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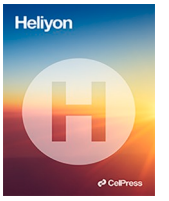

Research article

Distinguishing optimal candidates for primary tumor resection in patients with metastatic lung adenocarcinoma: A predictive model based on propensity score matching

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ABSTRACT

Background: Primary tumor resection is associated with survival benefits in patients with metastatic lung adenocarcinoma (mLUAD). However, there are no established methods to determine which individuals would benefit from surgery. Therefore, we developed a model to predict the patients who are likely to benefit from surgery in terms of survival.

Methods: Data on patients with mLUAD were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Depending on whether surgery was performed on the primary tumor, patients were categorized into two groups: cancer-directed surgery (CDS) and no-cancer-directed surgery (No-CDS). Propensity Score Matching (PSM) was utilized to address bias between the CDS and No-CDS groups. The prognostic impact of CDS was assessed using Kaplan-Meier analysis and Cox proportional hazard models. Subsequently, we constructed a nomogram to predict the potential for surgical benefits based on multivariable logistic regression analysis using preoperative factors.

Results: A total of 89,039 eligible patients were identified, including 6.4% (5705) who underwent surgery. Following PSM, the CDS group demonstrated a significantly longer median overall survival (mOS) compared with the No-CDS group (23 [21–25] vs. 7 [7–8] months; $P < 0.001$). The nomogram showed robust performance in both the training and validation sets (area under the curve [AUC]: 0.698 and 0.717, respectively), and the calibration curves exhibited high consistency. The nomogram proved clinically valuable according to decision curve analysis (DCA). According to this nomogram, surgical patients were categorized into two groups: no-benefit candidates and benefit candidates groups. Compared with the no-benefit candidate group, the benefit candidate group was associated with longer survival (mOS: 25 vs. 6 months, $P < 0.001$). Furthermore, no difference in survival was observed between the no-benefit candidates and the no-surgery groups (mOS: 6 vs. 7 months, $P = 0.9$).

Conclusions: A practical nomogram was developed to identify optimal CDS candidates among patients with mLUAD.

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1. Introduction

Lung cancer is globally recognized as one of the most severe malignant tumors because of its high morbidity and mortality rates [1]. Among its various pathological subtypes, lung adenocarcinoma (LUAD) stands out as the most prevalent. Typically, surgical resection is the primary treatment option for patients diagnosed in the early stages. However, most patients are diagnosed at advanced stages due to the mild early symptoms that are difficult to detect [2]. As the disease progresses to an advanced stage, chemotherapy, radiation, molecular targeted therapy, and immunotherapy become the primary treatment options. Despite a steady improvement in the survival rate of patients with metastatic lung adenocarcinoma (mLUAD) with the emergence of immunotherapy and molecular targeted therapies, the 5-year relative survival rate for patients with mLUAD is only approximately 20% [3], posing a serious threat to people's lives and health. Therefore, further improvement in the survival rate of these patients is urgently required.

In the past, the goal of treating patients with mLUAD was primarily centered on disease control rather than achieving a radical cure. Consequently, resection at the primary tumor site is not considered standard therapy for these patients [4]. Previous studies have shown that although the frequency of surgical treatment for advanced non-small cell lung cancer (NSCLC) is decreasing, the survival of surgical patients is on the rise [5]. Additionally, recent prospective and retrospective studies have indicated that carefully selected patients with mLUAD may benefit from surgery [6–15]. However, these studies are limited by their small sample sizes. Owing to significant variations in clinicopathological characteristics among these patients, only certain subpopulations with mLUAD benefit from cancer-directed surgery (CDS) [16]. To date, definitive criteria for accurately predicting which patients with mLUAD are likely to benefit from CDS remain elusive. Additionally, performing a phase III clinical trial proves challenging due to the high heterogeneity and poor prognosis associated with mLUAD. Therefore, this study aimed to develop a predictive model for identifying individuals with mLUAD who may benefit from CDS using a robust and statistically powerful sample from the Surveillance, Epidemiology, and End Results (SEER) database. To achieve this goal, we extracted extensive data from the SEER database, designed an individualized nomogram, and developed a web-based version. This comprehensive approach will assist physicians in easily identifying candidates for mLUAD who can benefit from CDS prior to surgery.

2. Materials and methods

2.1. Patient selection from the SEER database

The SEER database, managed by the National Cancer Institute, comprises 18 population-based cancer registries, covering almost 28 percent of the United States population. We selected patients from the incidence - SEER 18 Regs study database based on documents submitted in November 2020, utilizing SEER*Stat software version 8.4.0 (Seer. Cancer-gov/Seers TAT). Tumor, node, metastasis (TNM) stage was reclassified according to the eighth edition of the American Joint Committee on Cancer. Inclusion criteria for patients were as follows: (a) pathology identified as stage IV (2004–2015), (b) histopathological classification and coding of tumors (ICD-*O*-3): 8140–8141,8143–8146,8230,8250–8255,8260,8310,8323,8480,8481,8490,8550,8570,8571,8572,8574, (c) having data on the following inclusion variables: baseline demographic information (age, sex, race, marital status, survival state, and month of survival), tumor features (anatomical site, laterality, differentiation grade, T stage, N stage, CS tumor size [2004–2015], CS lymph nodes [2004–2015], CS extension [2004–2015], CS mets at dx [2004–2015]), and chemotherapy. Exclusion criteria were as follows: (a) diagnosis not being confirmed microscopically; (b) non-surgery due to other reasons (e.g., the patient died before the recommended surgery, patient or guardian refused surgery); and (c) having missing information.

2.2. Comparison of survival between the CDS and No-CDS groups after propensity score matching (PSM)

Based on whether surgery was performed on the primary tumor, the patients were categorized into two groups: CDS and No-CDS. PSM effectively addressed confounding biases between the two groups. Caliper matching was used to set the PSM criteria. Following PSM, chi-square tests were used to determine the significance of differences. Kaplan–Meier (K–M) analysis and log-rank tests were used to compare the overall survival (OS) of the two groups.

2.3. Development and validation of a predictive nomogram model

A nomogram is a statistical technique that calculates the likelihood of clinical occurrence by weighting each factor [17]. Numerous clinical studies have proven that nomograms combined with numerous factors achieve superior prognostic predictions compared to traditional score tables [18–20]. Consequently, it has been proposed as a substitute or even a new standard [21].

We selected the CDS group to build and verify a predictive model. To optimize data utilization for validation, we randomly allocated 70% of the patients to the training group and 30% to the validation cohort. We defined patients with mLUAD who underwent primary tumor surgery and lived longer than the median OS (mOS) of the No-CDS group as benefitting from surgery. Following this definition, patients in the CDS group were divided into two groups: surgery-beneficial and surgery-non-beneficial (results from the matched cohort). Based on the multivariate logistic regression analysis of the training set, a nomogram was developed as a quantitative tool to predict which patients with mLUAD may benefit from primary tumor surgery. Furthermore, we utilized the "DynNom" software to create a dynamic nomogram, accessible on the website in real-time. In both the training and validation sets, the area under the receiver operating characteristic curve (AUC) was used to measure the prediction performance of the nomogram. Calibration was graphically assessed using a calibration plot. Decision curve analysis (DCA) was used to calculate the clinical usefulness and net

benefit.

2.4. Clinical usefulness of the nomogram

In the CDS group, the predictive nomogram was used to calculate the probability of surgical benefits for each patient. A predictive benefit categorization algorithm was developed to classify individuals into two categories. If the overall prediction probability was >0.5, patients were classified as surgery-benefit candidates; otherwise, patients with total prediction probabilities less than 0.5 were classified as surgery-no-benefit candidates.

K–M analysis was used to determine whether the clinical application value of the nomogram could discriminate individuals who may benefit from primary tumor resection (surgery benefit-candidates vs. surgery no-benefit-candidates vs. no-surgery group).

2.5. Statistical analysis

All statistical analyses in this research were performed using R software (version 4.1)). A P value < 0.05 (two-sided) was considered statistically significant. Categorical variables were analyzed using chi-square or Fisher's exact tests.

3. Results

3.1. Patient characteristics before and after PSM

From 2004 to 2015, a total of 101,104 patients with mLUAD were identified from the SEER database, with 89,039 meeting the inclusion criteria (Fig. 1). Only 5705 (6.41%) patients underwent surgery, which is consistent with real-world results. Before PSM, there were significant disparities in age, sex, race, marital status, TN stage, location, lesion laterality, differentiation, and chemotherapy between the two treatment groups (Table 1). Notably, the CDS group exhibited a higher proportion of patients with pathological grades I–II (49.0%), T0–T2 (53.1%), and N0–1 (64.8%). A 1:1 PSM was applied to preoperatively available characteristics that

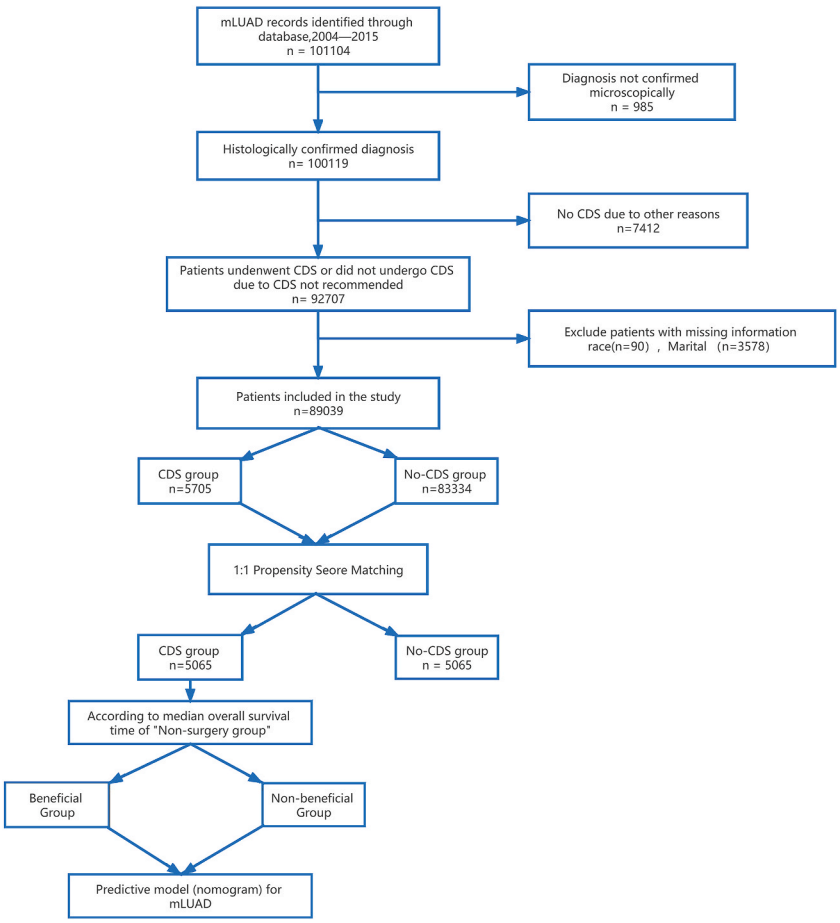

Fig. 1. Flow chart depicting the screening process.

Table 1
Baseline characteristics before and after PSM, including statistical comparisons between the CDS (highlighted in gray) and No-CDS groups (χ^2 test).

Factor	Pre-PSM				Post-PSM	
	No-CDS (n=83334)	Comparison	CDS (%) (n=5705)	CDS (%) (n=5065)	Comparison	No-CDS (n=5065)
Age (%)						
≤65	32875 (39.4%)	χ^2=40.65,	2450 (42.9%)	2108 (41.6%)	χ^2=0.040598	2119 (41.8%)
>65	50459(60.6%)	p<0.001	3255 (57.1%)	2957 (58.4%)	p=0.8403	2946 (58.2%)
Sex (%)						
Female	40365 (48.4%)	χ^2=108.27,	3170 (55.6%)	2781 (54.9%)	χ^2=0.001595	2784 (55.0%)
Male	42969 (51.6%)	p<0.001	2535 (44.4%)	2284 (45.1%)	p=0.9681	2281 (45.0%)
Race (%)						
Other	7958 (9.5%)		442 (7.7%)	320 (6.3%)		326 (6.4%)
White	65457 (78.5%)	χ^2=40.512, p<0.001	4683 (82.1%)	4306 (85.0%)	χ^2=0.68484 p=0.7101	4278 (84.5%)
Black	9919 (11.9%)		580 (10.2%)	439 (8.7%)		461 (9.1%)
Marital (%)						
Married	45721 (54.9%)		3403 (59.6%)	3082 (60.8%)		3067 (60.6%)
Unmarried	13450 (16.1%)	χ^2=50.017, p<0.001	804 (14.1%)	655 (12.9%)	χ^2=0.7101 p=0.5388	692 (13.7%)
Widowed	24163 (29.0%)		1498 (26.3%)	1328 (26.2%)		1306 (25.8%)
Site (%)						
Main bronchus	3124 (3.7%)		70 (1.2%)	60 (1.2%)		54 (1.1%)
Upper lobe	39348 (47.2%)		2575 (45.1%)	2486 (49.1%)		2443 (48.2%)
Middle lobe	3488 (4.2%)	χ^2=321.94,	351 (6.2%)	274 (5.4%)	χ^2=1.3556	280 (5.5%)
Lower lobe	19852 (23.8%)	p<0.001	1565 (27.4%)	1447 (28.6%)	p=0.9291	1478 (29.2%)
Overlapping	871 (1.0%)		154 (2.7%)	70 (1.4%)		76 (1.5%)
Unknown	16651 (20.0%)		990 (17.4%)	728 (14.4%)		734 (14.5%)

Laterality(%)						
Right	45237 (54.3%)		3423 (60.0%)	3015 (59.5%)		3018 (59.6%)
		χ^2=221.13,			χ^2=1.1495	
Left	30827 (37.0%)		2095 (36.7%)	1920 (37.9%)		1900 (37.5%)
		p<0.001			p=0.5628	
Both	7270 (8.7%)		187 (3.3%)	130 (2.6%)		147 (2.9%)
Grade (%)						
I-II	12392 (14.9%)	χ^2=5695,	2796 (49.0%)	2325 (45.9%)	χ^2=1.0386	2370 (46.8%)
III-IV	19056 (22.9%)	p<0.001	1906 (33.4%)	1762 (34.8%)	p=0.5949	1750 (34.6%)
Unknown	51886 (62.3%)		1003 (17.6%)	978 (19.3%)		945 (18.7%)
T (%)						
T0-T2	29687 (35.6%)		3031 (53.1%)	2623 (51.8%)		2610 (51.5%)
		χ^2=976.24,			χ^2=4.0013	
T3-4	38124 (45.7%)		2353 (41.2%)	2167 (42.8%)		2133 (42.1%)
		p<0.001			p=0.1352	
Tx	15523 (18.6%)		321 (5.6%)	275 (5.4%)		322 (6.4%)
N (%)						
N0-1	25135 (30.2%)		3698 (64.8%)	3195 (63.1%)		3160 (62.4%)
		χ^2=2929.3,			χ^2=3.0264	
N2-3	50831 (61.0%)		1758 (30.8%)	1683 (33.2%)		1684 (33.2%)
		p<0.001			p=0.2202	
Nx	7368 (8.8%)		249 (4.4%)	187 (3.7%)		221 (4.4%)
Chemotherapy (%)						
Yes	45960 (55.2%)	χ^2=1.2758,	3102 (54.4%)	2846 (56.2%)	χ^2=0.31486	2875 (56.8%)
No/Unknown	37374 (44.8%)	p=0.2587	2603 (45.6%)	2219 (43.8%)	p=0.5747	2190 (43.2%)

PSM: Propensity score matching; CDS: Cancer-directed surgery; No-CDS: No cancer-directed surgery.

PSM: Propensity score matching; CDS: Cancer-directed surgery; No-CDS: No cancer-directed surgery.

could potentially influence treatment outcomes, including age, sex, race, marital status, TN stage, location, lesion laterality, and differentiation. Before matching, the features of the two groups were quite different (Fig. 2a). After matching, the observed differences were successfully eliminated (Fig. 2b).

After 1:1 PSM, 5065 patients with mLUAD treated with CDS and 5065 patients without CDS were included in the study. Age, sex, race, marital status, TN stage, location, lesion laterality, and differentiation were all balanced ($P > 0.05$). The demographic and clinical features of the patients in the dataset are shown in Table 1.

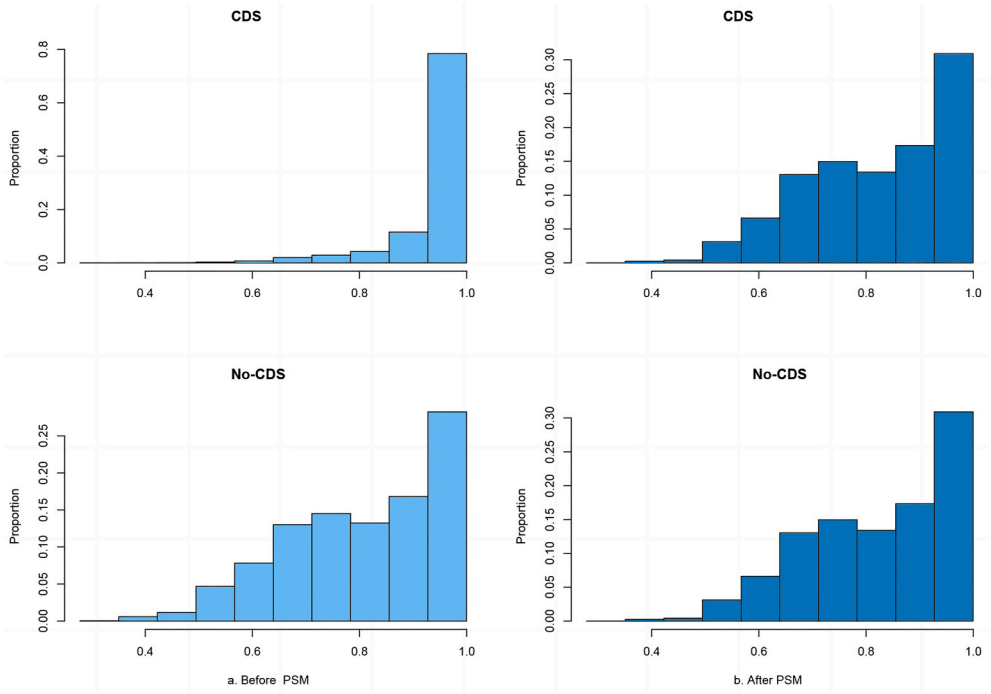

Fig. 2. Distribution of the propensity scores of the CDS and No-CDS groups: (a) before and (b) after PSM. CDS: cancer-directed surgery; No-CDS: no-cancer-directed surgery; PSM: propensity score-matching.

3.2. *Effect of CDS on survival outcomes in patients with mLUAD*

The influence of CDS on prognosis was assessed by comparing the mOS between the PSM groups (n = 5065 per group). Patients who received CDS demonstrated a significantly higher mOS(23 [21–25] months) compared with those who did not receive CDS (7 [7–8] months) (log-rank test: $\mathscr{X}^2 = 1384.0$, $P < 0.001$) (Fig. 3a).

Previous studies have shown that chemotherapy and sex affect the prognosis of advanced lung cancers [22–25]. We also explored the combined effects of these two variables on surgery. Our results suggest that chemotherapy and female sex have a positive impact on prognosis. As shown in Fig. 3b, survival differences were observed based on chemotherapy status and CDS utilization (chemotherapy + CDS [26 {25–27} months], non-chemotherapy + CDS [18 {16–20} months], chemotherapy + No-CDS [11 {11–12} months], and non-chemotherapy + No-CDS [3 {3–3} months], $P < 0.001$). As shown in Fig. 3c, survival differences were observed based on sex and CDS utilization (female + CDS [30 {28–32} months, male + CDS [16 {15–18} months, female + No-CDS [8 {8–9} months, male + No-CDS [6 {5–6} months, $P < 0.001$). (Fig. 3b and c).

3.3. *Nomogram to select optimal candidates for CDS patients*

The data above revealed that patients with mLUAD who underwent CDS had longer survival times. Within the CDS group, participants were categorized into two groups: 74.6% (3776) of patients who survived for more than 7 months were assigned to the surgery-beneficial group, whereas the remaining patients were assigned to the surgery-non-beneficial group.

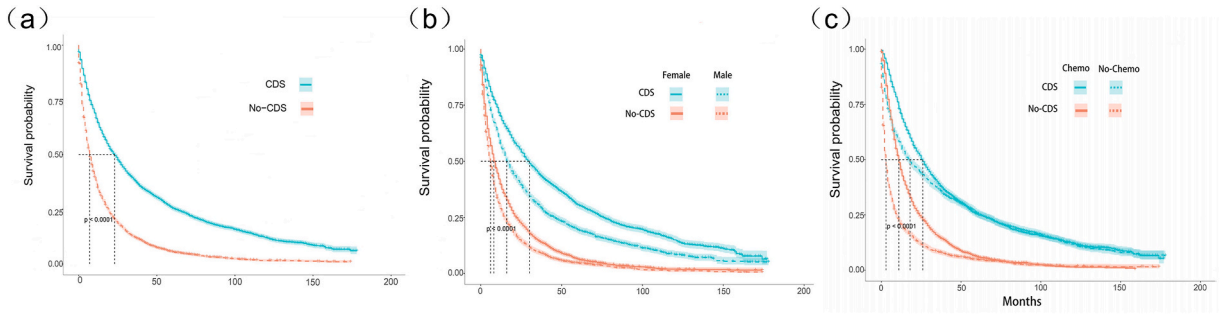

Fig. 3. Kaplan–Meier analysis for patients in the CDS and No-CDS groups: (a) the entire sample; grouped by (b) sex; and (c) chemotherapy.

We selected the CDS group to build and verify a predictive model. We randomly allocated 70% of the patients (n = 3545) to the training set and 30% (n = 1520) to the validation set. No significant differences were observed between training and validation sets (Table 2).

In the multivariate Cox analysis (Fig. 4), age, sex, marital status, TN stage, site, laterality, and differentiation grade were all independent predictors of survival in patients with mLUAD. Owing to practical clinical considerations, race was excluded from the model. Therefore, the clinical baseline parameters that could be retrieved preoperatively, such as age, sex, marital status, TN stage, site, laterality, and differentiation grade, were included in the nomogram. Based on multivariate logistic regression analysis, a predictive nomogram was established to identify patients with mLUAD who might benefit from surgical intervention. Fig. 5a illustrates the predictive nomogram for candidates who may benefit from surgery.

To assist researchers and clinicians in easily identifying individuals with mLUAD who would benefit from CDS, an online version of the nomogram is made available for access at https://dyna.shinyapps.io/mLUAD-DynNomapp/. The probability of surgical benefit can be readily predicted by entering clinical variables and reviewing the output figures and tables available on the website (Fig. 5b).

This prediction model accurately identified surgical candidates in both the training (AUC = 0.698) and validation (AUC = 0.717) groups (Fig. 6a and b). The actual findings from the calibration curve for the training and validation groups were consistent with the values predicted by the nomogram (Fig. 6c and d). DCA demonstrated that utilizing the nomogram to forecast surgery benefit probability produced a larger net benefit than either the “treat all with surgery” or “treat none with surgery” strategies for operable patients with mLUAD, supporting the clinical relevance of the nomogram (Fig. 6e and f).

3.4. Nomogram in clinical practice

Based on their overall score, candidates with a projected probability greater than the 0.5 cutoff point were classified as “surgical benefit candidates”. A schematic illustrating the application of the nomogram is shown in Fig. 7. For newly diagnosed patients with mLUAD, CDS is not directly performed if the patient cannot tolerate surgery. If patients with mLUAD can tolerate surgery, the probability of surgical benefit can be easily predicted by entering the preoperative clinical variables and reviewing the output chart

Table 2
Patient demographics and clinical characteristics.

Characteristics	All (%)	Training (%)	Validation (%)	χ^2	p
n	5065	3545	1520		
Age (%)				2.7977	0.0944
≤65	2108 (41.6%)	1448 (40.8%)	660 (43.4%)		
>65	2957 (58.4%)	2097 (59.2%)	860 (56.6%)		
Sex (%)				3.6309	0.05672
Female	2781 (54.9%)	1915 (54.0%)	866 (57.0%)		
Male	2284 (45.1%)	1630 (46.0%)	654 (43.0%)		
Race (%)				1.5534	0.4599
Other	320 (6.3%)	223 (6.3%)	97 (6.4%)		
White	4306 (85.0%)	3026 (85.4%)	1280 (84.2%)		
Black	439 (8.7%)	296 (8.3%)	143 (9.4%)		
Marital (%)				4.0158	0.1343
Married	3082 (60.8%)	2178 (61.4%)	904 (59.5%)		
Unmarried	655 (12.9%)	437 (12.3%)	218 (14.3%)		
Widowed	1328 (26.2%)	930 (26.2%)	398 (26.2%)		
Site (%)				3.6575	0.5997
Main bronchus	60 (1.2%)	39 (1.1%)	21 (1.4%)		
Upper lobe	2486 (49.1%)	1735 (48.9%)	751 (49.4%)		
Middle lobe	274 (5.4%)	193 (5.4%)	81 (5.3%)		
Lower lobe	1447 (28.6%)	1024 (28.9%)	423 (27.8%)		
Overlapping	70 (1.4%)	43 (1.2%)	27 (1.8%)		
Unknown	728 (14.4%)	511 (14.4%)	217 (14.3%)		
Laterality (%)				5.4205	0.06652
Right	3015 (59.5%)	2145 (60.5%)	870 (57.2%)		
Left	1920 (37.9%)	1307 (36.9%)	613 (40.3%)		
Both	130 (2.6%)	93 (2.6%)	37 (2.4%)		
Grade (%)				0.1718	0.9177
I-II	2325 (45.9%)	1621 (45.7%)	704 (46.3%)		
III-IV	1762 (34.8%)	1239 (35.0%)	523 (34.4%)		
Unknown	978 (19.3%)	685 (19.3%)	293 (19.3%)		
T (%)				2.191	0.3344
T0-T2	2623 (51.8%)	1857 (52.4%)	766 (50.4%)		
T3-4	2167 (42.8%)	1503 (42.4%)	664 (43.7%)		
Tx	275 (5.4%)	185 (5.2%)	90 (5.9%)		
N (%)				2.8142	0.2448
N0-1	3195 (63.1%)	2250 (63.5%)	945 (62.2%)		
N2-3	1683 (33.2%)	1174 (33.1%)	509 (33.5%)		
Nx	187 (3.7%)	121 (3.4%)	66 (4.3%)		

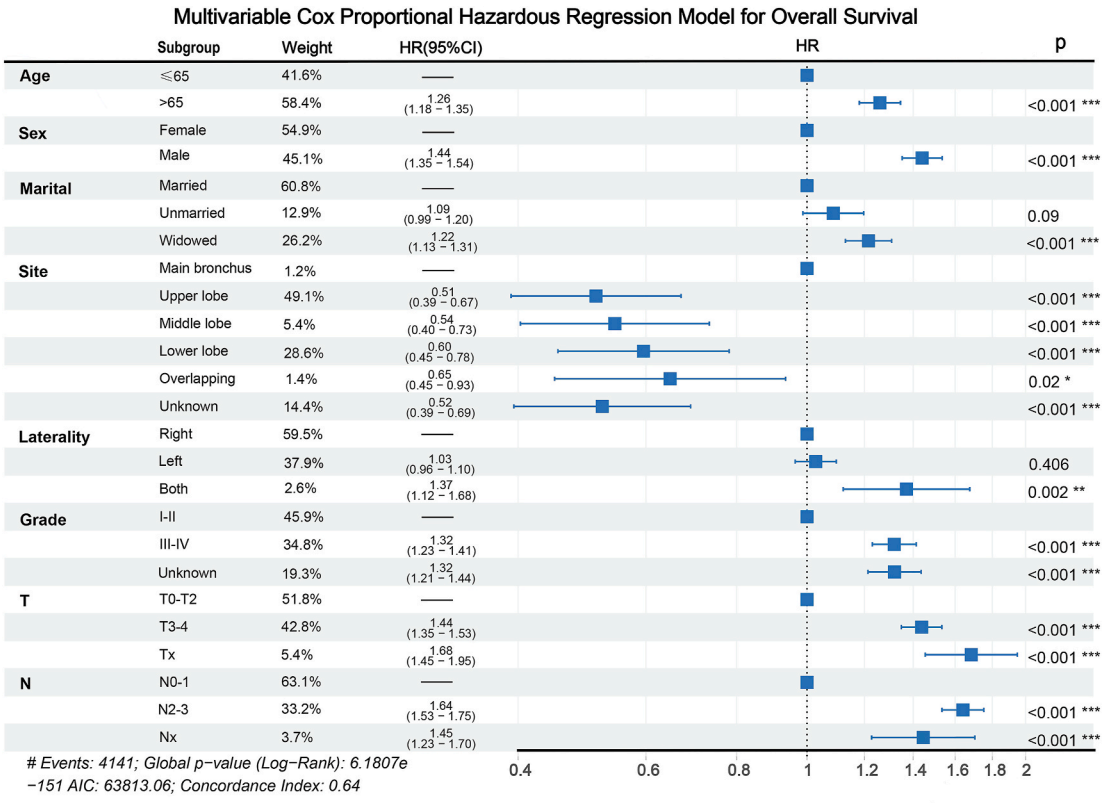

Fig. 4. The multivariate Cox regression forest graphic.

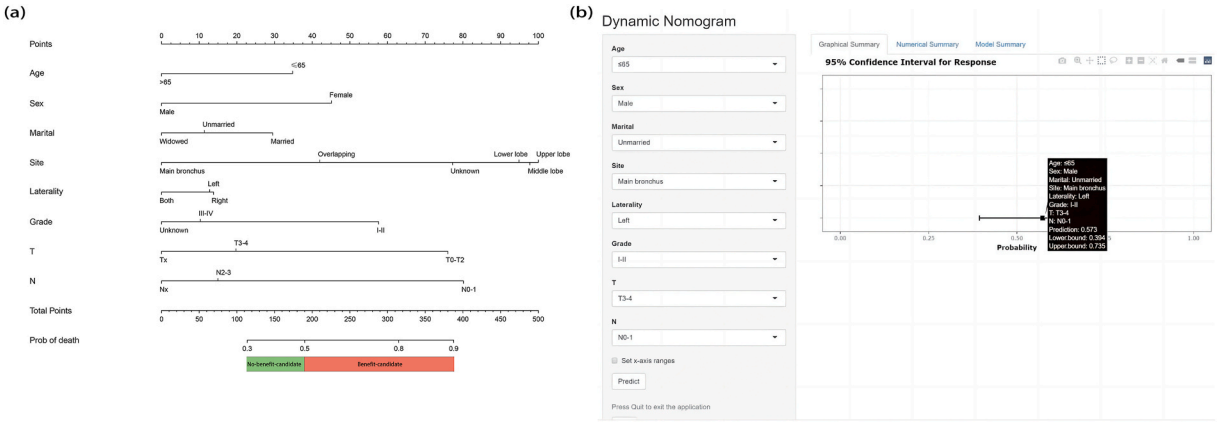

Fig. 5. (a) Nomogram to predict potential candidates likely to benefit from cancer-directed surgery among patients with metastatic lung adenocarcinoma. (b) To aid researchers and clinicians, an online version of the nomogram is made available at https://dyna.shinyapps.io/mLUAD-DynNomapp/.

provided by the website via our web-based nomogram. If no benefit is observed, surgery is not performed. Surgery is recommended if it offers any benefits. Certainly, some patients strongly refuse surgery, and in such cases, their opinion should be respected.

We compared the OS among the surgery benefit-candidate, surgery no-benefit-candidate, and no-surgery groups using K–M analysis (Fig. 8). Significant differences were observed (surgery benefit-candidate group, [25 {24–26} months]; surgery no-benefit-candidate group, [6 {5–8} months]; no-surgery group [7 {7–8} months]; $P < 0.0001$). Further pairwise comparisons revealed no significant differences between the surgery no-benefit-candidate group and the no-surgery group ($P = 0.9$).

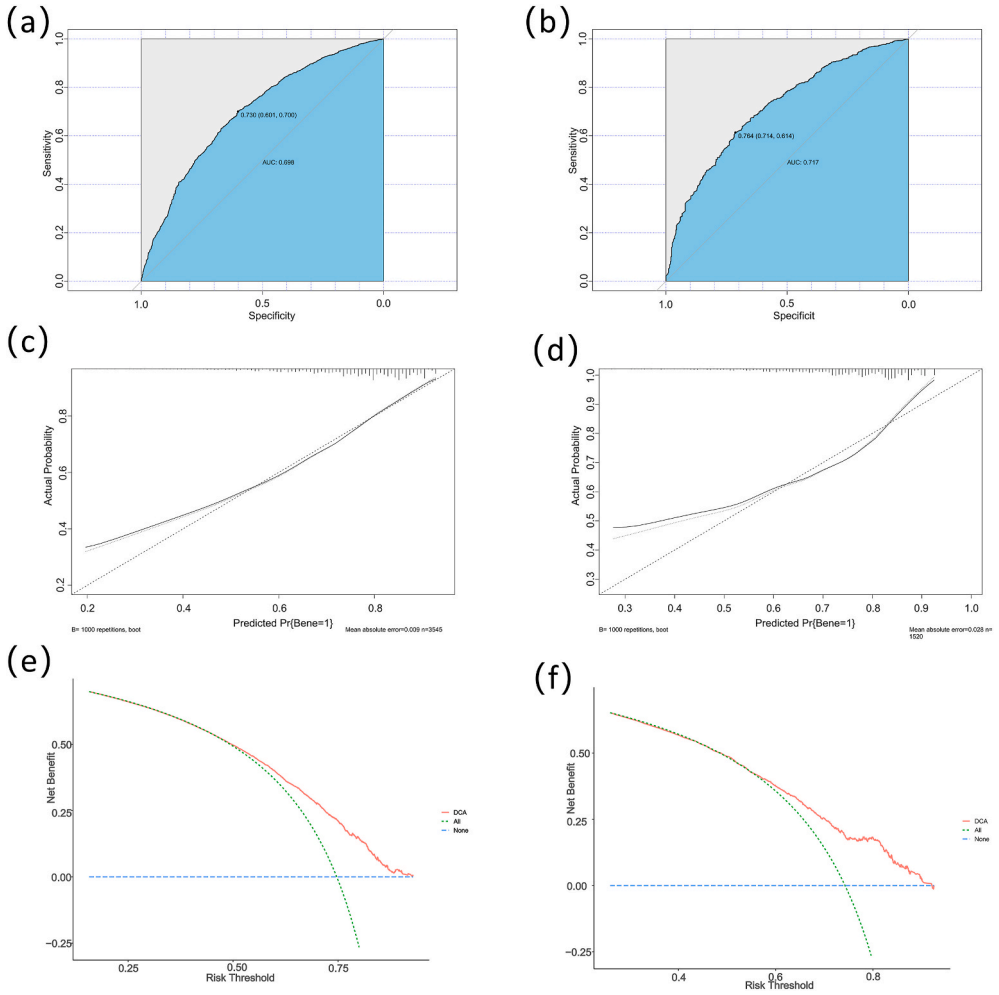

Fig. 6. Receiver operating characteristic curve of the (a) training and (b) validation sets. Calibration plot of the (c) training and (d) validation sets. Decision curve analysis of the (e) training and (f) validation sets.

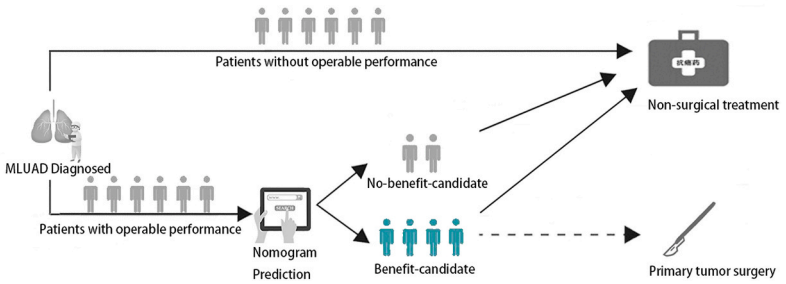

Fig. 7. A schematic diagram illustrating the application of the nomogram. In this study, a prediction model was developed to identify individuals with metastatic lung adenocarcinoma who might benefit from cancer-directed surgery and to offer these patients more precise therapy alternatives.

4. Discussion

To our knowledge, this is the most extensive research on surgical intervention for patients with mLUAD. The positive impact of CDS observed in this study underscores its potential in managing mLUAD. Ma et al. collected data from 2010 to 2015 in the SEER database and constructed a prognostic nomogram to assist clinicians in determining the prognosis of patients with mLUAD following primary site surgery. Liu's study was similar to Ma's, albeit with different variables. Both predictive models reported in previous studies only

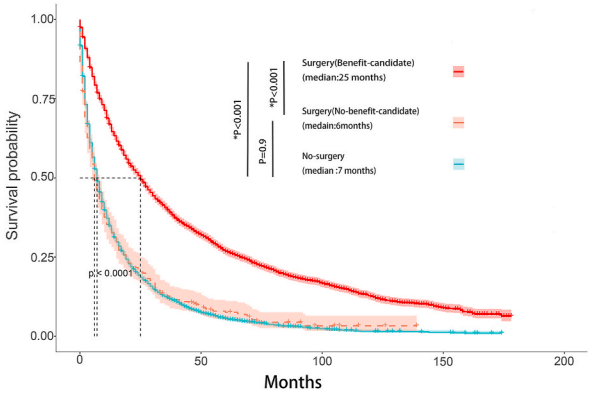

Fig. 8. Kaplan–Meier analysis curves for the patients with metastatic lung adenocarcinoma in the different groups according to the nomogram (No-surgery group, No-benefit-candidate group, and Benefit-candidate group).

analyzed the prognosis of patients with mLUAD undergoing surgery [26,27]. However, clear criteria for accurately predicting which mLUAD patients are likely to benefit from CDS remain undetermined. To address this gap, we devised a unique method for constructing a predictive model that can identify candidates who are likely to benefit from CDS. This model successfully stratified participants with mLUAD according to their surgical benefit potential, with readily obtainable predictive factors, enhancing its practicability in clinical applications. In addition, the nomogram demonstrated satisfactory predictive efficiency.

Surgery-related mortality has declined with advances in preoperative management and surgical techniques [28]. The continuous evolution of systemic therapy, coupled with increased awareness of clinical decision-making through multi-disciplinary teams (MDTs), has prompted a reevaluation of surgical intervention as part of the treatment of mLUAD [29]. Previous studies have shown that among 6644 resected NSCLC cases in Japan, the proportion of patients with stage IV NSCLC was 3.8% [30]. Sun et al. recommended surgical intervention for 4.8% of patients with stage IV extrathoracic metastatic NSCLC [6]. Our results indicate that 6.4% of patients with advanced LUAD underwent in situ surgical resection. Our study showed that only a small number of patients with advanced lung adenocarcinoma underwent in situ tumor resection. A meta-analysis involving 15 observational studies revealed a 31% reduction in mortality with the surgical removal of the primary tumor in patients with advanced disease [31]. Consistent with previous research [32–35], our study found an mOS of 23 months for patients who had undergone CDS, which is approximately 16 months longer than that for patients who did not undergo surgery. This could be attributed to a reduction in tumor burden. Notably, no difference in survival was observed between the no-benefit candidates in the CDS group and the no-surgery group (mOS: 6 vs. 7 months, $P = 0.9$), indicating that not all operable patients could derive a survival benefit from surgery.

The higher survival rates observed after surgical intervention may be attributable to a selection bias favoring individuals with favorable individual variables, such as better performance status and younger age. To mitigate this bias, we employed PSM to eliminate as much bias as possible. Our nomogram identified tumor site as the most significant predictor of surgical outcomes. Previous studies have shown that lung cancer affects the upper lobes more often than the lower lobes, and the right lung more frequently than the left [36]. Our study corroborates these findings, revealing a higher incidence of lung cancer in these positions. Specifically, 47.2% of patients had lesions in the upper lobes, whereas 59.5% had right-sided lung cancer. This finding can be attributed to the propensity for particles to deposit more easily in the upper and right lobes of the lungs. Additionally, our multivariate Cox analysis demonstrated that patients with mLUAD in the upper and right lobes were more likely to benefit from surgery. We suspect that this is related to the ease of total resection of these sites and the low incidence of postoperative complications. Traditional TNM staging has consistently associated high T and N levels with poor prognoses, aligning with the results of our prognostic model. In contrast, a high T stage was associated with a poor prognosis (HR = 1.44 [95% CI: 1.35–1.53], $P < 0.0001$), and a high N stage was also associated with a poor prognosis (HR = 1.64 [95% CI: 1.53–1.75], $P < 0.0001$). We hypothesize that this correlation is related to the challenges posed by surgical clearance in these cases.

TNM staging system is one of the main predictors of survival and treatment options [37]. Nonetheless, various patient-specific factors, including age, sex, and marital status [38], are associated with survival in a broad spectrum of cancers. Therefore, the development of an improved staging prediction system that considers the patient's condition is essential. For patients undergoing CDS, younger age is associated with a better prognosis [39]. Our findings are consistent with this observation. Older patients generally exhibit poorer health status, leading to a more cautious approach in their treatment compared with younger patients [40]. These findings underscore the significance of self-conditioning in the context of surgery for patients with advanced disease. Previous retrospective studies [22–25] have highlighted significant differences between male and female patients with NSCLC in terms of presentation, treatment, and prognosis. In the 1990s, Johnson et al. found that female patients with small cell lung cancer undergoing chemotherapy exhibited a survival advantage over their male counterparts. Subsequently, Ferguson et al. reported that women with various cell type tumors survived longer than men. In our study, sex emerged as an independent prognostic factor for survival, possibly because of the relation to hormonal control. There is evidence supporting the dependence of tumor cell growth on reproductive hormones, with NSCLC cells containing abundant estrogen receptors [41]. Marital status was also identified as an independent prognostic factor, with married patients demonstrating better health habits and economic support, including medication adherence

[42–44]. A happy marriage enhances the likelihood of shedding negative and pessimistic feelings, subsequently influencing physical health. Psychosomatic stress and negative emotions can interfere with an individual's immune system and hormone levels through various pathways [45].

This study has certain limitations, primarily stemming from insufficient information in the SEER database: First, the research is retrospective, and all data in this study were obtained from the SEER database, which may have introduced selection errors. Second, the SEER database often lacked information on gene alterations, tumor markers, smoking histories, detailed information on the nature and distribution of metastatic diseases, and data on other specific treatments. However, because the most recent data did not contain specific information about tumor size, lymph nodes, or metastasis, we were unable to perform restaging. Therefore, we excluded the most recent data. Finally, the SEER database only included information on patients from the United States, potentially limiting the generalizability of our findings globally. Therefore, well-designed multicenter studies are required to substantiate our claims.

5. Conclusions

We propose a novel nomogram for identifying patients with mLUAD who would benefit from CDS, using robust and statistically powerful data. Clinicians may devise a more targeted treatment plan for patients with mLUAD using our nomogram. Our predictive model incurs no further costs and merits further validation and improvement.

Ethics approval and consent to participate

The present study used previously collected anonymized and de-identified data from the SEER database. Therefore, no additional informed consent was required. The study was complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and deemed exempt from review by the Fourth Hospital of Hebei Medical University.

Consent for publication

Not applicable.

Availability of data and materials

This study utilized publicly available datasets- https://seer.cancer.gov/statistics/. Raw data can be downloaded from the software SEERStat according to the inclusion and exclusion criteria in this manuscript. The raw data can be consulted in the additional file 1.

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CRediT authorship contribution statement

Yuying Qi: Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Xiaojin Guo:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Zijie Li:** Writing – review & editing, Writing – original draft. **Bingzhang Ren:** Writing – review & editing, Writing – original draft. **Zhiyu Wang:** Writing – review & editing, Writing – original draft, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Zhiyu Wang reports financial support was provided by National Natural Science Foundation of China. We would like to thank Editage (www.editage.cn) for English language editing. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

mLUAD	Metastatic lung adenocarcinoma
SEER	Surveillance, Epidemiology, and End Results
CDS	Cancer-directed surgery
No-CDS	No cancer-directed surgery

PSM	Propensity score matching
OS	Overall survival
AUC	Area under the curve
DCA	Decision curve analysis
LUAD	Lung adenocarcinoma
MDT	Multi-disciplinary treatment
K–M	Kaplan –Meier
TNM	Tumor, Node, Metastasis
HR	Hazard ratio
CI	Confidence interval
AJCC	American Joint Committee on Cancer

Appendix A. Supplementary data

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References

[1] H. Sung, J. Ferlay, R.L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, et al., Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 71 (3) (2021) 209–4910, 3322/caac.21660.

[2] R.L. Siegel, K.D. Miller, H.E. Fuchs, A. Jemal, Cancer statistics, 2022, CA A Cancer J. Clin. 72 (1) (2022) 7–3310, 3322/caac.21708.

[3] A. Aupérin, C. Le Péchoux, E. Rolland, W.J. Curran, K. Furuse, P. Fournel, et al., Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 28 (13) (2010) 2181–9010, 1200/jco.2009.26.2543.

[4] T. Hanagiri, M. Takenaka, S. Oka, Y. Shigematsu, Y. Nagata, H. Shimokawa, et al., Results of a surgical resection for patients with stage IV non–small-cell lung cancer, Clin. Lung Cancer 13 (3) (2012) 220–410, 1016/j.cllc.2011.05.006.

[5] E.A. David, R.J. Canter, Y. Chen, D.T. Cooke, R.D. Cress, Surgical management of advanced non-small cell lung cancer is decreasing but is associated with improved survival, Ann. Thorac. Surg. 102 (4) (2016) 1101–1910, 1016/j.athoracsur.2016.04.058.

[6] Z. Sun, X. Sui, F. Yang, J. Wang, Effects of primary tumor resection on the survival of patients with stage IV extrathoracic metastatic non-small cell lung cancer: a population-based study, Lung Cancer 129 (2019) 98–106, https://doi.org/10.1016/j.lungcan.2018.11.012.

[7] O. Abdel-Rahman, Outcomes of surgery as part of the management of metastatic non-small-cell lung cancer: a surveillance, Epidemiology and End results database analysis, Cancer Invest. 36 (4) (2018) 238–4510, 1080/07357907.2018.1466895.

[8] E.A. David, S.W. Andersen, L.A. Beckett, J. Melnikow, K. Kelly, D.T. Cooke, et al., A model to predict the use of surgical resection for advanced-stage non-small cell lung cancer patients, Ann. Thorac. Surg. 104 (5) (2017) 1665–7210, 1016/j.athoracsur.2017.05.071.

[9] B.D. Kozower, J.M. Larner, F.C. Detterbeck, D.R. Jones, Special treatment issues in non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: Am. College of Chest Phys. Evid.-Based Clin. Prac. Guidelines. Chest 143 (5 Suppl) (2013) 12–2362, e369S-e99S10.1378/chest.

[10] T. Okamoto, T. Iwata, T. Mizobuchi, H. Hoshino, Y. Moriya, S. Yoshida, et al., Pulmonary resection for lung cancer with malignant pleural disease first detected at thoracotomy, Eur. J. Cardio. Thorac. Surg. : Off. J. Eur. Assoc. Cardio-Thoracic Surg. 41 (1) (2012) 25–30, https://doi.org/10.1016/j.ejcts.2011.04.010.

[11] Y.J. Ren, Y.L. She, C.Y. Dai, G.N. Jiang, K. Fei, C. Chen, Primary tumour resection showed survival benefits for non-small-cell lung cancers with unexpected malignant pleural dissemination, Interact. Cardiovasc. Thorac. Surg. 22 (3) (2016) 321–610, 1093/icvts/ivv353.

[12] C. Endo, T. Hasumi, Y. Matsumura, N. Sato, H. Deguchi, H. Oizumi, et al., A prospective study of surgical procedures for patients with oligometastatic non-small cell lung cancer, Ann. Thorac. Surg. 98 (1) (2014) 258, https://doi.org/10.1016/j.athoracsur.2014.01.052, 64.

[13] Y. Chikaishi, S. Shinohara, T. Kuwata, M. Takenaka, S. Oka, A. Hirai, et al., Complete resection of the primary lesion improves survival of certain patients with stage IV non-small cell lung cancer, J. Thorac. Dis. 9 (12) (2017) 5278–8710, 21037/jtd.2017.11.67.

[14] D. Li, X. Zhu, H. Wang, M. Qiu, N. Li, Should aggressive thoracic therapy be performed in patients with synchronous oligometastatic non-small cell lung cancer? A meta-analysis, J. Thorac. Dis. 9 (2) (2017) 310–710, 21037/jtd.2017.02.21.

[15] J. He, Y. Li, J. An, L. Hu, J. Zhang, Surgical treatment in non-small cell lung cancer with pulmonary oligometastasis, World J. Surg. Oncol. 15 (1) (2017) 36, https://doi.org/10.1186/s12957-017-1105-8.

[16] S. Zhu, T. Ge, J. Hu, G. Jiang, P. Zhang, Prognostic value of surgical intervention in advanced lung adenocarcinoma: a population-based study, J. Thorac. Dis. 13 (10) (2021) 5942, 5310.21037/jtd-21-997.

[17] Z. Pan, H. You, Q. Bu, X. Feng, F. Zhao, Y. Li, et al., Development and validation of a nomogram for predicting cancer-specific survival in patients with Wilms' tumor, J. Cancer 10 (21) (2019) 5299–30510, 7150/jca.32741.

[18] V.P. Balachandran, M. Gonen, J.J. Smith, R.P. DeMatteo, Nomograms in oncology: more than meets the eye, Lancet Oncol. 16 (4) (2015) e173–e8010, 1016/s1470-2045(14)71116-7.

[19] U. Rudloff, L.M. Jacks, J.I. Goldberg, C.A. Wynveen, E. Brogi, S. Patil, et al., Nomogram for predicting the risk of local recurrence after breast-conserving surgery for ductal carcinoma in situ, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 28 (23) (2010) 3762, 910.1200/jco.2009.26.8847.

[20] A.M. Thompson, R.M. Turner, A. Hayen, A. Aniss, S. Jalaty, D.L. Learoyd, et al., A preoperative nomogram for the prediction of ipsilateral central compartment lymph node metastases in papillary thyroid cancer, Thyroid : Off. J. Am. Thyroid Assoc. 24 (4) (2014) 675–8210, 1089/thy.2013.0224.

[21] A. Iasonos, D. Schrag, G.V. Raj, K.S. Panageas, How to build and interpret a nomogram for cancer prognosis, J. Clin. Oncol. : Off. J. Am. Soc. Clin. Oncol. 26 (8) (2008) 1364–7010, 1200/jco.2007.12.9791.

[22] M. Maemondo, A. Inoue, K. Kobayashi, S. Sugawara, S. Oizumi, H. Isobe, et al., Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR, N. Engl. J. Med. 362 (25) (2010) 2380, 810.1056/NEJMoa0909530.

[23] H. Kawai, Y. Saito, Y. Suzuki, Gender differences in the correlation between prognosis and postoperative weight loss in patients with non-small cell lung cancer, Interact. Cardiovasc. Thorac. Surg. 25 (2) (2017) 272–710, 1093/icvts/ivx092.

[24] J.M. Chatkin, C.M. Abreu, C.C. Fritscher, M.B. Wagner, J.A. Pinto, Is there a gender difference in non-small cell lung cancer survival? Gend. Med. 1 (1) (2004) 41–710, 1016/s1550-8579(04)80009-3.

[25] M. de Perrot, M. Licker, C. Bouchardy, M. Usel, J. Robert, A. Spiliopoulos, Sex differences in presentation, management, and prognosis of patients with non-small cell lung carcinoma, J. Thorac. Cardiovasc. Surg. 119 (1) (2000) 21–610, 1016/s0022-5223(00)70213-3.

[26] C. Ma, S. Peng, B. Zhu, S. Li, X. Tan, Y. Gu, The nomogram for the prediction of overall survival in patients with metastatic lung adenocarcinoma undergoing primary site surgery: a retrospective population-based study, Front. Oncol. 12 (2022) 916498, 10.3389/fonc.2022.916498.

[27] X. Tie, L. Chen, X. Li, W. Zha, Y. Liu, A nomogram model of postoperative prognosis for metastatic lung adenocarcinoma: a study based on the SEER database, Medicine 101 (41) (2022) e3108310, 1097/md.0000000000031083.

[28] H. Yavuz, A.K. Tekneci, A. Ozdil, U. Cagirici, Bibliometric analysis of 40 most cited articles comparing video-assisted thoracic surgery and robotic-assisted thoracic surgery in lung cancer (1997-2021), Heliyon 9 (10) (2023) e20765, https://doi.org/10.1016/j.heliyon.2023.e20765.
[29] B. Pillay, A.C. Wootten, H. Crowe, N. Corcoran, B. Tran, P. Bowden, et al., The impact of multidisciplinary team meetings on patient assessment, management and outcomes in oncology settings: a systematic review of the literature, Cancer Treat Rev. 42 (2016) 56–72, https://doi.org/10.1016/j.ctrv.2015.11.007.
[30] T. Goya, H. Asamura, H. Yoshimura, H. Kato, K. Shimokata, R. Tsuchiya, et al., Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study, Lung Cancer 50 (2) (2005) 227–3410, 1016/j.lungcan.2005.05.021.
[31] S. Ahmed, R.K. Shahid, A. Leis, K. Haider, S. Kanthan, B. Reeder, et al., Should noncurative resection of the primary tumour be performed in patients with stage iv colorectal cancer? A systematic review and meta-analysis, Curr. Oncol. 20 (5) (2013) e420–e4110, 3747/co.20.1469.
[32] S. Ahmed, A. Leis, A. Fields, S. Chandra-Kanthan, K. Haider, R. Alvi, et al., Survival impact of surgical resection of primary tumor in patients with stage IV colorectal cancer: results from a large population-based cohort study, Cancer 120 (5) (2014) 683–9110, 1002/cncr.28464.
[33] F.Y. Müsri, H. Mutlu, M. Karaağaç, M.K. Eryilmaz, Ş. Gündüz, M. Artaç, Primary tumor resection and survival in patients with stage IV gastric cancer, J. Gastric Cancer 16 (2) (2016) 78–84, 10.5230/jgc.2016.16.2.78.
[34] C.J. Yang, L. Gu, S.A. Shah, B.A. Yerokun, T.A. D'Amico, M.G. Hartwig, et al., Long-term outcomes of surgical resection for stage IV non-small-cell lung cancer: a national analysis, Lung Cancer 115 (2018) 75–83, https://doi.org/10.1016/j.lungcan.2017.11.021.
[35] R. Mudgway, C. Chavez de Paz Villanueva, A.C. Lin, M. Senthil, C.A. Garberoglio, S.S. Lum, The impact of primary tumor surgery on survival in HER2 positive stage IV breast cancer patients in the current era of targeted therapy, Ann. Surg Oncol. 27 (8) (2020) 2711, 2010.1245/s10434-020-08310-2.
[36] L.H. Garland, R.L. Beier, W. Coulson, J.H. Heald, R.L. Stein, The apparent sites of origin of carcinomas of the lung, Radiology 78 (1962) 1–1110, 1148/78.1.1.
[37] Z. Gao, J. Ni, H. Ding, C. Yan, C. Ren, G. Li, et al., A nomogram for prediction of stage III/IV gastric cancer outcome after surgery: a multicenter population-based study, Cancer Med. 9 (15) (2020) 5490, 910.1002/cam4.3215.
[38] W. Song, D.L. Miao, L. Chen, Nomogram for predicting survival in patients with pancreatic cancer, OncoTargets Ther. 11 (2018) 539–4510, 2147/ott.S154599.
[39] F. Tas, R. Ciftci, L. Kilic, S. Karabulut, Age is a prognostic factor affecting survival in lung cancer patients, Oncol. Lett. 6 (5) (2013) 1507, 1310.3892/ol.2013.1566.
[40] F. Yang, H. Xie, Y. Wang, Prognostic nomogram and a risk classification system for predicting overall survival of elderly patients with fibrosarcoma: a population-based study, J. Oncol. 2021 (2021) 9984217, 10.1155/2021/9984217.
[41] C.C. Canver, V.A. Memoli, P.L. Vanderveer, C.A. Dingivan, R.M. Mentzer Jr., Sex hormone receptors in non-small-cell lung cancer in human beings, J. Thorac. Cardiovasc. Surg. 108 (1) (1994) 153–157.
[42] Y. Wu, P.Z. Zhu, Y.Q. Chen, J. Chen, L. Xu, H. Zhang, Relationship between marital status and survival in patients with lung adenocarcinoma: a SEER-based study, Medicine 101 (1) (2022) e28492, https://doi.org/10.1097/md.0000000000028492.
[43] Z. Chen, K. Yin, D. Zheng, J. Gu, J. Luo, S. Wang, et al., Marital status independently predicts non-small cell lung cancer survival: a propensity-adjusted SEER database analysis, J. Cancer Res. Clin. Oncol. 146 (1) (2020) 67–7410, 1007/s00432-019-03084-x.
[44] J.Z. Ayanian, B.A. Kohler, T. Abe, A.M. Epstein, The relation between health insurance coverage and clinical outcomes among women with breast cancer, N. Engl. J. Med. 329 (5) (1993) 326–3110, 1056/nejm199307293290507.
[45] S. Goyal, K. Srivastava, C. Kodange, P.S. Bhat, Immunological changes in depression, Ind. Psychiatr. J. 26 (2) (2017) 201–610, 4103/ipj.ipj_22_18.