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Clinical characteristics and unique presentations of immune checkpoint inhibitor induced type 1 diabetes in Chinese patients from a single institution

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Immune checkpoint inhibitor-induced type 1 diabetes (ICI-T1D) is a rare immune-related adverse event (irAE) of immune checkpoint inhibitors (ICIs). This retrospective study aimed to characterize the clinical features and glucose patterns of ICI-T1D in Chinese individuals and compare them with those of traditional T1D. Between January 2019 and April 2024, 15 patients diagnosed with ICI-T1D were consecutively enrolled. Continuous glucose monitoring (CGM) data from 7 of these patients were compared with data from 14 traditional T1D patients, matched for age, sex, fasting C-peptide levels, and diabetes duration. Median time from ICI initiation to T1D onset was 16 weeks (IQR, 6–96). Notably, T1D developed in four participants at 144, 112, 108, and 96 weeks after PD-1 treatment, respectively. Three ICI-T1D had pre-existing type 2 diabetes (T2D). Moreover, two had concurrent hypothyroidism and adrenal insufficiency alongside ICI-T1D. CGM analysis suggested that ICI-T1D exhibited a higher overall coefficient of variation (CV) (36.3 ± 4.8% vs. 28.2 ± 6.5%; $p = 0.009$), a greater CV during the night (37.4 ± 8.4% vs. 23.4 ± 7.3%; $p = 0.001$), and an increased standard deviation (SD) during the night (3.3 ± 0.8 mmol/L vs. 2.1 ± 1.1 mmol/L; $p = 0.017$) compared to those with traditional T1D. The study highlighted diverse clinical presentations of ICI-T1D, including delayed onset and multiple endocrine organs dysfunctions after ICI treatment. Consequently, long-term glucose monitoring and early identification are crucial. Furthermore, the observed greater glucose variability in ICI-T1D emphasizes the critical importance of diabetes education and personalized insulin regimen.

Keywords Immune checkpoint inhibitors, Immune-related adverse events, Immunotherapy, Type 1 diabetes, Continuous glucose monitoring.

Immune checkpoint inhibitors (ICIs), designed to target immune checkpoints and induce anti-tumor immune response, have resulted in a paradigm shift in cancer therapy[1]. ICIs operate distinctly, distinguishing them from conventional cancer treatments. They function by releasing the brakes on the immune system, empowering it to specifically target and combat tumor cells[2]. A range of drugs have been created to achieve this, including anti-cytotoxic T lymphocyte antigen 4 (CTLA-4), anti-programmed cell death 1 (PD-1), and anti-programmed cell death ligand 1 (PD-L1) antibodies[3]. In addition to the stimulated anti-cancer immune response, there is a possibility of immune-related adverse events (irAEs) occurring, such as skin issues, digestive problems, liver damage, lung problems, nervous system disorders, and hormonal imbalances[2,4,5]. Immune checkpoint inhibitor-induced type 1 diabetes (ICI-T1D) is an irreversible endocrine irAE that happens in approximately 0.2–1.4% of patients under ICIs treatment[6–8]. Like traditional type 1 diabetes (T1D), ICI-T1D is characterized by the ongoing damage to β-cells, low levels of C-peptide, and the requirement for insulin therapy after onset[9].

In recent years, there has been a significant emphasis on ICI-T1D, driven by the growing prominence of ICIs in cancer treatment. Previous studies have indicated a mean time to onset ranging from 7 to 28 weeks[5,10,11], with the longest recorded duration being 94 weeks[12]. It has been suggested that autoantibody positivity is lower

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in ICI-T1D compared to traditional T1D[13]. Concomitant irAEs impacting other endocrine organs commonly involve the thyroid[14], and a few reported cases have documented the simultaneous occurrence of irAEs in three or more endocrine organs[15]. Risk factors associated with the development of ICI-T1D include the type of ICI therapy, younger age, and pre-existing non-type 1 diabetes[14]. Nevertheless, predicting the development of ICI-T1D continues to pose a challenge. Although there is growing recognition of ICI-T1D, substantial gaps in our comprehension of this condition remain. Specifically, only a limited number of studies have been performed on Chinese populations with small participant cohorts, resulting in an inadequate understanding of the disease[10,16,17]. Therefore, the present study primarily aims to investigate the clinical characteristics of ICI-T1D in Chinese patients to address this gap.

Materials and methods

Between January 2019 and April 2024, this study consecutively included individuals diagnosed with ICI-T1D from Peking University People's Hospital, a tertiary hospital in Beijing, China, affiliated with Peking University. The study has been reviewed by Peking University People's Hospital ethics committee (Approval No. 2022PHB407-002, 2024/4/29). All participants have been given their informed consent prior to their inclusion in the study. The diagnosis of ICI-T1D was confirmed by two endocrinologists using the following criteria: (1) no prior history of diabetes with new-onset T1D following ICI therapy; or (2) preexisting well-controlled type 2 diabetes with deteriorating glycemic control after ICI treatment; and (3) sustained reliance on insulin treatment with a low or undetectable C-peptide level during longitudinal follow-up. Clinical data collection included age, sex, diabetes history, primary tumor types, ICI types, ICI injection times, time to ICI-T1D onset, and the presence of diabetes ketoacidosis (DKA) at the time of diagnosis. For the analysis of continuous glucose monitoring (CGM) data, 7 patients with ICI-T1D who had available data were compared with 14 traditional T1D patients. These groups were matched based on age, sex, duration of diabetes, and fasting C-peptide levels.

Anthropometric and biochemical measurements

The body mass index (BMI) was calculated by dividing the weight (in kilograms) by the square of the height (in meters). Blood samples were collected following an 8-hour fast to measure fasting plasma glucose (FPG), serum C-peptide, insulin level, glycated albumin, glycated hemoglobin, and diabetes autoantibodies. Additionally, a blood sample was obtained 2 h after breakfast to evaluate postprandial glucose levels, serum C-peptide levels, and insulin levels.

Plasma glucose and glycated albumin were assessed using the enzyme immunoassay method with a biochemical analyzer (AU5800; Beckman Coulter). Glycated hemoglobin (HbA1c) was determined through automated high-performance liquid chromatography (Primus Ultra 2, Trinity Biotech, Bray, Co-Wicklow, Ireland). Serum insulin and C-peptide levels were measured using chemiluminescence (E601; Roche Diagnostics), with the lower limit of detection being 0.20 uU/mL and 0.01 ng/mL, respectively. Antibodies were tested in the hospital laboratory using RSR® antiglutamic acid decarboxylase antibodies (GAD) ELISA (RSR Limited, UK), ORGENTEC® anti-insulin antibody (IAA) radioimmunoassay (ORGENTEC Diagnostic GmbH, Germany), and BIOMERICA® anti-islet cell antibody (ICA) ELISA (BIOMERICA Inc, USA).

Continuous glucose monitoring

CGM (Freestyle Libre H 1.0, Abbott, US) data were collected and raw data were exported to the Matlab analysis program (Version 2023b.) for quantification and characterization of glucose level and glycemic variability. Coefficient of variation (CV), standard deviation (SD), mean of blood glucose (MG), time in range (TIR, the percent time with glucose level ranges from 3.9mmol/L to 10.0mmol/L), time below range (TBR, the percent time with glucose level ranges below 3.9mmol/L), time above range (TAR, the percent time with glucose level ranges above 10.0 mmol/L) and glycemic risk index (GRI) were analyzed. Among these metrics of CGM, GRI is a novel composite metric for assessing glycemic control quality, based on the percentage of time spent in glucose ranges of 3.0–3.9 mmol/L, < 3.0 mmol/L, 10.1–13.9 mmol/L, and > 13.9 mmol/L[18]. Standard Deviation (SD) is a CGM metric that reflects the magnitude of glucose fluctuations and is calculated as the square root of the average squared differences between each glucose value and the mean glucose level[19]. In addition, all of these metrics during the night (from 10:00 pm to 6:00 am) were also calculated, including CV during the night (CV night), SD during the night (SD night), TIR during the night (TIR night), TBR during the night (TBR night), TAR during the night (TAR night), and GRI during the night (GRI night).

Continuous variables were reported as medians with interquartile ranges (IQR), and categorical variables were presented as ratios calculated from the total number of non-missing values. Differences about CGM data and other clinical data were compared between participants in ICI-T1D and classic T1D, by using the student t-test or Mann-Whitney U test for parametric and nonparametric data. The categorical data were compared by Chi-square test. Statistical analysis was performed using SPSS statistical software, IBM version 25.0.

Results

Patient demographics and ICI therapy

A total of 15 participants (8 males, 7 females) with a median age of 50 years old (IQR, 25–75) were included in the study (Table 1). The median BMI was 23.57 kg/m^2 (IQR, 22.79–24.26). The primary cancer types observed in the participants included nasopharyngeal carcinoma (1/15), soft tissue sarcoma (1/15), renal cell carcinoma (1/15), esophageal cancer (1/15), pancreatic cancer (1/15), gastric cancer (1/15), lung cancer (4/15), breast cancer (2/15), sigmoid colon cancer (1/15), lymphoma (1/15), bladder cancer (1/15). All participants received treatment with PD-1 inhibitors, with 3 out of 14 receiving pembrolizumab, 4 out of 14 receiving tislelizumab, 2 out of 14 receiving camrelizumab, 1 out of 14 receiving nivolumab, 3 out of 14 receiving sintilimab, and 2 out of

	Median (IQR)/*N*	Reference value
Age (years, *N* = 15)	50 (25, 75)	-
Sex (male, *N* = 15)	8	-
BMI (kg/m^2, *N* = 13)	23.57 (22.79, 24.26)	-
Diabetes history (*N* = 15)	3/15	-
Tumor types (*N* = 15)	Nasopharyngeal carcinoma (1/15) Soft tissue sarcoma (1/15) Renal cell carcinoma (1/15) Esophageal cancer (1/15) Pancreatic cancer (1/15) Gastric cancer (1/15) Lung cancer (4/15) Breast cancer (2/15) Sigmoid colon cancer (1/15) Lymphoma (1/15) Bladder cancer (1/15)	-
Immune checkpoint inhibitor types (*N* = 15)	PD-1 inhibitor (15/15)	-
Immune checkpoint inhibitor (*N* = 14)	Pembrolizumab (3/14) Tislelizumab (4/14) Camrelizumab (2/14) Nivolumab (1/14) Sintilimab (3/14) Toripalimab (2/14)	-
Cycles of ICI injection before T1D onset (*N* = 14)	3 (2, 5)	-
Time to ICI-T1D onset after initiation of ICI (weeks, *N* = 15)	16 (6, 96)	-
Diabetic ketoacidosis (*N* = 15)	8/15	-
Daily insulin requirements (IU/kg, *N* = 9)	0.67 (0.55, 0.83)	-
FBG (mmol/L, *N* = 14)	14.1 (10.1, 18.7)	3.0–6.1
2hPG (mmol/L, *N* = 7)	18.0 (14.5 ,21.1)	3.3–7.8
HbA1c (%, *N* = 12)	8.2 (7.0, 9.8)	4.0–6.0
HbA1c < = 7.0% (*N* = 12)	3/12	-
GA (%, *N* = 10)	25.5 (22.6, 27.4)	11.0–16.0
Fasting C-peptide (ng/ml, *N* = 14)	0.01 (0.01, 0.30)	1.10–4.40
2 h post-prandial C-peptide (ng/ml, *N* = 12)	0.21 (0.03, 0.71)	-
Fasting insulin (IU/ml, *N* = 11)	1.42 (0.2, 4.14)	2.60–24.90
2 h post-prandial insulin (IU/ml, *N* = 6)	1.27 (0.87, 3.46)	-
IAA positivity (*N* = 12)	0/12	-
ICA positivity (*N* = 13)	2/13	-
GAD positivity (*N* = 14)	1/14	-
Other endocrinopathies adverse events (*N* = 14)	Hypothyroidism (4/14) Adrenal insufficiency (2/14)	-

Table 1. Demographic and clinical characteristics of ICI-T1D. Continuous variables are presented as medians (interquartile range, IQR). Categorical variables are presented as counts out of the total sample size. Abbreviation: N, number of non-missing subjects; BMI, body mass index; ICI, immune checkpoint inhibitor; ICI-T1D, immune checkpoint inhibitor induced type 1 diabete; FBG, fast blood glucose; 2 h PG, 2 h postprandial blood glucose; HbA1c, glycated hemoglobin A1c; GA, glycosylated albumin; IAA, insulin antibody; ICA, islet cell antibody; GAD, glutamic acid decarboxylase antibody.

14 receiving toripalimab. Notably, three participants had been diagnosed with type 2 diabetes for 20 years, 19 years, and 4 months before being diagnosed with ICI-T1D.

Presentation of ICI-T1D

The median number of PD-1 treatment cycles prior to the development of ICI-T1D was 3 cycles (IQR, 2–5), and the median time from ICI initiation to T1D onset was 16 weeks (IQR, 6–96) (Table 1). It is worth mentioning that one participant who underwent tislelizumab therapy for renal cell carcinoma developed ICI-T1D 144 weeks after the first cycle (Table 2). And another participant was diagnosed with ICI-T1D 108 weeks after PD-1 treatment (comprising 2 cycles of camrelizumab and 15 cycles of tislelizumab treatment) (Table 2). One participant was diagnosed with ICI-T1D 112 weeks after PD-1 treatment. One participant experienced T1D diagnosis 96 weeks after receiving camrelizumab treatment (Table 2). Eight participants experienced DKA at the onset of ICI-T1D (Table 2). All participants required insulin following the diagnosis of ICI-T1D, with a daily insulin dosage of 0.67 IU/kg (IQR, 0.55–0.83) (Table 1). In addition to T1D, four participants also experienced irAEs in other endocrine glands (Table 2). Two participants had concurrent hypothyroidism, while the other two developed both hypothyroidism and primary adrenal insufficiency.

The median HbA1c of the participants was 8.2% (IQR, 7.0–9.8), and the fasting blood glucose was 14.1 mmol/L (IQR, 10.1–18.7). Five of the thirteen participants had low fasting serum C-peptide, and eight had

	Age (years)	Sex	BMI (kg/m^2)	Diabetes history	Tumor types	Immune checkpoint inhibitor types	Immune checkpoint inhibitor	Times of ICI injection	Time to ICI-T1D onset (weeks)	DKA at onset	Daily insulin (IU/kg)	FBG (mmol/L)	2hPG (mmol/L)	HbA1c (%)	GA (%)	Fasting C-peptide (ng/mL)	2 h C-peptide (ng/mL)	Fast insulin (IU/mL)	2 h insulin (IU/mL)	IAA	ICA	GAD	Other irAEs
1	37	M	24.44	N	Nasopharyngeal carcinoma	PD-1	Camrelizumab	NA	96	N	NA	8.34	21.13	5.9	20.5	0.71	0.12	3.74	0.95	N	N	Y	Hypothyroidism
2	28	F	19.06	N	Soft tissue sarcoma	PD-1	Pembrolizumab	5	16	Y	0.57	9.36	NA	6.9	26.9	0.01	NA	1.07	NA	N	Y	N	N
3	60	M	NA	19 years T2DM	Renal cell carcinoma	PD-1	Tislelizumab	3	144	N	NA	9.84	NA	NA	NA	NA	NA	NA	NA	N	Y	N	N
4	76	F	23.28	N	Esophageal cancer	PD-1	Tislelizumab	2	3	N	NA	11.15	17.96	7.9	27.00	0.01	NA	9.22	NA	N	N	N	Hypothyroidism
5	59	M	24.22	4 months T2DM	Pancreatic cancer	PD-1	Pembrolizumab	3	12	N	0.71	17.96	27.59	10.4	NA	0.21	0.29	0.20	0.61	N	N	N	NA
6	71	F	19.53	N	Lung cancer	PD-1	NA	5	24	Y	NA	NA	NA	NA	NA	0.01	NA	NA	NA	NA	NA	N	N
7	29	F	25.78	N	Breast cancer	PD-1	Pembrolizumab	1	2	Y	0.59	45.71	NA	6.7	25.30	0.01	NA	0.20	NA	N	N	N	Adrenal insufficiency Hypothyroidism
8	59	F	NA	N	Lung cancer	PD-1	Nivolumab	2	32	Y	0.89	45.60	14.24	9.8	34.30	0.38	0.72	2.91	2.38	N	N	N	N
9	61	M	23.57	N	Gastric cancer	PD-1	Sintilimab	2	11	Y	NA	16.90	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Adrenal insufficiency Hypothyroidism
10	53	M	22.60	20 years T2DM	Lung cancer	PD-1	Toripalimab	3	12	N	NA	10.21	NA	8.4	23.15	0.01	NA	0.20	NA	N	N	N	N
11	69	M	23.90	N	Lung cancer	PD-1	Camrelizumab Tislelizumab	17	108	N	0.53	13.80	17.30	7.5	25.63	0.03	0.03	0.96	0.96	N	N	N	N
12	60	F	24.30	N	Breast cancer	PD-1	Toripalimab	3	6	Y	0.96	14.48	14.48	9.6	23.35	0.42	0.70	4.14	6.79	N	N	N	N
13	70	M	24.10	N	Sigmoid colon cancer	PD-1	Sintilimab	2	4	Y	0.77	15.39	20.04	10.9	28.43	0.01	0.01	1.42	1.58	N	N	N	N
14	61	F	23.14	N	Lymphoma	PD-1	Sintilimab	4	112	Y	0.67	12.60	NA	7.2	NA	0.01	NA	NA	NA	N	N	N	N
15	71	M	22.98	N	Bladder cancer	PD-1	Tislelizumab	7	22	N	0.36	20.76	NA	8.4	20.8	0.01	NA	0,20	NA	NA	N	N	N

Table 2. The characteristics of CGM metrics between ICI-T1D and traditional T1D. Abbreviation: BMI, body mass index; ICI, immune checkpoint inhibitor; ICI-T1D, immune checkpoint inhibitor induced type 1 diabete; DKA, diabetic ketoacidosis; FBG, fast blood glucose; 2 h PG, 2 h postprandial blood glucose; HbA1c, glycated hemoglobin; GA, glycosylated albumin; IAA, insulin antibody; ICA, islet cell antibody; GAD, glutamic acid decarboxylase antibody; M, male; F, female; NA, not availiable; Y, yes/positive; N, no/negative.

undetectable fasting serum C-peptide (< 0.01 ng/ml). The median fasting serum C-peptide was 0.01 ng/ml (IQR, 0.01–0.30).

Diabetes autoantibody status and other irAEs

One out of the fourteen participants tested positive for GAD antibodies, and two out of the thirteen participants tested positive for ICA antibodies. The analysis comparing the time from ICI initiation to T1D onset between the autoantibody-positive group ($N = 3$, 85 ± 64 weeks) and the negative group ($N = 11$, 30 ± 40 weeks) did not show a significant difference ($p = 0.139$).

Glucose pattern and glycemic variability

Compared to age, sex, diabetes duration, and fasting C-peptide level matched traditional T1D, the CGM data in ICI-T1D demonstrated a greater glycemic variability (Fig. 1). Overall CV (36.3 ± 4.8% vs. 28.2 ± 6.5%; $p = 0.009$), CV during the night (37.4 ± 8.4% vs. 23.4 ± 7.3%; $p = 0.001$) and SD during the night (3.3 ± 0.8 mmol/L vs. 2.1 ± 1.1 mmol/L; $p = 0.017$) were significantly higher in ICI-T1D (Fig. 2A and C; Table 3). Other glucose metrics including MG, TIR, TBR, TIR were similar between the two groups (Table 3).

Discussion

To the best of our knowledge, this is by far the largest case series report on ICI-T1D in Chinese. Some of the patients exhibited unique clinical characteristics, such as a prolonged onset of T1D after the initiation of ICI therapy, as well as multiple endocrine organ involvement in addition to T1D. ICI-T1D also present similar glycemic level to classic T1D, while showed more poorly glycemic variability than classic T1D.

Two main subtypes of ICI-T1D have been proposed[20]. The first subtype is fulminant T1D, which is characterized by a sudden onset of T1D accompanied by diabetic ketoacidosis. In this subtype, HbA1c levels are typically normal or near-normal. It is possible that three of our patients, with HbA1c levels below 7.0%, may fall into this subtype. The second proposed subtype is similar to a "decompensated" type 2 diabetes phenotype, which is characterized by elevated HbA1c levels and detectable C-peptide levels. Individuals with this subtype may have or may not have a history of type 2 diabetes. We observed seven patients with HbA1c levels above 7.0% and low C-peptide levels, which aligns with this subgroup.

Based on previous research, the onset of ICI-T1D typically occurred after a period of 12 weeks (with an interquartile range of 6–24 weeks) following ICI treatment[12]. Our study also suggested the similar median time of onset. Interestingly, we identified four patients who displayed significant variations on the timing of

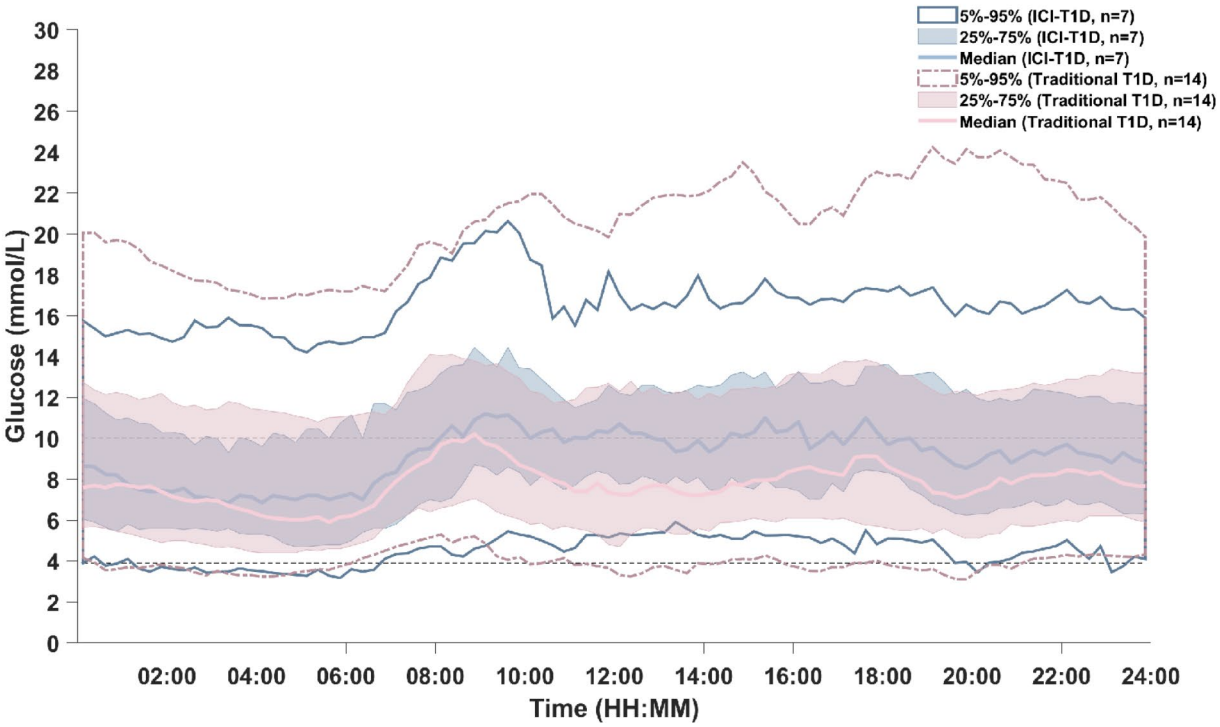

Fig. 1. The CGM profile of ICI-T1D vs. traditional T1D. The solid red line, shaded red area, and dashed red intervals represent the median blood glucose levels, the 25%~75% glucose range, and the 5%~95% glucose range in the traditional T1D group ($N = 14$). The solid blue line, shaded blue area, and solid blue intervals represent the median blood glucose levels, the 25%~75% glucose range, and the 5%~95% glucose range in the ICI-T1D group ($N = 7$). Abbreviation: ICI, immune checkpoint inhibitor; ICI-T1D, immune checkpoint inhibitor induced type 1 diabetes.

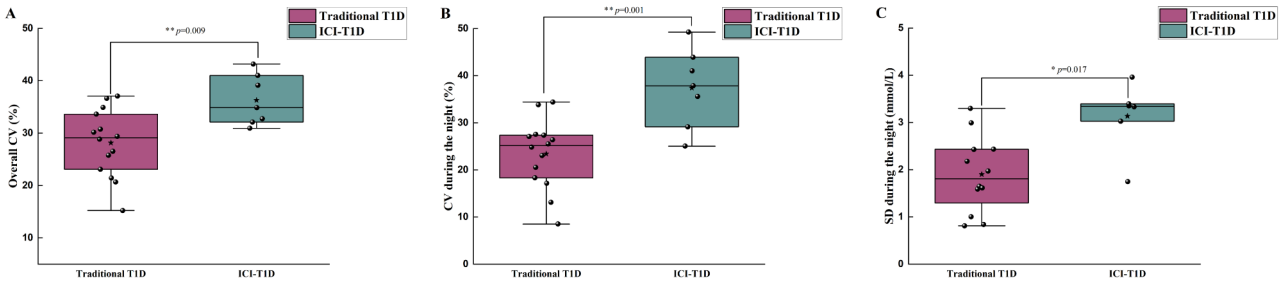

Fig. 2. The glucose metrics derived from CGM in ICI-T1D vs. traditional T1D. Comparison of glycemic variability between patients with ICI-T1D ($N=7$) and traditional T1D ($N=14$). (**A**) Overall CV. (**B**) CV during the night. (**C**) SD during the night. Abbreviation: ICI, immune checkpoint inhibitor; ICI-T1D, immune checkpoint inhibitor induced type 1 diabetes; CV, coefficient of variation; SD, standard deviation.

	Traditional T1D ($N=14$)	ICI-T1D ($N=7$)	*p*-value
Age (years)	48.0 ± 14.9	52.0 ± 20.0	0.667
Sex (male, %)	50.0	50.0	1
Diabetes duration (years)	4.3 ± 6.9	1.0 ± 0.0	0.228
BMI (kg/m^2)	23.4 ± 3.5	23.5 ± 2.1	0.947
Fasting C-peptide (ng/mL)	0.3 ± 0.3	0.2 ± 0.3	0.429
TIR (%)	58.5 ± 35.0	52.7 ± 14.7	0.684
MG (mmol/L)	9.8 ± 4.3	9.8 ± 1.5	0.995
SD (mmol/L)	2.7 ± 1.1	3.5 ± 0.6	0.072
TAR (%)	38.5 ± 37.3	43.9 ± 15.6	0.719
TBR (%)	3.1 ± 4.5	3.4 ± 3.1	0.477
GRI (%)	53.9 ± 46.1	55.9 ± 20.0	0.87
IQR (mmol/L)	3.3 ± 1.4	3.7 ± 0.6	0.179
Overall CV (%)	28.2 ± 6.5	36.3 ± 4.8	0.009
MG during the night (mmol/L)	9.1 ± 4.2	8.8 ± 1.5	0.551
GRI during the night (%)	49.9 ± 46.7	51.2 ± 25.3	0.944
SD during the night (mmol/L)	2.1 ± 1.1	3.3 ± 0.8	0.017
TIR during the night (%)	59.9 ± 39.3	59.0 ± 22.2	0.955
TBR during the night (%)	3.9 ± 6.0	6.2 ± 5.0	0.183
TAR during the night (%)	36.2 ± 42.2	34.8 ± 21.7	0.654
CV during the night (%)	23.4 ± 7.3	37.4 ± 8.4	0.001
IQR during the night (mmol/L)	2.1 ± 0.9	2.2 ± 0.9	0.551

Table 3. The CGM characteristic of ICI-T1D vs. traditional T1D. Abbreviation: T1D, type 1 diabetes mellitus; ICI-T1D, immune checkpoint inhibitors induced type 1 diabetes mellitus; BMI, body mass index; ICI, immune checkpoint inhibitor; ICI-T1D, immune checkpoint inhibitor induced type 1 diabetes; DKA, diabetic ketoacidosis; TIR, time in range; TAR, time above range; TBR, time below range; SD, standard deviation; MG, mean of blood glucose; GRI, glycemic risk index; IQR, inter quartile range; CV, coefficient of variation; Statistical significance was assessed by Mann-Whitney U test, student t-test, or Chi-square test.

T1D onset. One individual developed T1D 144 weeks after receiving tocilizumab treatment, while the other three were diagnosed 112 weeks, 108 weeks and 96 weeks after PD-1 treatment. To the best of our knowledge, these cases represent a highly unusual occurrence based on previous medical reports. These exceptional cases underscore the importance of closely monitoring blood glucose levels and early signs/symptoms of diabetes in patients even years after ICI therapy. Clinicians should remain vigilant regarding the onset of ICI-T1D following a patient's receipt of ICI treatment in order to prevent acute complications and irreversible consequences.

In addition to ICI-T1D, simultaneous involvement of other endocrine organs by irAEs has been observed. The thyroid was the most commonly reported concurrent irAE, with an incidence rate of 20.8%, followed by the pituitary gland at 8.9% and the adrenal gland at 1.6%[14,21]. However, there have been limited reports on irAEs affecting three endocrine organs simultaneously. Our study identified two unusual cases for whom ICI-T1D, adrenal insufficiency, and hypothyroidism occurred concurrently, and both patients were diagnosed with DKA

at onset. These findings serve as a reminder that when patients present with DKA and suspected ICI-T1D, considering further evaluation of other endocrine organs should be emphasized.

Pre-existing T2D has been identified as a risk factor for the development of ICI-T1D. Previous findings have suggested that 5.2% of patients with ICI-T1D had a prior non-T1D diagnosis[14]. Some researchers have hypothesized that ICI treatment may lead to a deterioration in β-cell function, resulting in a transition from T2D to T1D[14,22]. Interestingly, within our cohort, it was observed that two out of the three patients previously diagnosed with T2D had a duration of T2D for 19 and 20 years, respectively. This finding highlights the significance that pre-existing T2D should not be considered an exclusion criterion for the occurrence of newly developed ICI-T1D. In cases where patients experience unexplained hyperglycemia following ICI treatment, consideration should be given to the possibility of ICI-T1D diagnosis. Further research is necessary to investigate the underlying mechanisms and gain a better understanding of the pathogenesis of ICI-T1D.

In our case series, three out of the fourteen tested patients were found to have positive autoantibodies. This prevalence is similar to that reported in other published cohorts, which range from 40 to 50%. Previous studies investigating the association between positive autoantibodies and the time from treatment to the onset of T1D have yielded inconsistent results[13,23], our study indicates that there is no association between diabetes autoantibody positivity and the timing of T1D onset following ICI therapy. Previous studies on classic T1D have revealed a significant lower prevalence of positive diabetes autoantibodies in the Asian population compared to Caucasians[24]. Consequently, it is reasonable to speculate that since ICI serve as the main trigger in ICI-T1D, the autoimmune characteristics of ICI-T1D might exhibit greater similarities across diverse populations than those observed in traditional T1D.

Tsang et al. observed that glucose metrics captured by CGM in ICI-T1D appeared comparable to those in those with traditional T1D[13]. In our study, after accounting for clinical features that influence glucose levels, our findings indicated that while the metrics reflecting glucose levels were similar, glucose variability was significantly greater in ICI-T1D patients, particularly during the night. The underlying reasons for the higher glucose fluctuations in ICI-T1D may include the complex medication regimens associated with malignancy treatment, elevated levels of hormones that increase glucose levels, and challenges in adhering to proper carbohydrate counting. These results emphasize the critical need for diabetes education and proper insulin regimen selection in this patient group.

The study does have certain limitations. Firstly, it is a single-center study includes a limited number of participants. Additionally, the data were collected retrospectively, resulting in missing HbA1c and diabetes autoantibody data for some participants. However, it is worth highlighting that this study represents the largest case series focused on ICI-T1D in the Chinese population. The inclusion of exceptional clinical features, such as an extended duration of T1D onset following ICI therapy and the involvement of multiple endocrine organs, has contributed valuable new perspectives to our understanding of this disease.

In conclusion, this study suggests that ICI-T1D can develop even after a long period of ICI treatment initiation and can lead to irAEs affecting multiple endocrine organs. Furthermore, given the increased glycemic variability observed in ICI-T1D, enhanced diabetes education and personalized insulin regimen adjustments should be emphasized.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

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References

1. Carlino, M. S., Larkin, J. & Long, G. V. Immune checkpoint inhibitors in melanoma. *Lancet (London England)* **398**, 1002–1014. https://doi.org/10.1016/s0140-6736(21)01206-x (2021).
2. Johnson, D. B., Nebhan, C. A., Moslehi, J. J. & Balko, J. M. Immune-checkpoint inhibitors: long-term implications of toxicity. *Nat. Rev. Clin. Oncol.* **19**, 254–267. https://doi.org/10.1038/s41571-022-00600-w (2022).
3. Li, Q., Han, J., Yang, Y. & Chen, Y. PD-1/PD-L1 checkpoint inhibitors in advanced hepatocellular carcinoma immunotherapy. *Front. Immunol.* **13**, 1070961. https://doi.org/10.3389/fimmu.2022.1070961 (2022).
4. Naidoo, J. et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. *Ann. Oncol. Off. J. Eur. Soc. Med. Oncol.* **26**, 2375–2391. https://doi.org/10.1093/annonc/mdv383 (2015).
5. Barroso-Sousa, R. et al. Incidence of endocrine dysfunction following the use of different Immune checkpoint inhibitor regimens: a systematic review and Meta-analysis. *JAMA Oncol.* **4**, 173–182. https://doi.org/10.1001/jamaoncol.2017.3064 (2018).
6. Perdigoto, A. L., Quandt, Z., Anderson, M. & Herold, K. C. Checkpoint inhibitor-induced insulin-dependent diabetes: an emerging syndrome. *Lancet Diabets Endocrionol.* **7**, 421–423. https://doi.org/10.1016/s2213-8587(19)30072-5 (2019).
7. Kotwal, A., Haddox, C., Block, M. & Kudva, Y. C. Immune checkpoint inhibitors: an emerging cause of insulin-dependent diabetes. *BMJ open. Diabetes Res. care.* **7**, e000591. https://doi.org/10.1136/bmjdrc-2018-000591 (2019).
8. Shimada, K. et al. Real-world evidence of the incidence of and risk factors for type 1 diabetes Mellitus and Hypothyroidism as Immune-related adverse events associated with programmed cell Death-1 inhibitors. *Endocr. Pract. Offi. J. Am. Coll. Endocrinol. Am. Assoc. Clin. Endocrinol.* **27**, 586–593. https://doi.org/10.1016/j.eprac.2020.12.009 (2021).
9. Tittel, S. R. et al. Immune-checkpoint inhibitor-associated diabetes compared to other diabetes types - a prospective, matched control study. *J. Diabetes.* **13**, 1007–1014. https://doi.org/10.1111/1753-0407.13215 (2021).
10. Liu, Y. C., Liu, H., Zhao, S. L., Chen, K. & Jin, P. Clinical and HLA genotype analysis of immune checkpoint inhibitor-associated diabetes mellitus: a single-center case series from China. *Front. Immunol.* **14**, 1164120. https://doi.org/10.3389/fimmu.2023.1164120 (2023).
11. Marsiglio, J. et al. A single center case series of immune checkpoint inhibitor-induced type 1 diabetes mellitus, patterns of disease onset and long-term clinical outcome. *Front. Immunol.* **14** https://doi.org/10.3389/fimmu.2023.1229823 (2023).

12. Lo Preiato, V. et al. Diabetes mellitus induced by immune checkpoint inhibitors: type 1 diabetes variant or new clinical entity? Review of the literature. *Reviews Endocr. Metab. Disord.* **22**, 337–349. https://doi.org/10.1007/s11154-020-09618-w (2021).
13. Tsang, V. H. M. et al. Checkpoint inhibitor-associated autoimmune diabetes is distinct from type 1 diabetes. *J. Clin. Endocrinol. Metab.* **104**, 5499–5506. https://doi.org/10.1210/jc.2019-00423 (2019).
14. Wu, L. et al. Risk factors and characteristics of checkpoint inhibitor-associated autoimmune diabetes Mellitus (CIADM): a systematic review and delineation from type 1 diabetes. *Diabetes Care* **46**, 1292–1299. https://doi.org/10.2337/dc22-2202 (2023).
15. Iesaka, H. et al. Fulminant ACTH decrease following diabetic ketoacidosis induced by immune checkpoint inhibitor combination therapy with nivolumab and ipilimumab: a case report. *Medicine* **102**, e36664. https://doi.org/10.1097/md.0000000000036664 (2023).
16. Li, S., Zhang, Y., Sun, Z., Hu, J. & Fang, C. Anti-PD-1 pembrolizumab induced autoimmune diabetes in Chinese patient: a case report. *Medicine* **97**, e12907. https://doi.org/10.1097/md.0000000000012907 (2018).
17. Zhong, Z., Wang, Z., Li, Y. & Zhong, Y. Sintilimab treatment for ureteral carcinoma following bladder cancer leads to leukopenia: a case report. *Transl. Androl. Urol.* **11**, 277–284. https://doi.org/10.21037/tau-21-1146 (2022).
18. Piona, C. et al. Glycemia risk index as a novel metric to evaluate the safety of glycemic control in children and adolescents with type 1 diabetes: an observational, multicenter, real-life cohort study. *Diabetes. Technol. Ther.* **25**, 507–512. https://doi.org/10.1089/dia.2023.0040 (2023).
19. Battelino, T. et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabets Endocrionol.* **11**, 42–57. https://doi.org/10.1016/s2213-8587(22)00319-9 (2023).
20. Marchand, L. et al. The multifaceted nature of diabetes mellitus induced by checkpoint inhibitors. *Acta Diabetol.* **56**, 1239–1245. https://doi.org/10.1007/s00592-019-01402-w (2019).
21. Byun, D. J. et al. Immune Checkpoint inhibitor-Associated diabetes: a single-Institution experience. *Diabetes care*. **43**, 3106–3109. https://doi.org/10.2337/dc20-0609 (2020).
22. Chen, X. et al. Immune Checkpoint inhibitors and risk of type 1 diabetes. *Diabetes Care* **45**, 1170–1176. https://doi.org/10.2337/dc21-2213 (2022).
23. Qiu, J. et al. Characterization of immune checkpoint inhibitor-associated fulminant type 1 diabetes associated with autoantibody status and ethnic origin. *Front. Immunol.* **13**. https://doi.org/10.3389/fimmu.2022.968798 (2022).
24. Guo, Y. et al. Caucasian and Asian difference in role of type 1 diabetes on large-for-gestational-age neonates. *BMJ Open. Diabetes Res. Care* **8**. https://doi.org/10.1136/bmjdrc-2020-001746 (2020).

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Author contributions
Wei Liu designed the study. Chunmei Li and Wei Liu analyzed the data and drafted the article. All authors provided support for the analysis and interpretation of results, critically revised the article, and approved the final article.

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Declarations

Competing interests
The authors declare no competing interests.

Ethic statements
The study has been reviewed by Peking University People's Hospital ethics committee, and have been performed in accordance with the Declaration of Helsinki. All participants have been given their informed consent prior to their inclusion in the study.

Additional information
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