ORIGINAL RESEARCH

Fasting blood glucose levels and prognosis in patients with non-small-cell lung cancer: a prospective cohort study in China

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Purpose: Non-small-cell lung cancer (NSCLC) is the most diagnosed lung cancer and is associated with poor prognosis. This study aimed to analyze whether fasting blood glucose (FBG) levels could provide prognostic information in Chinese patients with NSCLC, using the Suzhou Lung Cancer Survival study.

Patients and methods: A prospective cohort study of adult patients with primary NSCLC was performed. The patients who were hospitalized between January 2016 and April 2018 in two hospitals affiliated with Soochow University were recruited. Patient information, including lifestyle habits and clinical and laboratory data, were collected through face-to-face interviews and evaluation of medical records. Follow-up was initiated from the date of patient enrollment until May 8, 2018 or until patient death. The long-term survival of patients was assessed every 6 months. Patient vital status was confirmed by using hospital records, telephone interview, or local death registration system. Cox proportional hazards regression was used to estimate hazard ratio and 95% confidence interval (CI) for death, with adjustment for cancer stage, medical treatments, smoking, and other potential confounders.

Results: A total of 387 patients were included in the analysis, and the numbers (percentages) of patients with stages I, II, III, and IV NSCLC were 53 (13.7%), 41 (10.6%), 64 (16.5%), and 215 (55.6%), respectively. The median duration of follow-up was 19.1 months. Compared with patients in the second tertile of FBG, the HRs for mortality were 2.16 (95% CI: 1.26–3.73) and 1.87 (95% CI: 1.03–3.42) for those in the lowest one and diabetic group, respectively. Subgroup analysis according to various patient characteristics confirmed these associations.

Conclusion: Diabetes and low FBG could be important predictors of death in patients with NSCLC. Maintaining appropriate blood glucose levels may improve prognosis in patients with NSCLC.

Keywords: non-small cell lung cancer, fasting blood glucose, diabetes, survival

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Introduction

Globally, lung cancer is one of the most common causes of cancer-related death and is associated with poor treatment outcome.[1] Non-small-cell lung cancer (NSCLC) is the most common type of lung cancer, accounting for >80% of all lung cancer cases.[2] The majority of patients with NSCLC are usually diagnosed at later stages when curative treatments are unavailable. In this regard, identifying prognostic factors is important because these factors could improve clinical decision making and, ultimately, patient prognosis. A number of prognostic factors in NSCLC have been described. In a systematic review of literature published between 1990 and 2001,

Brundage et al, found 169 potential prognostic factors that may be useful in predicting the survival of patients with NSCLC.[3] However, most of these factors are not readily available in routine practice.

The presence of multiple diseases is common among lung cancer patients. Notably, 8–18% of newly diagnosed cancer patients have diabetes. Although diabetes is the most common comorbidity associated with poor cancer survival,[4] the influence of diabetes on NSCLC prognosis remains equivocal.[5] Several observational studies found that diabetes was associated with poor prognosis in patients with NSCLC,[6–9] whereas other studies showed that diabetes was related to equal[10] or better survival.[11,12] Diabetes may affect lung cancer progression via several mechanisms, such as hyperinsulinemia, hyperglycemia, and chronic inflammation, which are associated with cell proliferation and cancer progression.[13,14] On the contrary, diabetes also impedes cancer cell invasion through the basocellular membrane by diabetic microangiopathy via microvascular changes, resulting in decreased metastatic ability and improved prognosis.[15] Thus far, only a few studies investigated the prognostic impact of fasting blood glucose (FBG) on NSCLC mortality and found that hyperglycemia may have significantly lower survival.[16,17] However, blood glucose has not been observed in a further stratification. Therefore, we used the data from the Suzhou Lung Cancer Survival (SLCS) study to investigate whether FBG in the low or high range could provide prognostic information in patients with NSCLC.

Materials and methods
Participant identification
The SLCS study is an ongoing patient cohort that was initiated in 2015 to explore the long-term predictors of lung cancer survival among patients living in Suzhou, China. Primary lung cancer patients aged 18 years old or older were included in the study. Although our inclusion criteria did not have other specific restrictions, such as status and type of medical treatments, data were carefully collected during the enrollment period and their influence on any examined association were explored through rigorous analysis. The patient enrollment was started in January 2016. In April 2018, a total of 455 patients with primary lung cancer were included. Considering the small number of small cell lung cancer cases (n=49), our present analysis only included patients with NSCLC (n=406). This study was approved by the Research Ethics Committee of Soochow University (Approval No. ESCU-2015–0002)

and written informed consent was obtained from each patient. This study was also conducted in accordance with the Declaration of Helsinki.

Data collection
In-person interviews were conducted using a structured questionnaire during recruitment to collect patients' characteristics on demographics and habitual lifestyle including smoking, alcohol drinking, and physical activity. Based on the collected data, smoking status was grouped into three categories (never, former, or current smoker) and drinking status was classified into two groups (yes or no). Former smokers were defined as patients who had smoked but already quitted smoking for at least one year, and current smokers were determined as those who are still smoking at the time of investigation or those who gave up smoking for less than one year. Patients who are drinking alcohol on average of at least once a week within the previous six months were considered as patients with drinking habit (yes). Anthropometric measurements (height, weight, waist, and hip circumference) were measured by trained personnel. The pathological type, cancer stage, and the treatments for lung cancer were identified through medical records.

Blood sample collection
A 5 mL whole blood was drawn from antecubital veins of each patient and then transferred into a tube with ethylenediaminetetraacetic acid during recruitment after an overnight fasting. The plasma was obtained through centrifugation (3000 rpm at 25°C for 10 mins) within 2 hrs after sample collection. All samples were numbered and stored at −80°C until further analysis.

Measurements of biomarkers
Measurement of FBG and albumin was conducted in laboratories of both institutions as a part of routine examination in each patient. FBG levels were measured by the hexokinase method using a fully automatic Siemens ADVIA 2400 Biochemical Analyzer System (Siemens Healthcare Diagnosis Inc, NY, USA). Albumin concentration was measured by bromocresol green staining method with an Olympus 5400 Automatic Biochemical Analyzer (Olympus Corporation, Tokyo, Japan).

Patient follow-up
This study primarily determined the overall survival, which was calculated from the date of the baseline

questionnaire to the date of death from any cause. Follow-up was initiated from the date of patient enrollment until May 8, 2018 or until patient death. The long-term survival of patients was assessed every 6 months. Data were collected from at least one of the following sources: 1) the hospital inpatient or outpatient records; 2) local death registration system; and 3) contacting patients or their family on phones. A small proportion of patients (4.7%, n=19) were excluded from the present analysis due to loss of follow-up. Finally, a total of 387 patients with NSCLC were included in the present analysis.

Statistical analysis

Continuous variables were expressed as the means with the standard deviation and were compared using one-way ANOVA. The Wilcoxon rank test was used to compare the categorical variables, which were presented as the number and percentage of patients. Cases with diabetes, information on treatment for diabetes, or FBG value of or higher than 126 mg/dL were included in a separate category (diabetic). For non-diabetic cases, FBG levels were categorized according to the following tertiles: <91 , 91–101 (reference), and >101 mg/dL.

The Hazard ratios (HR) and 95% confidence intervals (CI) for death were estimated using the Cox proportional hazards regression model. Two models with different covariates were constructed to account for potential confounders. The first model was adjusted for patient demographic and behavioral characteristics, including age at baseline interview (years), sex, body mass index (kg/m^2), albumin (<35 g/L or ≥35 g/L), family history of cancer (yes or no), patient history of chronic obstructive pulmonary disease (yes or no), smoking status (never smoker, former smoker, or current smoker), and drinking habit (yes or no). The second model included the variables in model 1 plus additional adjustment for clinical and pathological information, including tumor type (adenocarcinoma, squamous cell carcinoma, or other tumor types), cancer stage (I/II or III/IV), and treatment (with tumor resection, without resection but with other therapies such as chemotherapy and radiotherapy, without either resection or other therapies).

We also performed stratified analyses according to age (<60 years vs ≥60 years), sex, smoking status (never smoker vs ever smoker), tumor type (adenocarcinoma vs squamous cell carcinoma) , and cancer stage (I–III vs IV) to assess the potential effect modification by these characteristics. Statistical analyses were performed using the SAS 9.2 software. All tests were two-sided and statistical significance was set at $P<0.05$.

Results

A total of 387 patients with NSCLC were included in the final analysis. Mean age of the participants was 62.5 years. Two hundred and forty-one patients were male (62.3%), and the majority of them were at an advanced stage (72.1%). The median duration of follow-up was 19.1 months. Overall, 105 patients died by the end of May 2018. The baseline characteristics of the patients by FBG level are presented in Table 1. FBG levels were significantly associated with body mass index.

Results of multivariate analysis with adjustment for confounders are presented in Table 2. After adjustment of age, sex, body mass index, family history of cancer, patient history of chronic obstructive pulmonary disease, smoking status and drinking habit, albumin, the risk of death was significantly higher for those with the lowest tertile of blood glucose (HR =2.03; 95% CI: 1.19–3.46) and diabetic group (HR =1.81; 95% CI: 1.01–3.26), compared with those in the reference. Further adjustment for other clinical and pathological factors, such as tumor type, cancer stage, and treatment showed similar results. The HRs for mortality were 2.16 (95% CI: 1.26–3.73) and 1.87 (95% CI: 1.03–3.42) for those in the lowest tertile of FBG and diabetic group, respectively.

Results of subgroup analysis according to various patient characteristics confirmed these associations (Table 3). FBG levels of lower than 91 mg/dL or within a diabetic group were associated with a higher risk of death. Notably, the association between FBG and death evidently varied with tumor type and cancer stage. For patients with squamous cell carcinoma, FBG levels of lower than 91 mg/dL were not associated with an increased risk of mortality. Patients with diabetic status had no association with a higher risk of death in subgroup of stage I/II/III.

Discussion

The present study identified that FBG levels of lower than 91 mg/dL or within diabetic range were associated with poor survival in Chinese NSCLC patients. These associations remained robust even after adjustment for other potential confounders. Subgroup analysis according to various patient characteristics also confirmed these associations.

Several previous studies that classified patients according to the presence or absence of diabetes showed that diabetes was associated with poorer survival in patients with NSCLC.[6–9] The current study demonstrated that NSCLC patients with diabetes exhibited a significant increase in mortality risk,

Table 1 Baseline characteristics of patients by fasting blood glucose level

	Fasting blood glucose (mg/dL)				P-value
	<91	91–101	>101	diabetic	
Age	62.43±10.23	60.46±11.74	64.43±9.05	62.80±9.94	0.056
Gender					0.522
Male	66 (62.3)	66 (57.4)	62 (67.4)	47 (63.5)	
Female	40 (37.7)	49 (42.6)	30 (32.6)	27 (36.5)	
Smoking status					0.124
Never	49 (46.2)	63 (54.8)	40 (43.5)	31 (41.9)	
Former	26 (24.5)	22 (19.1)	27 (29.3)	27 (36.5)	
Current	31 (29.3)	30 (26.1)	25 (27.2)	16 (21.6)	
Tumor type					0.773
AC	70 (66.0)	81 (70.4)	64 (69.6)	44 (59.5)	
SCC	29 (27.4)	23 (20.0)	21 (22.8)	23 (31.1)	
Other	7 (6.6)	11 (9.6)	7 (7.6)	7 (9.5)	
Cancer stage					0.458
Stage I/II/III	39 (36.8)	50 (43.5)	39 (42.4)	30 (40.5)	
Stage IV	64 (60.4)	60 (52.2)	52 (56.5)	39 (52.7)	
Unknown	3 (2.8)	5 (4.3)	1 (1.1)	5 (6.8)	
Treatment					0.697
Surgery	38 (35.9)	60 (52.1)	39 (42.4)	32 (43.2)	
Other therapy	53 (50.0)	47 (40.9)	44 (47.8)	34 (46.0)	
None	15 (14.1)	8 (7.0)	9 (9.8)	8 (10.8)	
Albumin					0.462
<35 g/L	21 (19.8)	13 (11.3)	4 (4.4)	16 (21.6)	
≥35 g/L	85 (80.2)	102 (88.7)	88 (95.6)	58 (78.4)	
BMI					0.007
<18.5	16 (15.1)	12 (10.4)	6 (6.5)	3 (4.0)	
18.5–23.9	65 (81.3)	71 (61.7)	52 (56.5)	49 (66.2)	
24.0–27.9	17 (16.0)	24 (20.9)	30 (32.6)	19 (25.7)	
≥28.0	8 (7.6)	8 (7.0)	4 (4.4)	3 (4.1)	

Abbreviations: AC, adenocarcinoma; BMI, body mass index; SCC, squamous cell carcinoma.

Table 2 COX proportional hazards regression overall model of death and fasting blood glucose

FBG (mg/dL)	N	Model 1		Model 2	
		HR (95% CI)	P-value	HR (95% CI)	P-value
<91	106	2.03 (1.19–3.46)	0.009	2.16 (1.26–3.73)	0.006
91–101	115	1		1	
>101	92	1.33 (0.74–2.41)	0.34	1.54 (0.85–2.80)	0.159
Diabetic	74	1.81 (1.01–3.26)	0.049	1.87 (1.03–3.42)	0.041

Notes: Model 1 includes age at baseline interview, sex, body mass index, family history of cancer, patient history of chronic obstructive pulmonary disease, smoking status, drinking habit, and albumin. Model 2: model 1 plus tumor type, cancer stage, and treatment.
Abbreviations: CI, confidence interval; FBG, fasting blood glucose; HR, hazard ratio.

which is consistent with a meta-analysis showing that the association of diabetes with inferior prognosis was more prominent in the NSCLC group than that in the small-cell lung cancer group.[18] Two studies indicated that the risk of death increased with the increment of FBG without consideration of diabetic status in gastric carcinoma[19] or esophageal squamous

Table 3 COX proportional hazards regression stratified models of death and fasting blood glucose

	Death/total	Hazard ratio (95% confidence interval)			
		Fasting blood glucose (mg/dL)			
		<91	91–101	>101	Diabetic
Age					
<60	29/138	3.75 (1.13–12.49)	I	2.10 (0.54–8.26)	1.62 (0.44–5.93)
≥60	76/249	1.78 (0.92–3.44)	I	1.43 (0.71–2.87)	2.04 (1.00–4.14)
Gender					
Male	79/241	1.73 (0.94–3.18)	I	1.56 (0.80–3.04)	1.50 (0.72–3.11)
Female	26/146	4.96 (1.31–18.76)	I	1.50 (0.36–6.27)	3.38 (0.91–12.52)
Smoking					
Never	35/183	4.31 (1.46–12.75)	I	1.66 (0.52–5.35)	3.88 (1.28–11.73)
Ever	70/204	1.61 (0.84–3.10)	I	1.57 (0.75–3.28)	1.26 (0.57–2.77)
Tumor type					
AC	58/259	3.49 (1.55–7.90)	I	2.25 (0.97–5.22)	3.01 (1.18–7.66)
SCC	35/96	0.83 (0.82–2.13)	I	0.71 (0.21–2.41)	1.32 (0.46–3.81)
Cancer stage					
I/II/III	26/158	1.56 (0.51–4.79)	I	0.69 (0.20–2.34)	0.89 (0.27–2.34)
IV	76/215	1.96 (1.01–3.78)	I	1.34 (0.66–2.75)	2.11 (0.99–4.46)

Notes: Exclude stratification factor when the model was running. Model includes age at baseline interview, sex, body mass index, family history of cancer, patient history of chronic obstructive pulmonary disease, smoking status, drinking habit, albumin, tumor type, cancer stage, and treatment.
Abbreviations: AC, adenocarcinoma; SCC, squamous cell carcinoma.

cell carcinoma patients.[20] Park et al, found positive linear trends in lung cancer mortality with increasing fasting serum glucose in Korean patients, especially in patients with fasting serum level of 126 mg/dL or higher.[21] The biological mechanisms underlying the increased mortality risk in patients with NSCLC remain unclear. Diabetes is characterized by insulin resistance and hyperinsulinemia.[22] Experimental studies found that most cancer cells express insulin receptors, and hyperinsulinemia promotes carcinogenesis by directly stimulating the proliferating pathway after insulin receptors.[23] Cancer patients with diabetes may increase tumor cell proliferation and metastases as a consequence of the mitogenic environment of hyperinsulinemia.[24]

The present study identified that FBG levels lower than 91 mg/dL were associated with poor survival in patients with NSCLC. The reason for adverse effect of low blood glucose levels on NSCLC prognosis is unclear. In general, low FBG was significantly associated with malnutrition of patients with NSCLC and hence resulting poor survival in patients with NSCLC.[25] There is evidence that FBG lower than 90 mg/dL was associated with a reduced survival in esophageal cancer patient.[25] Minicozzi et al, also showed that breast cancer patients with FBG levels of 84 mg/dL or lower had a non-significant higher risk of death.[26] Further studies are needed to investigate the underlying mechanisms by which low FBG levels increase mortality risk in NSCLC patients.

The present study had several limitations. First, although a wide range of patient characteristics was considered in the analysis, the influence of unmeasured and residual confounders that may bias the observed findings could not be fully ruled out. Second, small number of patients included in the subgroup analyses may limit statistical power to detect a weak association. For example, no association was found when the results were further stratified by types of squamous cell carcinoma and stages of cancer. Ongoing patient enrollment could provide further opportunity to specifically investigate some of these associations. Third, the findings of the present study may not be applied to the general population because only patients in two hospitals were included.

Conclusion

In summary, the present study showed that low FBG levels and diabetes were associated with poor survival in Chinese patients

with NSCLC. Additional studies are still needed to verify the relationship between FBG levels and survival among patients with NSCLC.

Abbreviation list

AC, adenocarcinoma; BMI, body mass index; CI, confidence interval; FBG, fasting blood glucose; HR, hazard ratio; NSCLC, non-small cell lung cancer; SCC, squamous cell carcinoma; SLCS, Suzhou Lung Cancer Survival.

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Disclosure

The authors report no conflicts of interest in this work.

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