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Glycemic control was associated with nonprostate cancer and overall mortalities in diabetic patients with prostate cancer

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Abstract

Background: Diabetes mellitus (DM) can worsen the prognosis or survival in prostate cancer (PC) patients. We investigated whether glycemic control impacts mortality in PC patients with existing diabetes.

Methods: All PC patients with or without preexisting DM were enrolled from 2006 to 2017. Mean hemoglobin A1c (HbA1c) values (<7%, 7%-9%, ≥9%) were used to represent glycemic control. Major outcomes included all-cause, PC-specific, and non-PC mortalities. Statistical analyses were performed using Cox regression models with adjusted mean HbA1c and other related confounders.

Results: A total of 831 PC patients were enrolled (non-DM group, n = 690; DM group with a record of mean HbA1c values, n = 141). Results showed that the DM group with mean HbA1c level ≥ 9% (n = 14) had significantly increased risk for all-cause and non-PC mortality (hazard ratio [HR], 3.09; 95% CIs, 1.15-8.32; p=0.025 and HR, 5.49; 95% CIs, 1.66-18.16; p = 0.005, respectively), but not for PC-specific mortality (HR, 1.03; 95% CIs, 0.13-8.44; p = 0.975), compared with the non-DM group.

Conclusion: Our findings indicate that PC patients with DM who had a mean HbA1c level ≥ 9% had higher risks of all-cause and non-PC mortality compared with non-DM subjects. Further large and long-term studies are needed to verify the effect of glycemic control in PC patients with DM.

Keywords: Diabetes mellitus; Glycemic control; Mortality; Prostate cancer

1. INTRODUCTION

With the global prevalence of cancer and diabetes mellitus (DM) rising rapidly, it has been found that DM is associated with cancer prognosis and mortalities.[1,2] Studies have demonstrated that DM increased the risk of developing various cancers, including liver, pancreatic, breast, and colon cancers, with the exception of prostate cancer (PC), while a Japanese study showed similar results and found risk of PC was increased, suggesting that race might play a role.[3–6] A meta-analysis study demonstrated that patients with cancer and preexisting DM would have an increased risk of all-cause mortality.[7] DM or prediabetes status has been shown to increase the risk of death from several cancers.[8] Good glycemic control is extremely important consideration in the treatment of cancer patients with DM as concurrent chemotherapy or corticosteroid use affects serum glucose level, which increases the risks of infection, hospitalization, and even mortality.[9] Accordingly, good glycemic control in cancer patients with DM enhances survival.

PC is the second most common malignancy diagnosed in men next to lung cancer, and the estimated incidence and mortality are growing.[10,11] The incidence of PC in patients with DM is also on the rise in Taiwan.[12] The association between PC and DM, regarding mortality and progression, shows conflicting results. Some studies suggested that DM patients might have a reduced risk of PC development.[13,14] Research has shown that in DM patients with PC, further cancer progression or survival might be affected.[15–17] Other studies have suggested that DM may increase all-cause mortality in patients with PC and DM, while the results of PC-specific mortality were controversial.[18–20] None of the aforementioned studies adjusted for the potential confounding effect of glycemic status in the analyses. Moreover, some cancer treatments, such as hormone-based therapies, might affect glycemic control.[21] The androgen-deprivation treatment

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(ADT) was associated with elevation of hemoglobin A1c (HbA1c) level in PC patients with DM, compared with those without ADT.[22] It is necessary to maintain good glycemic control in order to prevent microvascular or macrovascular complications in DM patients.[23] Thus, glycemic control should be considered an important factor in the evaluation of mortalities in PC patients with DM, especially changes in glycemic levels.

Previous studies have indicated that age, gender, obesity, alcohol, smoking history, and medication (eg, metformin) might be associated with mortality rates in cancer patients with DM.[1,24,25] Obesity appears to be associated with increased PC-specific mortality.[26–28] The severity of PC, represented as Gleason score, was also found to be a risk factor.[29,30] Overall, it is necessary to adjust for all potential confounders to assess the relationship between variations in glycemic levels and mortality in PC patients with DM.

HbA1c is an important biomarker that can be used to reflect recent changes of glycemic level.[23] How changes of HbA1c level influence PC outcomes is uncertain. The studies mentioned above primarily investigated the relationship between PC progression and glycemic control in PC patients with DM, or the relationship between PC mortality and those with or without DM comorbidity, but the effects of changes in glycemic status were not evaluated. Therefore, in this retrospective cohort study, we investigated the relationship between PC mortality and preexisting DM with adjustment for changes in HbA1c levels.

2. METHODS

2.1. Data source

Data were extracted from electronic medical records and merged with data from the cancer registry database by the Clinical Informatics Research and Development Center of Taichung Veterans General Hospital. After approval was obtained by the Institution Review Board (CE18226A), delinked data were transferred to the authors for further analysis.

The patients' characteristics included age at initial diagnosis of PC, body mass index (BMI), follow-up years of PC, smoking status, drinking habit, Charlson Comorbidity Index (CCI) score calculated from medical diagnosis, clinical stage of PC (classified by the tumor-node-metastasis staging system according to the American Joint Committee on Cancer),[31,32] Gleason score, prostate-specific antigen (PSA) level, and cancer-related treatment (chemotherapy, hormone therapy, operation, and radiation therapy in the following period). Diabetes medication records and related laboratory data were also collected.

Mean HbA1c level was used to represent individual glycemic changes instead of a single baseline value. The HbA1c values were collected from the initial diagnosis of PC to the end of the study (patients expired or censored data).

2.2. Study population

All PC patients (age 20 years old and above), diagnosed between January 1, 2006, and December 31, 2017, were eligible for this study. The definition of DM diagnosis was (1) had one DM diagnosis and prescribed antihyperglycemic medication in an inpatient setting, (2) had two DM diagnoses or one DM diagnosis with a prescription for a antihyperglycemic medication in an outpatient setting, or (3) had an HbA1c level greater than 6.5% or a random serum glucose level above 200 mg/dL before the initial PC diagnosis. The exclusion criteria were short follow-up duration (< 14 days), any missing record in the Taichung Veterans General Hospital (TCVGH) Cancer Registry and Clinical Informatics Research and Development Center database, or patients with DM who did not have any HbA1c record. The study period was from the initial PC diagnosis day to June 30, 2018, or the patient expired before June 30, 2018. The patient selection process is presented in Figure 1. Due to the retrospective nature of this study and all the subjects' information were encoded without identification. The study was approved by the Institutional Review Board (CE18226A) of Taichung Veterans General Hospital in Taichung, Taiwan.

2.3. Outcome measures

The primary outcomes included all-cause mortality, PC-specific mortality, and non-PC mortality. All-cause mortality was defined as any cause of death during the study period. PC-specific mortality was defined as death due to PC. Non-PC mortality was defined as any cause of death, excluding death due to PC. All of the records of survival status described above were obtained from the TCVGH Cancer Registry and the Clinical Informatics Research and Development Center database. Further propensity score matching was performed to minimize bias between groups. Both continuous and categorical mean HbA1c were used in this study for model adjustment. All of the death diagnoses were coded based on the 9th or 10th version of the International Classification of Diseases (ICD).

2.4. Statistical analysis

Baseline characteristics were presented as mean ± SD for continuous variable and counts with percentage for categorical variables. The Kruskal-Wallis test, Mann-Whitney *U* test, Chi-square test, or Fisher exact test were used for continuous and categorical variables to analyze baseline characteristics for PC patients with DM and non-DM. The glycemic status was grouped as mean HbA1c levels less than 7%, between 7% and 9%, as well as equal to or greater than 9%. Kaplan-Meier curves were performed for the survival analysis and Cox regression models were used to calculate the hazard ratio (HR) and 95% CIs for all-cause mortality, non-PC mortality, and PC mortality. Multivariate Cox regression models were performed to adjust for related confounders listed in Table 1. We further used propensity score matching by one-to-four ratio as age for matching variable to implemented advanced multivariate Cox regression models analysis. Statistical significance was defined as a p value of less than 0.05. All of the analyses were performed by Stata statistical computer program version 13 (StataCorp, College Station, TX, USA) and SPSS version 22 (IBM Corporation, Armonk, NY, USA).

3. RESULTS

A total of 831 subjects met our inclusion and exclusion criteria and were recruited into this study. Patients' characteristics are presented in Table 1. There were 141 PC patients with DM with a record of mean HbA1c values, whereas there were 690 PC patients without DM. Compared with non-DM patients, DM patients tended to be older, had a higher BMI, had more comorbidities, and had a higher PSA level, as well as a greater proportion of concurrent hormone therapy, and a lower proportion of surgeries.

The HRs for unadjusted models of all-cause mortality (HR, 2.86; 95% CIs, 1.72-4.75; $p < 0.001$) and non-PC mortality (HR, 4.00; 95% CIs, 2.05-7.82; $p < 0.001$) were significantly higher in PC patients with DM, compared with those without DM (Table 2). After adjusting for related confounders, PC patients with DM had significantly higher risk for all-cause mortality (HR, 2.02; 95% CIs, 1.15-3.54; $p = 0.014$) and non-PC mortality (HR, 2.29; 95% CIs, 1.04-5.03; $p = 0.040$), compared with those without DM. After adding metformin to the adjustment model (model 2), the results did not show any statistical differences in any mortality in PC patients with DM compared with those without DM. There was no statistical difference in

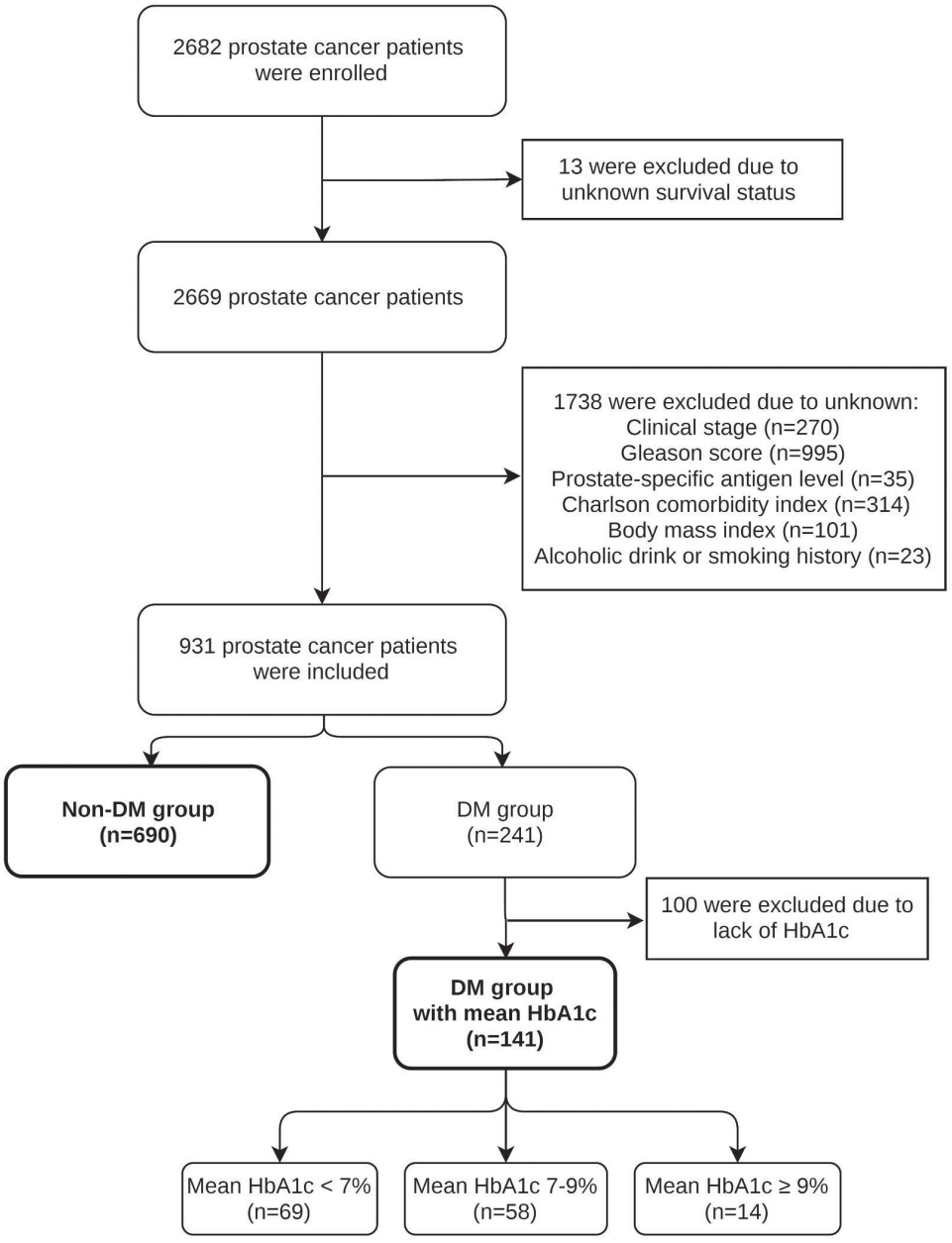

Fig. 1 Flow chart for patient selection. DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus.

PC-specific mortality in any of the models. In addition, there were no statistical differences in all major mortality outcomes, with or without adjustment for confounders, when continuous mean HbA1c level was included (Table 2).

The HR for mortality rates with different groups of mean HbA1c values, compared with those of the non-DM group are presented in Table 3. PC mortality did not differ significantly based on any of the different HbA1c groups, compared with the non-DM group. However, there were significant differences in all-cause mortality and non-PC mortality. Mean HbA1c subgroup analysis showed that higher mean HbA1c level (≥9%) increased the risk of all-cause mortality (HR, 7.57; 95% CIs, 2.99-19.17; $p < 0.001$ for univariate analysis; HR, 3.09; 95% CI, 1.15-8.32; $p = 0.025$ for multivariate analysis; and HR, 2.96; 95% CIs, 1.04-8.41; $p = 0.041$ for multivariate analysis with metformin confounder, respectively) and non-PC mortality (HR, 12.99; 95% CIs, 4.42-38.17; $p < 0.001$ for univariate analysis; HR, 5.49; 95% CIs, 1.66-18.16; $p = 0.005$ for multivariate analysis; and HR, 5.56; 95% CIs, 1.61-19.23; $p = 0.007$ for multivariate analysis with adjustment for metformin, respectively; Table 3).

Hormone therapy increased the risk of all-cause mortality in the univariate analysis (HR, 3.12; 95% CIs, 1.91-5.10; $p < 0.001$ for all-cause mortality; HR, 2.28; 95% CIs, 1.17-4.42; $p = 0.015$ for non-PC mortality; and HR, 4.56; 95% CIs, 2.15-9.69; $p < 0.001$ for PC-specific mortality, respectively), but not in the multivariate analysis (Table 3). Moreover, risk of all-cause mortality was positively associated with higher Gleason scores (HR, 1.92; 95% CIs, 1.59-2.32; $p<0.001$ for univariate analysis; HR, 1.41; 95% CIs, 1.12-1.80; $p = 0.004$ for multivariate analysis; and HR, 1.4; 95% CIs, 1.10-1.80; $p = 0.006$ for multivariate analysis with adjustment for metformin, respectively)

Table 1

Baseline characteristics of prostate cancer patients with preexisting diabetes mellitus grouped by mean HbA1c level and those without diabetes mellitus

		DM group with mean HbA1c (n = 141)			
	Non-DM group (n = 690)	<7% (n = 69)	7%-9% (n = 58)	≥9% (n = 14)	*p*
Age at diagnosis[a]	67.9 ± 0.3	72.5 ± 1.3	71.6 ± 1.1	75.6 ± 3.1	**<0.001**
Charlson Comorbidity Index[a]	1.8 ± 0.1	2.1 ± 0.3	1.9 ± 0.2	2.5 ± 0.5	**0.022**
Mean BMI (kg/m^2)[a]	24.4 ± 0.1	25.1 ± 0.4	25.9 ± 0.6	23.2 ± 0.8	**0.023**
Follow-up years on prostate cancer[a]	2.3 ± 0.1	2.3 ± 0.2	2.1 ± 0.2	1.8 ± 0.4	0.418
Smoking[b]					
Never (%)	551 (79.9)	52 (75.4)	44 (75.9)	8 (57.1)	0.159
Ever (%)	139 (20.1)	17 (24.6)	14 (24.1)	6 (42.9)	
Alcoholic drink[b]					
Never (%)	624 (90.4)	65 (94.2)	53 (91.4)	11 (78.6)	0.304
Ever (%)	66 (9.6)	4 (5.8)	5 (8.6)	3 (21.4)	
Prostate cancer stage[c]					
Stage 0–I (%)	126 (18.3)	16 (23.2)	9 (15.5)	1 (7.1)	0.193
Stage II (%)	397 (57.5)	32 (46.4)	33 (56.9)	8 (57.2)	
Stage III (%)	57 (8.3)	2 (2.9)	4 (6.9)	1 (7.1)	
Stage IV (%)	110 (15.9)	19 (27.5)	12 (20.7)	4 (28.6)	
Total Gleason score[b]					
≤ 6 (low risk) (%)	283 (41.0)	28 (40.6)	21 (36.2)	4 (28.6)	0.500
7 (intermediate risk) (%)	194 (28.1)	16 (23.2)	21 (36.2)	3 (21.4)	
8–10 (high risk) (%)	213 (30.9)	25 (36.2)	16 (27.6)	7 (50.0)	
PSA level (ng/mL)[c]					
< 20 (%)	450 (65.2)	32 (46.4)	35 (60.3)	5 (35.7)	**0.001**
20–97 (%)	138 (20.0)	21 (30.4)	8 (13.8)	3 (21.4)	
≥ 98 (%)	102 (14.8)	16 (23.2)	15 (25.9)	6 (42.9)	
Primary surgery[b]					
No (%)	148 (21.4)	26 (37.7)	16 (27.6)	9 (64.3)	**<0.001**
Yes (%)	542 (78.6)	43 (62.3)	42 (72.4)	5 (35.7)	
Radiotherapy[c]					
No (%)	642 (93.0)	65 (94.2)	53 (91.4)	10 (71.4)	0.053
Yes (%)	48 (7.0)	4 (5.8)	5 (8.6)	4 (28.6)	
Chemotherapy[c]					
No (%)	684 (99.1)	69 (100)	58 (100)	14 (100)	0.745
Yes (%)	6 (0.9)	0 (0)	0 (0)	0 (0)	
Hormone therapy[b]					
No (%)	483 (70.0)	37 (53.6)	31 (53.4)	6 (42.9)	**0.001**
Yes (%)	207 (30.0)	32 (46.4)	27 (46.6)	8 (57.1)	

Bold type indicates statistically significant difference (p<0.05)

BMI = body mass index; DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus; PSA level = prostate-specific antigen level.

[a]Kruskal-Wallis test.

[b]Chi-square test.

[c]Fisher exact test.

and PC-specific mortality (HR, 2.64; 95% CIs, 1.94-3.59; $p < 0.001$ for univariate analysis; HR, 1.54; 95% CIs, 1.08-2.21; $p = 0.017$ for multivariate analysis; and HR, 1.52; 95% CIs, 1.06-2.19; $p = 0.023$ for multivariate analysis with adjustment for metformin, respectively). Gleason score only showed a statistical difference in the unadjusted model (HR, 1.50; 95% CIs, 1.17-1.94; $p = 0.001$) for non-PC mortality.

Further propensity score matching analysis also showed a similar risk elevation in all-cause and non-PC mortality in PC patients with DM and HbA1c ≥ 9% (HR, 4.83; 95% CIs, 1.19-19.63; $p = 0.028$ and HR, 15.06; 95% CIs, 3.05-74.31; $p = 0.001$ after model 2 adjustment, respectively), while PC-specific mortality only showed a significantly increased risk in PC patients with DM and HbA1c < 7% after adjusting model 1 (HR, 4.33; 95% CIs, 1.02-18.50; $p = 0.048$). When continuous mean HbA1c was adjusted for, all-cause and non-PC mortality only showed increased risk in the univariate analysis (HR, 2.32; 95% CIs, 1.21-4.47; $p = 0.012$ and HR, 3.06; 95% CIs, 1.23-7.61; $p = 0.016$), but not in further multivariate analysis, and PC-specific mortality was not significantly affected (Table 4).

There were 100 patients who were excluded because they did not have HbA1c values. Table 5 lists baseline information of patients in the DM group with HbA1c values (n = 141) and without HbA1c values (n = 100). Patients without HbA1c values had higher rates of surgery, as well as lower proportions of hormone therapy and metformin use, compared with patients with HbA1c values.

The all-cause, non-PC, and PC-specific mortality rates were 7.94% (66/831), 4.21% (35/831), and 3.73% (31/831), separately. The survival curves (Kaplan-Meier plot) of mortalities were plotted to determine the median and overall survival status during the follow-up time (Figs. 2–4). Overall, PC patients with DM had lower median and overall survival rates compared with those without DM, especially when HbA1c was ≥ 9% in all-cause mortality (median: 55.92% vs 91.62%; overall: 39.94% vs 87.38%) and non-PC mortality (median: 64.76% vs 95.16%; overall: 46.26% vs 93.74%) (Tables 6 and 7). Compared with

Table 2

Mortality outcomes of prostate cancer patients with diabetes mellitus compared with those without diabetes mellitus (n = 831) and those with mean HbA1c (n = 141)

		Model without adjustment		Adjustment model 1[a]		Adjustment model 2[b]	
	Death (n)	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
n = 831 (141 DM patients grouped by mean HbA1c and 690 non-DM patients)							
All-cause mortality	66						
Non-DM	43	Reference		Reference		Reference	
DM	23	2.86 (1.72-4.75)	**<0.001**	2.02 (1.15-3.54)	**0.014**	1.90 (0.92-3.93)	0.082
Non-PC mortality	35						
Non-DM	20	Reference		Reference		Reference	
DM	15	4.00 (2.05-7.82)	**<0.001**	2.29 (1.04-5.03)	**0.040**	2.39 (0.94-6.03)	0.066
PC-specific mortality	31						
Non-DM	23	Reference		Reference		Reference	
DM	8	1.87 (0.84-4.18)	0.128	1.58 (0.66-3.76)	0.305	1.25 (0.34-4.59)	0.738
n = 141 (with continuous mean HbA1c)							
All-cause mortality	23	1.23 (0.97-1.55)	0.090	1.23 (0.88-1.70)	0.225	1.24 (0.89-1.73)	0.206
Non-PC mortality	15	1.28 (0.97-1.68)	0.081	1.49 (0.96-2.30)	0.072	1.51 (0.97-2.35)	0.071
PC-specific mortality	8	1.12 (0.71-1.76)	0.638	0.87 (0.38-1.99)	0.735	0.82 (0.35-1.90)	0.641

Cox regression.

Bold type indicates statistically significant difference (p<0.05)

DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; non-DM = non-diabetes mellitus; non-PC mortality = nonprostate cancer mortality; PC-specific mortality = prostate cancer-specific mortality.

[a]Model 1: age, body mass index, smoking status, alcoholic drink, Charlson Comorbidity Index, primary surgery, radiation therapy, chemotherapy, hormone therapy, Gleason score, clinical stage, prostate-specific antigen level.

[b]Model 2: model 1 and metformin use.

the non-DM group, the survival curve showed a significant difference in all HbA1c subgroups of all-cause mortality and both HbA1c < 7% and HbA1c ≥ 9% subgroups in non-PC mortality ($p < 0.05$) (Fig. 2; Fig. 4A, B, and D). There was no significant difference in survival when the non-DM group was compared with all HbA1c subgroups in PC-specific mortality and the HbA1c 7%-9% subgroup in non-PC mortality ($p > 0.05$) (Fig. 3; Fig. 4C). These results were similar to those of the Cox regressions.

4. DISCUSSION

In this study, we investigated the possible relationship between changes of glycemic levels and mortalities in PC patients with DM. Mortality rates between PC patients with or without DM were compared. The baseline characteristics in the DM and non-DM groups were generally similar, although there were differences in some confounders. Studies have indicated that PC patients with preexisting DM had increased all-cause mortality and non-PC mortality, compared with those without DM, which was similar to our findings, but the results of PC-specific mortality were controversial.[15,18–20] However, the aforementioned studies did not primarily investigate the impact of glycemic changes, such as changes of HbA1c levels, on mortality rates. Our study indicates that poor glycemic control had a negative impact on overall and non-PC mortalities, while PC-specific mortality was not affected by mean glycemic levels or after adjusting for related confounders. We further used continuous mean HbA1c in the same analyses, but there were no statistical differences in the adjusted mortality outcomes. To verify that the selection bias was minimized, we performed the same analyses using propensity score matching. The results showed a similar elevation in the risks of all-cause and non-PC mortality in PC patients with DM. To the best of our knowledge, this is the first study to investigate the mortalities of PC patients with DM using mean HbA1c level to represent glycemic control.

A significant number of DM patients without mean HbA1c levels were excluded from this study (n = 100). In order to confirm that the excluded population did not bias the mortality outcomes in this study, we performed separate analyses and compared the baseline characteristics between DM patients with or without mean HbA1c levels. The results were unchanged, that is, PC-specific mortality showed no statistical difference, and overall and non-PC mortalities were significantly different. Thus, it appears that any bias in our study likely had a minimal effect on the final outcomes.

There were 35 patients who died from a non-PC cause, including nine deaths due to other cancers, 17 due to noncancer causes, and nine due to an unknown cause. It was not possible to analyze the causes of death in more detail (non-PC or unknown death) because of the limitation of the data source. These patients were older than our study population (mean age was 75.63 years), had more comorbidities (average CCI was 2.14), 71.43% (25/35), had intermediate to high risk of Gleason score (≥7) status in combination with hormone therapy, 42.86% (15/35) had DM status, and 40% (14/35) were at clinical stage 3 or 4 of PC. These variables might have contributed to more deaths in patients with non-PC. The lower PC mortality found in this study might have been due to the shorter follow-up time compared with other studies.[16–19,33] However, CCI score and other important confounders were adjusted for and propensity score matching was performed to minimize possible bias.

Some studies showed that obesity (define as BMI ≥ 30 kg/m^2) or overweight (BMI ≥ 25 kg/m^2) were related to increased PC-specific mortality,[27,28] and results from a meta-analysis also supported this finding.[26] However, average BMI in our population was 25.21 kg/m^2, which was close to the cutoff value between normal weight and overweight in PC patients with a record of HbA1c levels (Table 1 and Table 5). Possibly, PC-specific mortality was not affected by changes of glycemic levels in our study. According to the National Comprehensive Cancer Network (NCCN) guideline, for a number of years,

Table 3

Mortality outcomes of prostate cancer patients with diabetes mellitus based on mean HbA1c levels compared with those without diabetes mellitus (n = 831)

	Model without adjustment		Adjustment model 1[a]		Adjustment model 2[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
All-cause mortality						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	2.45 (1.23-4.88)	**0.011**	1.52 (0.69-3.33)	0.295	1.44 (0.59-3.50)	0.419
DM with mean HbA1c 7%-9%	2.42 (1.14-5.17)	**0.021**	2.21 (1.00-4.92)	0.051	2.04 (0.75-5.56)	0.161
DM with mean HbA1c ≥ 9%	7.57 (2.99-19.17)	**<0.001**	3.09 (1.15-8.32)	**0.025**	2.96 (1.04-8.41)	**0.041**
Without hormone therapy	Reference		Reference		Reference	
Hormone therapy	3.12 (1.91-5.10)	**<0.001**	0.98 (0.50-1.90)	0.946	0.98 (0.50-1.90)	0.942
Gleason score	1.92 (1.59-2.32)	**<0.001**	1.41 (1.12-1.80)	**0.004**	1.40 (1.10-1.80)	**0.006**
Non-PC mortality						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	3.63 (1.53-8.60)	**0.003**	1.46 (0.52-4.11)	0.471	1.49 (0.48-4.57)	0.488
DM with mean HbA1c 7%-9%	2.64 (0.90-7.75)	0.076	2.37 (0.75-7.46)	0.142	2.43 (0.63-9.37)	0.197
DM with mean HbA1c ≥ 9%	12.99 (4.42-38.17)	**<0.001**	5.49 (1.66-18.16)	**0.005**	5.56 (1.61-19.23)	**0.007**
Without hormone therapy	Reference		Reference		Reference	
Hormone therapy	2.28 (1.17-4.42)	**0.015**	1.00 (0.39-2.51)	0.992	1.00 (0.39-2.51)	0.992
Gleason score	1.50 (1.17-1.94)	**0.001**	1.29 (0.92-1.80)	0.140	1.29 (0.92-1.82)	0.143
PC-specific mortality						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	1.40 (0.42-4.66)	0.584	1.47 (0.38-5.76)	0.577	1.25 (0.25-6.28)	0.789
DM with mean HbA1c 7%-9%	2.24 (0.77-6.47)	0.137	1.89 (0.60-5.98)	0.279	1.51 (0.30-7.62)	0.620
DM with mean HbA1c ≥ 9%	2.85 (0.38-21.10)	0.306	1.03 (0.13-8.44)	0.975	0.90 (0.10-8.21)	0.926
Without hormone therapy	Reference		Reference		Reference	
Hormone therapy	4.56 (2.15-9.69)	**<0.001**	0.74 (0.28-1.92)	0.531	0.73 (0.28-1.92)	0.526
Gleason score	2.64 (1.94-3.59)	**<0.001**	1.54 (1.08-2.21)	**0.017**	1.52 (1.06-2.19)	**0.023**

Cox regression.

Bold type indicates statistically significant difference (p<0.05)

DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; non-DM = non-diabetes mellitus; non-PC mortality = nonprostate cancer mortality; PC-specific mortality = prostate cancer-specific mortality; PSA = prostate-specific antigen.

[a]Model 1: age, body mass index, smoking status, alcoholic drink, Charlson Comorbidity Index, primary surgery, radiation therapy, chemotherapy, hormone therapy, Gleason score, clinical stage, PSA level, and categorical mean HbA1c.

[b]Model 2: model 1 and metformin use.

Table 4

Mortality outcomes of prostate cancer patients with diabetes mellitus grouped by mean HbA1c after propensity score matching (1:4 matched) and mean HbA1c values

	Model without adjustment		Adjustment model 1[a]		Adjustment model 2[b]	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
n = 550 (110 DM patients grouped by mean HbA1c and 440 non-DM patients)						
All-cause mortality[c]						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	1.75 (0.67-4.58)	0.253	1.48 (0.50-4.41)	0.484	0.97 (0.23-4.11)	0.969
DM with mean HbA1c 7%-9%	2.06 (0.85-5.03)	0.112	1.61 (0.61-4.23)	0.331	1.07 (0.29-3.93)	0.921
DM with mean HbA1c ≥ 9%	11.22 (3.34-37.7)	**<0.001**	4.53 (1.10-18.70)	**0.037**	4.83 (1.19-19.63)	**0.028**
Non-PC mortality[c]						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	1.60 (0.35-7.21)	0.543	0.81 (0.15-4.36)	0.803	0.32 (0.03-3.84)	0.372
DM with mean HbA1c 7%-9%	2.44 (0.68-8.74)	0.171	1.85 (0.43-7.92)	0.406	0.77 (0.09-6.43)	0.806
DM with mean HbA1c ≥ 9%	22.46 (6.12-82.50)	**<0.001**	17.23 (3.40-87.30)	**0.001**	15.06 (3.05-74.31)	**0.001**
PC-specific mortality[c]						
Non-DM	Reference		Reference		Reference	
DM with mean HbA1c < 7%	2.03 (0.58-7.06)	0.267	4.33 (1.02-18.50)	**0.048**	4.66 (0.84-25.89)	0.078
DM with mean HbA1c 7%-9%	1.86 (0.53-6.46)	0.331	1.34 (0.34-5.38)	0.675	1.45 (0.27-7.73)	0.664
DM with mean HbA1c ≥ 9%	0 (0.00-0.00)	0.986	0 (0.00-0.00)	0.995	0 (0.00-0.00)	0.994
n = 110 (with continuous mean HbA1c)						
All-cause mortality[d]	2.32 (1.21-4.47)	0.012	1.85 (0.90-3.78)	0.093	1.71 (0.68-4.27)	0.252
Non-PC mortality[d]	3.06 (1.23-7.61)	0.016	2.24 (0.79-6.33)	0.127	2.11 (0.58-7.73)	0.258
PC-specific mortality[d]	1.90 (0.73-4.95)	0.189	1.90 (0.65-5.52)	0.238	1.81 (0.43-7.58)	0.415

Cox regression.

Bold type indicates statistically significant difference (p<0.05)

DM = diabetes mellitus; HbA1c = hemoglobin A1c; HR = hazard ratio; non-DM = non-diabetes mellitus; non-PC mortality = nonprostate cancer mortality; PC-specific mortality = prostate cancer-specific mortality; PSA = prostate-specific antigen.

[a]Model 1: age, body mass index, smoking status, alcoholic drink, Charlson Comorbidity Index, primary surgery, radiation therapy, chemotherapy, hormone therapy, Gleason score, clinical stage, PSA level, and mean HbA1c as; [c]categorical or; [d]continuous variable.

[b]Model 2: model 1 and metformin use.

Table 5

Baseline characteristics of prostate cancer patients with or without mean HbA1c levels in diabetes mellitus group

	DM group without mean HbA1c (n = 100)	DM group with mean HbA1c (n = 141)	*p*
Age at diagnosis[a]	70.5 ± 0.8	72.5 ± 0.8	0.206
Charlson Comorbidity Index[a]	1.6 ± 0.1	2.1 ± 0.2	0.251
Mean BMI (kg/m^2)[a]	24.7 ± 0.4	25.2 ± 0.3	0.418
Follow-up years on prostate cancer[a]	2.2 ± 0.2	2.2 ± 0.2	0.743
Smoking[b]			
Never (%)	79 (79.0)	104 (73.8)	0.348
Ever (%)	21 (21.0)	37 (26.2)	
Alcoholic drink[b]			
Never (%)	90 (90.0)	129 (91.5)	0.692
Ever (%)	10 (10.0)	12 (8.5)	
Prostate cancer stage[b]			
Stage 0–I (%)	9 (9.0)	26 (18.4)	0.181
Stage II (%)	62 (62.0)	73 (51.8)	
Stage III (%)	6 (6.0)	7 (5.0)	
Stage IV (%)	23 (23.0)	35 (24.8)	
Total Gleason score[b]			
≤ 6 (low risk) (%)	31 (31.0)	53 (37.6)	0.521
7 (intermediate risk) (%)	29 (29.0)	40 (28.4)	
8–10 (high risk) (%)	40 (40.0)	48 (34.0)	
PSA level (ng/mL)[b]			
< 20 (%)	56 (56.0)	72 (51.1)	0.423
20–97 (%)	25 (25.0)	32 (22.7)	
≥ 98 (%)	19 (19.0)	37 (26.2)	
Primary surgery[b]			
No (%)	21 (21.0)	51 (36.2)	**0.011**
Yes (%)	79 (79.0)	90 (63.8)	
Radiotherapy[b]			
No (%)	92 (92.0)	128 (90.8)	0.741
Yes (%)	8 (8.0)	13 (9.2)	
Chemotherapy[c]			
No (%)	99 (99.0)	141 (100)	0.415
Yes (%)	1 (1.0)	0 (0)	
Hormone therapy[b]			
No (%)	66 (66.0)	74 (52.5)	**0.036**
Yes (%)	34 (34.0)	67 (47.5)	
Metformin use[b]			
No (%)	95 (95.0)	71 (50.4)	**<0.001**
Yes (%)	5 (5.0)	70 (49.6)	

Bold type indicates statistically significant difference (p<0.05)

BMI = body mass index; DM = diabetes mellitus; HbA1c = hemoglobin A1c; PSA = prostate-specific antigen.

[a]Mann-Whitney *U* test.

[b]Chi-square test.

[c]Fisher exact test.

Gleason score has been used as a variable to evaluate progression risk and prognosis in PC patients.[34] Therefore, it may have also been correlated with survival in PC patients. This study showed a significantly increased risk not only in all-cause mortality but also in PC-specific mortality, which was consistent with other studies showing that higher Gleason score was related to higher PC-specific mortality, even when metformin was adjusted for in the model in this study.[29,30] This finding indicates that Gleason score might have a greater impact on PC-specific mortality compared with mean HbA1c. Nevertheless, good glycemic control, such as mean HbA1c level less than 9%, is still important for all DM patients in clinical practice whether PC exists or not, in order to reduce non-PC mortality, and the Gleason score is likely also a crucial concern due to its association with PC-specific mortality. Other important variables also affect glycemic status in cancer patients with DM, including antihyperglycemic agents, such as metformin, and hormone therapy for PC patients.[1,21] A meta-analysis study showed metformin reduced all-cause mortality but not PC-specific mortality in diabetic cancer patients.[25] Our results are similar to the above-mentioned studies. Mean HbA1c was an important confounder, irrespective of DM group, that was associated with a risk reduction of all-cause mortality (HR values from 3.09 to 2.96) after adjusting for metformin in PC patients with DM compared with those without DM. The NCCN guideline revealed the importance of hormone therapy in PC patients, so it should be considered in our population.[34] However, hormone therapy in this study did not have a significant influence on mortality outcomes after adjusting for related confounders. It should be noted that we used mean HbA1c values as an indicator of glycemic changes, instead of baseline HbA1c, which might explain, at least in part, why our results differed from previous studies.[22]

Some possible mechanisms have been proposed to explain the relationship between survival and PC patients with DM. High insulin serum level and insulin-like growth factor (IGF)-1 signaling pathway activation are associated with prostate growth.[17,35]

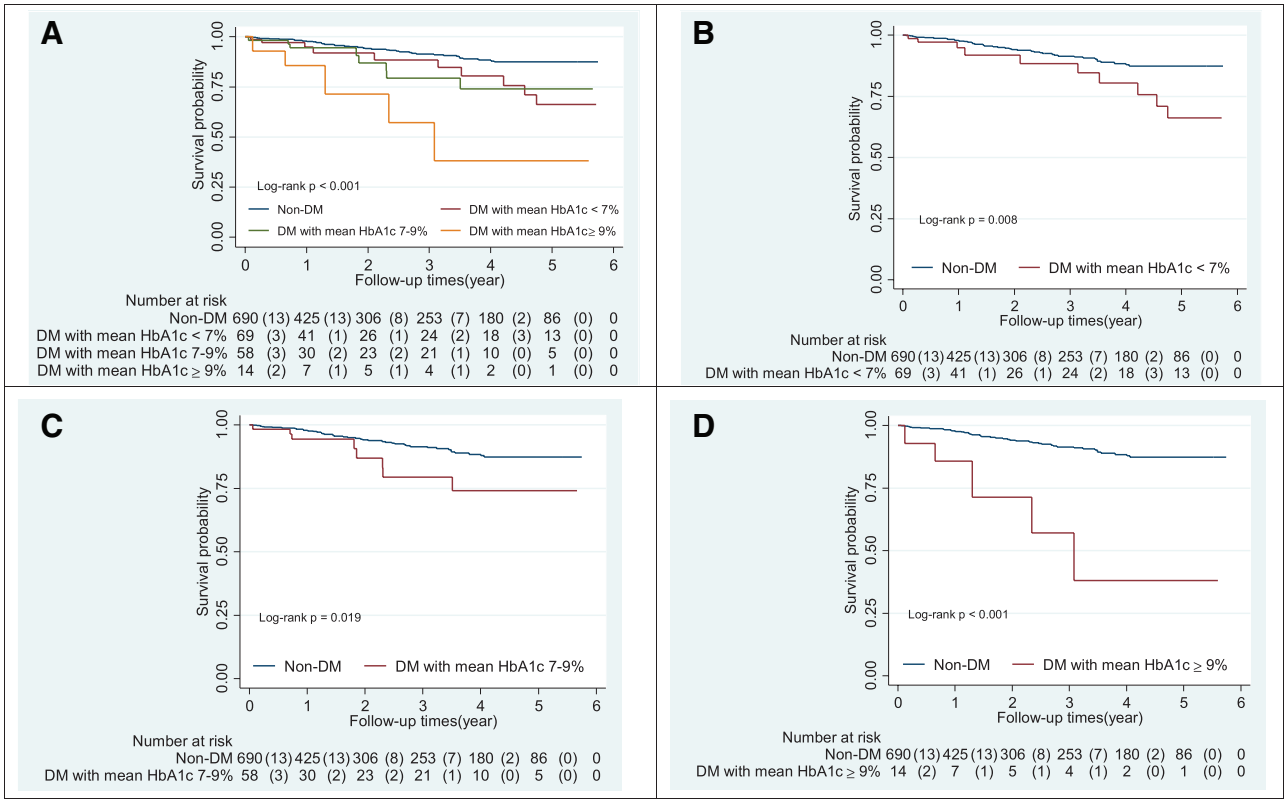

Fig. 2 Survival curve (Kaplan-Meier plot) of all-cause mortality in different group comparison. A, All group; (B) non-DM and DM with mean HbA1c < 7%; (C) non-DM and DM with mean HbA1c 7%-9%; (D) non-DM and DM with mean HbA1c ≥ 9%. DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus.

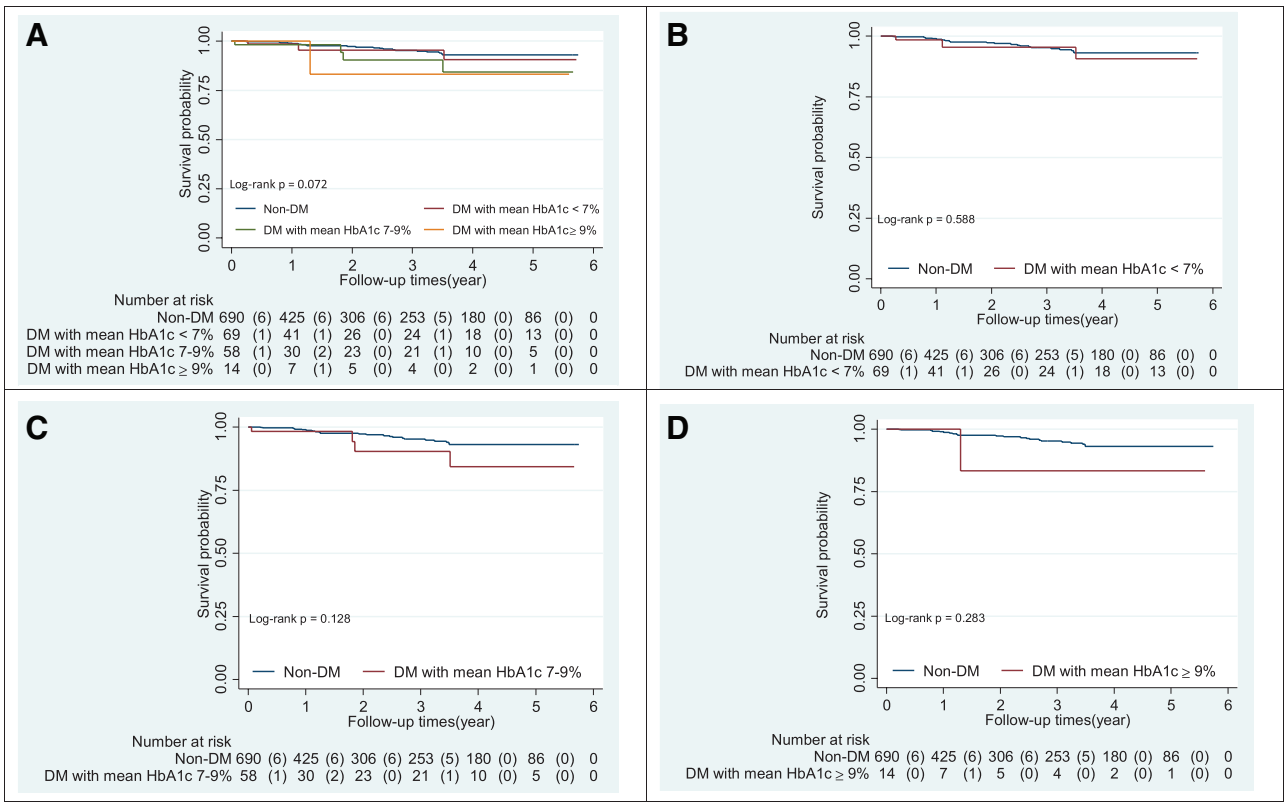

Fig. 3 Survival curve (Kaplan-Meier plot) of PC-specific mortality in different group comparison. A, All group; (B) non-DM and DM with mean HbA1c < 7%; (C) non-DM and DM with mean HbA1c 7%-9%; (D) non-DM and DM with mean HbA1c ≥ 9%. DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus; PC-specific mortality = prostate cancer-specific mortality.

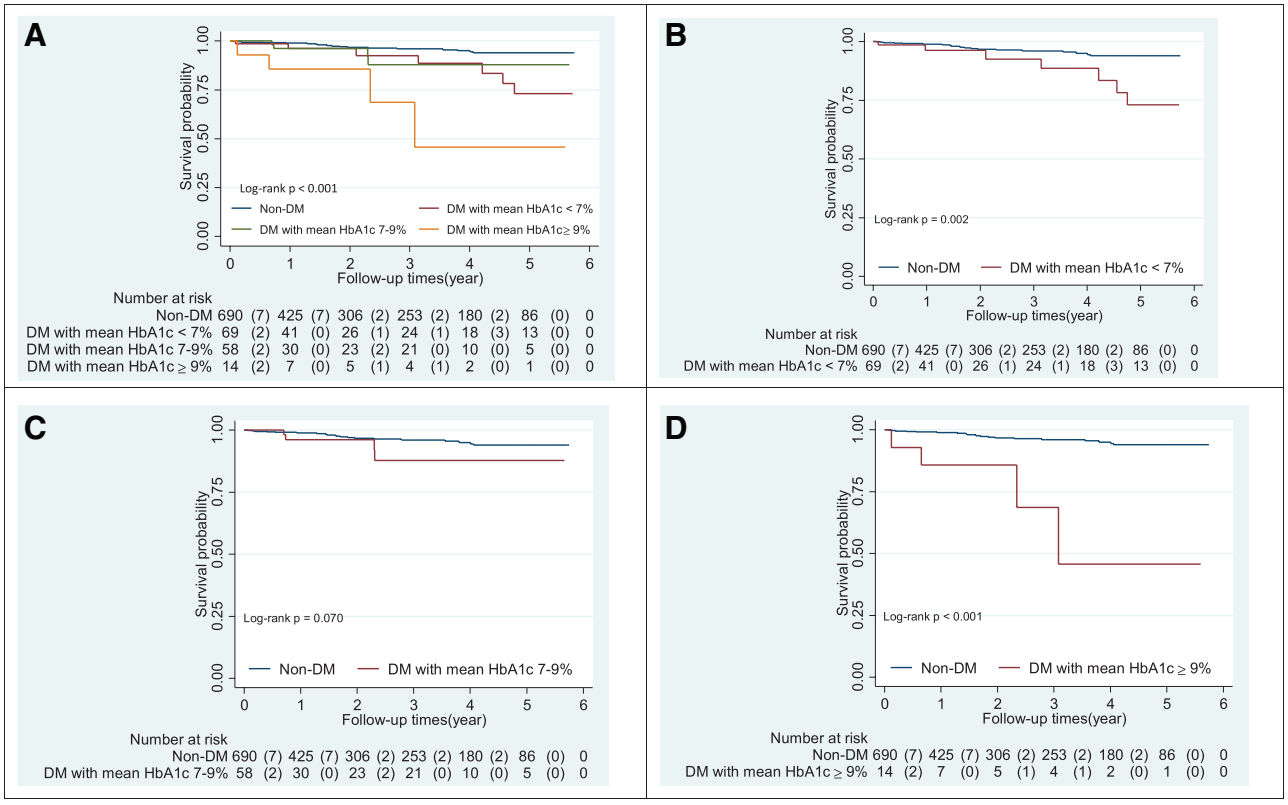

Fig. 4 Survival curve (Kaplan-Meier plot) of non-PC specific mortality in different group comparison. A, All group; (B) non-DM and DM with mean HbA1c < 7%; (C) non-DM and DM with mean HbA1c 7%-9%; (D) non-DM and DM with mean HbA1c ≥ 9%. DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus; PC-specific mortality = prostate cancer-specific mortality.

Table 6

Median and overall survival rate in different mortality outcomes (non-DM group and DM group)

	Non-DM, %		DM, %	
	Median	Overall	Median	Overall
All-cause mortality	91.62	87.38	81.87	69.78
Non-PC mortality	95.16	93.74	86.53	78.16
PC-specific mortality	95.14	92.94	93.25	87.60

DM = diabetes mellitus; non-DM = non-diabetes mellitus; non-PC mortality = nonprostate cancer mortality; PC-specific mortality = prostate cancer-specific mortality.

However, it was not possible to obtain these values in this study, and thus the possible effects of these variables on our study population could not be explored. Hyperglycemia status was related to cancer progression or comorbidities. Hence, it is reasonable to postulate that PC patients with DM and poor glycemic control might have increased all-cause or non-PC mortality.[17,36] The results of the current study support this postulation.

There were several limitations in this study. First, we excluded patients who had missing values of any variables before entering this study, which might have influenced the univariate analyses of outcomes. Nevertheless, we believe the important outcomes, which needed to be adjusted by all of the confounders, were not affected. We used aggregated mean HbA1c levels to represent the changes of glycemic status. However, in this retrospective observational study, it was not possible to obtain HbA1c levels from every patient as some of them may have sought health care in other health institutes. Also, the sample size was somewhat limited as we only analyzed data from our hospital after 2011, when the Gleason values became available in our hospital information system. Other important and related laboratory data may also have affected the results. However, due to the limited sample size, we were not able to include all of the antihyperglycemics and related laboratory data. The National Health Insurance (NHI) Administration in Taiwan has developed a cloud system that includes the HbA1c level of all DM patients, as well as other related laboratory data. We believe future studies using NHI real-world data will be able to minimize these limitations. Antihyperglycemic medications other than metformin may have

Table 7

Median and overall survival rate in different mortality outcomes (non-DM group and all HbA1c subgroups)

	Non-DM, %		DM with mean HbA1c < 7%, %		DM with mean HbA1c 7%-9%, %		DM with mean HbA1c ≥ 9%, %	
	Median	Overall	Median	Overall	Median	Overall	Median	Overall
All-cause mortality	91.62	87.38	88.30	66.11	79.08	74.14	55.92	39.94
Non-PC mortality	95.16	93.74	92.33	72.42	86.53	86.53	64.76	46.26
PC-specific mortality	95.14	92.94	94.60	89.35	84.32	84.32	77.78	77.78

DM = diabetes mellitus; HbA1c = hemoglobin A1c; non-DM = non-diabetes mellitus; non-PC mortality = nonprostate cancer mortality; PC-specific mortality = prostate cancer-specific mortality.

had an impact on PC mortality. Lastly, data from the cancer registry database may not have been up-to-date. Although these data are updated regularly by Health Promotion Administration (HPA), Ministry of Health and Welfare, and survival status of patients is largely determined by telephone interviews with patients or their family members, it is still possible that death status might have been underestimated.

In conclusion, this study provides evidence that the treatment of PC patients with DM should aim to maintain a mean HbA1c level of less than 9% to reduce overall and non-PC mortalities. Lower Gleason score was associated with lower risk of all-cause and PC-specific mortalities in PC patients with DM. Further large studies using cloud data from the NHI should be conducted to verify the effect of mean glycemic levels in this population.

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