ORIGINAL ARTICLE

Long-term survival analysis of patients with non-small cell lung cancer complicated with type 2 diabetes mellitus

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Abstract

Background: This study aimed to investigate the effect of type 2 diabetes mellitus on survival of patients with non-small cell lung cancer (NSCLC).
Methods: We retrospectively analyzed NSCLC patients who had undergone radical lung cancer surgery from January 2011 to December 2014 in the Anhui Medical University affiliated Anhui Provincial Hospital. Kaplan-Meier plots, log-rank tests, and Cox proportional hazards regression models were used to describe the effect of type 2 diabetes mellitus on the overall survival of patients with NSCLC.
Results: A total of 769 patients with NSCLC were enrolled, including 126 in the diabetic mellitus group and 643 in the nondiabetic mellitus group. The one, three, and five-year survival for patients with and without diabetes mellitus were 86.1% versus 89.6%, 49.5% versus 62.4%, and 33.3% versus 40.6%, respectively. The Cox model showed that type 2 diabetes mellitus was a poor independent prognostic factors for NSCLC patients. In addition, metformin is a good independent prognostic factor for patients with non-small cell lung cancer with type 2 diabetes mellitus.
Conclusions: NSCLC patients without type 2 diabetes mellitus have an increased survival rate compared with those with type 2 diabetes mellitus.

Introduction

The incidence and mortality of lung cancer ranks first among all malignancies worldwide.[1] The prognosis of lung cancer patients is related to tumor stage, pathological type and concomitant disease, among which concomitant disease is an important factor affecting the prognosis.[2] Diabetes mellitus is one of the most common endocrine diseases, mostly type 2 diabetes mellitus (type 2 DM). Epidemiological data show that the prevalence of type 2 DM is as high as 9.7%–11.6%, and type 2 DM is a risk factor for the occurrence, development and prognosis of various tumors.[3–5] It has been reported in the literature that diabetes mellitus has a significant impact on the prognosis of gastric cancer, colorectal cancer, breast cancer and other malignant tumors,[6–8] while there is no consistent conclusion

on the impact of type 2 DM on the prognosis of lung cancer patients. Research investigating how pre-existing diabetes mellitus influences lung cancer outcomes is critical to inform the proper care of these patients. The aim of this study was to examine the effects of type 2 DM at the time of cancer diagnosis on the overall survival (OS) of patients with NSCLC treated by surgery. In addition, we analyzed whether metformin could affect the prognosis of NSCLC patients with type 2 DM.

Methods

Sample setting and study population

This retrospective study was conducted with approval of the Institutional Review Boards of the Anhui Medical

University-affiliated Anhui Provincial Hospital. Hospital, and departmental tumor registries were used to identify all patients undergoing curative resection of stages I-IIIA NSCLC from January 2011 and August 2014. The patients were screened, and their hospital records were extracted if patients met the following criteria: (i) histopathologically proven NSCLC; (ii) no neoadjuvant therapy; (iii) no known distant metastasis; and (iv) R0 resection. Patients were excluded if they had: (i) palliative resection; (ii) type 1 diabetes mellitus; or (iii) incomplete medical records.

Patient characteristics

The initial hospitalization during the years under study was identified as the index visit. Patients characteristics and clinical laboratory data during the index visit were extracted from hospital records, including the patient's age, sex, smoking history, surgical procedure, histological classification, pathological stage, tumor diameter, postoperative adjuvant radiotherapy and postoperative adjuvant chemotherapy. TNM staging was based on the International Association for Lung Cancer Research (IASLC) guidelines, eighth edition. The OS was calculated from the date of the operation for NSCLC until death from any cause. The disease-free survival (DFS) was measured from the date of surgery to the date of locoregional recurrence, type 2 DM or death from any cause.

Type 2 DM recorded during the index visit was considered the main prognostic factor of interest in the study. The dependent variable in this analysis were OS and DFS. Of all patients, 662 (86.1%) patients were followed up until the end of 2019.

Statistical analysis

For quantitative variables, the *t*-test was used for evaluating normally distributed data. Non-normally distributed data

Table 1 Characteristics of NSCLC patients by type 2 diabetes mellitus (DM) (*n* = 769)

Variable	A group (*n* = 643)	B group (*n* = 126)	χ^2	*P*-value
Sex			1.878	0.171
Male	451	96		
Female	192	30		
Age (year)			0.443	0.506
≤65	428	80		
>65	215	46		
Smoking history			0.017	0.896
Yes	241	48		
No	402	78		
Surgical procedure			0.186	0.666
Lobectomy	552	110		
Pneumonectomy	91	16		
Tumor diameter (cm)			0.122	0.727
≤3	312	59		
>3	331	67		
Histological classification			0.628	0.890
Adenocarcinoma	360	68		
Squamous cell carcinoma	241	49		
Adenosquamous carcinoma	23	6		
Other	19	3		
TNM stage			0.440	0.802
I	312	59		
II	195	37		
III	136	30		
Postoperative chemotherapy			0.723	0.395
Yes	343	62		
No	300	64		
Postoperative radiotherapy			0.735	0.391
Yes	56	14		
No	587	112		
Complications			0.001	0.973
Yes	142	28		
No	501	98		

were analyzed with the Mann-Whitney test. Qualitative variables were examined with Pearson's $\chi 2$ test when appropriate. Data are expressed as the median and interquartile range. Survival curves for the two groups were estimated using the Kaplan-Meier method and compared by a log-rank test. Both univariate and multivariate Cox proportional hazards models were fitted to assess the association between type 2 DM with OS and DFS and to evaluate potential independent predictors of survival. The variables included in the Cox proportional hazards models were age, sex, smoking history, surgical procedure, tumor diameter, histological classification, TNM stage, type 2 DM, postoperative adjuvant chemotherapy, postoperative adjuvant radiotherapy and complications.

All analyses were performed using SPSS (IBM SPSS Statistics for Windows, Version 24.0).

Results

Baseline patient characteristics

A total of 769 patients with newly diagnosed NSCLC between January 2011 and August 2014 were included in the final analysis. The median follow-up was 46 months (range: 0–108 months). The mean age of the study population was 67.8 years. Of all patients, 547 (71.1%) were males, and the majority (82.4%) did not have type 2 DM. Overall, 662 patients (86.1%) died by the end of 2019.

Table 2 Univariate and multivariate analyses of prognostic factors and overall survival (OS) in patients with NSCLC (*n* = 769)

Variable	Case	Median survival time (month) (95% CI)	Five-year survival rate (%)	*P*-value	RR (95% CI)	*P*-value
		Univariate analysis			Multivariate analysis	
Sex				0.385	—	0.625
Male	547	44 ± 2.527	37.6%			
Female	222	48 ± 4.723	41.6%			
Age (year)				0.432	—	0.202
≤65	508	47 ± 2.582	38.9%			
>65	261	46 ± 4.106	39.3%			
Smoking history				0.336	—	0.451
Yes	289	42 ± 2.852	35.0%			
No	480	48 ± 2.850	41.1%			
Surgical procedure				0.003	1.333(1.070–1.662)	0.010
Lobectomy	662	48 ± 2.571	40.6%			
Pneumonectomy	107	36 ± 3.775	27.5%			
Tumor diameter (cm)				0.296	—	0.234
≤3	335	47 ± 3.174	39.5%			
>3	434	46 ± 2.729	38.1%			
Histological classification				0.073	—	0.148
Adenocarcinoma	428	48 ± 3.644	41.8%			
Squamous-cell carcinoma	290	45 ± 2.632	36.0%			
Adenosquamous carcinoma	29	33 ± 0.893	24.1%			
Other	22	31 ± 11.770	21.2%			
TNM stage				<0.001	1.240(1.124–1.369)	<0.001
I	371	55 ± 2.686	45.2%			
II	232	44 ± 4.930	37.6%			
III	166	37 ± 2.625	26.3%			
Type 2 DM				0.045	0.787(0.641–0.967)	0.023
Yes	126	36 ± 4.370	33.3%			
No	643	48 ± 2.236	40.6%			
Postoperative chemotherapy				<0.001	—	0.112
Yes	405	39 ± 1.888	33.4%			
No	364	56 ± 3.355	45.0%			
Postoperative radiotherapy				0.055	—	0.994
Yes	70	36 ± 2.007	27.9%			
No	699	48 ± 2.154	39.9%			
Complications				0.067		0.074
Yes	170	37 ± 2.944	32.3%			
No	599	48 ± 2.285	40.5%			

There were 276 stage IA cases, 95 stage IB cases, 129 stage IIA cases, 103 stage IIB cases and 166 stage IIIA cases. According to the type 2 DM, the patients were divided into the without diabetes mellitus group ($n = 643$; 16.4%; A group) and the diabetes mellitus group ($n = 126$; 83.6%; B group). The two groups were similar in terms of age, sex, smoking history, surgical procedure, tumor diameter, histological classification, TNM stage, type 2 DM, postoperative adjuvant chemotherapy, postoperative adjuvant radiotherapy and complications, with no significant differences ($P > 0.05$) (Table 1).

Prognostic factor analysis

The results of the univariate analysis of factors associated with the OS in the patients are presented in Table 2. The

univariate survival analysis revealed the following patient characteristics to be significant prognostic factors for poor survival: pneumonectomy, later stage, postoperative adjuvant chemotherapy, and type 2 DM. According to DFS calculations, the univariate survival analysis revealed the following patient characteristics to be significant prognostic factors for poor survival: pneumonectomy, later stage, postoperative adjuvant chemotherapy, postoperative adjuvant radiotherapy and type 2 DM. Detailed results are listed in Table 3.

The further multivariate analysis identified that, for the NSCLC patients, type 2 DM ($P = 0.023$), TNM stage ($P < 0.001$) and surgical procedure ($P = 0.010$) were independent factors associated with OS (Table 2), while the type 2 DM ($P = 0.013$), TNM stage ($P < 0.001$) and

Table 3 Univariate and multivariate analyses of prognostic factors and disease-free survival (DFS) in patients with NSCLC ($n = 769$)

		Univariate analysis			Multivariate analysis	
Variable	Case	Median survival time (month) (95% CI)	Five-year survival rate (%)	*P*-value	RR (95% CI)	*P*-value
Sex				0.383	—	0.597
Male	547	36 ± 2.454	12.6%			
Female	222	41 ± 3.765	17.3%			
Age (year)				0.686	—	0.402
≤65	508	37 ± 2.202	13.2%			
>65	261	38 ± 3.742	15.8%			
Smoking history				0.265	—	0.368
Yes	289	34 ± 2.987	11.5%			
No	480	39 ± 2.878	15.5%			
Surgical procedure				0.009	1.333(1.070–1.662)	0.030
Lobectomy	662	39 ± 2.298	14.6%			
Pneumonectomy	107	26 ± 3.995	10.2%			
Tumor diameter (cm)				0.265	—	0.238
≤3	335	38 ± 2.916	15.2%			
>3	434	36 ± 2.811	13.0%			
Histological classification				0.114	—	0.148
Adenocarcinoma	428	42 ± 2.917	15.4%			
Squamous-cell carcinoma	290	36 ± 2.305	13.8%			
Adenosquamous carcinoma	29	21 ± 15.249	3.4%			
Other	22	19 ± 12.181	5.6%			
TNM stage				<0.001	1.240(1.124–1.369)	<0.001
I	371	45 ± 2.353	16.9%			
II	232	37 ± 4.135	14.5%			
III	166	25 ± 2.898	6.7%			
Type 2 DM				0.023	0.787(0.641–0.967)	0.013
Yes	126	25 ± 5.241	10.2%			
No	643	38 ± 2.091	14.7%			
Postoperative chemotherapy				<0.001	—	0.138
Yes	405	30 ± 2.277	10.4%			
No	364	46 ± 2.171	18.0%			
Postoperative radiotherapy				0.035	—	0.877
Yes	70	24 ± 1.744	10.2%			
No	699	38 ± 1.973	14.4%			
Complications				0.115		0.087
Yes	170	28 ± 4.485	14.9%			
No	599	39 ± 2.431	13.7%			

surgical procedure ($P = 0.030$) were identified as independent prognostic factor for DFS (Table 3).

The Kaplan-Meier curve for OS displayed a statistically significant association with survival and type 2 DM (Fig 1a). The one-, three-, and five-year OS rates for patients with and without type 2 DM were 86.1% versus 89.6%, 49.5% versus 62.4%, and 33.3% versus 40.6%, respectively, and the corresponding DFS rates were 73.6% versus 79.9%, 41.4% versus 51.9%, and 10.2% versus 13.3%, respectively (Fig 1b).

Further analyses

According to whether metformin was used in group B, the patients were divided into the metformin group ($n = 35$; 27.8%) and the nonmetformin group ($n = 91$; 72.2%). The two groups were similar in terms of age, sex, smoking history, surgical procedure, tumor diameter, histological classification, TNM stage, type 2 DM, postoperative adjuvant chemotherapy, postoperative adjuvant radiotherapy and complications, with no significant differences ($P > 0.05$) (Table 4).

The univariate analyses were conducted, and the detailed result was that the patients with young age, later stage, postoperative adjuvant chemotherapy, postoperative adjuvant radiotherapy, complications and metformin use have a worse OS and DFS. Detailed results are listed in Tables 5 and 6. The further multivariate analysis identified that the

TNM stage ($P < 0.001$) and metformin use ($P = 0.016$) were independent factors associated with OS (Table 5), while the TNM stage ($P < 0.001$) and metformin use ($P = 0.019$) were identified as independent prognostic factor for DFS (Table 6).

The Kaplan-Meier curve for OS displayed a statistically significant association between survival and metformin (Fig 2a). The one-, three-, and five-year survival rates for patients treated with and without metformin were 91.4% versus 84.0%, 65.2% versus 42.9%, and 43.5% versus 28.9%, respectively, and the corresponding DFS rates were 85.7% versus 68.7%, 53.8% versus 36.2%, and 12.7% versus 6.1%, respectively (Fig 2b).

Discussion

Diabetes mellitus is one of the most common endocrine diseases.[9] As the world's population ages, the number of patients with lung cancer and diabetes mellitus appear to be on the rise. The literature reports that diabetes mellitus has a significant impact on the prognosis of gastric cancer, colorectal cancer, breast cancer and other malignant tumors.[6–8] However, there are few studies on the impact of diabetes mellitus on lung cancer, and there are differences in their findings.[10–12] At present, most of the studies on lung cancer with diabetes mellitus are on patients with advanced disease who are receiving chemoradiotherapy, while there are relatively few studies on patients with lung
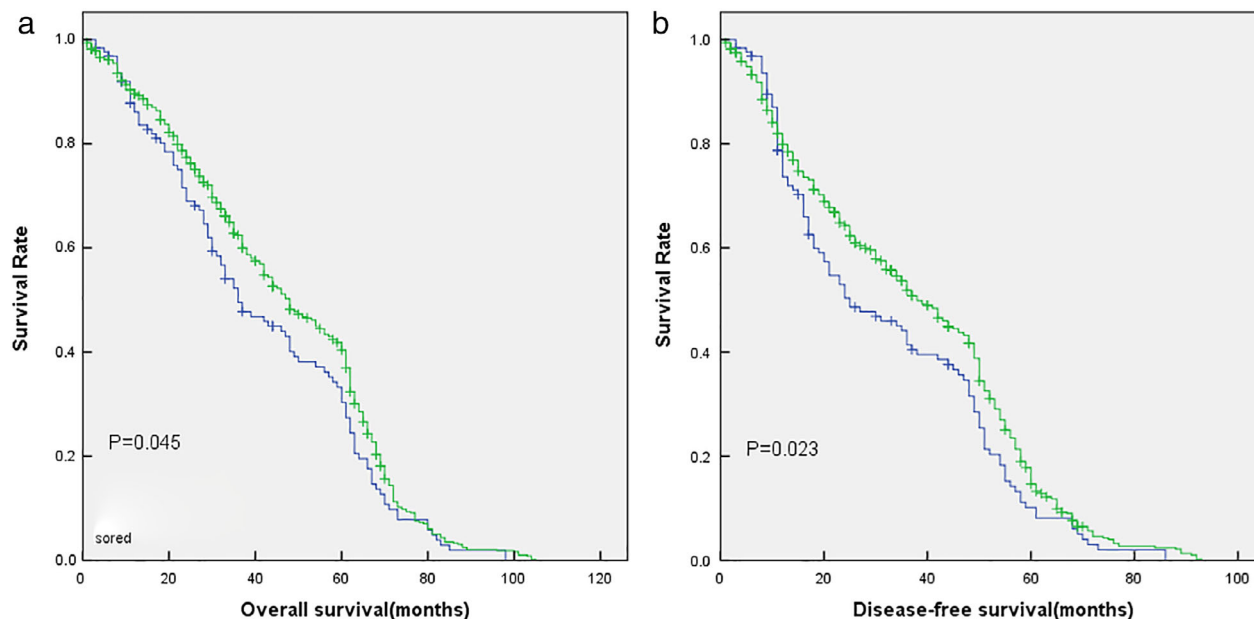

Figure 1 Kaplan-Meier survival curves for A group and B group. (**a**) The median overall survival (OS) was significantly better in the A group. (**b**) The patients without type 2 DM (A group) had better median disease-free survival (DFS). (**a**) (⎽⎯⎤) B group, (⎽⎯⎤) A group, (⊢+⊣) B group censored, (⊢+⊣) A group censored. (**b**) (⎽⎯⎤) B group, (⎽⎯⎤) A group, (⊢+⊣) B group censored, (⊢+⊣) A group censored.

Table 4 Characteristics of NSCLC patients with type 2 DM by metformin (*n* = 126)

Variable	Metformin group (*n* = 35)	Nonmetformin group (*n* = 91)	χ^2	*P*-value
Sex			1.187	0.276
Male	29	67		
Female	6	24		
Age (year)			0.008	0.927
≤65	22	58		
>65	13	33		
Smoking history			0.913	0.339
Yes	11	37		
No	24	54		
Surgical procedure			1.349	0.245
Lobectomy	33	77		
Pneumonectomy	2	14		
Tumor diameter			0.096	0.757
≤3	18	44		
>3	17	47		
Histological classification			2.028	0.567
Adenocarcinoma	19	49		
Squamous-cell carcinoma	22	37		
Adenosquamous carcinoma	3	3		
Other	1	2		
TNM stage			0.397	0.820
I	17	42		
II	11	26		
III	7	23		
Postoperative chemotherapy			1.643	0.200
Yes	14	48		
No	21	43		
Postoperative radiotherapy			0.061	0.806
Yes	3	11		
No	32	80		
Complications			0.138	0.710
Yes	7	21		
No	28	70		

cancer and diabetes mellitus undergoing surgery in the early and middle stages.[13–15] This study found that type 2 DM was significantly associated with long-term survival in patients with NSCLC who underwent surgery, and long-term survival was significantly lower in patients with type 2 DM. In addition, further studies have found that patients with NSCLC using metformin, a hypoglycaemic agent, have better long-term survival than patients with NSCLC using nonmetformin hypoglycaemic agents.

This study found that NSCLC patients with type 2 DM who underwent radical surgery had a worse five-year survival than NSCLC patients without type 2 DM. Inal *et al.* found that 442 patients with advanced NSCLC who received chemotherapy had better survival than NSCLC patients without diabetes mellitus, and diabetes mellitus was an independent prognostic factor for advanced NSCLC patients.[16] Peter *et al.* analyzed 1852 patients with advanced lung cancer from three databases, HUNT, PEG and NLCB. Among them, 84 patients had lung cancer and

diabetes mellitus and 1768 patients had lung cancer without diabetes mellitus. Patients with advanced lung cancer and diabetes mellitus have worse survival than patients with advanced lung cancer without diabetes mellitus, and multivariate analysis found that diabetes mellitus is an independent prognostic factor for patients with advanced lung cancer.[17] This is similar to our findings.

With regard to the causes of type 2 DM that affect the prognosis of NSCLC patients, the current study believes that, first, insulin and IGF-1 activate pathways such as P13K/Akt kinase and Ras/MAP kinase, which stimulate tumor cell proliferation, metastasis, and progression. The P13K/Akt kinase pathway plays an important role in tumor resistance. In addition, studies have shown that inhibition of the PI3K/Akt kinase pathway can increase the killing of tumor cells by chemotherapy and radiotherapy. Insulin resistance in type 2 DM leads to hyperinsulinaemia, and hyperinsulinaemia indirectly affects the carcinogenic effects of IGF-1. High insulin enhances tumor risk by

Table 5 Univariate and multivariate analyses of prognostic factors and overall survival (OS) in patients with NSCLC with type 2 DM (*n* = 126)

		Univariate analysis			Multivariate analysis	
Variable	Case	Median survival time (month) (95% CI)	Five-year survival rate (%)	*P*-value	RR (95% CI)	*P*-value
Sex				0.497	—	0.927
Male	96	36 ± 6.735	32.3%			
Female	30	36 ± 4.397	23.2%			
Age (year)				0.037	—	0.171
≤65	80	36 ± 3.732	26.7%			
>65	46	46 ± 8.261	34.6%			
Smoking history				0.435	—	0.496
Yes	48	43 ± 10.590	37.4%			
No	78	36 ± 2.232	25.7%			
Surgical procedure				0.223	—	0.992
Lobectomy	110	37 ± 5.649	31.5%			
Pneumonectomy	16	33 ± 11.686	22.2%			
Tumor diameter (cm)				0.247	—	0.694
≤3	62	46 ± 7.329	30.8%			
>3	64	36 ± 3.806	29.7%			
Histological classification				0.649	—	0.552
Adenocarcinoma	68	43 ± 5.817	34.1%			
Squamous-cell carcinoma	49	36 ± 5.352	27.8%			
Adenosquamous carcinoma	6	26 ± 3.674	0.0%			
Other	3	23 ± 4.899	0.0%			
TNM stage				0.002	1.582(1.099–2.546)	<0.001
I	59	54 ± 7.893	43.0%			
II	37	30 ± 4.198	22.0%			
III	30	24 ± 5.613	14.4%			
Metformin				0.039	1.673(1.099–2.546)	0.016
Yes	35	49 ± 7.644	40.4%			
No	91	33 ± 3.031	26.0%			
Postoperative chemotherapy				0.008	—	0.851
Yes	62	30 ± 3.749	24.2%			
No	64	48 ± 8.208	36.3%			
Postoperative radiotherapy				0.004	—	0.112
Yes	14	24 ± 5.727	0.0%			
No	112	39 ± 5.967	34.0%			
Complications				0.023		0.105
Yes	28	30 ± 2.433	9.5%			
No	98	42 ± 5.750	34.7%			

inhibiting the binding of IGF-1 to proteins, thereby increasing the bioavailability of IGF-1.[18] Second, hyperinsulinaemia produces too much peroxide by destroying the mitochondria. Oxidative stress caused by peroxide can cause a series of complications and increase the DNA damage of the cells, thereby increasing the possibility of damage to the body caused by mutations in tumor cell-related genes in patients. In addition, the metabolism of tumor cells is completed under anaerobic conditions, so the demand for glucose is great, and the hyperglycaemia in diabetic patients creates better conditions for the survival of tumor cells.[19] Finally, the inflammatory response is accompanied by the whole process of tumorigenesis and development, and various signaling pathways, such as interleukin-6, TNF-a and STAT3, can activate inflammation-related responses and affect the progression of the tumor.[20]

Our study divided the patients with diabetes mellitus into the metformin group and the nonmetformin group. Through multivariate and survival analysis, we found that patients with metformin have longer survival and that metformin use is an independent prognostic factors for NSCLC patients with type 2 DM. A study by Dhillon *et al.* of 409 patients with stage I NSCLC with diabetes mellitus found that patients taking metformin had longer survival and that metformin was an independent prognostic factor for NSCLC with diabetes mellitus.[15] Tseng *et al.* studied the survival of 15 414 patients who had never used metformin and 280 159 patients who had used metformin.

Table 6 Univariate and multivariate analyses of prognostic factors and DFS in patients with NSCLC with type 2 DM (*n* = 126)

Variable	Case	Median survival time (month) (95% CI)	Five-year survival rate (%)	*P*-value	RR (95% CI)	*P*-value
		Univariate analysis			Multivariate analysis	
Sex				0.546	—	0.986
Male	96	25 ± 6.772	9.0%			
Female	30	25 ± 4.603	0.0%			
Age (year)				0.024	—	0.126
≤65	80	24 ± 4.295	2.9%			
>65	46	34 ± 12.360	19.9%			
Smoking history				0.511	—	0.551
Yes	48	34 ± 10.314	10.3%			
No	78	24 ± 2.282	6.7%			
Surgical procedure				0.254	—	0.983
Lobectomy	110	27 ± 5.265	8.2%			
Pneumonectomy	16	21 ± 5.196	7.5%			
Tumor diameter (cm)				0.202	—	0.820
≤3	62	35 ± 7.557	13.0%			
>3	64	24 ± 3.858	3.8%			
Histological classification				0.540	—	0.401
Adenocarcinoma	68	34 ± 7.285	13.8%			
Squamous cell carcinoma	49	24 ± 5.261	9.5%			
Adenosquamous carcinoma	6	14 ± 3.674	0.0%			
Other	3	11 ± 0.816	0.0%			
TNM stage				0.002	1.534(1.208–1.948)	<0.001
I	59	45 ± 7.879	14.8%			
II	37	18 ± 4.044	3.2%			
III	30	16 ± 3.134	0.0%			
Metformin				0.041	1.649(1.649–2.508)	0.019
Yes	35	44 ± 7.655	12.7%			
No	91	21 ± 2.916	6.1%			
Postoperative chemotherapy				0.009	—	0.976
Yes	62	18 ± 2.625	2.1%			
No	64	38 ± 7.638	13.8%			
Postoperative radiotherapy				0.012	—	0.216
Yes	14	17 ± 4.640	0.0%			
No	112	30 ± 6.193	9.1%			
Complications				0.017		0.065
Yes	28	18 ± 3.603	5.5%			
No	98	34 ± 6.553	9.0%			

Patients with lung cancer and type 2 DM who used metformin had better survival than type 2 DM patients who did not use metformin.[21]

Metformin primarily reduces circulating glucose levels in patients with AMPK activation mediated by liver kinase B1, a tumor suppressor protein that responds during metabolic stress.[22] The anticancer effect of metformin inhibits mammalian target of rapamycin via the hepatic kinase B1/AMPK pathway, leading to protein synthesis, cell cycle arrest and apoptosis inhibition.[23] A recent study suggested that AMPK activation may promote cell growth,[24] but metformin also inhibits mammalian rapamycin targets through the GTP-activated protein-dependent pathway.[25] Since elevated levels of insulin-like growth factor 1 (IGF-1) may be carcinogenic, a study explored the role of metformin in reducing IGF-1-mediated tumorigenesis, demonstrating that metformin reduces IGF-1 levels independent of the AMPK pathway. In mice treated with metformin, it has been shown that activation of the protein-dependent pathway by GTPase and regulation of receptor tyrosine kinase activity can significantly reduce tumorigenesis, regardless of the decrease in IGF-1 levels.[26] It has also been reported that metformin clinically enhances the response of NSCLC cells to radiotherapy through the AMPK-dependent pathway.[27,28] Metformin has been confirmed as a first-line drug for the treatment of diabetes mellitus. However, its antitumour mechanism remains unclear, and further experimental research is needed. At the same time, it also provides new ideas and methods for the treatment of lung cancer. In addition, many studies are aimed at patients
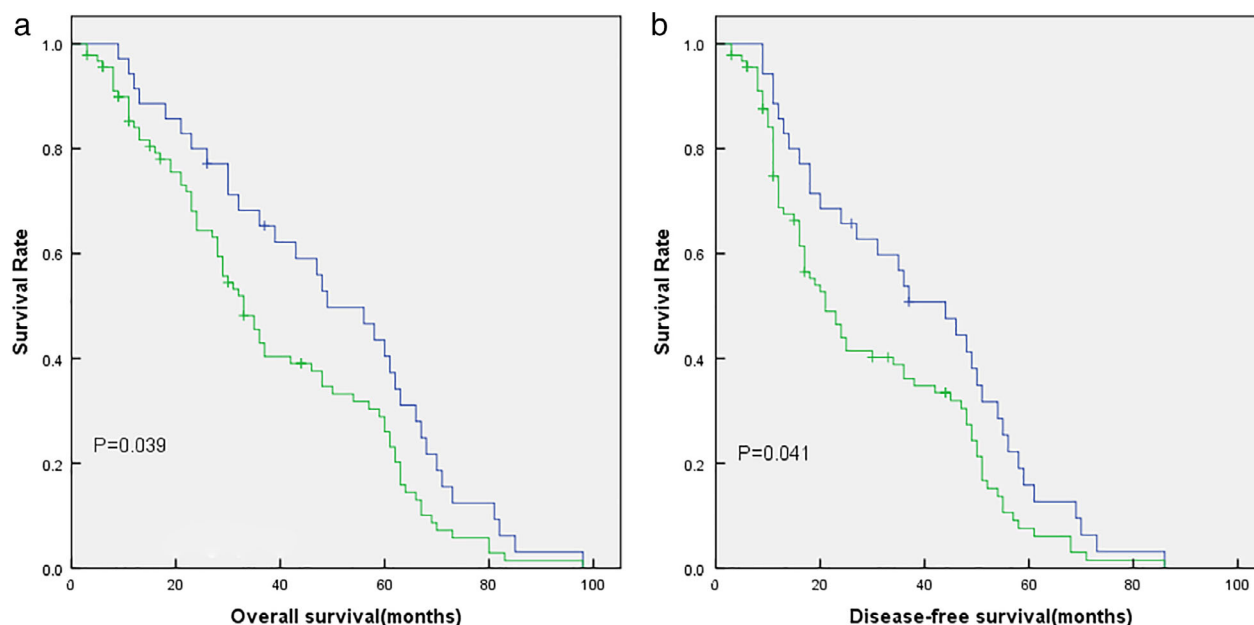
Figure 2 Kaplan-Meier survival curves for metformin users and nonusers. (**a**) The median overall survival was significantly better in the metformin user group. (**b**) The patients using metformin had better median disease-free survival (DFS). (**a**) (▭) Metformin group, (▭) Nonmetformin group, (—+—) Metformin group censored, (—+—) Nonmetformin group censored. (**b**) (▭) Metformin group, (▭) Nonmetformin group, (—+—) Metformin group censored, (—+—) Nonmetformin group censored.

with diabetes mellitus with lung cancer. For nondiabetic lung cancer patients, the antitumour effect of metformin needs further study.

Univariate and multivariate analyses of the study found that the five-year survival rates after lobectomy and pneumonectomy were 41.0% and 25.8%, respectively, and the surgical approach was an independent prognostic factor for patients with NSCLC. There are some potential explanations for this difference. First, in this study, a total of 658 patients with lobectomy accounted for 85.6% of the entire group, and patients with pneumonectomy accounted for 14.4%, so there was a certain statistical bias. Second, the pathological stage of patients with pneumonectomy is generally late, so the patient survival is generally short and the prognosis is poor. Finally, patients with pneumonectomy are more likely to have multiple organ failure, such as respiratory and heart failure, than patients with lobectomy, thus affecting the prognosis of patients.

This study has the following shortcomings. First, because this study is a retrospective study, it is not possible to accurately assess the severity of diabetes and glycaemic control in postoperative patients. In addition, the study used a randomized fasting blood glucose of more than 126 mg/dL and a previous diagnosis of type 2 DM by endocrinologists as the basis for diagnosis, so there is a diagnostic bias. Second, this study did not specifically calculate the specific dose of metformin in patients and the dose may affect the antitumor effect of metformin. Third, there are no other

factors associated with the complications associated with chronic diseases and surgery that may affect surgical outcomes and long-term survival.

In conclusion, type 2 DM was independently associated with a significantly higher risk of all-cause mortality in patients with NSCLC. To further extend the current understanding, future studies applying large prognostic evaluations with longer follow-ups to confirm the prognostic utility of type 2 DM are needed. In addition, the antitumor effect and mechanism of metformin remain to be further studied.

Acknowledgments

Disclosure

No authors report any conflict of interest.

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