8-1-2022

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10.21037/tlcr-22-493

Shen, Y., Li, J., Qiang, H., Lei, Y., Chang, Q., Zhong, R., ... & Chu, T. (2022). A retrospective study for prognostic significance of type II diabetes mellitus and hemoglobin A1c levels in non-small cell lung cancer patients treated with pembrolizumab. Translational Lung Cancer Research, 11(8), 1619-1630. https://doi.org/10.21037/tlcr-22-493

Original Article

A retrospective study for prognostic significance of type II diabetes mellitus and hemoglobin A1c levels in non-small cell lung cancer patients treated with pembrolizumab

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Contributions: (I) Conception and design: J Qian, T Chu; (II) Administrative support: None; (III) Provision of study materials or patients: Y Shen, R Zhong, J Qian, T Chu; (IV) Collection and assembly of data: Y Shen, J Li, H Qiang; (V) Data analysis and interpretation: Y Shen, J Li, H Qiang, Y Lei, Q Chang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Diabetes mellitus (DM) is common and recognized as a risk factor for developing non-small cell lung cancer (NSCLC) while the prognostic evaluation is still controversial. As immunotherapy is widely used in clinical practice, its efficacy and survival should be investigated in patients with DM.

Methods: We retrospectively recruited 266 locally advanced and metastatic NSCLC patients who received pembrolizumab alone or in combination with chemotherapy. Patients' clinicopathological data, including age, history of DM, hemoglobin A1c (HbA1c), genetic tumor profiling, and survival data were collected. Associations between clinical characteristics and survival were evaluated by univariate and multivariate analyses.

Results: In this cohort, 15.04% (40/266) of the patients had a history of DM. Fifty-nine (22.2%) patients had a HbA1c level ≥6.5%. A total of 169 (63.5%) patients received 1st-line therapy, and 97 (36.5%) received 2nd- or subsequent-line therapy. Patients with high (≥6.5%) HbA1c and lower (<35 g/L) albumin levels at baseline had worse survivals, and epidermal growth factor receptor (*EGFR*) mutants significantly associated with worse outcomes at normal HbA1c (<6.5%) levels (all P<0.05). Among the 1st-line therapy patients, a higher HbA1c level (≥6.5%) at baseline indicated a worse overall survival (OS) (2-year survival rate: 31.25% *vs.* 27.03%, P=0.045), tumor protein p53 (*TP53*) alternations and high programmed death-ligand 1 (PD-L1) expression (≥50%) were significantly associated with better outcomes (P<0.05). For 2nd- or subsequent-line patients, *EGFR* mutants and non-squamous carcinomas (non-SCs) indicated worse survivals, and the normal peripheral blood markers of the carcinoembryonic antigen (CEA), C-reactive protein (CRP), albumin levels were favorable prognostic factors for survivals. In non-SCs, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutations, high PD-L1 expression, and normal alkaline phosphatase (ALP) levels favored better progression-free survival (PFS), while *EGFR* mutants indicated poor PFS (P<0.05).

Conclusions: Among patients treated with 1st-line immunotherapy, a higher HbA1c level (≥6.5%) indicated dismal OS, while history of DM, baseline blood glucose levels, and glucose changes during the treatment process were not significantly associated with any of the outcomes.

Keywords: Diabetes mellitus (DM); hemoglobin A1c (HbA1c); non-small cell lung cancer (NSCLC); immunotherapy

Submitted Apr 20, 2022. Accepted for publication Jul 26, 2022.
doi: 10.21037/tlcr-22-493
View this article at: https://dx.doi.org/10.21037/tlcr-22-493

Introduction

Immunotherapy has made great advances in the management of advanced stage non-small cell lung cancer (NSCLC), which is the leading cause of cancer-related deaths worldwide (1,2). Immune checkpoint inhibitors (ICIs), including monoclonal antibody targeting anti-programmed death-1, anti-programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), have achieved an objective response rate (ORR) of 14–31%, and significantly prolonged the survival of patients compared to chemotherapy in the 2nd-line setting of NSCLC (3-5). When combined with chemotherapy or another kind of inhibitor, immunotherapy could further promote the survival of lung cancer patients regardless of histology or PD-L1 expression status (6-8). Notably, the addition of immunotherapy maintenance following standard chemo-radiotherapy has greatly improved the progression-free survival (PFS) and overall survival (OS) of locally advanced staged-III patients as described in the PACIFIC study (9,10). Thus, immunotherapy has become the cornerstone of the treatment of NSCLC patients. However, lung cancer patients always had kinds of comorbidities, of which diabetes mellitus (DM) is common while the impact of DM on efficacy, survival in lung cancer was still unclear, especially in immunotherapy era.

Concurrently, DM is increasing all over the world (11). Previous reports have indicated an increased risk of cancer in patients with type II DM (12,13), while the associations between survival and DM in NSCLC are still controversial (14-16). However, since immunotherapy has been implemented widely in clinical practice, the effect of DM among patients treated with ICIs should be clarified. Additionally, the peripheral blood glycated hemoglobin A1c (HbA1c) was a regular indicator for DM diagnosis and treatment evaluation, previous studies have reported the negative prognostic role of higher HbA1c levels in patients who underwent surgical resection, while the reported results are too scarce for a robust conclusion to be drawn in these patients received ICIs at present, although pembrolizumab therapy has achieved obvious clinical benefits (17-20).

To extend understandings of immunotherapy and DM and associated blood glucose markers in NSCLC treated with ICI, we conducted a retrospective study while correlating DM and HbA1c with clinical outcome, response and survival. We present the following article in accordance with the REMARK reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-493/rc).

Methods

Study population

We recruited 266 patients who had been diagnosed with locally advanced or metastatic NSCLC and received immunotherapy between July 2016 and January 2020 in Shanghai chest hospital. All the patients had been treated with pembrolizumab alone or in combination with chemotherapy. The present study was a retrospective study and conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Chest Hospital (No. IS21110). Individual consent for this retrospective analysis was waived.

Data extraction, treatment, assessment, and follow-up

Detailed data on patients' clinical characteristics were collected from the electronic database, including age, gender, smoking history, combined diseases, type II DM history, tumor histology, baseline blood glucose/HbA1c level before ICI treatment, blood glucose levels after 2–4 cycles treatment, tumor (T) stage, node (N) stage, tumor-node-metastasis (TNM) stage, PD-L1 expression level (antibody: 22C3), and driver-gene mutation status. Pre-treatment blood results: peripheral blood tumor marker carcinoembryonic antigen (CEA), cytokeratin-19 fragment (CYFRA21-1), alkaline phosphatase (ALP), albumin, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels were also analyzed.

The abnormal values of these blood biomarkers applied in present study are listed as follow: CEA (>5 ng/mL), ALP (>120 U/L), CYFRA21-1 (>5 ng/mL), ESR (>40 mm/1 h), albumin (<35 g/L), CRP (>10 mg/L). Gene mutations or rearrangement profiles were detected by targeted next generation sequencing with commercially available gene panels consisted of 68 cancer-related genes (Burning Rock Biotech, Guangzhou, China). All tumor staging was performed according to the staging system of the American Joint Committee on Cancer (8th edition). All patients received intravenously administered pembrolizumab monotherapy (200 mg) or the monotherapy combined with chemotherapy/anti-angiogenesis therapy every 3 weeks. Patients who received pemetrexed were prepared with folic acid, vitamin B12, and glucocorticoids according to local guidelines.

All patients were recommended to receive sequential physical examination and image evaluation (every 6 weeks) after initial treatments, survival details were evaluated mainly by phone communication and outpatient visit (every 6–9 weeks). OS was defined as the time from 1st treatment administration to death from any cause or last follow-up. PFS was defined as the time from 1st treatment administration to disease progression or death. The tumor assessments were performed using the whole treatment process in accordance with the Response Evaluation Criteria in Solid Tumors guidelines (RECIST; version 1.1). At the last follow-up date (set as June 2021), the median follow-up time was 22.5 months [95% confidence interval (CI): 21.2–23.8 months].

Statistical analysis

The clinicopathological characteristic comparison was conducted using the Chi-square (χ^2) test or Fisher's exact test. The survival differences were analyzed using the Kaplan-Meier (K-M) survival function with the log-rank test. Further, clinical characteristics which showed statistically significant association with the survivals were subjected to final regression analysis, multivariate relationships were evaluated by fitting logistic regression analysis using a backward stepwise (likelihood ratio) method. Statistical significance was defined as a two-sided P value <0.05, and all statistical analysis were performed using SPSS 19.0 statistical software (SPSS, Inc., Chicago, IL, USA).

Results

Characteristics of the study patients

A total of 266 NSCLC patients were recruited for the present study, of whom 218 (81.95%) were male and 48 were female (18.05%). Of the patients, 173 (65.04%) were aged >60 years, 63.3% (133/210) were former or current smokers, and 190 had stage IV tumors. More than half (140, 52.63%) of the patients had adenocarcinoma (AC), 100 (37.59%) had squamous carcinoma (SC), and 26 had other NSCLC histological types (3 had lymphoepithelioma-like carcinoma, 1 had sarcoma, 3 had adenosquamous carcinoma, and 19 NSCLC-not otherwise specified). Among 159 tumor samples evaluable for PD-L1 expression, 52 (32.7%) tumors showed low expression (LP; PD-L1 <1%), 43 (27.04%) middle expression (MP; PD-L1 1–49%) and 64 (40.26%) samples had high expression levels (HP; PD-L1 ≥50%). In total, 169 (63.53%) patients received 1st-line therapy and the remaining 97 (36.47%) patients as 2nd- or further-line therapy. Additionally, 15.04% (40/266) of the patients had a known history of type II DM before their ICI treatments, 59 (22.2%) patients had a HbA1c level ≥6.5% at the baseline, 42.63% (107/251) had a fasting blood glucose level >7 mmol/L, besides, 93 patients showed a blood glucose level increase after ICI therapy. The details of the patients are listed in *Table 1*.

Genetic alternations and peripheral blood tumor markers profiles

Driver mutant genes were detected in this cohort. Specifically, 12.96% (28/216) of the tumors harbored epidermal growth factor receptor (*EGFR*) alterations, including 16 (57.1%) sensitizing mutations. All other gene alterations are reported in *Table 1*. The baseline peripheral blood tumor markers were also detected, and the abnormal/positive rates of these biomarkers were 55.88% (95/170) for CEA (>5 ng/mL), 25.95% (68/262) for ALP (>120 U/L), 49.40% (83/168) for CYFRA21-1 (>5 ng/mL), 59.59% (87/146) for ESR (>40 mm/1 h), 22.66% (46/203) for albumin (<35 g/L), and 49.36% (77/156) for CRP (>10 mg/L).

Efficacy and outcome analysis of patients with high or normal HbA1c levels in the whole population

We found that baseline HbA1c level (≥6.5% or <6.5%),

Table 1 Clinicopathological characteristics of the 266 NSCLC patients treated with pembrolizumab

Characteristics	Number (%)
Gender	
Male	218 (81.95)
Female	48 (18.05)
Age (years)	
>60	173 (65.04)
≤60	93 (34.96)
History of DM	
Yes	40 (15.04)
No	207 (77.82)
Missing	19 (7.14)
Smoking history	
Yes	133 (50.00)
No	77 (28.90)
Missing	56 (21.10)
Tumor histology	
AC	140 (52.63)
SC	100 (37.59)
Other	26 (9.78)
HbA1c	
≥6.5%	59 (22.18)
<6.5%	120 (45.11)
Missing	87 (32.71)
Tumor stage	
II	6 (2.26)
III	66 (24.81)
IV	190 (71.43)
Missing	4 (1.50)
EGFR mutants (n=28)	
19del	8 (28.57)
L858R	8 (28.57)
T790M	1 (3.57)
20ins	5 (17.86)
Amplification	6 (21.43)
Other driver genes	
ALK	2 (0.75)
ROS1	1 (0.37)
KRAS	32 (12.03)
BRAF	3 (1.13)
PD-L1 expression	
<1%	52 (32.70)
1–49%	43 (27.04)
≥50%	64 (40.26)
CEA (ng/mL)	
High (>5)	95 (55.88)
Normal (≤5)	75 (44.12)
ALP (U/L)	
High (>120)	68 (25.95)
Normal (≤120)	194 (74.05)
CYFRA21-1 (ng/mL)	
High (>5)	83 (49.40)
Normal (≤5)	85 (50.60)
ESR (mm/1 h)	
High (>40)	87 (59.59)
Normal (≤40)	59 (40.41)
Albumin (g/L)	
Low (<35)	46 (22.66)
Normal (≥35)	157 (77.34)
CRP (mg/L)	
High (>10)	77 (49.36)
Normal (≤10)	79 (50.64)

NSCLC, non-small cell lung cancer; DM, diabetes mellitus; AC, adenocarcinoma; SC, squamous carcinoma; HbA1c, hemoglobin A1c; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; *ROS1*, c-ros oncogene 1; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; PD-L1, programmed death-ligand 1; CEA, carcinoembryonic antigen; ALP, alkaline phosphatase; CYFRA21-1, cytokeratin-19 fragment; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

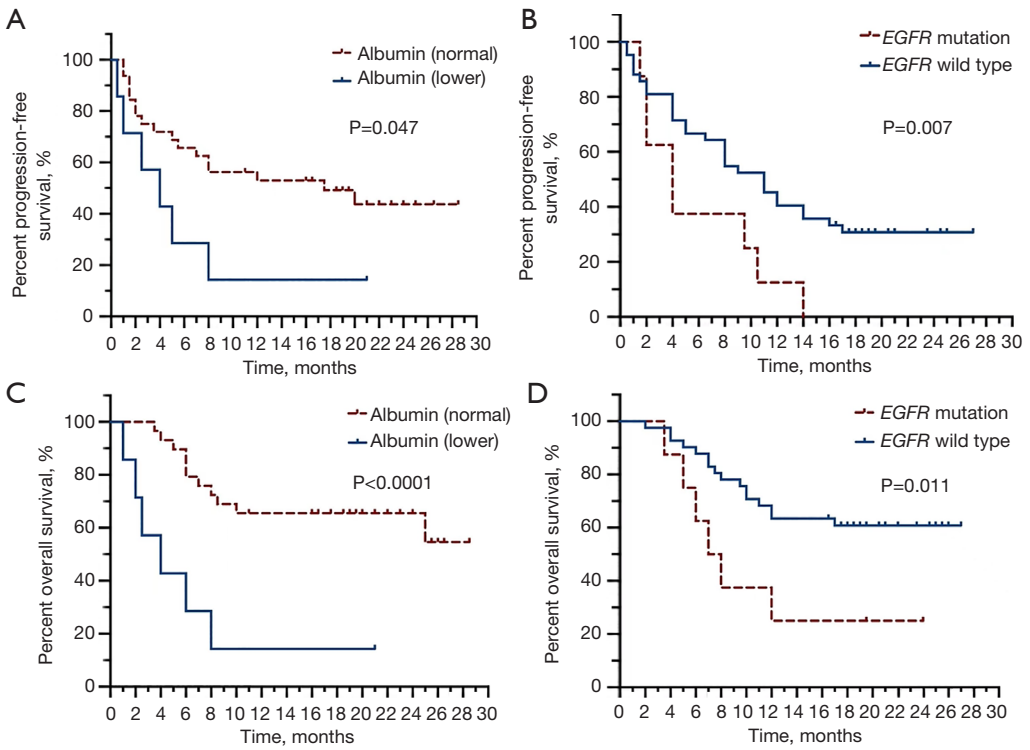

Figure 1 K-M estimates of PFS (A) and OS (C) for different blood albumin levels (normal ≥35 g/L) for patients with high HbA1c level (≥6.5%). Estimates of PFS (B) and OS (D) for different *EGFR* statuses for patients with a normal HbA1c level (<6.5%). *EGFR*, epidermal growth factor receptor; K-M, Kaplan-Meier; PFS, progression-free survival; OS, overall survival; HbA1c, hemoglobin A1c.

blood glucose level (> or ≤7 mmol/L) and blood glucose level changes between and post-ICIs treatment were all not significantly associated with response to ICIs treatment or survivals in the whole population. In 59 patients with a HbA1c level ≥6.5% at baseline, 23 (46.0%) had partial response (PR), 22 (44.0%) had stable disease (SD), and 5 (10.0%) had progressive disease (PD). As for patients (n=120) with normal HbA1c levels (<6.5%), 1 (0.9%, 1/109) had complete response (CR), 41 (37.7%) had PR, 54 (49.5%) had SD, and 13 (11.9%) had PD, while the ORR and disease control rate (DCR) were not significantly differed compared with those in high HbA1c levels patients (all P>0.05). In patients (n=59) with HbA1c level ≥6.5%, PFS differed significantly between the peripheral blood albumin levels [median: 17.5 months (normal) *vs.* 4 months (abnormal), P=0.047], and abnormal/lower albumin levels (<35 g/L) also indicated poor OS [median: not reached (NR) *vs.* 4 months, P<0.0001], while clinicopathological characteristics, such as age, gender, smoking history, genetic mutations, and PD-L1 expression, were not associated with outcomes. In patients with normal HbA1c levels (<6.5%), *EGFR* mutants were significantly associated with worse outcomes [PFS: 4 months (mutant) *vs.* 12 months (wild type), P=0.007; and OS: 8 months (mutant) *vs.* NR months (wild type), P=0.011; see *Figure 1*]. Additionally, PD-L1 expression was also a predictive factor for PFS, such that higher levels (PD-L1 <1%, 1–49%, and ≥50% expression) indicated better survival (9 months *vs.* 11.5 months *vs.* NR, respectively, P=0.008). Baseline abnormal ALP and CRP levels were also significantly associated with worse PFS [ALP: 6 months (abnormal) *vs.* 14 months (normal), P=0.001; and CRP: 8 months (abnormal) *vs.* 12 months (normal), P=0.043]. Further, abnormal baseline ALP and CYFRA21-1 levels were prognostic biomarkers for inferior OS [ALP: 10 months (abnormal) *vs.* NR months (normal), P=0.006; and CYFRA21-1: 11 months (abnormal) *vs.* NR months (normal), P=0.009].

Efficacy and outcome analysis of patients who received 1st-line ICI therapy

Of all involved patients, 169 received 1st-line treatment, 2

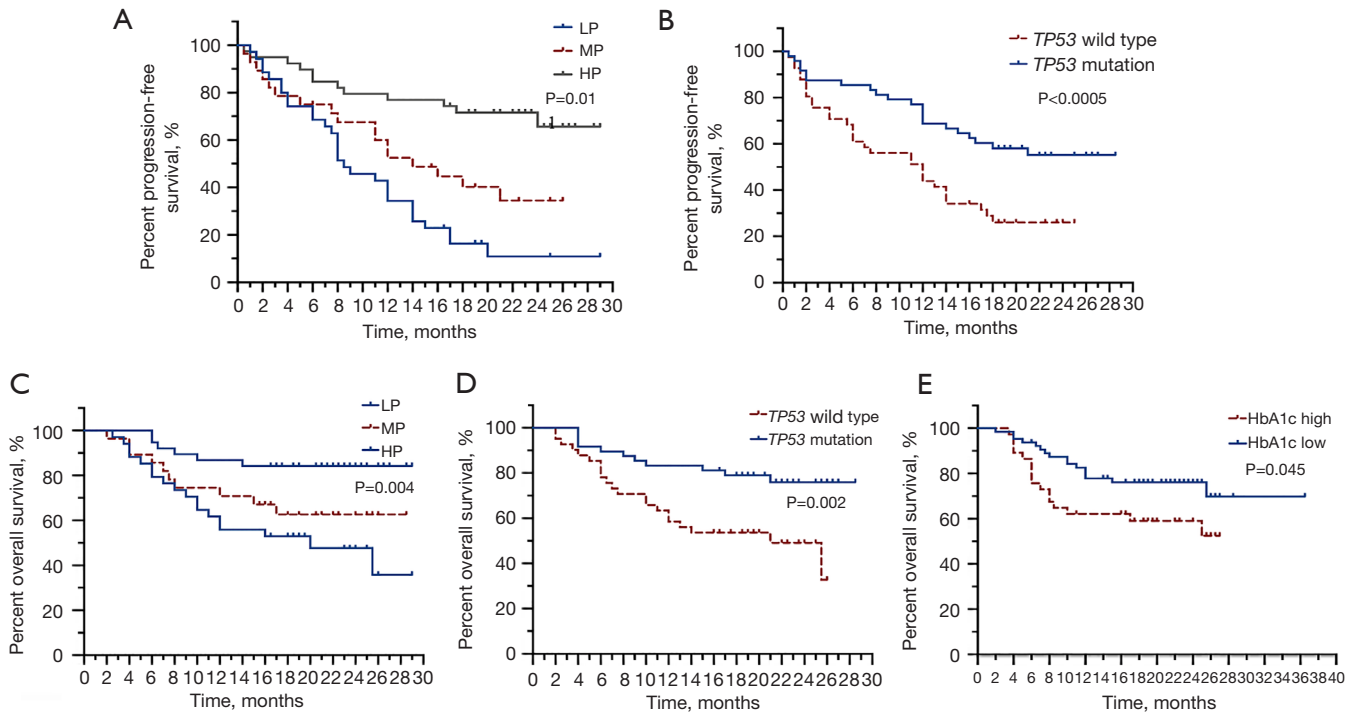

Figure 2 For NSCLC patients who received 1st-line therapy. K-M estimates of PFS for different PD-L1 expression levels (A) and *TP53* alternations (B). K-M estimates of OS for different PD-L1 expression levels (C), *TP53* alternations (D), and HbA1c levels (E). LP: low PD-L1 expression <1%; MP: middle PD-L1 expression 1–49%; HP: high PD-L1 expression ≥50%; HbA1c high: ≥6.5%; HbA1c low: <6.5%. TP53, tumor protein p53; HbA1c, hemoglobin A1c; NSCLC, non-small cell lung cancer; K-M, Kaplan-Meier; PFS, progression-free survival; PD-L1, programmed death-ligand 1; OS, overall survival.

(1.3%, 2/154) had CR, 77 had PR (50%), 64 had SD (41.6%) and 11 had PD (7.1%). DM history, smoking history, blood glucose level (>7 or ≤7 mmol/L) and blood glucose level changes between and post-ICIs treatment were all not significantly associated with tumor progression and response to ICIs. Tumor protein p53 (*TP53*) alternations were associated with longer PFS (NR *vs.* 12 months, P=0.011). Different PD-L1 expression also indicated different PFS, such that a higher level (PD-L1 <1% *vs.* 1–49% *vs.* ≥50% expression) indicated better survival (8 months *vs.* 12 months *vs.* NR, respectively, P<0.0005). Additionally, *TP53* (NR for mutant *vs.* 21 months for wild type, P=0.002) and PD-L1 expression (20 months for PD-L1 negative *vs.* NR for PD-L1 1–49% and PD-L1 ≥50%, P=0.004) were also prognostic factors for OS. A HbA1c level ≥6.5% at the baseline indicated worse OS compared to a HbA1c <6.5% (2-year survival rate: 31.25% *vs.* 27.03%, P=0.045; see *Figure 2*). The baseline blood glucose level and blood glucose level changes were not associated with PFS or OS. ALP was a prognostic factor for survival [PFS: 8 months (abnormal) *vs.* 18 months (normal), P=0.003; and OS: 14 months (abnormal) *vs.* NR (normal), P=0.003].

Outcomes of NSCLC patients who received ICIs as 2nd- or further-line therapies

The efficacy and outcomes of patients treated with ICIs as 2nd- or further-line therapies did not significantly differ in relation to whether or not they had a history of DM, and their baseline HbA1c level, blood glucose levels, and glucose changes pre- and post-treatment. Smoking history indicated a better PFS (median 8 *vs.* 4 months, P<0.01), *EGFR* mutants were significantly associated with poor survival, [PFS: 2.5 months (mutant) *vs.* 7.5 months (wild type); and OS: 6 months (mutant) *vs.* 14 months (wild type); both P=0.001]. Further, the histology results also indicated different OS among patients, such that non-SC patients had a shorter OS than SC patients (non-SC: 8.5 months *vs.* SC: 20 months, P=0.013). An abnormal baseline CRP (positive) indicated worse PFS [2.5 months (abnormal) *vs.* 9 months

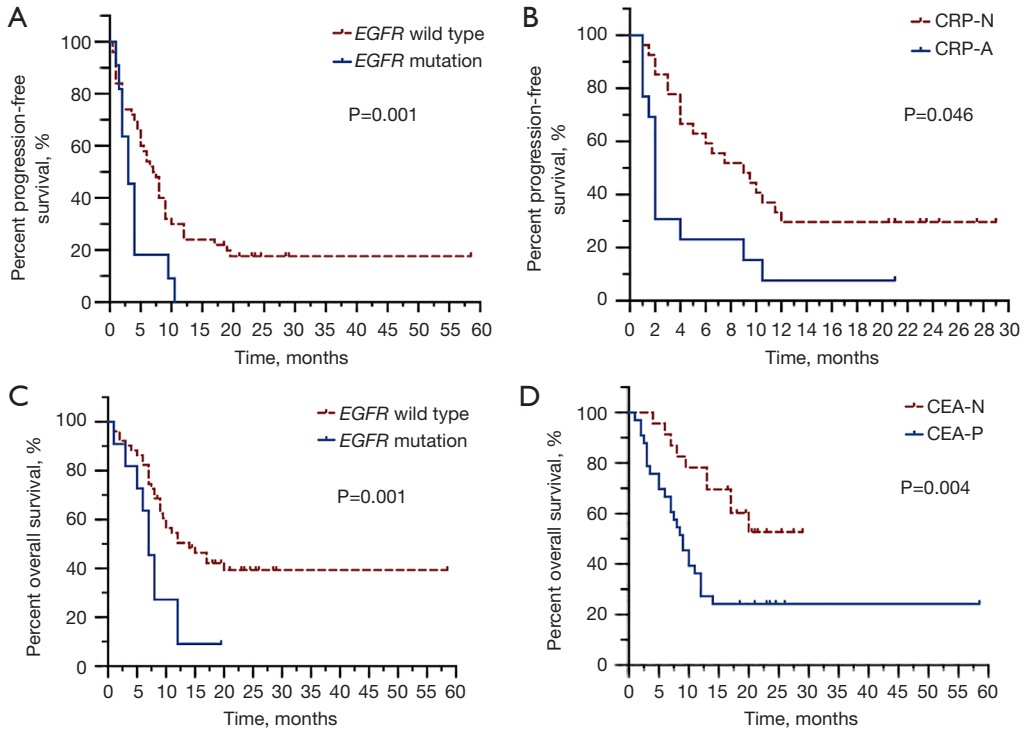

Figure 3 For NSCLC patients who received 2nd- or further-line therapy. K-M estimates of PFS for different *EGFR* statuses (A) and CRP levels (B). Estimates of OS for different *EGFR* statuses (C) and CEA levels (D). CRP-N: ≤10 mg/L; CRP-A: >10 mg/L; CEA-N: ≤5 ng/mL; CEA-P: >5 ng/mL. *EGFR*, epidermal growth factor receptor; CRP, C-reactive protein; CEA, carcinoembryonic antigen; NSCLC, non-small cell lung cancer; K-M, Kaplan-Meier; PFS, progression-free survival; OS, overall survival.

(normal), P=0.046]. CEA, CYFRA21-1, and albumin also acted as prognostic biomarkers for OS [CEA: 9 months (high) *vs.* NR (normal), P=0.004; *Figure 3*; CYFRA21-1: 19 months (high) *vs.* NR (normal), P=0.022; and albumin: 9 months (abnormal) *vs.* 13 months (normal), P=0.021].

Outcomes analysis of different types of histology for NSCLC patients who received ICI therapy

We also evaluated prognosis based on tumor histology. In relation to the non-SC patients, we did not find any statistically significant differences between the outcomes and a history of DM/smoking, baseline HbA1c, blood glucose levels, and glucose changes pre- and post-treatment. Patients with *EGFR* mutants had worse PFS [4 months (mutant) *vs.* 11 months (wild type), P=0.02], and patients with the Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation had better PFS [8 months (wild type) *vs.* 16.5 months (mutant), P=0.039]. Higher PD-L1 expression (PD-L1 <1% *vs.* 1–49% *vs.* ≥50% expression) indicated better PFS (8 months *vs.* 11.5 months *vs.* NR, respectively, P=0.001), normal albumin [4 months (abnormal) *vs.* 9.5 months (normal), P=0.001] and ALP levels [6 months (abnormal) *vs.* 11 months (normal), P=0.005] also indicated longer PFS. Further, *TP53* mutations indicated better OS compared to wild-type mutations (13 months *vs.* NR; P=0.042). Normal ALP [10 months (abnormal) *vs.* NR months (normal), P=0.001], CEA [12 months (abnormal) *vs.* NR months (normal), P=0.014], and albumin levels [7.5 months (abnormal) *vs.* NR months (normal), P=0.001] also indicated longer OS (see *Figure 4*). In the SC group, only PD-L1 expression level was found to be a significant prognostic marker for OS, but the median survival period was NR when the data were cut-off (P=0.046).

Multivariate analysis of outcome predictors in NSCLC patients treated with ICIs

We selected DM history, tumor histology, *TP53* alternations, PD-L1 expression, ALP, and HbA1c level as variates in

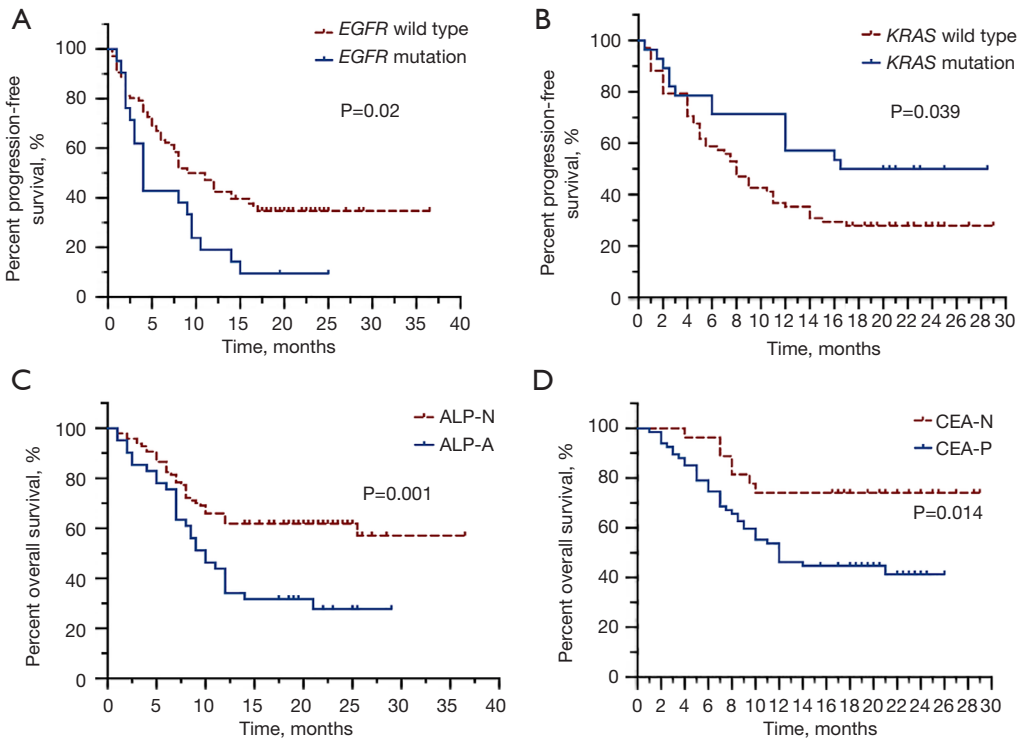

Figure 4 For NSCLC patients with non-SCs. K-M estimates of PFS for different *EGFR* statuses (A) and *KRAS* statuses (B). Estimates of OS for different ALP (C) and CEA levels (D). ALP-N: ≤120 U/L; ALP-A: >120 U/L; CEA-N: ≤5 ng/mL; CEA-P: >5 ng/mL. *EGFR*, epidermal growth factor receptor; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; ALP, alkaline phosphatase; CEA, carcinoembryonic antigen; NSCLC, non-small cell lung cancer; non-SCs, non-squamous carcinomas; K-M, Kaplan-Meier; PFS, progression-free survival; OS, overall survival.

the prognostic evaluation of PFS and OS for patients who received ICIs as a 1st-line therapy. We found that HbA1c level could not predicted survivals in this population, while PD-L1 was an independent prognostic factor for PFS (P=0.001) and OS (P=0.034), and *TP53* alternation also indicated better PFS (P=0.039) and OS (P=0.009). In patients treated with ICIs as a 2nd- or further-line therapy, DM history, tumor histology, *EGFR* mutants, CEA, CRP, and HbA1c levels were included in the multivariate analysis, and we only discovered *EGFR* mutants and CEA acted as prognostic biomarkers for OS (P=0.018 and 0.023; see *Table 2*).

Discussion

DM occurs frequently and has been recognized as a risk factor in the development of cancer in previous reports (12,13), however, the treatment effects and outcomes for NSCLC patients with DM have not been evaluated adequately. As ICIs are widely implemented in clinical practice, the question of whether a history of DM, the baseline peripheral blood HbA1c level, and glucose levels affect prognosis requires careful analysis. In the present retrospective study, we recruited 266 NSCLC patients who had received pembrolizumab monotherapy or combined therapy and discovered that lower albumin level had worse survival in patients with a high HbA1c level (≥6.5%) at the baseline. Additionally, for 1st-line patients, a higher HbA1c level (≥6.5%) indicated a worse OS compared to a lower HbA1c level (P=0.045), while a history of DM, glucose levels (>7 or ≤7 mmol/L), and blood glucose level changes during the treatment process were not significantly associated with efficacy and outcomes.

Locally advanced or metastatic NSCLC patients have dismal long-term survival outcomes. Recently, pembrolizumab therapy was shown to improve the 5-year OS rate by >30% among patients with a PD-L1 tumor proportion score ≥50 (18). In the present study, we found

Table 2 Multivariate analysis of outcome predictors for NSCLC patients who received pembrolizumab

Prognostic characteristics	PFS			OS		
	P value	HR	95% CI	P value	HR	95% CI
ICIs as 1st-line therapy						
DM history	0.718	0.784	0.209–2.940	0.506	0.554	0.097–3.158
Histology	0.771	1.154	0.441–3.018	0.786	1.219	0.292–5.084
TP53 alternations	0.039	0.462	0.221–0.963	0.009	0.234	0.079–0.693
PD-L1 expression	0.001	0.459	0.291–0.724	0.034	0.499	0.262–0.950
ALP	0.965	0.977	0.344–2.775	0.661	0.690	0.131–3.630
HbA1c	0.896	1.073	0.373–3.086	0.183	2.525	0.645–9.884
ICIs as second or further therapy						
DM history	0.399	3.718	0.176–78.533	0.148	10.141	0.439–234.407
Histology	0.339	2.364	0.406–13.779	0.072	3.897	0.885–17.153
EGFR mutants	0.159	2.193	0.734–6.546	0.018	4.485	1.297–15.504
CEA	0.121	2.579	0.778–8.548	0.023	4.215	1.216–14.614
CRP	0.358	1.643	0.570–4.738	0.256	1.907	0.626–5.810
HbA1c	0.247	0.294	0.037–2.341	0.803	0.763	0.091–6.399

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; DM, diabetes mellitus; *TP53*, tumor protein p53; PD-L1, programmed death-ligand 1; ALP, alkaline phosphatase; HbA1c, hemoglobin A1c; *EGFR*, epidermal growth factor receptor; CEA, carcinoembryonic antigen; CRP, C-reactive protein; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; OS, overall survival.

that a high HbA1c level was a prognostic factor for worse OS in the 1st-line ICI therapy patients. Jacobi *et al.* found that a history of DM was significantly and negatively correlated with PFS and OS in metastatic NSCLC patients treated with ICIs (17), but did not find any such positive relationship for HbA1c levels or metformin use. Motoishi *et al.* found that a higher HbA1c level (≥6.5%) indicated poor OS in postoperative elderly NSCLC patients (19). Ogawa *et al.* also evaluated the preoperative HbA1c levels of AC patients who underwent surgery and found that a HbA1c level ≥8% was associated with the worst 5-year OS, and the tumors were more likely to undergo distant metastasis in the follow-up period (20). Other studies have collected data from lung cancer patients with DM; however, results on the prognostic value of DM status have not been consistent in survival analyses (14-16,21). Further, research on ICI therapy is scarce. Thus, the prognostic value of DM or HbA1c levels for patients treated with ICIs needs to be further evaluated. Reports on DM status range from 4.59–18.87% in the published data (14-16,21). In the present study, 15.04% of the patients had a history of DM before treatment. Thus, a more balanced sample-selection procedure should be employed in the future.

Previous studies have evaluated ICI monotherapy or combined therapy in NSCLC patients with *EGFR* mutants, and most of these studies have found a poor response and survival benefits (5,22-26) among both 1st-line or further-line patients, while another study with anti-angiogenesis treatment resulted in a better clinical outcome (8). More related clinical trials need to be conducted to evaluate the effects of ICI therapy in *EGFR*-mutant populations. Our study showed that in patients who received 2nd- or subsequent-line therapy, *EGFR* was an unfavorable predictive and prognostic biomarker, and resulted in inferior PFS and OS. Our multivariate analysis also confirmed that *EGFR* mutants were independent prognostic factors for worse OS. However, *KRAS* mutations indicated favorable outcomes in non-SC patients. As the use of mature *KRAS*-tyrosine kinase inhibitors (TKIs) are limited in the G12C type at present (27), ICIs represent a potential therapy for these patients, which is consistent with previous findings (28,29). We also discovered the *TP53* alternations indicated

superior survival and acted as an independent prognostic biomarker. Previously, the co-mutation for *TP53/KRAS* has been proven to improve immunotherapy outcomes for AC patients (29-31). More clinical research might delineate a specific subgroup of patients with driver-gene mutant tumors who would benefit from ICI therapies.

Peripheral blood tumor marker detection is non-invasive and convenient in regular clinical practice. The survival outcomes of patients treated with 1st-line ICIs differed significantly depending on ALP levels. Additionally, baseline CEA, CRP, and albumin levels were statistically predictive and had prognostic value in further-line treatments. CEA is widely used to provide supportive information in efficacy and survival evaluations, and baseline high level (>5 ng/mL) appears to indicate shorter PFS and OS. High level CEA is also significantly associated with poorer OS in non-SC patients. Chen *et al.* reported that a post-treatment CEA decrease was an indicator of better survival after ICI therapy (32). Another study revealed that an increase in CEA levels appeared to predict progression in NSCLC patients treated with ICIs (33). Similar results have also been reported in several other studies (34-36). We also found that clinical laboratory test markers, such as CRP and albumin levels, had prognostic value in the outcome analyses. Research has revealed that the baseline CRP: albumin ratio (CAR) and subsequent changes in CAR may be predictive of treatment responses and long-term survival (37). As more data are gathered, more precise conclusions will be able to be drawn about the value of these peripheral blood markers in the survival evaluations of NSCLC patients treated with ICIs in the future.

The present study had several limitations. First, we could not collect all the patients' data, and some information was missing in this retrospective study, including information on DM history and HbA1c level, PD-L1 expression, peripheral tumor markers, and genetic profiling detection results. Second, the use of single-center samples in this study may affect the generalizability of our findings. Finally, the relatively small sample size and relatively low proportion of patients with DM may have led to biases.

In conclusion, in patients with baseline higher HbA1c level (≥6.5%) group, lower baseline albumin levels indicated worse outcomes. And in NSCLC patients who received 1st-line pembrolizumab monotherapy or combined therapy, higher HbA1c levels (≥6.5%) indicated dismal outcomes, interventions for reducing HbA1c may improve the prognosis, which should be further investigated in the future. *TP53* gene alternations and PD-L1 expression were also independent prognostic biomarkers. In 2nd- or further-line treatments, *EGFR* mutants and the peripheral blood markers of CEA, CRP, and albumin could be used for outcome predictions, and would be convenient and cost-effective in clinical practice.

Acknowledgments

The authors appreciate the academic support from the AME Lung Cancer Collaborative Group.
Funding: This work was supported by the "Star of SJTU" Plan Medical-Engineering Cross Fund of Shanghai Jiao Tong University (No. YG2019QNA48), the Western Medicine Guide Project of the Shanghai Committee of Science and Technology (No. 18411968500), and the Medical Innovation Project of Scientific and Technological Innovation Action Plan of the Shanghai Committee of Science and Technology (No. 21Y11913500).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-493/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-493/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-22-493/coif). FG reports personal fees from AstraZeneca and honoraria for advisory board participation from Eli-Lilly, outside the submitted work. The other authors have no conflicts of interest to declare.

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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Chest Hospital (No. IS21110). Individual consent for this retrospective analysis was waived.

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(English Language Editor: L. Huleatt)

Cite this article as: Shen Y, Li J, Qiang H, Lei Y, Chang Q, Zhong R, Stella GM, Gelsomino F, Kim YW, Abed A, Qian J, Chu T. A retrospective study for prognostic significance of type II diabetes mellitus and hemoglobin A1c levels in non-small cell lung cancer patients treated with pembrolizumab. Transl Lung Cancer Res 2022;11(8):1619-1630. doi: 10.21037/tlcr-22-493