et al's study suggests that women who receive radiation therapy exhibit a longer median survival time compared to men (6.3 months vs 5.5 months).[40] The immune microenvironment and gene expression profiles exhibit significant gender-related disparities. Female patients demonstrate a tumor microenvironment characterized by substantially heightened T cell dysfunction, elevated expression of inhibitory immune checkpoint molecules, and increased infiltration of immunosuppressive cellular components. Concurrently, females exhibit higher mutation rates in EGFR and KRAS mutations. Consequently, female patients may benefit from expanded therapeutic options. The enhanced therapeutic efficacy observed in female patients undergoing radiotherapy is attributable to synergistic effects between radiotherapy and targeted therapies or immunotherapeutic interventions. Stereotactic ablation radiotherapy offers precise and high-dose radiation therapy, leading to favorable local control rates for both primary and metastatic tumors. Advanced technology is appealing due to its potential for enhancing accuracy and reducing radiotherapy toxicity. However, it also entails substantial costs, with the average expense of a 90-day course of stereotactic radiotherapy reaching as high as $11,122.[41] An analysis conducted by Matthew Koshy et al, involving 46,803 diagnosed with stage IV lung cancer who underwent chest radiotherapy, revealed that individuals possessing private insurance were more likely to receive prolonged and intensified courses of radiotherapy.[42] Additionally, another study conducted by the same researchers demonstrated that higher doses of radiotherapy were associated with improved survival rates among patients with metastatic lung cancer.[39] Consequently, we hypothesize that affluent households are more likely to undergo aggressive radiotherapeutic interventions, thereby increasing the likelihood of survival by up to 0.5 years. Whole brain irradiation and stereotactic radiotherapy are conventional treatments for brain malignancies to their ability to

penetrate the blood-brain barrier where chemotherapeutic agents cannot reach effectively. Recent research has demonstrated that stereotactic ablation radiotherapy yields superior outcomes in terms of local control rates, reduced neurological deterioration, and decreased incidence of complications among patients with BM from NSCLC.[43] Radiotherapy demonstrates potent local control efficacy in managing cerebral metastases from lung carcinoma, with documented capacity to suppress neoplastic proliferation and metastatic dissemination. This intervention significantly reduces intracranial lesion burden (both in quantity and volumetric dimensions), ameliorates neurological symptomatology, and delays disease progression. Mechanistically, radiation-induced modulation of blood-brain barrier permeability enhances intracerebral bioavailability of chemotherapeutic agents and other therapeutic compounds, thereby potentiating systemic treatment outcomes. Furthermore, radiotherapy induces immunogenic modulation of the local tumor microenvironment through stromal remodeling and activation of immune surveillance mechanisms. This radiation-primed immunostimulatory milieu synergistically augments the efficacy of immunotherapeutic regimens by promoting antigen presentation and lymphocyte infiltration, establishing a favorable therapeutic foundation for combinatorial treatment approaches.

Several limitations exist in our study. Firstly, the SEER database lacks information regarding the utilization of targeted drugs and immune checkpoint inhibitors, while specific regimens and doses of chemotherapy and radiotherapy were not available; these particular treatment choices could potentially impact patient survival outcomes. Secondly, certain variables within the SEER database are missing, such as data on metastatic organ involvement, which may introduce confounding factors into the statistical analysis of our study results. Thirdly, being a retrospective analysis based on a public database, it lacks validation from real-world data; therefore, further validation through a real-world multicenter study is warranted to corroborate our findings.

5. Conclusion

We developed and validated the nomogram to predict survival probability in patients with NSCLC with DBIM, providing valuable insights for prognostic assessment and clinical decision-making. Although chemotherapy, as a crucial treatment modality, along with the addition of radiotherapy did not improve OS rates, it demonstrated potential benefits specifically in female patients, those with BM, and individuals from higher income backgrounds.

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