Original Article

Effect of type 2 diabetes mellitus on systemic treatment for advanced non-small cell lung cancer

Yasuhiro Kato[1]^, Eri Kuramochi[1], Rei Yamaguchi[1], Erika Mikami[1], Kaoruko Shinbu[1], Jyunichi Aoyama[1], Shunsuke Kobayashi[2], Fumitaka Okajima[2], Masahiro Seike[3], Tetsuya Okano[1]

[1]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School Chiba-Hokusoh Hospital, Chiba, Japan; [2]Department of Diabetes, Endocrinology and Metabolism, Nippon Medical School Chiba-Hokusoh Hospital, Chiba, Japan; [3]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan

Contributions: (I) Conception and design: Y Kato, T Okano; (II) Administrative support: None; (III) Provision of study materials or patients: S Kobayashi, F Okajima; (IV) Collection and assembly of data: E Kuramochi, R Yamaguchi, E Mikami, K Shinbu, J Aoyama, Y Kato, T Okano; (V) Data analysis and interpretation: Y Kato, T Okano; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yasuhiro Kato, MD, PhD. Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School Chiba-Hokusoh Hospital, 1715, Kamakari, Inzai, Chiba, Japan. Email: y-kato@nms.ac.jp.

Background: The effect of type 2 diabetes mellitus (T2DM) on treatments for advanced non-small cell lung cancer (NSCLC) remains unelucidated. We aimed to assess the effect of T2DM on the treatment for advanced NSCLC.

Methods: We retrospectively investigated clinicopathological character, treatment effect, and adverse events (AEs) in advanced NSCLC patients started on systemic treatment at Nippon Medical School Chiba-Hokusoh Hospital from 2018 to 2024.

Results: The numbers of T2DM and non-T2DM patients among those undergoing immune checkpoint inhibitor (ICI) therapy, molecular targeted therapy (MTT), and cytotoxic chemotherapy (CTT) were 37 and 78, 30 and 86, 9 and 17, respectively. The overall survival (OS) of patients complicated T2DM was significantly worse in total (19.3 *vs.* 34.5 months, P=0.001), the ICI (11.5 *vs.* 34.2 months, P=0.005) and the MTT cohort (27.4 *vs.* 43.4 months, P=0.03). Median progression-free survival (PFS) was significantly poor for T2DM patients in the ICI cohort (5.7 *vs.* 12.5 months, P=0.04). However, a significant difference was not found for the MTT cohort (13.3 *vs.* 12.7 months, P=0.91). There were no significant differences in AEs in either cohort. Hemoglobin A1c (HbA1c) was significantly higher in patients with derived neutrophil lymphocyte ratio (dNLR) ≥3. The PFS in T2DM patients in the ICI cohort was investigated with regard to clinicopathological factors and T2DM treatments. Specialist consultation was identified as a factor that improved PFS of ICI.

Conclusions: Our research suggests that T2DM is an independent poor prognostic factor in advanced NSCLC and affects ICI treatment.

Keywords: Immune checkpoint inhibitor (ICI); non-small cell lung cancer (NSCLC); systemic treatment; type 2 diabetes mellitus (T2DM)

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^ ORCID: 0000-0001-8585-1995.

Introduction

Until recently, the prognosis for patients with non-small cell lung cancer (NSCLC) was notoriously poor. Nowadays, therapies targeting oncogene mutations demonstrate good efficacy for NSCLC harboring any oncogenic driver mutation (1). In particular, NSCLC with an *EGFR* mutation, *ALK* fusion, *ROS1* fusion, *BRAF V600E* mutation, *RET* fusion, and *MET* exon 14 skipping mutation respond extremely well to tyrosine kinase inhibitors. Therefore, molecular targeted therapies (MTTs) are considered standard first-line treatment for this disease (2). In addition, immune checkpoint inhibitors (ICIs), as novel types of drugs for malignant tumors, show good efficacy in advanced NSCLCs (3,4). ICIs have also demonstrated positive effects when combined with cytotoxic anticancer drugs (5-7). Therefore, molecular targeted therapies, ICIs, and cytotoxic chemotherapy (CTT) are considered as standard therapies for advanced NSCLCs.

Type 2 diabetes mellitus (T2DM) is one of the metabolic diseases of global concern. Previous reports have shown that 15% of patients with cancer have concomitant T2DM, and the risk of developing several types of cancer from diabetes has also been reported (8-11). Assessing the effect of T2DM complications and treatment on cancer and its systemic treatment is therefore an important issue. Although previous research reported that T2DM was one of the prognostic factors for shorter survival, other studies showed that T2DM was not associated with worse survival (12-16). Whether T2DM is a prognostic factor or not remains controversial. In addition, since most studies were published over 10 years ago, there is a paucity of studies examining the effect of T2DM on the diverse treatments for cancers that have emerged in recent years. The effect of T2DM on the therapeutic efficacy of ICI is of particular interest since it is well known that T2DM has a suppressive effect on immunity and alters metabolic functions (17). Recent studies have reported a negative effect of T2DM on ICI treatment for several kinds of cancer (18,19). This research reported advanced NSCLC patients with T2DM patients showed lower neutrophil lymphocyte ratio (NLR) (18). The impact of T2DM on the systemic and tumor immune environment has received much attention. However, these previous studies only investigated cohorts treated with ICI for several types of cancer. It is difficult to determine whether T2DM is a predictor of ICI efficacy or prognosis in NSCLC based on current studies' results. There are also no studies assessing the effect of T2DM on various systemic treatments, including ICI for NSCLC, and knowledge is lacking.

We conducted a multi-cohort retrospective study with the aim of comprehensively investigating the effect of T2DM on advanced NSCLC with particular attention to differences in the effect between treatments. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-302/rc).

Highlight box

Key findings

- Type 2 diabetes mellitus (T2DM) affects advanced non-small cell lung cancer (NSCLC) prognosis and immune checkpoint inhibitor (ICI) treatment efficacy.

What is known and what is new?

- It was known that T2DM could worsen the prognosis of advanced NSCLC, however the finding remained controversial.
- This study suggests that T2DM affects prognosis and ICI treatment efficacy for advanced NSCLC.

What is the implication, and what should change now?

- Interventions for glycemic control may be important in the systemic treatment of advanced-stage NSCLC, especially when ICIs are administered.

Methods

Patients and clinicopathological features

The clinical records of consecutive patients with advanced NSCLC, for whom systemic treatment was initiated between April 2018 and August 2024 at the Nippon Medical School Chiba-Hokusoh Hospital in Japan, were reviewed. As first-line treatment: patients treated with ICI monotherapy or a combination with a platinum doublet were defined as the ICI cohort; those treated with some form of MTT for NSCLC harboring targetable oncogenic mutations were labeled the MTT cohort; and patients treated with cytotoxic chemotherapy (CTT) without ICIs were the CTT cohort.

T2DM was diagnosed according to 2019 World Health Organization (WHO) diagnostic criteria or a history of T2DM or medication use, such as insulin or oral hypoglycemic agents (20). Baseline characteristics included the presence of T2DM, age, sex, Eastern Cooperative Oncology Group performance status (PS), smoking history, clinical stage, histology, body mass index

(BMI), hemoglobin A1c (HbA1c), NLR, derived NLR (dNLR), tumor proportion score (TPS) of programmed death ligand 1 (PD-L1), central nervous system metastasis, Charlson Comorbidity Index (CCI), interstitial lung disease (ILD) at baseline, and treatment regimens for NSCLC. T2DM treatment [control hyperglycemia by diabetes specialist intervention, any medication for T2DM, insulin, metformin or dipeptidyl peptidase-4 (DPP4) inhibitor], and treatment adverse events (AEs) for NSCLC were obtained retrospectively from medical charts (21). Each cohort of patients placed on medication for T2DM was defined as a treatment group if medication was continued for at least one month or until systemic treatment for lung cancer was completed from the start. Specialist consultation was defined as an intervention group if diabetes specialists were consulted for T2DM treatment prior to the start of systemic treatment for NSCLC. Genetic mutations were screened for by a Oncomine Dx target test, AmoyDx pan lung cancer PCR panel, the Lung Cancer Compact Panel™, cobas® EGFR Mutation Test v2 and immunohistochemical or fluorescence in situ hybridization assays for *ALK* rearrangement. These were performed within the Japanese insurance system for cases deemed necessary according to the judgement of the attending physician. We analyzed the TPS of PD-L1 using a 22C3 pharm Dx assay on tumor samples, which is known to be a predictor of the effectiveness of ICI (3,22,23). The NLR and dNLR was calculated according to previous studies (24,25). Missing data were treated appropriately, but were rarely observed in either cohort.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Institutional Review Board of the Nippon Medical School Chiba-Hokusoh Hospital (No. 2024-246) and informed consent was obtained from all individual participants.

Evaluation of the efficacy of systemic treatment

The efficacy of any systemic treatments for patients with NSCLC was retrospective analyzed. Whole-body computed tomography and brain magnetic resonance imaging or computed tomography were conducted before the start of treatment; whole-body bone scintigraphy or positron emission tomography were employed. All patients underwent computed tomography of the chest and abdomen every 8 to 12 weeks. Overall response rate (ORR) was assessed using the Response Evaluation Criteria in Solid Tumors (version 1.1) and median (26). AEs were assessed using the common terminology criteria for AEs in version 5.0 (27).

Statistical analysis

Associations between patients' characteristics and T2DM were examined using Fisher's exact test. Progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan-Meier method. The effect of treatment efficacy and the prognostic value of each clinical factor was assessed using the Cox regression method for univariate and multivariate analyses. A Mann-Whitney *U* test was used to statistically verify the association between HbA1c and dNLR. Missing data was rarely observed, but when it did occur, complete data analysis was performed. Patients for whom follow-up observation was not possible were censored on the final confirmation date. All analyses were performed using EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan), a graphical user interface for R that is designed for biostatistics. P values <0.05 were considered statistically significant (28).

Results

Patients' baseline characteristics

A total of 354 consecutive patients diagnosed with advanced NSCLC were screened and 257 patients started on a systemic treatment (*Figure 1*). The number of patients included in ICI, MTT, and CTT cohorts were 115, 116, and 26 patients (*Figure 1*, *Table 1*). *Table 1* shows the clinicopathological characteristics of NSCLC patients, with or without T2DM, in the total and individual cohorts.

Elderly people aged over 70 years were more common, around 65% in both groups with and without T2DM complications. In addition, more cases of poor PS and squamous cell carcinoma were observed in patients with T2DM from among total patients. Among total patients and the ICI cohort, squamous cell carcinoma was significantly more common in patients with T2DM. In the ICI cohort, a trend was observed toward significantly higher NLR and dNLR in advanced NSCLC patients with T2DM compared to without T2DM (*Table 1*). No other clinicopathological factors showed statistically significant differences between T2DM and non-T2DM patients in the total and individual cohorts.

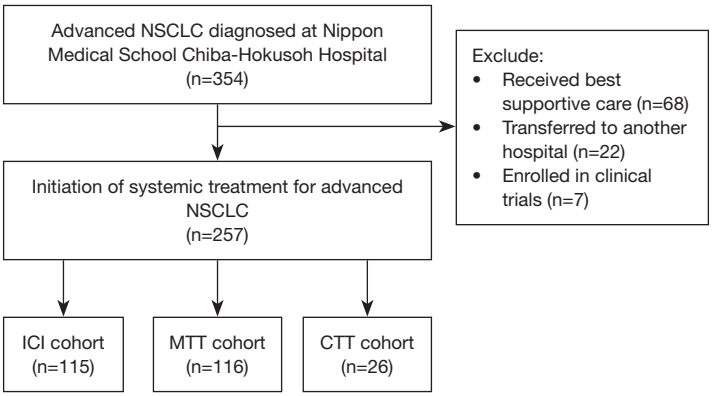

Figure 1 Flow chart to select patients with advanced NSCLC who underwent systemic treatment. CTT, cytotoxic chemotherapy; ICI, immune checkpoint inhibitor; MTT, molecular targeted therapy; NSCLC, non-small cell lung cancer.

Prognosis and efficacy of each systemic treatment with T2DM or non-T2DM

The total cohort median follow-up period was 16.4 months, with 13.6 months for the ICI cohort, 21.4 months for the MTT cohort, and 11.2 months for the CTT cohort. In every cohort, ORRs were not significantly different between NSCLC patients with or without T2DM (total: 61.8% *vs.* 58.6%, odds ratio 1.14, P=0.68; ICI cohort: 62.2% *vs.* 52.6%, odds ratio 1.48, P=0.42; MTT cohort: 70.0% *vs.* 68.6%, odds ratio 1.07, P value >0.99; CTT cohort, 33.3% *vs.* 35.3%, odds ratio 1.07, P value >0.99; *Table 2*). Overall, cardiovascular and infection events were many in patients with T2DM complications, particularly in the ICI cohort, where the incidence of cardiovascular disease was relatively higher in patients with T2DM complications (*Table 2*). However, there is no significant differences were observed (*Table 2*).

For total patients, the median OS was significantly different between T2DM and non-T2DM patients [19.3 *vs.* 34.5 months, hazard ratio (HR) 1.76, 95% confidence interval (CI): 1.24–2.51, P=0.001; *Figure 2*]. We conducted univariate and multivariate analyses using a logistic regression test on the OS in total patients with T2DM and general prognostic factors, including the CCI, which reflect the prevalence of comorbidities. T2DM likewise PS stage and histology was an independent prognostic factor in advanced NSCLC patients introduced to systemic treatment (*Table 3*). In addition, the median OS was significantly different between T2DM and non-T2DM patients in ICI and MTT cohorts (ICI cohort 11.5 *vs.* 34.2 months, HR 2.13, 95% CI: 1.24–3.66, P=0.005; MTT cohort 27.4 *vs.* 43.4 months, HR 1.81, 95% CI: 1.05–3.13, P=0.03; *Figure 3A*,*3B*). No differences in median OS were observed between T2DM and non-T2DM patients in the CTT cohort (10.7 *vs.* 11.4 months, HR 1.81, 95% CI: 1.05–3.13, P=0.56; *Figure 3C*) likely due to small sample size. The median PFS was significantly different between T2DM and non-T2DM patients in the ICI cohort (5.7 *vs.* 12.5 months, HR 1.60, 95% CI: 1.03–2.51, P=0.04; *Figure 4A*). On the contrary, no differences were noted in the median OS between T2DM and non-T2DM patients in the MTT cohort and CTT cohort (*Figure 4B*,*4C*). Univariate analysis and multivariate analysis for PFS of ICI cohort showed T2DM is an independent ineffective factor for ICI (*Table 4*).

These results suggest that T2DM may affect the efficacy of ICI treatment for advanced NSCLC. In addition, we assessed the relationship between AEs and T2DM. The frequency of Grade 3 or higher AEs did not show a clear difference between T2DM and non-T2DM patients; a trend toward more ILDs and AE discontinuations in T2DM compared to non-T2DM patients was observed in the overall population, and ICI and MTT cohorts. However, none of these differences reached statistical significance (*Table 2*).

Relationship between dNLR and HbA1c

We investigated the relationship between HbA1c and dNLR using a Mann-Whitney *U* test in the ICI cohort. A higher HbA1c trend was observed in patients with a NLR of 5 or higher and a statistically significant higher level of HbA1c was found in patients with a dNLR of 3 or higher (NLR: 6.1%±0.3% *vs.* 6.4%±0.4%, P=0.051, dNLR: 6.0%±0.4%

Table 1 Patients characteristics

Variables	Total			ICI cohort			MTT cohort			CTT cohort		
	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P
Total	76	181	–	37	78	–	30	86	–	9	17	–
HbA1c (range, %)	6.9 (5.8–9.8)	5.9 (4.9–6.4)	–	7 (6.5–9.6)	5.9 (4.9–6.4)	–	6.7 (5.8–9.8)	5.8 (5–6.4)	–	7.0 (6.4–7.4)	5.8 (5.4–6.3)	–
Age (years)			0.67			0.41			0.83			0.67
<70	25 (32.9)	65 (35.9)		11 (29.7)	30 (38.5)		11 (36.7)	29 (33.7)		3 (33.3)	6 (35.3)	
≥70	51 (67.1)	116 (64.1)		26 (70.3)	48 (61.5)		19 (63.3)	57 (66.3)		6 (66.7)	11 (64.7)	
Sex			0.12			0.77			0.38			0.63
Men	54 (71.1)	109 (60.2)		33 (89.2)	67 (85.9)		13 (43.3)	29 (33.7)		8 (88.9)	13 (76.5)	
Women	22 (28.9)	72 (39.8)		4 (10.8)	11 (14.1)		17 (56.7)	57 (66.3)		1 (11.1)	4 (23.5)	
PS			<0.001*			0.34			0.79			0.66
PS 0–1	60 (78.9)	173 (95.6)		31 (83.8)	71 (91.0)		24 (80.0)	71 (82.6)		5 (55.6)	11 (64.7)	
PS 2–4	16 (21.1)	8 (4.4)		6 (16.2)	7 (9.0)		6 (20.0)	15 (17.4)		4 (44.4)	6 (35.3)	
Smoking			0.35			0.13			>0.99			0.74
Never	11 (14.5)	40 (22.1)		1 (2.7)	9 (11.5)		10 (33.3)	30 (34.9)		0 (0.0)	1 (5.9)	
Former	47 (61.8)	97 (53.6)		22 (59.5)	33 (42.3)		18 (60.0)	50 (58.1)		7 (77.8)	14 (82.4)	
Current	18 (23.7)	44 (24.3)		14 (37.8)	36 (46.2)		2 (6.7)	6 (7.0)		2 (22.2)	2 (11.8)	
BMI (kg/m^2)			0.60			0.39			0.55			0.17
<18	7 (9.2)	22 (12.2)		4 (10.8)	6 (7.7)		3 (10.0)	15 (17.4)		0 (0.0)	1 (5.9)	
18≤ to <25	48 (63.2)	119 (65.7)		22 (59.5)	56 (71.8)		20 (66.7)	48 (55.8)		6 (66.7)	15 (88.2)	
≥25	21 (27.6)	40 (22.1)		11 (29.7)	16 (20.5)		7 (23.3)	23 (26.7)		3 (33.3)	1 (5.9)	
Stage			0.53			0.11			0.59			0.44
Recurrence	13 (17.1)	43 (23.8)		5 (13.5)	21 (26.9)		7 (23.3)	22 (25.6)		1 (11.1)	0 (0.0)	
IIIA-C	11 (14.5))	26 (14.4)		5 (13.5)	18 (23.1)		4 (13.3)	6 (7.0)		2 (22.2)	4 (23.5)	
IVA-B	52 (68.4)	112 (61.9)		27 (73.0)	39 (50.0)		19 (63.3)	58 (67.4)		6 (66.7)	13 (76.5)	
Histology			0.006*			0.007*			0.49			0.61
Ad	45 (59.2)	139 (76.8)		11 (29.7)	46 (59.0)		29 (96.7)	83 (96.5)		5 (55.6)	10 (58.8)	
Sq	23 (30.3)	33 (18.2)		19 (51.4)	26 (33.3)		1 (3.3)	0 (0.0)		3 (33.3)	7 (41.2)	
Adsq	0 (0.0)	3 (1.7)		0 (0.0)	1 (1.3)		0 (0.0)	2 (2.3)		0 (0.0)	0 (0.0)	
Other	8 (10.5)	6 (3.3)		7 (18.9)	5 (6.4)		0 (0.0)	1 (1.2)		1 (11.1)	0 (0.0)	
PD-L1			0.07			0.30			0.59			0.74
≥50%	17 (22.4)	32 (17.7)		14 (37.8)	23 (29.5)		2 (6.7)	8 (9.3)		1 (11.1)	1 (5.9)	
1–49%	8 (10.5)	44 (24.3)		4 (10.8)	20 (25.6)		4 (13.3)	21 (24.4)		0 (0.0)	3 (17.6)	
0%	31 (40.8)	60 (33.1)		15 (40.5)	26 (33.3)		11 (36.7)	26 (30.2)		5 (55.6)	8 (47.1)	
Unknown	20 (26.3)	45 (24.9)		4 (10.8)	9 (11.5)		13 (43.3)	31 (36.0)		3 (33.3)	5 (29.4)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total			ICI cohort			MTT cohort			CTT cohort		
	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P
Gene mutation			0.53			>0.99			0.67			–
None or unknown	45 (59.2)	92 (50.8)		36 (97.3)	75 (96.2)		0 (0.0)	0 (0.0)		9 (100.0)	17 (100.0)	
EGFR mutation	27 (35.5)	72 (39.8)		0 (0.0)	0 (0.0)		27 (90.0)	72 (83.7)		0 (0.0)	0 (0.0)	
ALK fusion	1 (1.3)	8 (4.4)		0 (0.0)	0 (0.0)		1 (3.3)	8 (9.3)		0 (0.0)	0 (0.0)	
Other	3 (3.9)	9 (5.0)		1 (2.7)	3 (3.8)		2 (6.7)	6 (7.0)		0 (0.0)	0 (0.0)	
CNS metastasis			0.87			>0.99			0.35			>0.99
Yes	16 (21.1)	36 (19.9)		5 (13.5)	12 (15.4)		10 (33.3)	21 (24.4)		1 (11.1)	3 (17.6)	
No	60 (78.9)	145 (80.1)		32 (86.5)	66 (84.6)		20 (66.7)	65 (75.6)		8 (88.9)	14 (82.4)	
CCI			0.12			0.54			0.37			0.42
0–1	51 (67.1)	139 (76.8)		23 (62.2)	53 (67.9)		24 (80.0)	75 (87.2)		4 (44.4)	11 (64.7)	
≥2	25 (32.9)	42 (23.2)		14 (37.8)	25 (32.1)		6 (20.0)	11 (12.8)		5 (55.6)	6 (35.3)	
ILD			0.45			0.32			–			0.72
Yes	8 (10.5)	13 (7.2)		2 (5.4)	8 (10.3)		0 (0.0)	0 (0.0)		6 (66.7)	5 (29.4)	
No	68 (89.5)	168 (92.8)		35 (94.6)	70 (89.7)		30 (100.0)	86 (100.0)		3 (33.3)	12 (70.6)	
NLR			0.04*			0.02*			0.82			0.67
<5.0	44 (57.9)	130 (71.8)		18 (48.6)	56 (71.8)		21 (70.0)	62 (72.1)		5 (55.6)	12 (70.6)	
≥5.0	32 (42.1)	51 (28.2)		19 (51.4)	22 (28.2)		9 (30.0)	24 (27.9)		4 (44.4)	5 (29.4)	
dNLR			0.06			0.006*			>0.99			>0.99
<3.0	43 (56.6)	126 (69.6)		17 (45.9)	57 (73.1)		23 (76.7)	64 (74.4)		3 (33.3)	5 (29.4)	
≥3.0	33 (43.4)	55 (30.4)		20 (54.1)	21 (26.9)		7 (23.3)	22 (25.6)		6 (66.7)	12 (70.6)	
Regimen			0.84			>0.99			0.67			–
Platinum + ICI	29 (38.2)	59 (32.6)		29 (78.4)	59 (75.6)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
ICI monotherapy	8 (10.5)	19 (10.5)		8 (21.6)	19 (24.4)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
EGFR-TKI	27 (35.5)	72 (39.8)		0 (0.0)	0 (0.0)		27 (90.0)	72 (83.7)		0 (0.0)	0 (0.0)	
ALK-TKI	1 (1.3)	8 (4.4)		0 (0.0)	0 (0.0)		1 (3.3)	8 (9.3)		0 (0.0)	0 (0.0)	
Other targeted therapy	2 (2.6)	6 (3.3)		0 (0.0)	0 (0.0)		2 (6.7)	6 (6.9)		0 (0.0)	0 (0.0)	
Cytotoxic chemotherapy	9 (11.8)	17 (9.4)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		9 (100.0)	17 (100.0)	

Data are presented as median (range) or n (%). *, statistically significant difference recognized. Ad, adenocarcinoma; Adsq, adenosquamous; ALK, anaplastic lymphoma kinase; BMI, body mass index; CCI, Charlson Comorbidity Index; CNS, central nervous system; CTT, cytotoxic chemotherapy; dNLR, derived neutrophil lymphocyte ratio; EGFR, epidermal growth factor receptor; HbA1c, hemoglobin A1c; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; MTT, molecular targeted therapy; PD-L1, programmed death ligand 1; PS, performance status; Sq, squamous cell carcinoma; T2DM, type 2 diabetes mellitus; TKI, tyrosine kinase inhibitor.

Table 2 Response of systemic treatment and T2DM

Variables	Total			ICI cohort			MTT cohort			CTT cohort		
	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P	T2DM	Non-T2DM	P
CR	4	3	–	2	2	–	2	1	–	0	0	–
PR	43	103	–	21	39	–	19	58	–	3	6	–
SD	12	35	–	7	21	–	3	11	–	2	3	–
PD	14	34	–	5	15	–	5	11	–	4	8	–
NE	3	6	–	2	1	–	1	5	–	0	0	–
ORR (%)	61.8 (50.0–72.8)	58.6 (51.0–68.6)	0.68	62.2 (44.8–77.5)	52.6 (40.9–64.0)	0.42	70.0 (50.6–85.3)	68.6 (57.7–78.2)	>0.99	33.3 (7.5–70.1)	35.3 (14.2–61.7)	>0.99
AEs > Grade 3	25 (32.9)	55 (30.4)	0.77	12 (32.4)	25 (32.1)	>0.99	10 (33.3)	24 (27.9)	0.64	3 (42.9)	6 (31.6)	0.66
ILD	17 (22.4)	25 (13.8)	0.10	10 (27.0)	14 (17.9)	0.33	7 (23.3)	23 (26.7)	0.79	0 (0.0)	0 (0.0)	>0.99
Treatment discontinuation	21 (24.4)	35 (19.3)	0.34	16 (43.2)	24 (30.8)	0.21	5 (16.7)	11 (12.8)	0.56	0 (0.0)	0 (0.0)	>0.99
Cardiovascular event	1 (1.3)	2 (1.1)	>0.99	1 (2.7)	1 (1.3)	0.54	0 (0.0)	1 (1.2)	>0.99	0 (0.0)	0 (0.0)	>0.99
Infection event	1 (1.2)	4 (2.2)	>0.99	1 (2.7)	1 (1.3)	0.54	0 (0.0)	3 (3.6)	0.57	0 (0.0)	0 (0.0)	>0.99
Treatment related death	0 (0.0)	2 (1.1)	>0.99	0 (0.0)	1 (1.3)	>0.99	0 (0.0)	1 (1.2)	>0.99	0 (0.0)	0 (0.0)	>0.99

Data are presented as n, median (range) or n (%). AEs, adverse events; CR, complete response; CTT, cytotoxic chemotherapy; ICI, immune checkpoint inhibitor; ILD, interstitial lung disease; MTT, molecular targeted therapy; NE, not evaluated; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; T2DM, type 2 diabetes mellitus.

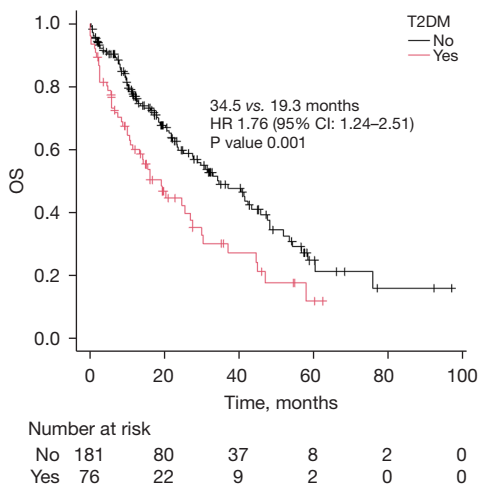

Figure 2 Kaplan-Meier curves for OS in total patients comparing T2DM and non-T2DM. CI, confidence interval; HR, hazard ratio; OS, overall survival; T2DM, type 2 diabetes mellitus.

vs. 6.4%±0.5%, P=0.02; *Figure 5A,5B*). Interestingly, no differences existed between HbA1c and dNLR in MTT cohort patients (NLR: 6.0%±0.3% *vs.* 6.0%±0.3%, P=0.76, dNLR 6.0%±0.4% *vs.* 5.9%±0.4%, P=0.78; *Figure 5C,5D*). These results suggest that a close association exists between dNLR and blood glucose levels in NSCLC without a targetable gene mutation, and that this may influence the efficacy of ICI treatment.

Effect of T2DM treatment on ICI treatment for advanced NSCLC

The effect of T2DM treatment on ICI treatment for advanced NSCLC was exploratory assessed. Characteristics of DM treatment in NSCLC patients diagnosed with T2DM in the ICI cohort are shown in *Table 5*. We conducted univariate and multivariate analyses of PFS of ICI cohort patients for each T2DM treatment and general prognostic factors. NLR and dNLR was not included in the multivariate analysis due to multicollinearity with glycemic control from our study result. Diabetes specialist consultation, PS and stage was identified as a statistically significant factor having a positive effect on ICI treatment (*Table 6*). In contrast, any medication, insulin, metformin, and DPP4 inhibitors were not clearly significant factors for PFS.

Table 3 Univariate analysis and multivariate analysis predictive factor for OS in total patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (<70 *vs*. ≥70 years)	0.85	0.60–1.21	0.37			
PS (0–1 *vs*. 2–4)	0.37	0.24–0.57	<0.001*	0.37	0.23–0.58	<0.001*
Sex (male *vs*. female)	1.67	1.16–2.40	0.005*	1.02	0.61–1.71	0.93
Smoking status (smoker *vs*. never smoker)	1.83	1.25–2.67	0.002*	1.29	0.73–2.29	0.38
BMI (<25 *vs*. ≥25 kg/m^2)	1.37	0.90–2.09	0.14			
Stage (recurrence or III *vs*. IV)	0.63	0.44–0.91	0.01*	0.58	0.39–0.84	0.005*
Histology (Sq *vs*. non-Sq)	1.74	1.18–2.57	0.005*	1.64	1.02–2.63	0.04*
PD-L1 status (positive *vs*. negative or unknown)	0.94	0.66–1.33	0.72			
Gene mutation status (positive *vs*. negative or unknown)	0.58	0.41–0.82	0.002*	0.84	0.52–1.37	0.49
CNS metastasis (positive *vs*. negative)	1.48	0.99–2.20	0.050			
CCI score (0–1 *vs*. ≥2)	0.91	0.62–1.35	0.65			
T2DM (yes *vs*. no)	1.76	1.24–2.51	0.001*	1.56	1.11–2.29	0.01*

*, statistically significant difference recognized. BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1; PS, performance status; Sq, squamous cell carcinoma; T2DM, type 2 diabetes mellitus.

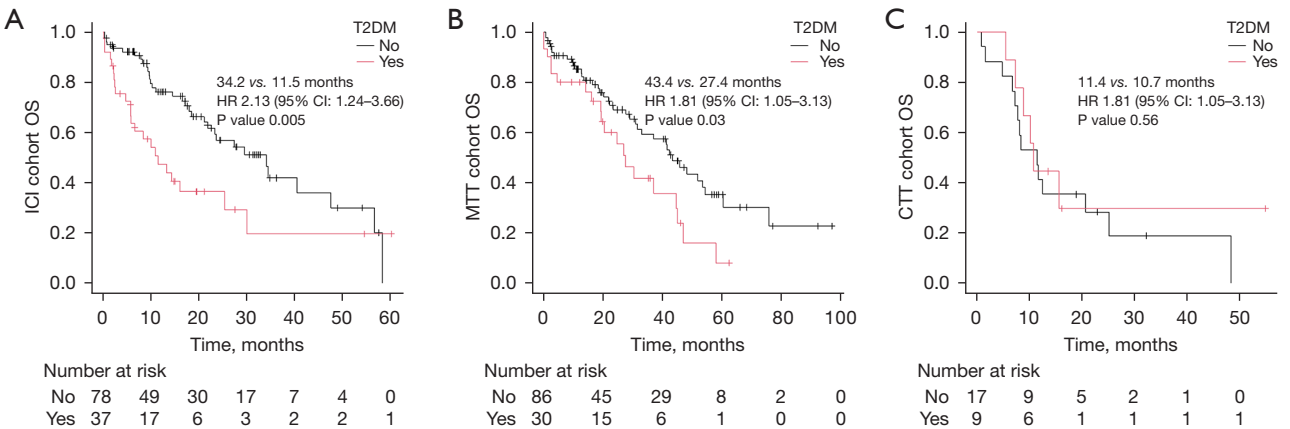

Figure 3 Kaplan-Meier curves for OS in ICI (A), MTT (B), and CTT (C) cohort patients comparing T2DM and non-T2DM. CI, confidence interval; CTT, cytotoxic chemotherapy; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; MTT, molecular targeted therapy; T2DM, type 2 diabetes mellitus.

Discussion

Few studies have assessed the effect of T2DM on various systemic treatments for NSCLC. Previous research has suggested that T2DM is prognostic factor in advanced NSCLC (12-14). However, other studies have reported that T2DM does not affect the prognosis of NSCLC, and the effect of DM on advanced NSCLC remains controversial (15,16). Several recent studies have reported that DM has an effect on the prognosis of NSCLC; however, most studies have reported on only a small number of cases and have not been able to analyze the specific effect of DM on treatment (16,29,30). Our findings suggested that T2DM was an independent prognostic factor in patients with

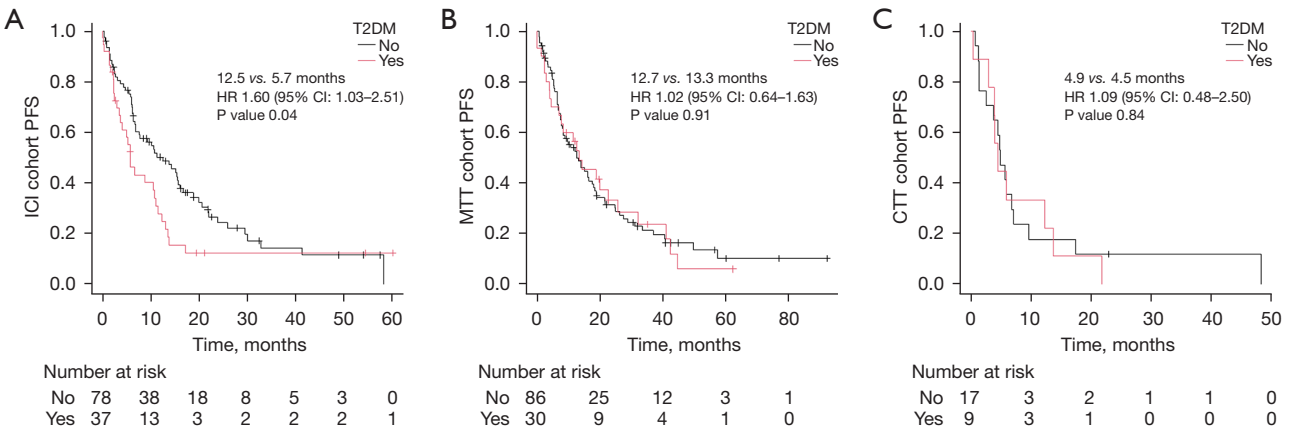

Figure 4 Kaplan-Meier curves for PFS in ICI (A), MTT (B), and CTT (C) cohort patients comparing T2DM and non-T2DM. CI, confidence interval; CTT, cytotoxic chemotherapy; PFS, progression-free survival; HR, hazard ratio; ICI, immune checkpoint inhibitor; MTT, molecular targeted therapy; T2DM, type 2 diabetes mellitus.

Table 4 Univariate analysis and multivariate analysis clinicopathological factors for PFS in ICI cohort patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (<70 *vs*. ≥70 years)	0.78	0.49–1.21	0.26			
PS (0–1 *vs*. 2–4)	0.48	0.25–0.90	0.02*	0.54	0.26–0.95	0.03*
Sex (male *vs*. female)	0.63	0.35–1.14	0.13			
Smoking status (smoker *vs*. never smoker)	0.67	0.32–1.40	0.28			
BMI (<25 *vs*. ≥25 kg/m^2)	1.04	0.64–1.69	0.86			
Stage (recurrence or III *vs*. IV)	0.56	0.36–0.87	0.009*	0.61	0.39–0.95	0.03*
Histology (Sq *vs*. non-Sq)	0.84	0.54–1.30	0.43			
PD-L1 status (positive *vs*. negative or unknown)	0.91	0.60–1.38	0.64			
CNS metastasis (positive *vs*. negative)	1.67	0.95–2.92	0.07			
CCI score (0–1 *vs*. ≥2)	1.56	0.98–2.47	0.06	1.56	0.97–2.52	0.07
T2DM (yes *vs*. no)	1.60	1.03–2.51	0.04*	1.68	1.06–2.67	0.03*

*, statistically significant difference recognized. BMI, body mass index; CCI, Charlson Comorbidity Index; CI, confidence interval; CNS, central nervous system; HR, hazard ratio; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status; Sq, squamous cell carcinoma; T2DM, type 2 diabetes mellitus.

systemically treated advanced NSCLC. This trend was similar in the ICI and MTT cohorts. The observation of a similar phenomenon between patients treated by anticancer agents of different mechanisms is considered to be strongly support T2DM as a prognostic factor.

To the best of our knowledge, this is the first study to analyze the relationship between T2DM and systemic treatment efficacy, including ICI and MTT, for advanced NSCLC. Interestingly, no significant difference in PFS was observed between T2DM and non-T2DM patients on MTT and CTT therapies, whereas a statistically significant difference in PFS was observed for the ICI cohort. A previous comprehensive analysis of various cancer types suggested that T2DM affects the efficacy of ICI treatment

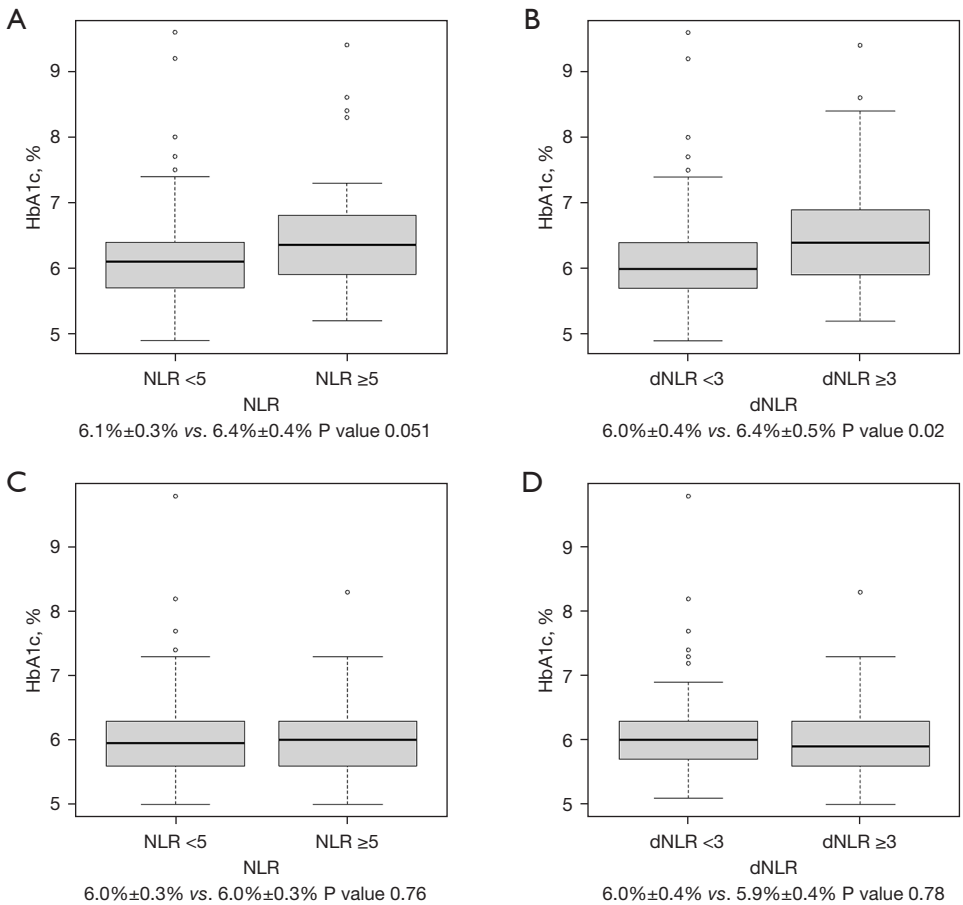

Figure 5 Association between NLR or dNLR and HbA1c. (A,B) A higher HbA1c trend and a statistically significant higher level of HbA1c was found in patients with a NLR of 5 or higher and dNLR of 3 or higher (6.1%±0.3% *vs.* 6.4%±0.4%, P=0.051; 6.0%±0.4% *vs.* 6.4%±0.5%, P=0.02). (C,D) Similar trend of the ICI cohort was not observed in the MTT cohort (6.0%±0.3% *vs.* 6.0%±0.3%, P=0.76; 6.0%±0.4% *vs.* 5.9%±0.4%, P=0.78). dNLR, derived neutrophil lymphocyte ratio; HbA1c, hemoglobin A1c; ICI, immune checkpoint inhibitor; MTT, molecular targeted therapy; NLR, neutrophil lymphocyte ratio.

(18,19). T2DM has been suggested to influence ICI treatment through the induction of systemic and tumor inflammation in previous research (18). A specific analysis of candidate genes for specimens showed a reduction of gene expression related to the inflammatory response (CXCL9, CXCL11, and BIRC5) and modulation of T-cell function (LAG3) in the specimens of diabetic patients (18). More interestingly, despite the association between the dNLR and HbA1c observed in the ICI cohort, a similar trend was not observed in the MTT cohort. These results suggest that the immune environment, including NLR and dNLR, is altered by T2DM to affect ICI treatment. It also suggests that the immune environment in patients, such as NLR and dNLR, may also be altered by the nature of the cancer, such as the presence or absence of targetable gene mutations.

Previous studies have variously reported that the treatment of DM influences the efficacy of anticancer agents. In particular, metformin has attracted attention as preclinical studies have shown potential anti-cancer activity and synergistic effects with epidermal growth factor receptor tyrosine kinase inhibitors in a prospective clinical study (31-33). In comparison, DPP4 and sodium-glucose transporter inhibitors have been suggested to have a positive effect on the therapeutic efficacy of ICI treatment for cancer. Studies have suggested that metformin may have a negative effect on ICI and chemoradiotherapy; the evaluation of this effect remains an ongoing issue (18,34-37).

Our study identified consultation with a DM specialist as

Table 5 T2DM treatment characteristics of ICI cohort patients with T2DM

Variables	ICI cohort with T2DM (N=37)
HbA1c	
<7.0%	20 (54.1)
≥7.0%	17 (45.9)
Diabetes specialist consultation	
Yes	8 (21.6)
No	29 (78.4)
Any medication	
Yes	16 (43.2)
No	21 (56.8)
Insulin	
Yes	10 (27.0)
No	27 (73.0)
Metformin	
Yes	8 (21.6)
No	29 (78.4)
DPP4 inhibitor	
Yes	10 (27.0)
No	27 (73.0)

Data are presented as n (%). DPP4, dipeptidyl peptidase-4; HbA1c, hemoglobin A1c; ICI, immune checkpoint inhibitor; T2DM type 2 diabetes mellitus.

the only independent factor affecting PFS in the treatment of T2DM, but did not identify the effect of individual drugs as a clear factor. These results may be because of the small sample size used in this study. However, they indicate that specialist consultation is more important for an appropriate T2DM assessment as well as the introduction of adequate hypoglycemic treatment in the ICI treatment of advanced NSCLC.

Our study has several limitations. First, it was a single-center, retrospective study with a small sample size so there was likely an element of selection bias in NSCLC and T2DM treatments. For example, all results of CTT cohort or the effect of any diabetes treatment on ICI treatment are likely to be false negatives because the sample size is too small. Furthermore, treatment selection bias may not be negligible, in a retrospective cohort study with this sample size. Further research will be required, particularly in relation to the association between diabetes treatment and ICI treatment, as the study was conducted on a very small group and bias is likely to be present. It cannot be excluded that the small sample size may also have influenced the fact that the PFS did not change in the MTT group. In addition, the data were analysed only for the Japanese population, and further studies with a new cohort are needed to determine whether the data can be generalised to other races. In addition, our study lacks consideration of diabetes severity, complications, and blood glucose trends during systemic treatment for advanced NSCLC due to its retrospective nature. We used HbA1c as a surrogate for blood glucose since it is difficult to assess blood glucose appropriately due to the mix of fasting and casual glucose in blood samples. HbA1c reflects the blood glucose status for 2–3 months but may not be sufficient to assess dynamic markers such as blood glucose (38). HbA1c was not identified as an independent poor prognostic factor in this study. Pre-treatment HbA1c was not identified as an independent poor prognostic factor in this study, but specialist intervention was identified as an independent factor. This result suggests that glycemic control during treatment may influence the prognosis of advanced NSCLC. However, more direct and dynamic studies of observations in blood sugar trends during systemic treatment for advanced NSCLC will be needed in the future to prove this. Furthermore, it was difficult to examine the immune environment of patients other than NLR and dNLR in this study. In particular, few studies have been conducted on the tumor immune environment and further large-scale studies, including those related to glycemic control, are needed (18). Finally, changes in the tumor microenvironment due to T2DM needs attention in future as it has recently been reported that metabolites in tumors differ between T2DM and non-T2DM patients with NSCLC (39).

Conclusions

Our findings suggest that T2DM is an independent poor prognostic factor in advanced NSCLC and affects the efficacy of ICI treatment. The study of T2DM highlighted the importance of glycemic control by T2DM specialist intervention to reduce this. T2DM can alter the dNLR through hyperglycemia and cause the deterioration of the immune environment. Glycemic control with appropriate intervention by a diabetes specialist may have a positive

Table 6 Univariate analysis and multivariate analysis for T2DM treatment and PFS of ICI treatment

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P	HR	95% CI	P
Age (<70 *vs*. ≥70 years)	1.95	0.86–4.44	0.06	1.00	0.42–2.40	0.99
PS (0–1 *vs*. 2–4)	0.28	0.12–0.77	0.01*	0.27	0.09–0.77	0.01*
Sex (male *vs*. female)	0.63	0.20–1.79	0.34			
BMI (<25 *vs*. ≥25 kg/m^2)	1.04	0.64–1.69	0.86			
Stage (recurrence or III *vs*. IV)	0.23	0.08–0.61	0.007*	0.24	0.08–0.73	0.01*
Histology (Sq *vs*. non Sq)	0.82	0.39–1.65	0.43			
PD-L1 status (positive *vs*. negative or unknown)	0.76	0.39–1.64	0.72			
CNS metastasis (positive *vs*. negative)	1.36	0.51–3.65	0.81			
NLR (≥5 *vs*. <5)	2.36	1.52–3.66	<0.001*			
dNLR (≥3 *vs*. <3)	3.85	0.86–17.31	0.08*			
HbA1c (≥7.0% *vs*. <7.0%)	0.69	0.29–1.63	0.40			
Diabetes specialist consultation (yes *vs*. no)	0.44	0.15–1.28	0.22	0.24	0.09–0.97	0.045*
Any medication (yes *vs*. no)	0.80	0.38–1.69	>0.99			
Insulin (yes *vs*. no)	0.62	0.25–1.54	0.48			
Metformin (yes *vs*. no)	1.78	0.69–4.61	0.47			
DPP4 inhibitor (yes *vs*. no)	0.57	0.24–1.35	0.41			

*, statistically significant difference recognized. BMI, body mass index; CI, confidence interval; CNS, central nervous system; dNLR, derived neutrophil lymphocyte ratio; DPP4, dipeptidyl peptidase-4; HbA1c, hemoglobin A1c; HR, hazard ratio; ICI, immune checkpoint inhibitor; NLR, neutrophil lymphocyte ratio; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; PS, performance status; Sq, squamous cell carcinoma; T2DM, type 2 diabetes mellitus.

impact in ICI treatment.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-302/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-2025-302/dss

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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 and its subsequent amendments. The study was approved by the Institutional Review Board of the Nippon Medical School Chiba-Hokusoh Hospital (No. 2024-246) and informed consent was obtained from all individual participants.

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