Long-term survival analysis of patients with stage IIIB-IV non-small cell lung cancer complicated by type 2 diabetes mellitus: A retrospective propensity score matching analysis

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Abstract

Background: This study aimed to determine the effect of type 2 diabetes mellitus (T2DM) on overall survival (OS) of patients with stage IIIB–IV non-small cell lung cancer (NSCLC).

Methods: We retrospectively analyzed patients with stage IIIB–IV NSCLC from January 2015 to December 2018 in the Department of Oncology at the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine. Kaplan–Meier plots, log-rank tests, and Cox proportional hazards regression models were used to describe the effect of T2DM on the OS of patients with stage IIIB–IV NSCLC.

Results: This study collected data on 76 patients with NSCLC and T2DM (group A) and 214 NSCLC patients without T2DM (group B). After propensity score matching (PSM) analysis, 74 patients were included in each group. The mean OS of all patients was 17 months (range, 11–31 months). The mean OS of group A was 15 months (range, 8–25 months) and the mean OS of group B was 20 months (range, 14–39 months). The mean OS of group B was longer than group A, and the difference was statistically significant. Univariate analysis of the clinical data showed that T2DM and complications were significantly correlated with the prognosis of patients with stage IIIB–IV NSCLC (p = 0.003 and p = 0.034). Multivariate Cox model analysis showed that T2DM and complications were independent prognostic factors for patients with stage IIIB–IV NSCLC (p = 0.002 and p = 0.024, respectively).

Conclusion: Stage IIIB–IV NSCLC patients without T2DM have an increased OS compared to patients with stage IIIB–IV NSCLC and T2DM.

KEYWORDS
non-small cell lung cancer, diabetes mellitus, chemotherapy, survival

INTRODUCTION

According to the latest cancer data released by the International Research Institute of the World Health Organization, lung cancer is the deadliest malignant tumor worldwide.¹,² Lung cancer is the leading cause of morbidity and mortality amongst malignant tumors in China. Furthermore, 80% of the lung cancer cases in China are non-small cell lung cancer (NSCLC) with a 5-year survival rate < 20%.³,⁴ As a result of an aging population and changes in lifestyle, an increasing number of lung cancer patients have other major diseases, such as diabetes mellitus (DM), hypertension, and cerebral infarction. Previous studies have shown that DM affects the prognosis of cancer patients, including patients with breast, colorectal, and liver cancers.⁵–⁷ In addition, it has been shown that type 2 DM (T2DM) promotes tumor cell proliferation and metastasis vis-à-vis hyperglycaemia and...
insulin-like growth factor-1 (IGF-1). In addition, it has been shown that DM-induced modification of advanced glycation end-products hinders invasive metastasis of lung cancer cells. Therefore, we reviewed the medical records of patients with NSCLC diagnosed in our hospital from January 2015 to December 2018 to analyze the clinicopathological characteristics of patients with T2DM, determine the effect of T2DM on the overall survival (OS) of patients with NSCLC, and evaluate whether T2DM affects the long-term prognosis of patients with NSCLC.

### METHODS

#### General information

This retrospective study was conducted with approval of the Institutional Review Board of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine. Data were collected from 76 patients with NSCLC and T2DM and 214 NSCLC patients without T2DM who were treated in the Department of Oncology of the First Affiliated Hospital of Anhui University of Traditional Chinese Medicine.

#### TABLE 1 Characteristics of NSCLC patients by T2DM

| Variable                  | PSM 前 A group (n = 76) | B group (n = 214) | χ² | p-value | PSM 后 A group (n = 74) | B group (n = 74) | χ² | p-value |
|---------------------------|------------------------|-------------------|----|---------|------------------------|-------------------|----|---------|
| Sex                       |                        |                   |    |         |                        |                   |    |         |
| Male                      | 54 (71.1%)             | 152 (71.0%)       | 0.000 | 0.997   | 52 (70.3%)             | 52 (70.3%)        | 0.000 | 1.000   |
| Female                    | 22 (28.9%)             | 62 (29.0%)        | 0.285 | 0.594   | 22 (29.7%)             | 22 (29.7%)        | 0.029 | 0.866   |
| Age (year)                |                        |                   |    |         |                        |                   |    |         |
| ≤ 60                      | 30 (39.5%)             | 92 (43.0%)        | 0.083 | 0.773   | 28 (37.8%)             | 29 (39.2%)        | 0.142 | 0.707   |
| > 60                      | 46 (60.5%)             | 122 (57.0%)       | 0.000 | 0.997   | 46 (62.2%)             | 45 (60.8%)        | 0.000 | 1.000   |
| Smoking history           |                        |                   |    |         |                        |                   |    |         |
| Yes                       | 20 (26.3%)             | 60 (28.0%)        | 2.129 | 0.712   | 20 (27.0%)             | 18 (24.3%)        | 2.157 | 0.707   |
| No                        | 56 (73.7%)             | 154 (72.0%)       | 0.000 | 0.997   | 54 (73.0%)             | 56 (75.7%)        | 0.000 | 1.000   |
| Tumor location            |                        |                   |    |         |                        |                   |    |         |
| RUL                       | 14 (18.4%)             | 48 (22.4%)        | 5.253 | 0.072   | 14 (18.9%)             | 12 (16.2%)        | 1.817 | 0.403   |
| RML                       | 4 (5.3%)               | 20 (9.3%)         | 0.000 | 0.997   | 4 (5.4%)               | 5 (6.8%)          | 0.108 | 0.742   |
| RLL                       | 18 (23.7%)             | 46 (21.5%)        | 0.005 | 0.944   | 18 (24.3%)             | 16 (21.6%)        | 0.015 | 0.902   |
| LUL                       | 24 (31.6%)             | 62 (29.0%)        | 0.000 | 0.997   | 24 (32.4%)             | 20 (27.0%)        | 0.000 | 1.000   |
| LLL                       | 16 (21.1%)             | 38 (17.8%)        | 1.091 | 0.579   | 16 (21.6%)             | 21 (28.4%)        | 0.109 | 0.742   |
| Pathological type         |                        |                   |    |         |                        |                   |    |         |
| Adenocarcinoma            | 42 (55.3%)             | 140 (65.4%)       | 2.143 | 0.143   | 42 (56.8%)             | 41 (55.4%)        | 0.353 | 0.632   |
| Squamous cell carcinoma   | 26 (34.2%)             | 66 (30.8%)        | 0.005 | 0.944   | 24 (32.4%)             | 29 (39.2%)        | 0.108 | 0.742   |
| Other                     | 8 (10.5%)              | 8 (3.7%)          | 0.000 | 0.997   | 8 (10.8%)              | 4 (5.4%)          | 0.000 | 1.000   |
| TNM stage                 |                        |                   |    |         |                        |                   |    |         |
| IIIB stage                | 38 (50.0%)             | 106 (49.5%)       | 0.000 | 0.997   | 38 (51.4%)             | 40 (54.1%)        | 0.108 | 0.742   |
| IV stage                  | 38 (50.0%)             | 108 (50.5%)       | 0.000 | 0.997   | 38 (48.6%)             | 34 (45.9%)        | 0.000 | 1.000   |
| PS score                  |                        |                   |    |         |                        |                   |    |         |
| 0                         | 20 (26.3%)             | 76 (35.5%)        | 2.143 | 0.143   | 20 (27.0%)             | 19 (25.7%)        | 0.035 | 0.852   |
| 1                         | 56 (73.7%)             | 138 (64.5%)       | 0.000 | 0.997   | 54 (73.0%)             | 55 (74.3%)        | 0.000 | 1.000   |
| Chemotherapy regimen      |                        |                   |    |         |                        |                   |    |         |
| TP                        | 10 (13.2%)             | 38 (17.8%)        | 0.714 | 0.403   | 10 (13.5%)             | 12 (16.2%)        | 0.000 | 1.000   |
| DP                        | 16 (21.1%)             | 48 (22.4%)        | 0.714 | 0.403   | 16 (21.6%)             | 19 (14.9%)        | 0.000 | 1.000   |
| PC                        | 50 (65.8%)             | 128 (59.8%)       | 0.714 | 0.403   | 48 (63.8%)             | 43 (13.5%)        | 0.000 | 1.000   |
| Complications             |                        |                   |    |         |                        |                   |    |         |
| Yes                       | 32 (42.1%)             | 46 (21.5%)        | 12.116 | <0.001 | 30 (40.5%)             | 30 (40.5%)        | 0.000 | 1.000   |
| No                        | 44 (57.9%)             | 168 (78.5%)       | 0.000 | 1.000   | 44 (59.5%)             | 44 (59.5%)        | 0.000 | 1.000   |

Abbreviations: DP, docetaxel + cisplatin regimen; LLL, left lower lobe; LUL, left upper lobe; PC, pemetrexed + cisplatin regimen; PS, performance status; PSM, propensity score matching; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; T2DM, type 2 diabetes mellitus; TNM stage, tumor node metastasis stage; TP, paclitaxel plus cisplatin regimen.
Hospital at Anhui University of Traditional Chinese Medicine from January 2015 to December 2018. The patients were
divided into two groups based on NSCLC that was or was not
complicated by T2DM: group A with T2DM; and group B
without T2DM. The case inclusion criteria were as follows:
(1) histopathological confirmation of NSCLC, (2) pathological
stage IIIB–IV, (3) treatment with first-line platinum-
containing dual-drug chemotherapy, (4) no history of other
tumors, (5) no prior chemoradiotherapy, (6) performance sta-
tus (PS) score of 0–1, and (7) T2DM diagnosed by an endo-
crinologist. The exclusion criteria were as follows: (1) NSCLC
diagnosis preceding the diagnosis of T2DM, (2) a diagnosis of
type 1 DM, (3) failure to complete first-line chemotherapy,
and (4) incomplete data. Group A met inclusion criteria 1–7
and group B met inclusion criteria 1–6. TNM staging was
based on the eighth edition of the International Association
for Lung Cancer Research (IASLC).

Observation index

The clinicopathological data of the two groups of NSCLC
patients were compared, the OS times of NSCLC patients
with and without T2DM were compared, and the clinicopatho-
logical factors affecting the prognosis of NSCLC
patients were analyzed.

Chemotherapy regimen

All patients received paclitaxel plus cisplatin (TP regimen),
docetaxel + cisplatin (DP regimen), or pemetrexed +
cisplatin (PC regimen). Treatment efficacy was evaluated
every two cycles. Patients who responded to treatment com-
pleted at least four cycles of chemotherapy, while nonrespon-
sive patients were switched to other regimens or other
treatments, including docetaxel, pemetrexed, and epidermal
growth factor receptor tyrosine kinase inhibitors
(EGFR-TKIs).

Prognostic follow-up

Patient prognosis was determined by outpatient re-examina-
tion, telephone contact, or social networking software. The
patients were followed once monthly in the first 6 months
and every 3 months thereafter. The follow-up cutoff date
was December 31, 2021, and the content of the follow-up
evaluation was related to OS, which refers to the time from
the diagnosis of NSCLC to the date of death, the last follow-
up date, or the follow-up deadline.

Statistical analysis

The patient data (sex, age, smoking history, tumor location,
pathological type, TNM staging, complications, performance
status (PS) score, and chemotherapy regimen) were analyzed
using SPSS 26.0 statistical software. The variables with the
closest tendency score between the two groups were
matched at a ratio of 1:1, and the clamp value was 0.02.
Then, survival analysis was performed between the two
groups. A t-test was used to compare the mean of the mea-
sured data, and a χ2 test was used to compare the counted
data. The survival rate was calculated using the Kaplan–Meier method, and the difference in survival rate between groups was analyzed using the log-rank and trend tests. The Cox model was used for multivariate survival analysis. OS is expressed as P50 (P25 and P75). The difference was statistically significant at \( p < 0.05 \).

### RESULTS

#### Clinicopathological characteristics of patients in the two groups

Before propensity score matching (PSM) analysis, there were no significant differences in sex, age, smoking history, tumor location, pathological type, TNM stage, PS score, or chemotherapy regimen between the two groups. The number of complications in group A was greater than group B \( (p < 0.001) \). After PSM analysis, 74 patients were included in each group. There were no significant differences in sex, age, smoking history, tumor location, pathological type, TNM stage, PS score, chemotherapy regimen, or complications between the two groups (Table 1).

#### Effect of T2DM on OS in patients with stage IIIB–IV NSCLC

The mean OS of all patients was 17 months (range, 11–31 months). The mean OS of group A was 15 months (range, 8–25 months), and the mean OS of group B was 20 months (range, 14–39 months). The mean OS of group B was longer than group A; the difference was statistically significant (Figure 1).

#### Univariate and multivariate analyses of prognostic factors in patients with stage IIIB–IV NSCLC

Univariate analysis of the clinical data showed that T2DM and complications were significantly correlated with the prognosis of patients with stage IIIB–IV NSCLC \( (p = 0.003 \) and \( p = 0.034 \), respectively; Table 2). Multivariate Cox model analysis showed that T2DM and complications were independent prognostic factors for patients with stage IIIB–IV NSCLC \( (p = 0.002 \) and \( p = 0.024 \), respectively; Table 3).

### DISCUSSION

As long ago as the 19th century, it was thought that DM affected the prognosis and OS of cancer patients. In recent years, related studies have reported that DM is a poor prognostic factor in patients with liver, gastric, and breast cancers. In addition, whether concomitant DM has an adverse effect on the prognosis of patients with NSCLC is controversial. Few studies have determined if T2DM has different outcomes on the prognosis of patients with stage IIIB–IV NSCLC. Univariate and multivariate analyses showed that T2DM is a prognostic factor in patients with stage IIIB–IV NSCLC.
Stage IIIB–IV NSCLC patients without T2DM had longer survival. A history of other chronic diseases is also a prognostic factor for patients with stage IIIB–IV NSCLC. Kirakli et al.14 studied the effect of the blood glucose level in 71 patients with stage IIIA–IIIB NSCLC on OS, disease-free survival (DFS), and local recurrence after treatment, and showed that patients with hyperglycaemia and DM had a shorter survival time than patients with a normal blood glucose level. Diabetic patients had higher rates of relapse during treatment, and blood glucose levels were significantly higher in relapsed patients. Bergamino et al.15 retrospectively compared 56 advanced NSCLC patients with T2DM and 114 advanced NSCLC patients without T2DM and reported that the median progression-free survival (PFS) and OS of patients with a fasting plasma glucose (FPG) ≥7 mmol/l was 8 and 15 months, respectively, and the median PFS and OS of patients with a FPG <7 mmol/l were 20 and 31 months, respectively. Thus, the fasting blood glucose level was an independent prognostic factor for advanced NSCLC.

The main pathological features of diabetic patients are hyperinsulinaemia and insulin resistance, and the concentration of insulin in the blood is increased.16 Insulin interferes with the synthesis of insulin-like growth factor (IGF)-binding protein in the liver, thereby increasing the level of free circulating IGF-1 and promoting the IGF-1 receptor (IGF-1R) expression. Insulin and IGF-1 are considered to be important factors in promoting the occurrence and development of tumors, and the activation of insulin receptors and IGF-1R promote cell mitosis, inhibit cell apoptosis, and induce neovascularization.17,18 Adequate energy supply is the premise for cancer cells to proliferate, invade, and metastasize rapidly and indefinitely. Tumors are preferentially powered by glycolysis. The higher the degree of tumor malignancy, the greater the energy demand and the more active glycolysis is. In addition, tumor cells are still preferentially powered by glycolysis under aerobic conditions, thus the “Warburg” effect.19 Hyperglycaemia not only provides sufficient energy for tumor cell proliferation to drive anabolism and cell division, but also a large number of intermediates produced in the process of glycolysis can provide raw materials for the synthesis of tumor organelles, so it is also conducive to tumor cell proliferation. In addition, the blood glucose of diabetic patients is more unstable, and tumor cells grow faster and are more likely to shed and metastasize when the blood glucose concentration fluctuates. Kim et al.20 showed that keratoblastoma pleomorphic lesions gradually increase without cell shedding when there is a continuous supply of glucose maintained at a specific concentration level, and the tumor lesions grow faster and tumor cells shed and metastasize when the glucose concentration fluctuates due to an intermittent supply of glucose.

This study has the following limitations. First, it was a single-center retrospective analysis with a small sample size, and there was case selection bias. Thus, the results need to be confirmed by a large-sample prospective study. Second, this study did not classify the hypoglycaemic drugs used by the patients and the statistics on the doses used, which may have led to bias in the results. Third, the impact of distant metastases on the prognosis of patients with stage IIIB–IV NSCLC was not analyzed.

In conclusion, concomitant T2DM is an independent factor that can affect the prognosis of patients with stage IIIB–IV NSCLC. Therefore, we should pay more attention to patients with stage IIIB–IV NSCLC with T2DM who are treated with chemotherapy.

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CONFLICT OF INTEREST
No authors report any conflict of interest.
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