Association between time in range and cancer mortality among patients with type 2 diabetes: a prospective cohort study

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Abstract

Background: Little was known about the association among time in range (TIR), time above range (TAR), time below range (TBR), and cancer mortality among patients with type 2 diabetes. We aimed to investigate the association among TIR, TAR, TBR, and the risk of cancer mortality among patients with type 2 diabetes.

Methods: A total of 6225 patients with type 2 diabetes were prospectively recruited in Shanghai, China. TIR was measured with continuous glucose monitoring at baseline and was defined as the average percentage of time in the target glucose range during a 24 h period. Cox proportion hazard regression analysis was used to determine the association between TIR and the risk of cancer mortality.

Results: During a mean follow-up of 7.10 years, we confirmed 237 death events related to cancer. The multivariable-adjusted hazard ratio (HR) for cancer mortality was 1.32 (95% confidence interval [CI]: 1.01–1.75) in patients with TIR ≤70% compared with those with TIR >70%. When TIR was considered as a continuous variable, the multivariable-adjusted HR for cancer mortality associated with each 10% decrease in TIR was 1.07 (95% CI: 1.02–1.14). In the site-specific analysis, a significant association between TIR as a continuous variable and the risk of hepatocellular cancer was found (HR: 1.24; 95% CI: 1.09–1.41). However, no relationship between hemoglobin A1c and cancer mortality was observed (HR: 1.04; 95% CI: 0.97–1.10).

Conclusions: The present study found an inverse association of TIR with the risk of cancer mortality among patients with type 2 diabetes. New evidence of TIR was added into the clinical practice that TIR may be an optimal target of glycemic control among patients with type 2 diabetes.

Keywords: Time in range; HbA1c; Type 2 diabetes; Cancer mortality; Cohort study; Hepatocellular cancer

Introduction

Robust evidence has shown that there is a close relationship between diabetes and cancer.[1] These two diseases share many risk factors such as obesity, multiple metabolic disorders, physical inactivity, unhealthy diet, alcohol consumption, and smoking.[1] A recent meta-analysis showed that diabetes was associated with an increased risk of cancer mortality by nearly 25%.[2] In addition, hemoglobin A1c (HbA1c), a marker for mean glycemic levels, was also found to be associated with incident cancer or cancer-related mortality among a mixed population with and without diabetes.[3] However, one study reported among patients with diabetes that no associations between HbA1c and risk of all cancers or site-specific cancers were observed, after adjusting for insulin treatment, duration of diabetes, and body mass index (BMI).[4] Another study in China also supported the null association between HbA1c and overall cancer risks.[5] Although HbA1c is one certain metric for hyperglycemia,

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it provides no information on glycemic variability as well as the daily pattern of glycemic levels. With the development of advanced technologies in the field of glucose monitoring, percentage time within a certain glycemic threshold has become a novel discovered risk factor associated with diabetic complications.[6] Percentage time within a certain glycemic threshold can reflect exposure to both hyperglycemia and hypoglycemia based on continuous glucose monitoring (CGM).[7] Previously, we have reported several times that time in range (TIR) was associated with diabetic complications such as retinopathy,[8] carotid atherosclerosis,[9] and even all-cause and cardiovascular disease (CVD) mortality[10] among patients with type 2 diabetes. Very little is known about the association of TIR with the risks of cancer mortality and site-specific cancer mortality among patients with diabetes. We have conducted a prospective cohort with available CGM data to investigate the association of TIR with the risk of total and site-specific cancer mortality among patients with type 2 diabetes.

Methods

Ethical approval

The study protocol was approved by the Ethics Committees of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Written informed consent was obtained from each participant.

Study population

The study design of the INDices of Continuous Glucose Monitoring and Adverse Outcomes of Diabetes study has been described previously.[10] Inpatients who were admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital during January 2005 to December 2015 were prospectively recruited. Eligible patients should be: (1) age ≥18 years with the diagnosis of type 2 diabetes; (2) a stable glucose-lowering regimen for previous 3 months; and (3) with available data on CGM. We excluded those with other types of diabetes (eg, gestational diabetes or type 1 diabetes), and those who had experienced severe and recurrent hypoglycemic events within the previous 3 months.

Calculation of TIR as well as time above range (TAR) and time below range (TBR)

A retrospective CGM system (CGMS GOLD; Medtronic Inc., Northridge, CA, USA) was used for glucose monitoring, as previously described.[8] In brief, the sensor of the CGM system was inserted on day 0 and removed after 72 h, generating a daily record of 288 continuous sensor values. At least four capillary blood glucose readings per day were measured by a SureStep blood glucose meter (LifeScan, Milpitas, CA, USA) to calibrate the CGM system. TIR was defined as the average percentage of time in the target glucose range of 70 to 180 mg/dL (3.9–10.0 mmol/L) during a 24 h period. TAR was defined as the average percentage of time above the target glucose range of 180 mg/dL (10.0 mmol/L). TBR was defined as the average percentage of time below the target glucose range of 70 mg/dL (3.9 mmol/L).

Baseline characteristics

Age, sex, smoking status, and health condition (history of cancer and CVD) were collected at the baseline interview by self-report. Each patient underwent a physical examination that included measurements of height, weight, and blood pressure. BMI was calculated as weight (kg) divided by squared height (m). Blood pressure was measured three times using a standard mercury sphygmomanometer and the measurements were averaged. Biochemical measurements, including triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and HbA1c were assayed as previously described.[8]

Outcomes

Causes and time of death were obtained from the database of the Shanghai Municipal Center for Disease Control and Prevention and were linked with study data through the personal identification number. The death causes were identified with the use of the codes in the International Classification of Disease 10th version (ICD-10). ICD-10 codes C00 through C99 were classified as death of cancer. The rate of missing death events in Shanghai was proven to be 0.7‰. We used chart review to evaluate the confirmation of death (COD) via the Shanghai adaptation of the Medical Record Audit Form. Trained physicians have reviewed the medical records of a death event and reassigned the COD, which provided a gold standard method to measure the quality of routine COD data. The death events identified by Shanghai Civil Registration and Vital Statistics routine monitoring were thus reported with high sensitivity and specificity of 85.7% and 90.0%, respectively. In the current study, the primary outcome was cancer mortality and the secondary outcome was site-specific cancer mortality. All patients were followed up until a death event occurred or until December 31, 2018, whichever occurred first.

Statistical analysis

Student's *t* test was used for continuous variables with normal distributions for comparisons between groups. For continuous variables with skewed distributions, Mann-Whitney *U* tests were conducted. The Chi-square test was used to compare the categorical data. Cox proportional hazards regression was used to estimate hazard ratios (HRs) for cancer mortality according to TIR, TAR, TBR, and HbA1c as either categorical groups or continuous variables (per 10% decrease of TIR, TAR, and TBR). The significance of the trend across categories of TIR was tested in the same models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models. In general, all proportionality assumptions were appropriate. A backward stepwise selection procedure of candidate covariates was conducted. All analyses were conducted after adjusting first for age, and sex, and then for systolic blood pressure (SBP), LDL-C, use

of thiazolidinediones (TZD), antiplatelet medication and smoking status, and baseline values of HbA1c. Subgroup analyses were performed in groups of patients with different ages, sexes, BMI, smoking status, baseline ALT levels, baseline HBsAg, baseline HbA1c levels, and the proportion of patients receiving and not receiving glucose-lowering, lipid-lowering, and antihypertensive medications. We used the restricted cubic spline nested in Cox models to test whether there was a dose-response or non-linear association of TIR or HbA1c as a continuous variable with the risk of cancer mortality. Sensitivity analyses were performed excluding participants with a history of self-reported cancer. A P value < 0.050 (two-tailed) was considered statistically significant. Statistical analyses were performed using SAS for Windows, version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 6225 patients with type 2 diabetes were enrolled in the final analysis with a mean age of 61.7 ± 11.9 years. The baseline characteristics are listed in Table 1. Compared to patients with TIR ≤70%, those with TIR >70% were younger and had a shorter duration of diabetes. The metabolic profiles including blood pressure, lipids, and glucose were all better in patients with TIR >70% than

Table 1: Baseline characteristics of the study population.

Items	TIR ≤70%			TIR >70%		
	With prior history of cancer	Without prior history of cancer	*P* value	With prior history of cancer	Without prior history of cancer	*P* value
Participants (*n*)	151	3148		134	2792	
Age (years)	68.4 ± 9.7	62.3 ± 11.9	<0.001	64.9 ± 9.6	60.5 ± 11.9	<0.001
Male (%)	49.7	53.6	0.394	44.0	56.7	0.005
BMI (kg/m^2)	24.8 ± 3.3	24.7 ± 3.5	0.583	25.4 ± 3.2	25.1 ± 3.5	0.428
Duration (years)	11.55 ± 8.14	10.53 ± 7.53	0.105	9.79 ± 7.45	8.55 ± 7.01	0.046
Blood pressure (mmHg)						
Systolic	136 ± 21	134 ± 17	0.188	133 ± 18	132 ± 16	0.408
Diastolic	80 ± 10	80 ± 10	0.599	80 ± 10	80 ± 9	0.719
HbA1c (%)	9.6 ± 2.2	9.8 ± 2.1	0.351	7.6 ± 1.8	7.9 ± 1.9	0.051
HbA1c (mmol/mol)	81.4 ± 23.6	83.2 ± 22.5	0.351	59.5 ± 20.0	63.2 ± 21.1	0.051
TC (mmol/L)	4.82 ± 1.21	4.86 ± 1.31	0.681	4.64 ± 0.94	4.61 ± 1.03	0.787
LDL-C (mmol/L)	3.02 ± 0.99	3.01 ± 1.00	0.937	2.87 ± 0.81	2.90 ± 0.89	0.668
HDL-C (mmol/L)	1.12 ± 0.32	1.12 ± 0.32	0.981	1.14 ± 0.30	1.12 ± 0.30	0.481
TG (mmol/L)	1.78 ± 1.23	1.90 ± 2.13	0.491	1.67 ± 1.18	1.67 ± 1.37	0.983
ALT (U/L)	25.3 ± 25.4	25.5 ± 29.3	0.923	22.4 ± 16.4	24.1 ± 19.3	0.299
Hepatitis B virus surface antigen (%)						
Negative	76.2	80.7	0.206	82.1	75.1	0.085
Positive	2.0	0.8	0.295	0	0.5	0.899
No information	21.9	18.5	0.352	17.9	24.4	0.107
Current smoker (%)	15.9	24.4	0.022	9.0	24.2	<0.001
Use of medications (%)						
Lipid-lowering	40.4	40.4	0.996	44	36.0	0.060
Antihypertensive	58.9	54.6	0.340	61.2	53.4	0.093
Glucose-lowering						
Metformin	20.5	25.5	0.201	29.1	36.0	0.123
Insulin	85.4	81.7	0.296	53	49.8	0.531
Sulfonylurea	19.2	19.8	0.935	24.6	28.0	0.451
DPP4 inhibitors	0	0.8	0.536	0	0.3	0.535
α-Glucosidase inhibitors	47.0	45.5	0.781	43.3	44.1	0.918
GLP-1 receptor agonists	0	0.2	0.591	0	0.2	0.624
Thiazolidinediones	3.3	6	0.226	0.7	5.8	0.021
Antiplatelet or anticoagulant	42.4	49.1	0.126	44	45.3	0.834
CGM metrics (%)						
TIR	45.5 ± 18.4	46.1 ± 17.9	0.652	84.7 ± 8.6	85.4 ± 8.7	0.368
TAR	52.7 ± 20.3	52.6 ± 19.4	0.943	14.1 ± 10.1	13.0 ± 9.1	0.197
TBR	1.1 ± 2.8	1.4 ± 4.2	0.319	1.5 ± 2.8	1.8 ± 4.0	0.482

Data are expressed as mean ± standard deviation, *n* or %. ALT: Alanine aminotransferase; BMI: Body mass index; CGM: Continuous glucose monitoring; DPP4: Dipeptidyl peptidase 4; GLP-1: Glucagon-like peptide-1; HbA1c: Hemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; TAR: Time above range; TBR: Time below range; TIR: Time in range; TC: Total cholesterol; TG: Triglycerides.

those with TIR ≤70% except for HDL cholesterol. The use of insulin, lipid-lowering drugs, and antiplatelet or anticoagulant was less frequent in patients with TIR >70% compared with those with TIR ≤70%.

TIR and cancer mortality

During a mean follow-up of 7.10 ± 2.82 years, we confirmed 237 death events because of cancer. The multivariable-adjusted (age, sex, SBP, LDL-C, use of TZD, antiplatelet medication, smoking status, and baseline HbA1c) HR for cancer mortality was 1.32 (95% confidence interval [CI]: 1.01–1.75) in patients with TIR ≤70% compared with those with TIR >70% [Table 2]. When TIR was considered as a continuous variable, the multivariable-adjusted HR for cancer mortality associated with each 10% decrease in TIR was 1.07 (95% CI: 1.02–1.14) [Table 2 and Figure 1A].

Sensitivity and subgroup analysis

In the sensitivity analysis, we excluded patients with a prior history of malignancy ($N = 285$). The multivariable-adjusted HR was 1.25 (95% CI: 0.92–1.70) in patients with TIR ≤70% compared with those with TIR >70% [Table 2]. When TIR was considered as a continuous variable, the multivariable-adjusted HR for cancer mortality associated with each 10% decrease in TIR was 1.08 (95% CI: 1.01–1.15). Similar results were found among patients with different ages, smoking status, and different categories of lipid-lowering drugs [Table 3]. To identify the

Table 2: Association between TIR and cancer mortality among patients with type 2 diabetes.

Items	TIR>70%	TIR≤70%	Each 10% decrease in TIR
Major analysis			
No. of patients	2926	3299	
No. of deaths	92	145	
Person-years	21,732	22,475	
HR-Model 1 (95% CI)	1.00	1.44 (1.11–1.88)	1.09 (1.04–1.15)
HR-Model 2 (95% CI)	1.00	1.43 (1.10–1.86)	1.09 (1.03–1.14)
HR-Model 3 (95% CI)	1.00	1.32 (1.01–1.75)	1.07 (1.02–1.14)
Sensitivity analysis			
No. of patients	2835	3105	
No. of deaths	80	118	
Person-years	20,912	21,567	
HR-Model 1 (95% CI)	1.00	1.37 (1.03–1.83)	1.11 (1.06–1.17)
HR-Model 2 (95% CI)	1.00	1.36 (1.02–1.81)	1.09 (1.03–1.15)
HR-Model 3 (95% CI)	1.00	1.25 (0.92–1.70)	1.08 (1.01–1.15)

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, SBP, LDL-C, use of TZD, antiplatelet medication, and smoking status. Model 3 adjusted for variables in model 2 plus baseline HbA1c. CI: Confidence interval; HbA1c: Hemoglobin A1c; LDL-C: Low-density lipoprotein cholesterol; TIR: Time in range.

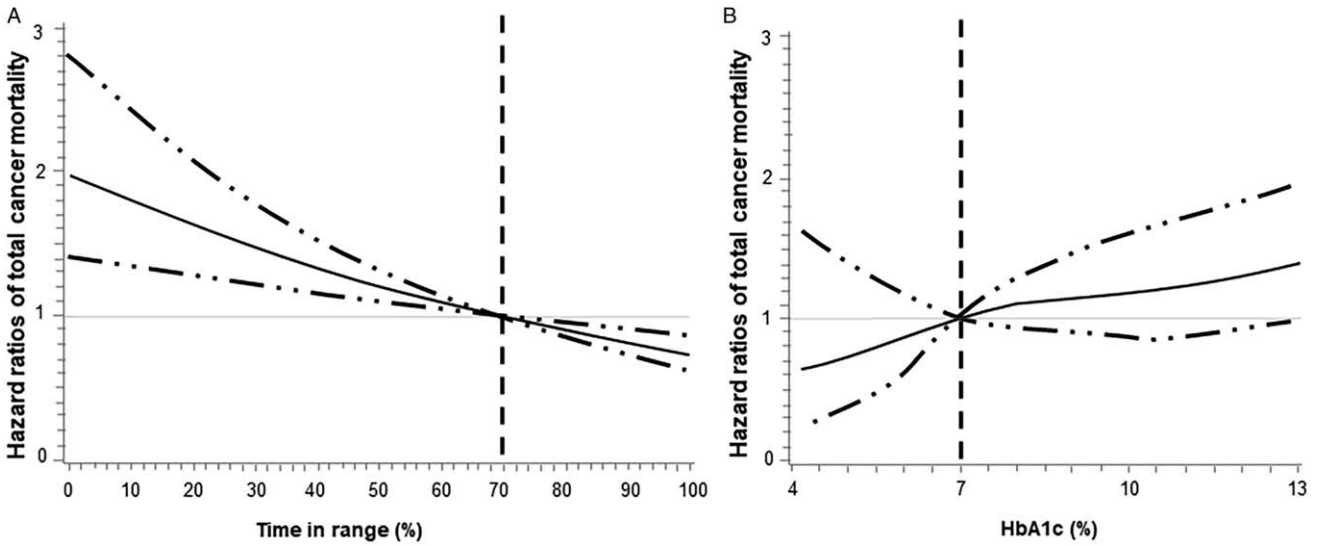

Figure 1: Hazard ratios of cancer mortality by TIR (A) and HbA1c (B) as continuous variables. Adjustments were made for age, sex, SBP, LDL-C, use of TZD, antiplatelet medication, and smoking status. For analysis of TIR, baseline HbA1c level was further adjusted in the model. HbA1c: hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; TIR: Time in range.

Table 3: Association between TIR and cancer mortality among patients with type 2 diabetes in different subgroups.

Items	No. of patients	No. of cases	Person-years	HR (95% CI)		
				TIR>70%	TIR≤70%	Each 10% decrease in TIR
Age						
<65 years	2348	148	16,050	1.00	1.60 (1.05–2.45)	1.15 (1.06–1.24)
≥65 years	3877	89	28,157	1.00	1.37 (0.98–19.20)	1.07 (1.01–1.15)
Sex						
Men	3404	162	23,917	1.00	1.41 (1.03–1.93)	1.11 (1.05–1.19)
Women	2821	75	20,290	1.00	1.37 (0.84–2.22)	1.04 (0.95–1.15)
BMI						
<24.0 kg/m^2	2644	103	18,998	1.00	1.83 (1.21–2.78)	1.19 (1.09–1.28)
24.0–27.9 kg/m^2	2509	89	17,850	1.00	1.33 (0.87–2.05)	1.05 (0.96–1.14)
≥28.0 kg/m^2	1072	45	7359	1.00	0.87 (0.47–1.60)	0.99 (0.88–1.12)
Current smoker						
Yes	1478	63	10,266	1.00	1.61 (0.96–2.71)	1.07 (1.01–1.14)
No	4747	174	33,941	1.00	1.27 (0.94–1.73)	1.12 (1.01–1.24)
Baseline ALT levels						
<65 U/L	5950	224	42,154	1.00	1.33 (1.00–1.72)	1.07 (1.02–1.14)
≥65 U/L	275	13	2052	1.00	1.20 (0.34–4.26)	1.19 (0.91–1.55)
Baseline HBsAg						
Negative	4863	142	32,244	1.00	1.17 (1.01–1.34)	1.08 (1.03–1.13)
Positive	42	7	204	1.00	8.13 (0.50–133.00)	3.47 (0.98–12.00)
No information	1320	88	11,759	1.00	1.61 (1.01–2.57)	1.10 (1.00–1.20)
Baseline HbA1c						
<7%	1521	42	10,979	1.00	2.55 (1.30–5.00)	1.29 (1.11–1.50)
≥7%	4704	195	33,228	1.00	1.09 (0.81–1.48)	1.04 (0.98–1.11)
Glucose lowering drugs						
Insulin	4164	185	29,388	1.00	1.17 (0.85–1.59)	1.05 (1.01–1.12)
Others	2061	52	14,819	1.00	1.32 (0.73–2.37)	1.08 (0.95–1.22)
Antihypertensive drugs						
Yes	2755	127	19,102	1.00	1.17 (0.82–1.67)	1.06 (0.99–1.14)
No	3470	110	25,105	1.00	1.65 (1.12–2.45)	1.12 (1.03–1.20)
Lipid lowering drugs						
Yes	2397	72	29,483	1.00	1.35 (0.84–2.19)	1.11 (1.01–1.22)
No	3828	165	14,724	1.00	1.39 (1.01–1.90)	1.08 (1.01–1.15)
Antiplatelet drugs						
Yes	2935	113	20,335	1.00	1.12 (0.77–1.64)	1.01 (0.94–1.10)
No	3290	124	23,872	1.00	1.66 (1.15–2.41)	1.15 (1.07–1.23)

Adjusted for age, sex, SBP, LDL-C, use of TZD, antiplatelet medication, smoking status, and baseline HbA1c other than the variable for stratification. ALT: Alanine aminotransferase; BMI: Body mass index; CI: Confidence interval; HbA1c: Hemoglobin A1c; HBsAg: Hepatitis B virus surface antigen; HR: Hazard ratio; LDL-C: Low-density lipoprotein cholesterol; TIR: Time in range.

risks of cancer mortality within 3, 5, and 10 years at follow-ups, another subgroup analysis of TIR was performed [Supplementary Table 1, http://links.lww.com/CM9/A751]. TIR was found not associated with the risk of cancer mortality with 3 years at follow-up after multivariable adjustments (HR: 1.47; 95% CI: 0.90–2.38). In addition, patients with TIR ≤70% showed a higher risk of cancer mortality within 5 years at follow-up (HR: 1.60; 95% CI: 1.09–2.36), while the HR reduced to 1.32 (95% CI: 1.01–1.73) within 10 years at follow-up.

TIR and site-specific cancer mortality

The multivariable-adjusted HRs for site-specific cancer mortality by TIR categories were presented in Supplementary Table 2, http://links.lww.com/CM9/A751. Site-specific cancer mortality included death because of endometrial or breast cancer, prostate cancer, bladder cancer, gastric cancer, colorectal cancer, hepatocellular cancer, lung cancer, and pancreas cancer. A significant association between TIR as a continuous variable and the risk of hepatocellular cancer was observed (HR: 1.24; 95% CI: 1.09–1.41).

When HbA1c was considered as a continuous variable by using restricted cubic splines, no significant association was observed between HbA1c and the risk of cancer mortality (HR: 1.04; 95% CI: 0.97–1.10) [Figure 1B].

TAR, TBR, and cancer mortality

Since TAR and TBR reflect different clinical meanings, further additional analysis on the association between TAR and TBR and cancer mortality was performed [Supplementary Tables 3, http://links.lww.com/CM9/A751 and 4, http://

links.lww.com/CM9/A751]. There was a significant association between TAR and cancer mortality when multivariable-adjusted Cox models were applied both in the major analysis (HR: 1.08; 95% CI: 1.02–1.14, TAR as a continuous variable) and sensitivity analysis (HR: 1.08; 95% CI: 1.01–1.14, TAR as a continuous variable). However, no association between TBR and cancer mortality was detected.

Discussion

In this prospective cohort study, we demonstrated an inverse association between TIR assessed by CGM and the risk of total and hepatocellular cancer mortality among patients with type 2 diabetes. Patients with TIR $\leq$70% showed the highest risk of cancer mortality within 5 years at follow-up. These findings have added new insights into the clinical application of TIR as an optimal marker for diabetic comorbidities.

The association between diabetes and the risks of cancer and cancer-related mortality is still of great interest worldwide. Previous evidence has supported a strong association between diabetes and cancer risk.[1,11] However, there are conflicting reports in terms of the association of glycemic control with cancer-related mortality among patients with type 2 diabetes. Most of the previous studies suggested a significantly positive association between HbA1c and the risk of cancer mortality among the general population.[12-14] The Atherosclerosis in Communities Study observed a U-shaped relationship between HbA1c and cancer incidence and mortality among the general population.[15] With the development of advanced technologies in diabetes, TIR has become a robust marker associated with multiple diabetic complications.[16] Here, we are not surprised to find that TIR is moderately associated with cancer-related mortality especially mortality due to hepatocellular cancer. However, non-significant association between HbA1c and cancer mortality was observed, although TIR was well correlated with HbA1c. We failed to observe a significant association between HbA1c and cancer mortality, indicating that HbA1c was a good marker for glycemic control but not an optimal marker for diabetic comorbidities such as cancer. In addition, TIR is significantly associated with glycemic variability, which is associated with hypoglycemia events. Hypoglycemia events have been proved to be a key factor in relation to mortality in clinical trials among patients with diabetes.[17,18] Our findings were consistent with one previous study[4] and suggest that TIR seems to be superior to HbA1c in relation to the prediction of comorbidities among patients with diabetes. More studies are needed to confirm our findings.

In a pooled analysis in 2017, diabetes was associated with a 26% increased risk of death from any cancer.[2] One Chinese study indicated that diabetes was positively associated with the risks of specific-type cancers of colorectal, liver, bile duct, gallbladder, pancreas, breast, endometrium, ovary, prostate, kidney, and thyroid, as well as lymphoma among patients with type 2 diabetes.[19] The large sample size of this Chinese study allowed sufficient power to detect the association between diabetes and site-specific cancer mortality risk. Because of the limited death events of cancer, we only found that TIR was well associated with hepatocellular cancer, which was consistent with the findings above. By using TIR that is generated from CGM, we can assess exposures to hyperglycemia, hypoglycemia, and glycemic variability beyond a single measurement of HbA1c. HbA1c is a marker of mean glucose levels, but may not be an optimal marker of hyperglycemia. For instance, in certain patients with both hypoglycemia and hyperglycemia, HbA1c can be in the falsely "normal" range and be misleading.[6] This phenomenon is most often observed in patients with a high degree of glycemic variability. Therefore, TIR is a useful metric of glycemic control and glucose patterns. More evidence linking TIR with comorbidities among patients with diabetes are encouraged. For additional discussion on TIR, further analysis of the association among TAR, TBR, and cancer mortality was performed as was shown in the Supplementary Materials, http://links.lww.com/CM9/A751. We demonstrated that hyperglycemia may contribute to cancer mortality among patients with type 2 diabetes. However, no association between hypoglycemia, presented by TBR, and cancer mortality was observed. Most of the evidence supported the association between hypoglycemia or severe hypoglycemia and cardiovascular events and even CVD mortality.[20] Whether there was a link between hypoglycemia and cancer morality or not remained uncertain.

The potential mechanism underlying the association between hyperglycemia and cancer mortality is limited. Hyperglycemic conditions may have an adverse effect on the DNA 5-hydroxymethylome. A novel "phospho-switch" regulates tumor suppressor [ten-eleven translocation protein 2 (TET2)] stability and a regulatory pathway that links glucose and AMP-activated kinase to TET2 and 5-hydroxymethylcytosine, which connects diabetes to cancer.[21] In hyperglycemic environment, tumor cells can promote the progress of cancer mechanism by enhancing glucose intake, up-regulating glycolysis, and controlling cell cycle imbalance. The indirect effects of hyperinsulinemia, insulin resistance, chronic inflammation, and hormones imbalance have also been suggested as contributing factors.[22] Genetically predicted high insulin levels and obesity, but not diabetes, were associated with breast, endometrial, and pancreatic cancer incidence.[23,24] Most of the cancer cells express insulin and insulin-like growth factor (IGF) receptors. Therefore, insulin or IGF can stimulate the proliferation or metastasis of cancer cells.[25] In addition to the direct effect of insulin or IGF on cancer cells, other pathway such as inflammatory cytokines may also result in the progression of cancer. More researches are encouraged to further clarify the interaction between hyperglycemia or other common risk factors and cancer.[26]

The major strength of our study is the large sample size of patients with type 2 diabetes with available CGM data. The duration of follow-up is also long. There are several limitations that should be clarified. First, socio-economic or lifestyle factors were not available in the present study. Whether these factors were associated with cancer mortality or not could not be determined. Second, TIR was only measured for 72 h at the beginning of the study. Whether multiple and longer measurements of TIR and

further adjustments on medication could contribute to the outcomes or not was not sure. Finally, our study subjects were all inpatients, which may introduce selection bias. In addition, all patients were diagnosed as type 2 diabetes in the present study. Whether there is a significant association among patients with type 1 diabetes is unknown.

In conclusion, an independent and inverse association between TIR, but not HbA1c, and the risk of cancer mortality was observed among patients with type 2 diabetes. New evidence of TIR was added into the clinical practice that TIR may be an optimal target of glycemic control among patients with type 2 diabetes.

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Conflicts of interest

None.

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