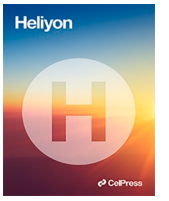
Heliyon 10 (2024) e36657

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Distant metastatic patterns in young and old non-small cell lung cancer patients: A dose–response analysis based on SEER population

Yingxian Dong [a,b,d,1], Sicheng Zhou [a,b,d,1], Jue Li [a,b,d], Yin Zhang [c,e], Guowei Che [a,b,d,*]

[a] Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[b] Lung Cancer Center/Lung Cancer Institute, West China Hospital, Sichuan University, Chengdu, Sichuan, China
[c] Department of Respiratory and Critical Care Medicine, Clinical Research Center for Respiratory Diseases, West China Hospital, Sichuan University, Chengdu, China
[d] West China Clinical Medical College, Sichuan University, Chengdu, Sichuan, China
[e] Laboratory of Pulmonary Immunology and Inflammation, Frontiers Science Center for Disease-related Molecular Network, Sichuan University, Chengdu, China

ARTICLE INFO

Keywords:
Distant metastases
dose–response analysis
Young
Non–small cell lung cancer

ABSTRACT

Background: Few research has explored the risk of distant metastasis dynamically changes with age in non-small cell lung cancer patients. The objective of this study was to explore the risk factors of developing distant metastasis with changing age.
Methods: This retrospective cohort study was based on a large population of patients with non-small cell lung cancer from the SEER database. Logistic regression was applied to identify risk factors for distant metastasis. The clinicopathological features were compared between the young group (≤50 years old) and the old group (>50 years old). Dose-response analyses were conducted to explore risk of distant metastasis changes with age.
Results: A total of 18,711 patients were studied in this study. According to the univariate and multivariate logistic regression analyses, ten factors were found to be risk factors for distant metastasis. Young patients have a greater incidence of each pattern of metastasis. However, the survival time of younger patients was longer. Dose-response analyses indicated that the risks of pleural or pericardial metastasis and overall distant metastasis gradually decreased with age at younger ages, but they intend to increase at older ages.
Conclusions: Age, sex, ethnicity, histology, T category, N category, differentiation grade, primary site of the tumor, ipsilateral metastases are factors associated with distant metastasis in NSCLC patients. Young patients have a greater risk of distant metastasis. The distant metastasis may decrease with the increasing age in patients younger than 70 years, but increase with the climb of age for patients older than 70 years.

* Corresponding author. Lung Cancer Center/Lung Cancer Institute, West China Hospital, Sichuan University, Chengdu, 610041, Sichuan, China.
E-mail address: cheguoweixw@126.com (G. Che).
[1] Yingxian Dong and Sicheng Zhou share first authorship and contributed equally.

https://doi.org/10.1016/j.heliyon.2024.e36657
Received 1 June 2024; Received in revised form 19 August 2024; Accepted 20 August 2024
Available online 22 August 2024
2405-8440/© 2024 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC license (http://creativecommons.org/licenses/by-nc/4.0/).

1. Introduction

Lung cancer is the leading cause of cancer deaths globally, and the number of new cases continues to increase annually [1–3]. A significant proportion of patients diagnosed with NSCLC, representing about 85 % of lung cancer [4]. Distant Metastasis (DM) occurs in the advanced stage of NSCLC, which indicates increased treatment difficulty and poor prognosis [5]. These included contralateral tumor nodules, pleural or pericardial invasion, and distant lymph node or organ metastasis [6]. The occurrence of DM often indicates fewer chance to receive radical operation, and fewer opportunities to benefit from systematic therapy [7–9]. Compared with patients with no metastasis, NSCLC patients with DM have worse 5-year survival rate [10]. Therefore, early detection of metastasis in NSCLC patients is essential for reasonable medical decision making and prognostic prediction in clinical practice.

A previous epidemiological study indicated that the incidence of NSCLC peaks between ages of 60 and 70, with patients under the age of 50 comprising less than 15 % of cases [11]. Some researchers demonstrated discrepant clinicopathological features and prognoses between young and old patients with NSCLC (12). The race, sex, histology, and survival status of younger NSCLC patients differ from older patients [13,14]. Although previous researchers found that younger patients were more likely to develop regional lymph node or distant metastasis [12,15–17], no research has further explored the risk of DM with age dynamics in NSCLC patients.

To enhance comprehension of the relationship between the attributes and metastatic patterns of NSCLC patients across different age demographics, we conducted this population-based study to ascertain risk factors associated with DM and investigate the pattern by which the risk of DM fluctuates with age in NSCLC patients.

2. Methods

2.1. Study population

This retrospective cohort study was based on a large population of NSCLC patients from the Surveillance, Epidemiology, and End Results (SEER) database. The SEER database is an authoritative source that collects patient information from 18 cancer registries [18]. In this study, data on patients with non-small cell lung cancer (NSCLC) were obtained from 2010 to 2015 using the SEER Program software (version 8.3.9, http://seer.cancer.gov/seerstat/software/). The username is 14238-Nov2020.

Inclusion criteria for this study were as follows: (i) Patients were required to be at least 18 years of age and diagnosed between 2010 and 2015. (ii) NSCLC was the only primary tumor at diagnosis. (iii) The diagnosis was confirmed by pathological tests. (iv) The follow-up duration was required to be at least one month. The exclusion criteria included: (i) Patient information was unavailable. (ii) Paired tumor sites were absent (insufficient data were available to determine whether the paired lesion was separate from the primary lung cancer or metastatic foci). This study was conducted in accordance with the STROBE reporting checklist.

2.2. Data processing

The extracted clinicopathological information included patient ID, sex, age, ethnicity, marriage, primary tumor location, histological type, pathological grade, T category, N category and M category according to the 7th edition American Joint Cancer Committee (7th AJCC Staging), tumor size, ipsilateral metastasis, pleural or pericardial metastasis, distant lymph node metastasis, distant organ metastases (i.e., brain metastasis, liver metastasis, bone metastasis), single DM, multiple DM, overall DM and survival months.

The following histologic codes were used to define NSCLC: 8010, 8012, 8013, 8014, 8015, 8020, 8021, 8022, 8031, 8032, 8046, 8050–8052, 8070–8078, 8140–8147, 8250–8255, 8260, 8310, 8323, 8430, 8480, 8481, 8482, 8490, 8560, and 8570–8575. For information extraction, patients were divided into young group (aged $\leq$50 years) and old group (aged >50 years), as a previous study indicated that the cut-off age for young and old lung cancer patients was 50 years [19]. Patients were treated as unmarried if they were divorced, separated, single (never married), widowed or had a domestic partner. Tumor size was divided into three groups ($\leq$5 cm, 5–7 cm, >7 cm). Ipsilateral metastasis indicated separate metastatic tumor nodules in the same or/and different lobes of the ipsilateral lung. Single DM, multiple DM and overall DM were identified according to “CS METS AT DX (2004–2015)” in the SEER database.

2.3. Statistical analysis

In selecting the risk factors for overall DM, age was treated as a categorical variable ($\leq$50 years old vs. >50 years old), while age was treated as a continuous variable in the dose–response analyses to determine the dynamic trend in the risk of DM.

To ascertain the risk factors associated with overall DM, logistic regression was employed. The variables that demonstrated statistical significance in the univariate logistic regression were selected to construct the multivariate logistic regression model using the stepwise forward selection method. The variables identified as statistically significant in the multivariate logistic regression analysis were found to be risk factors for overall DM. A series of pre-specified subgroup analyses was performed with the objective of determining whether the association between age categorization and the incidence of DM was modified by sex, ethnicity, tumor histology, tumor size, and nodal status. To assess the robustness of the results, sensitivity analyses were conducted by excluding patients at extreme ages (in the range of age <1 % or >99 %), excluding patients whose primary site was unclear, and excluding patients with extreme tumor sizes (in the range of tumor size <1 % or >99 %).

Dose–response analyses were conducted to investigate the associations between age and the occurrence of pleural or pericardial invasion, distant lymph node metastasis, distant organ metastasis (bone, brain, and liver, as recorded in the SEER database), single metastasis, multiple metastases, and overall DM. We constructed unadjusted logistic models with the variable as a restricted cubic

spline with four knots at the 5th, 35th, 65th, and 95th percentiles, with the median value of age (68 years old) serving as the reference level. The Wald test was employed to ascertain the correlation between continuous age and the risk estimates. In the tables, the mean value of survival time is presented with the standard deviation (SD) in parentheses [20,21]. K–M analysis with the log-rank test was used to evaluate the differences between two groups. Categorical data are expressed as numbers and percentages and were analyzed by the chi-square test. A two-tailed p value less than 0.05 was considered significant. The statistical analyses were conducted using SPSS 25.0 and R 3.6.1 software.

3. Results

3.1. Patient characteristics

A total of 41,938 patients with non-small cell lung cancer (NSCLC) were included in the study, with data extracted from the SEER database. After excluding patients who met the exclusion criteria, a total of 18,711 patients were included in this study, 12,522 of them were divided into the non-DM group, the rest 6,189 patients experienced DM were divided into DM group by contrast. The flow chart of patient screening is shown in Fig. 1.

Approximately 95 % of patients were late-stage NSCLC, while the remaining 5 % were early-stage. Among the patients, 9,855 (52.67 %) were male, and 8,856 (47.33 %) were female. Ethnicity was predominantly Caucasian (78.43 %), other ethnic groups like Asians, Latinos were included. Approximately 54.28 % of patients were married, the rest was unmarried. More than half primary tumors (58.52 %) were located in the left site. Meanwhile, the upper lobe was the most common primary site (59.11 %), followed by the lower lobe (29.98 %). About histological types, Lung Adenocarcinoma (LUAD) was the most common histological type (58.45 %), Lung Squamous Cell Carcinoma (LUSC) accounted for 32.3 %, and undifferentiated types accounted for the minimum proportion, rated 2.19 %. A total of 20.20 % patients developed ipsilateral metastasis. A greater proportion of the cohort (68.53 %) was comprised of patients with tumors $\leq$5 cm in size than patients with tumors larger than 5 cm. The mean overall survival (OS) was 41.79 months. Table 1 presents a summary of the T and N categories of the patients. Significant differences were observed between the DM and non-DM groups with respect to age, sex, ethnicity, primary site of the tumor, histological type, tumor differentiation grade, T category, N category, tumor size, ipsilateral metastasis, and survival months. However, no significant differences were observed between the two groups with regard to marital status or laterality of the tumor.

3.2. Risk factors associated with DM

The univariate analysis revealed that ten variables exhibited significant differences between the two groups. In the multivariate analysis, all ten variables (age, sex, ethnicity, primary site of the tumor, histological type, tumor differentiation grade, T category, N category, tumor size, and ipsilateral metastasis) were found to be significantly related to DM. Patients who developed DM at an earlier age, males, and those of African descent exhibited an increased risk. Moreover, in comparison to LUAD and other histological types,

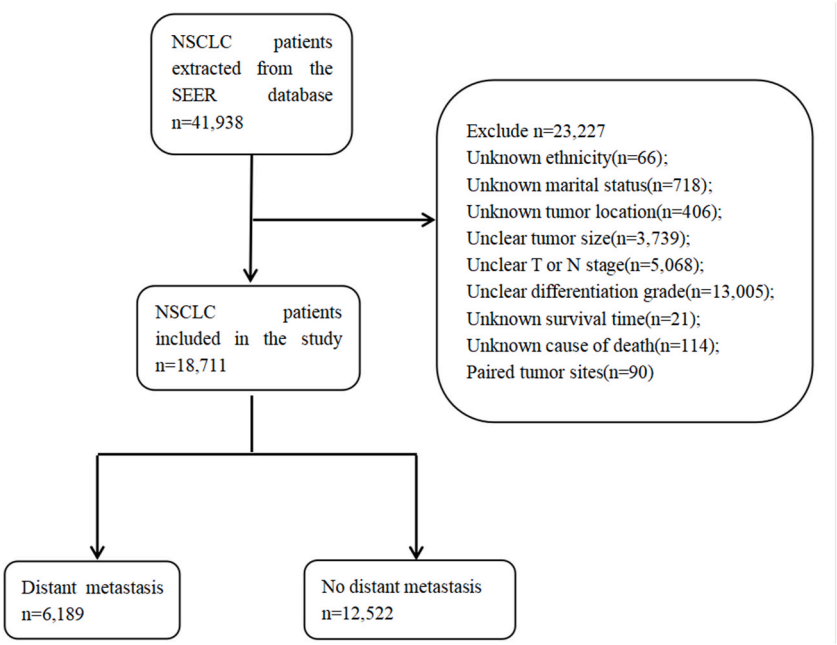


Fig. 1. Flow diagram of the selected cases.

Table 1
The clinicopathological features in NSCLC patients between DM and Non-DM groups.

	Overall (n = 18,711)	Non-DM(n = 12,522)	DM(n = 6,189)	p
Age group(n,%)				<0.001
Early onset	936 (5.00 %)	526 (4.2 %)	410 (6.62 %)	
Late onset	17775 (95.00 %)	11996 (95.8 %)	5779 (93.38 %)	
Gender(n,%)				<0.001
Male	9855 (52.67 %)	6400 (51.11 %)	3455 (55.82 %)	
Female	8856 (47.33 %)	6122 (48.89 %)	2734 (44.18 %)	
Ethnicity(n,%)				<0.001
Black	2181 (11.66 %)	1324 (10.57 %)	857 (13.85 %)	
White	14675 (78.43 %)	10000 (79.86 %)	4675 (75.54 %)	
Other	1855 (9.91 %)	1198 (9.57 %)	657 (10.62 %)	
Marital status(n,%)				0.87
Married	10156 (54.28 %)	6802 (54.32 %)	3354 (54.19 %)	
Unmarried	8555 (45.72 %)	5720 (45.68 %)	2835 (45.81 %)	
Laterality(n,%)				0.19
Left	10949 (58.52 %)	7369 (58.85 %)	3580 (57.84 %)	
Right	7762 (41.48 %)	5153 (41.15 %)	2609 (42.16 %)	
Primary site(n,%)				<0.001
Main bronchus	463 (2.47 %)	220 (1.76 %)	243 (3.93 %)	
Upper lobe	11060 (59.11 %)	7514 (60.01 %)	3546 (57.3 %)	
Middle lobe	866 (4.63 %)	587 (4.69 %)	279 (4.51 %)	
Lower lobe	5609 (29.98 %)	3841 (30.67 %)	1768 (28.57 %)	
Overlapping lesion	209 (1.12 %)	144 (1.15 %)	65 (1.05 %)	
Lung, NOS	504 (2.69 %)	216 (1.72 %)	288 (4.65 %)	
Differentiation(n,%)				<0.001
Well differentiated	2027 (10.83 %)	1692 (13.51 %)	335 (5.41 %)	
Moderately differentiated	6991 (37.36 %)	5254 (41.96 %)	1737 (28.07 %)	
Poorly differentiated	9283 (49.61 %)	5362 (42.82 %)	3921 (63.35 %)	
Undifferentiated	410 (2.19 %)	214 (1.71 %)	196 (3.17 %)	
Histology(n,%)				<0.001
SCC	6044 (32.3 %)	4413 (35.24 %)	1631 (26.35 %)	
ADC	10936 (58.45 %)	7280 (58.14 %)	3656 (59.07 %)	
Others	1731 (9.25 %)	829 (6.62 %)	902 (14.57 %)	
T stage(n,%)				<0.001
T0	4 (0.02 %)	1 (0.01 %)	3 (0.05 %)	
T1	4920 (26.29 %)	4363 (34.84 %)	557 (9 %)	
T2	6335 (33.86 %)	4681 (37.38 %)	1654 (26.72 %)	
T3	3884 (20.76 %)	2158 (17.23 %)	1726 (27.89 %)	
T4	3568 (19.07 %)	1319 (10.53 %)	2249 (36.34 %)	
N stage(n,%)				<0.001
N0	9513 (50.84 %)	7987 (63.78 %)	1526 (24.66 %)	
N1	1955 (10.45 %)	1432 (11.44 %)	523 (8.45 %)	
N2	5436 (29.05 %)	2570 (20.52 %)	2866 (46.31 %)	
N3	1807 (9.66 %)	533 (4.26 %)	1274 (20.58 %)	
Ipsilateral metastasis(n,%)				<0.001
Yes	3780 (20.20 %)	1316 (10.51 %)	2464 (39.81 %)	
No	14931 (79.80 %)	11206 (89.49 %)	3725 (60.19 %)	
Tumor size(cm)				<0.001
<5	12823 (68.53 %)	9434 (75.34 %)	3389 (54.76 %)	
5~7	3168 (16.93 %)	1765 (14.1 %)	1403 (22.67 %)	
>7	2720 (14.54 %)	1323 (10.57 %)	1397 (22.57 %)	
Survival time(months)	41.79 (0.32)	55.35 (0.40)	14.24 (0.30)	<0.001

Note: ADC,adenocarcinoma; SCC,squamous cell carcinoma.

LUSC is unlikely to be associated with the development of DM. In general, the risk of developing DM increases with increasing tumor differentiation grade, T category, N category, and tumor size. The presence of different tumor sites also indicated different risks. Patients with ipsilateral metastasis exhibited a significantly elevated risk of developing DM compared to those who did not develop ipsilateral metastasis (Table 2).

3.3. Young patients had greater risk of DM

The study population was divided into two groups: those NSCLC patients with young age (≤50 years old) and old age (>50 years old). The clinicopathological characteristics of the two groups were then compared. The young group comprised 936 patients (5.0 %), while the old group consisted of 17,775 patients (95.0 %). In addition to marital status and tumor laterality, significant differences were found in sex, ethnicity, primary site of the tumor, histological type, tumor differentiation grade, T category, N category, tumor size, and ipsilateral metastasis between the two groups. The young patients population exhibited a greater proportion of female patients (50.85 % vs 47.14 %, $p < 0.001$). Poorly differentiated and undifferentiated tumors in young patients were more than old

Table 2
The univariate and multivariate logistic regression for analyzing the risk factors of DM.

	Univariate logistic regression	Multivariate logistic regression
	OR (95%CI)	OR (95%CI)
Age group		
Early-onset	(Reference)	(Reference)
Late-onset	0.62 (0.54–0.71)*	0.84 (0.72–0.99)*
Gender		
Male	(Reference)	(Reference)
Female	0.83 (0.78–0.88)*	0.91 (0.84–0.98)*
Ethnicity		
Black	(Reference)	(Reference)
White	0.72 (0.66–0.79)*	0.83 (0.74–0.93)*
Others	0.85 (0.75–0.96)*	0.86 (0.74–1.005)
Marital status		
Married	(Reference)	
Unmarried	1.01 (0.95–1.07)	
Laterality		
Left	(Reference)	
Right	1.04 (0.98–1.11)	
Histology		
SCC	(Reference)	(Reference)
ADC	1.36 (1.27–1.46)*	1.79 (1.65–1.95)*
Others	2.94 (2.64–3.29)*	2.37 (2.08–2.71)*
Differentiation		
Well differentiated	(Reference)	(Reference)
Moderately differentiated	1.7 (1.47–1.90)*	1.36 (1.17–1.58)*
Poorly differentiated	3.7 (3.27–4.19)*	2.11 (1.82–2.44)*
Undifferentiated	4.6 (3.69–5.80)*	2.25 (1.71–2.96)*
Primary site		
Main bronchus	(Reference)	(Reference)
Upper lobe	0.43 (0.35–0.51)*	0.75 (0.60–0.93)*
Middle lobe	0.43 (0.34–0.54)*	0.77 (0.59–1.02)
Lower lobe	0.42 (0.34–0.50)*	0.83 (0.66–1.04)
Overlapping lesion of lung	0.41 (0.29–0.57)*	0.52 (0.35–0.78)*
Lung, NOS	1.21 (0.94–1.56)	1.11 (0.82–1.49)
Tumor size(cm)		
<5	(Reference)	(Reference)
5-7	2.21 (2.04–2.40)*	1.31 (1.18–1.44)*
>7	2.94 (2.70–3.20)*	1.47 (1.30–1.67)*
T stage		
T0/T1	(Reference)	(Reference)
T2	2.75 (2.48–3.06)*	1.89 (1.69–2.13)*
T3	6.23 (5.60–6.95)*	1.98 (1.71–2.31)*
T4	13.29 (11.90–14.86)*	3.14 (2.69–3.67)*
N stage		
N0	(Reference)	(Reference)
N1	1.91 (1.70–2.10)*	1.39 (1.23–1.57)*
N2	5.84 (5.41–6.30)*	3.53 (3.24–3.84)*
N3	12.51 (11.16–14.00)*	6.94 (6.12–7.87)*
Ipsilateral metastases		
No	(Reference)	(Reference)
Yes	5.63 (5.22–6.08)*	2.99 (2.66–3.36)*

Note: ADC,adenocarcinoma; SCC,squamous cell carcinoma.

patients (55.02 % vs 51.64 % $p < 0.001$). For young patients diagnosed with LUSC, which is associated with a lower risk of DM, was found to be lower than that of old group. Similarly, young patients had a higher incidence of worse T category (both size and invasion of adjacent structure), N category. In contrast, patients in young group exhibited a higher prevalence of ipsilateral metastasis, single metastasis, multiple metastases, and overall distant metastasis. The same results were observed for pleural or pericardial metastasis, distant lymph node metastasis, and distant organ metastasis. In the NSCLC patients included in the study, the highest incidence of DM occurred in the pleura or pericardium, while bone was the organ with the highest incidence of DM, followed by the brain and liver. However, the incidence of brain metastasis was the highest in young patients, while the incidence of pleural or pericardial metastasis was the highest in old patients. Despite the greater risk of DM, the survival time of young patients was longer than that of old patients. The details are presented in Table 3.

In subgroup analysis, the association between categorical age and overall DM in NSCLC patients was stratified. In patients with SCC and ADC, younger age still indicated a greater risk of DM, while the effect was not statistically significant for other types of tumors. Furthermore, the association between tumor onset age and DM risk was not significant in patients with large tumors (>7 cm). Nevertheless, the association between age and DM status was not found to be modified by sex, ethnicity, or lymph node status (Fig. 2).

Table 3
The clinicopathological features and metastatic patterns in NSCLC patients between early-onset and late-onset groups.

	Early-onset (n = 936)	Late-onset (n = 17,775)	p
Gender(n,%)			<0.001
Male	460 (49.15 %)	9395 (52.86 %)	
Female	476 (50.85 %)	8380 (47.14 %)	
Ethnicity(n,%)			<0.001
Black	161 (17.2 %)	2020 (11.36 %)	
White	647 (69.12 %)	14028 (78.92 %)	
Other	128 (13.68 %)	1727 (9.72 %)	
Marital status(n,%)			0.42
Married	496 (52.99 %)	9660 (54.35 %)	
Unmarried	440 (47.01 %)	8115 (45.65 %)	
Laterality(n,%)			0.47
Left	537 (57.37 %)	10412 (58.58 %)	
Right	399 (42.63 %)	7363 (41.42 %)	
Primary site(n,%)			<0.001
Main bronchus	44 (4.7 %)	419 (2.36 %)	
Upper lobe	545 (58.23 %)	10515 (59.16 %)	
Middle lobe	42 (4.49 %)	824 (4.64 %)	
Lower lobe	262 (27.99 %)	5347 (30.08 %)	
Overlapping lesion	13 (1.39 %)	196 (1.1 %)	
Lung, NOS	30 (3.21 %)	474 (2.67 %)	
Differentiation(n,%)			<0.001
Well differentiated	92 (9.83 %)	1935 (10.89 %)	
Moderately differentiated	329 (35.15 %)	6662 (37.48 %)	
Poorly differentiated	481 (51.39 %)	8802 (49.52 %)	
Undifferentiated	34 (3.63 %)	376 (2.12 %)	
Histology(n,%)			<0.001
SCC	165 (17.63 %)	5879 (33.07 %)	
ADC	660 (70.51 %)	10276 (57.81 %)	
Others	111 (11.86 %)	1620 (9.11 %)	
T stage(n,%)			<0.001
T0	0 (0 %)	4 (0.02 %)	
T1	200 (21.37 %)	4720 (26.55 %)	
T2	275 (29.38 %)	6060 (34.09 %)	
T3	237 (25.32 %)	3647 (20.52 %)	
T4	224 (23.93 %)	3344 (18.81 %)	
N stage(n,%)			<0.001
N0	362 (38.68 %)	9151 (51.48 %)	
N1	102 (10.9 %)	1853 (10.42 %)	
N2	328 (35.04 %)	5108 (28.74 %)	
N3	144 (15.38 %)	1663 (9.36 %)	
Tumor size(cm)			<0.001
<5	595 (63.57 %)	12228 (68.79 %)	
5~7	163 (17.41 %)	3005 (16.91 %)	
>7	178 (19.02 %)	2542 (14.3 %)	
Ipsilateral metastasis(n,%)	234 (25 %)	3546 (19.95 %)	<0.001
Pleural or pericardial metastasis(n,%)	144 (15.38 %)	2306 (12.97 %)	0.033
Distant lymph node metastasis(n,%)	57 (6.09 %)	607 (3.41 %)	<0.001
Dsitant organ metastases(n,%)			
Brain	174 (18.59 %)	1686 (9.49 %)	<0.001
Liver	67 (7.16 %)	817 (4.6 %)	<0.001
Bone	152 (16.24 %)	2083 (11.72 %)	<0.001
Single metastasis(n,%)	276 (29.49 %)	3973 (22.35 %)	<0.001
Multiple metastases(n,%)	134 (14.32 %)	1806 (10.16 %)	<0.001
Overall distant metastasis(n,%)	410 (43.8 %)	5779 (32.51 %)	<0.001
Survival time(months)	50.16 (1.49)	41.34 (0.32)	<0.001

Note: ADC,adenocarcinoma; SCC,squamous cell carcinoma.

A sensitivity analysis was conducted to assess the impact of excluding patients at extreme ages (n = 437), patients whose primary site was unclear (n = 534), and patients with extreme tumor sizes (n = 448) on the initial association between age and DM risk. The results demonstrated that these exclusions did not substantially alter the direction or magnitude of this association. (Table 4).

3.4. Dose–response analyses

To investigate the dynamic trend in the occurrence of DM with age, we conducted dose-response analyses. Nonlinear associations between age and pleural or pericardial metastasis (p for nonlinear <0.001) (Fig. 3h)), brain metastasis (p for nonlinear = 0.03) (Fig. 3f)), single metastasis (p for nonlinear <0.001) (Fig. 3b)), multiple metastases (p for nonlinear = 0.02) (Fig. 3c)), and overall DM

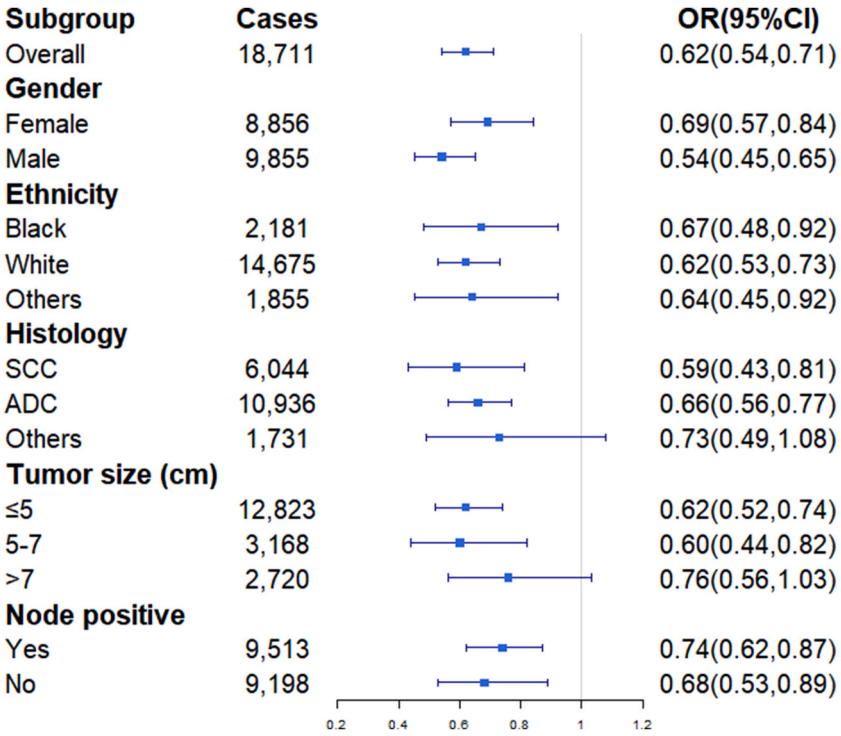


Fig. 2. Subgroup analyses evaluating the association of tumor onset age (young vs old) with DM modified by gender, ethnicity, histology, tumor size and node status.

Table 4
Sensitivity analyses to assess the robustness of the association between tumor onset age (early-onset v.s. late-onset) and DM risk.

	Excluding cases	OR (95%CI)
Primary analysis	0	0.62 (0.54,0.71)
Excluding patients at extreme age	437	0.61 (0.52,0.70)
Excluding patients with extreme tumor size	448	0.61 (0.53,0.70)
Excluding patients whose primary site was unclear	504	0.62 (0.55,0.72)

(p for nonlinear <0.001) were identified (Fig. 3a)). However, a linear association was found between age and distant lymph node metastasis (p for nonlinear = 0.27) (Fig. 3d)), liver metastasis (p for nonlinear = 0.37) (Fig. 3g)), and bone metastasis (p for nonlinear = 0.87) (Fig. 3e)). The risk of distant lymph node metastasis and distant organ metastasis (i.e., bone metastasis, brain metastasis, and liver metastasis) decreased with increasing age. In contrast, the risk of pleural or pericardial metastasis, single metastasis, multiple metastases, and overall distant metastasis gradually decreased with age at younger ages, but there was a slight trend that they increased at older ages. Specifically, the risk of pleural or pericardial metastasis exhibited a "U"-shaped pattern with age.

4. Discussion

This retrospective cohort study with large population investigated the risk factors associated with DM and the relationship between continuous age and risk of different patterns of DM in NSCLC patients. Our study found that young age, male, and black race patients exhibited a higher risk of developing DM. We also found that patients with SCC had a lower DM risk than those with LUAD or other histological types. Worse T and N category, as well as poorer pathological grade was closely related to the risk of DM, which had been proved by previous studies [22–24]. Moreover, the primary site of the tumor is also associated with the development of DM, tumors located in the main bronchus are more likely to develop DM. Furthermore, our study found it possible that patients may have already developed multiple latent metastases if intrapulmonary ipsilateral metastases occurred. Subgroup analyses indicated that the risk of DM was not significantly greater in young patients than in old patients with large tumors (>7 cm) or histological type excluding LUSC and LUAD. The reason could be that a tumor size often indicates advanced stage with higher incidence of metastasis [25]. Future research should be conducted to explore the relationship between age and DM in patients with other types of histology.

A definitive correlation exists between the incidence of lung cancer and age [26]. Population-based statistics indicate that the incidence of lung cancer is relatively low in younger age groups, with a notable increase observed after the age of 50, often exceeding a

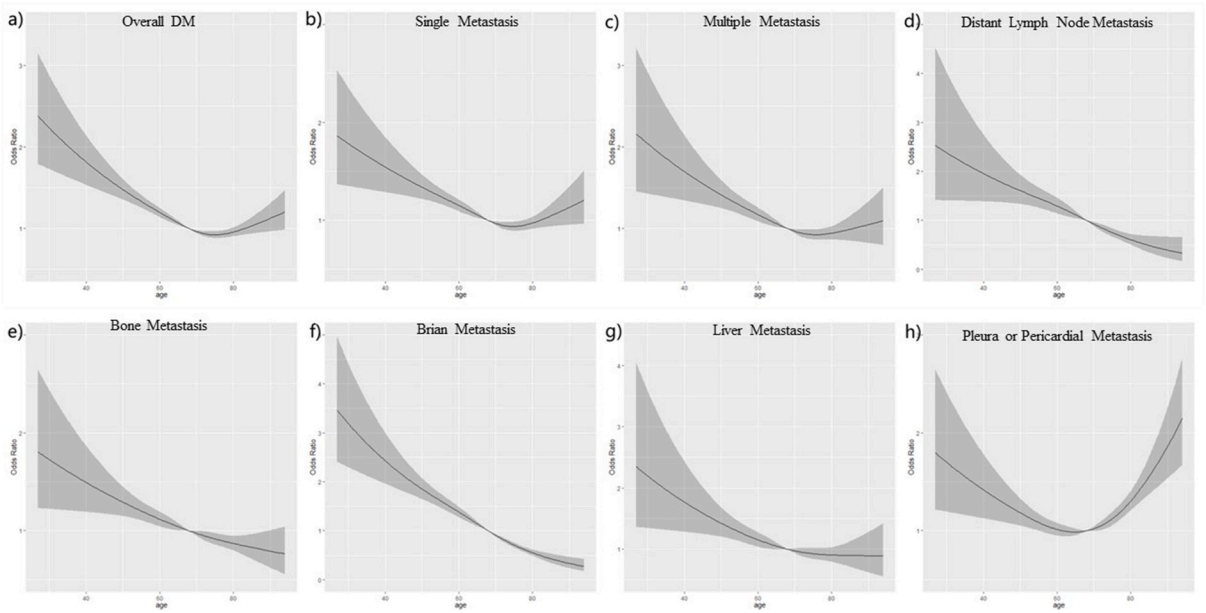


Fig. 3. Dose-response relationship between age (continuous) and risk of a) overall DM(p for nonlinear<0.001), b) single metastasis (p for nonlinear<0.001), c) multiple metastases (p for nonlinear = 0.02), d) distant lymph node metastasis (p for nonlinear = 0.27), e) bone metastasis (p for nonlinear = 0.87), f) brain metastasis (p for nonlinear = 0.03), g) liver metastasis (p for nonlinear = 0.37), h) pleural or pericardial metastasis (p for nonlinear<0.001).

fivefold to tenfold increase, a decline may be observed at the extremely advanced ages (e.g., over 85 years), and epidemiological studies conducted on larger populations, such as those in the United States and China, also demonstrate this phenomenon [3,27]. Therefore, it can be posited that patients diagnosed with lung cancer under age of 50 will exhibit distinctive characteristics when compared to other age groups. Young NSCLC patients are underrepresented with considerable heterogeneity in clinicopathologic characteristic compared with old patients [28]. Several studies have indicated that younger age had greater risk of lymph node or distant metastasis when diagnosed initially [15,16,29]. Our study partially indicates these differences, like more LUAD proportion, poorer pathological grading and more prone to developing DM. Metastases to relatively rare sites and organs were not fully recorded in the SEER database and we could not describe the detailed status. We still found that young patients had a greater incidence of each type of metastasis, including pleural or pericardial metastasis, distant lymph node metastasis, distant organ metastasis and overall distant metastasis. However, the survival time of young patients was longer than that of old patients. This may be attributed to differences in the genotypes targeted and the effects of treatments between early- and old patients, physical condition and treatment intention are considered as well [19,30].

Although this study indicated that young NSCLC patients (≤50 years) have a greater risk of DM than late-onset patients (>50 years), interestingly, the dose–response analyses suggest that DM risk changes nonlinearly. The overall risk of DM decreases with age before 70 years old but increases with age older than that. The risk of distant lymph node metastasis and distant organ metastases (i.e., bone metastasis, brain metastasis and liver metastasis) decreased with increasing age, while the risks of pleural or pericardial metastasis, single metastasis, multiple metastases and overall DM decreased at younger ages, but they tended to increase at older ages, which had not been reported in previous studies. Specifically, the risk of pleural or pericardial metastasis significantly increases after the seventh decade, and thus, the risk changes with age in a U-shaped manner. In clinical practice, it is necessary to comprehensively evaluate whether a patient has DM before surgery because of the unsatisfactory effect of surgery on patients with DM. This study suggested that although old patients were generally at lower risk of developing DM, the decision still should be drawn with caution when considering surgery.

The following strengths should be noted in this study. First, this study is based on a large population. Second, this is the first study exploring the factors related to the development of DM in NSCLC patients and evaluating how the risk of DM dynamically changes with age using dose–response analysis. Because DM is closely related to quality of life and survival probability, earlier risk evaluation can help clinicians identify patients at greater risk of DM and provide a faster reference for active medical decision making. Moreover, the sensitivity analysis indicated that age plays an excellent and robust role in the risk stratification of DM risk for NSCLC patients.

Our study also has limitations: First, the study is a retrospective study based on public database, the real-world large scale prospective studies may be required to explore risk factors for DM risk by including more parameters in the future. Second, Caucasian ethnicity dominates the cohort, while there is considerable heterogeneity in lung cancer between racial groups [31,32], which may produce research bias. Third, driven gene mutation is not fully explored, although a few researchers found ALK refusion may be risk factor of NSCLC recurrence [33], but the relationship between DM and driven genes has not been investigated systematically. More studies are needed to reveal their correlation in the future.

5. Conclusions

This retrospective cohort study suggested that age, sex, ethnicity, histology, T category, N category, differentiation grade, primary site of the tumor, and ipsilateral metastases are factors associated with DM in NSCLC patients. Young NSCLC patients (≤50 years) have a greater risk of DM than old patients (>50 years). Dose–response analysis revealed that the risk of DM may decrease with increasing age in patients under 70 years old, but there is a trend toward a slight increase with increasing age in patients older than seven decades. Large prospective studies may be required to explore risk factors for DM risk by including more parameters in the future.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Because the data were obtained from SEER database with permission (username: 14238-Nov2020) and all information was deidentified for patients, the ethics approval and consent were waived.

Data availability statement

The data supporting this study's findings are available from the corresponding author upon reasonable request.

CRediT authorship contribution statement

Yingxian Dong: Software, Methodology, Investigation, Conceptualization. **Sicheng Zhou:** Writing – review & editing, Writing – original draft, Data curation. **Jue Li:** Visualization, Software. **Yin Zhang:** Visualization, Investigation. **Guowei Che:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Not applicable.

References

[1] Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet (London, England) 396 (10258) (2020) 1204–1222.
[2] 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) 209–249.
[3] R.L. Siegel, A.N. Giaquinto, A. Jemal, Cancer statistics, 2024, CA A Cancer J. Clin. 74 (1) (2024) 12–49.
[4] D.S. Ettinger, D.E. Wood, D.L. Aisner, W. Akerley, J.R. Bauman, A. Bharat, et al., NCCN Guidelines® insights: non-small cell lung cancer, version 2.2023, J. Natl. Compr. Cancer Netw. : J. Natl. Compr. Cancer Netw. 21 (4) (2023) 340–350.
[5] A.A. Thai, B.J. Solomon, L.V. Sequist, J.F. Gainor, R.S. Heist, Lung cancer, Lancet (London, England) 398 (10299) (2021) 535–554.
[6] K.M. Fong, A. Rosenthal, D.J. Giroux, K.K. Nishimura, J. Erasmus, Y. Lievens, et al., The international association for the study of lung cancer staging project for lung cancer: proposals for the revision of the M descriptors in the forthcoming ninth edition of the TNM classification for lung cancer, J. Thorac. Oncol. : official publication of the International Association for the Study of Lung Cancer 19 (5) (2024) 786–802.
[7] W.L. Tan, K.L.M. Chua, C.C. Lin, V.H.F. Lee, L.M. Tho, A.W. Chan, et al., Asian thoracic oncology research group expert consensus statement on optimal management of stage III NSCLC, J. Thorac. Oncol. : official publication of the International Association for the Study of Lung Cancer 15 (3) (2020) 324–343.
[8] Y. Wang, F. Shi, R. Tao, J. Wu, J. Gu, R. Yang, et al., The relationship between UBE2C and AGGF1 overexpression and tumor angiogenesis in non-small cell lung cancer, Cancer Manag. Res. 13 (2021) 5919–5930.
[9] F. Waechter, J. Passweg, M. Tamm, M. Brutsche, R. Herrmann, M. Pless, Significant progress in palliative treatment of non-small cell lung cancer in the past decade, Chest 127 (3) (2005) 738–747.
[10] R.L. Siegel, K.D. Miller, N.S. Wagle, A. Jemal, Cancer statistics, 2023, CA A Cancer J. Clin. 73 (1) (2023) 17–48.
[11] N. Howlader, A.M. Noone, M. Krapcho, N. Neyman, Z.J.N.C.I. Tatalovich, SEER Cancer Statistics Review, vols. 1975–2003, 2013.
[12] J. Subramanian, D. Morgensztern, B. Goodgame, M.Q. Baggstrom, F. Gao, J. Piccirillo, et al., Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis, J. Thorac. Oncol. : official publication of the International Association for the Study of Lung Cancer 5 (1) (2010) 23–28.
[13] A. Dell'Amore, M. Monteverde, N. Martucci, F. Davoli, G. Caroli, E. Pipitone, et al., Surgery for non-small cell lung cancer in younger patients: what are the differences? Heart Lung Circ. 24 (1) (2015) 62–68.
[14] A. Thomas, Y. Chen, T. Yu, M. Jakopovic, G. Giaccone, Trends and characteristics of young non-small cell lung cancer patients in the United States, Front. Oncol. 5 (2015) 113.
[15] W. Xia, A. Wang, M. Jin, Q. Mao, W. Xia, G. Dong, et al., Young age increases risk for lymph node positivity but decreases risk for non-small cell lung cancer death, Cancer Manag. Res. 10 (2018) 41–48.
[16] L. Yang, F. Fang, J. Chan, B. Chen, W. Luo, Q. Zhu, et al., Metastatic patterns and prognosis of young lung cancer patients: a population-based study by age, Ann. Transl. Med. 9 (14) (2021) 1159.
[17] D.J. Hughes, M. Kapiris, A. Podvez Nevajda, H. McGrath, C. Stavraka, S. Ahmad, et al., Non-small cell lung cancer (NSCLC) in young adults, age < 50, is associated with late stage at presentation and a very poor prognosis in patients that do not have a targeted therapy option: a real-world study, Cancers 14 (24) (2022).

[18] P.A. Wingo, P.M. Jamison, R.A. Hiatt, H.K. Weir, P.M. Gargiullo, M. Hutton, et al., Building the infrastructure for nationwide cancer surveillance and control–a comparison between the national Program of cancer registries (NPCR) and the surveillance, epidemiology, and end results (SEER) Program (United States), Cancer Causes Control : CCC (Cancer Causes Control) 14 (2) (2003) 175–193.
[19] A.G. Sacher, S.E. Dahlberg, J. Heng, S. Mach, P.A. Jänne, G.R. Oxnard, Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer, JAMA Oncol. 2 (3) (2016) 313–320.
[20] A.K. Nowak, K. Chansky, D.C. Rice, H.I. Pass, H.L. Kindler, L. Shemanski, et al., The IASLC mesothelioma staging project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for pleural mesothelioma, J. Thorac. Oncol. : official publication of the International Association for the Study of Lung Cancer 11 (12) (2016) 2089–2099.
[21] L. Desquilbet, F. Mariotti, Dose-response analyses using restricted cubic spline functions in public health research, Stat. Med. 29 (9) (2010) 1037–1057.
[22] B. Wang, S. Chen, H. Xiao, J. Zhang, D. Liang, J. Shan, et al., Analysis of risk factors and gene mutation characteristics of different metastatic sites of lung cancer, Cancer Med. 11 (1) (2022) 268–280.
[23] J.J. Hung, W.J. Jeng, W.H. Hsu, T.Y. Chou, B.S. Huang, Y.C. Wu, Predictors of death, local recurrence, and distant metastasis in completely resected pathological stage-I non-small-cell lung cancer, J. Thorac. Oncol. : official publication of the International Association for the Study of Lung Cancer 7 (7) (2012) 1115–1123.
[24] J. Yang, A. Peng, B. Wang, A.M. Gusdon, X. Sun, G. Jiang, et al., The prognostic impact of lymph node metastasis in patients with non-small cell lung cancer and distant organ metastasis, Clin. Exp. Metastasis 36 (5) (2019) 457–466.
[25] Y. Aksoy, N. Citak, C. Obuz, B. Acikmese, A. Pekcolaklar, M. Metin, et al., Prognostic factors and survival in resected T4 non-small cell lung cancer: is there any difference in the T4 subgroups? Zentralblatt fur Chirurgie 146 (3) (2021) 335–343.
[26] F. Bray, M. Laversanne, H. Sung, J. Ferlay, R.L. Siegel, I. Soerjomataram, et al., Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, CA A Cancer J. Clin. 74 (3) (2024) 229–263.
[27] R. Zheng, S. Zhang, S. Wang, R. Chen, K. Sun, H. Zeng, et al., Lung cancer incidence and mortality in China: updated statistics and an overview of temporal trends from 2000 to 2016, Journal of the National Cancer Center 2 (3) (2022) 139–147.
[28] S. Ramalingam, K. Pawlish, S. Gadgeel, R. Demers, G.P. Kalemkerian, Lung cancer in young patients: analysis of a Surveillance, Epidemiology, and End Results database, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 16 (2) (1998) 651–657.
[29] B. Wang, L. Chen, C. Huang, J. Lin, X. Pan, Z. Shao, et al., The homogeneous and heterogeneous risk factors for occurrence and prognosis in lung cancer patients with bone metastasis, Journal of bone oncology 17 (2019) 100251.
[30] L. Corrales-Rodríguez, O. Arrieta, L. Mas, R. Báez-Saldaña, O. Castillo-Fernández, N. Blais, et al., An international epidemiological analysis of young patients with non-small cell lung cancer (AduJov-CLICaP), Lung cancer (Amsterdam, Netherlands) 113 (2017) 30–36.
[31] L. Ellis, A.J. Canchola, D. Spiegel, U. Ladabaum, R. Haile, S.L. Gomez, Racial and ethnic disparities in cancer survival: the contribution of tumor, sociodemographic, institutional, and neighborhood characteristics, J. Clin. Oncol. : official journal of the American Society of Clinical Oncology 36 (1) (2018) 25–33.
[32] A.M. Johnson, A. Johnson, R.B. Hines, R. Mohammadi, Neighborhood context and non-small cell lung cancer outcomes in Florida non-elderly patients by race/ethnicity, Lung cancer (Amsterdam, Netherlands) 142 (2020) 20–27.
[33] S.H. Shin, H. Lee, B.H. Jeong, Y.S. Choi, M.H. Shin, S. Kim, et al., Anaplastic lymphoma kinase rearrangement in surgically resected stage IA lung adenocarcinoma, J. Thorac. Dis. 10 (6) (2018) 3460–3467.