Original Article

Impact of diabetes on prognosis of gastric cancer patients performed with gastrectomy

Xinhua Chen, Yuehong Chen, Tao Li, Luo Jun, Tian Lin, Yanfeng Hu, Huilin Huang, Hao Chen, Hao Liu, Tuanjie Li, Guoxin Li, Jiang Yu

Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China

Correspondence to: Prof. Jiang Yu, MD, PhD. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Email: balbc@163.com; Prof. Guoxin Li, MD, PhD, FRCS. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Email: gzliguoxin@163.com; Prof. Tuanjie Li, MD, PhD. Department of General Surgery, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. Email: ehbhltj@hotmail.com.

Abstract

Objective: This study aimed to determine the impact of type 2 diabetes mellitus (T2DM) on clinical outcomes of gastric cancer (GC) patients and explore whether metformin use and good glycemic control could reverse it.

Methods: Clinicopathologic data of consecutive GC patients who underwent gastrectomy at Nanfang Hospital between October 2004 and December 2015 were included. Propensity score matching (PSM) was performed to balance the important factors of the disease status between non-T2DM and T2DM group. The last follow-up time was January 2019.

Results: A total of 1,692 eligible patients (1,621 non-T2DM *vs.* 71 T2DM) were included. After PSM, non-T2DM group (n=139) and T2DM group (n=71) were more balanced in baseline variables. The 5-year cancer-specific survival (CSS) rate in T2DM group (47.0%) was inferior to that in non-T2DM group (58.0%), but did not reach statistical significance [hazard ratio (HR)=1.319, 95% confidence interval (95% CI): 0.868−2.005, P=0.192]. While the 5-year progress-free survival (PFS) rate of T2DM group (40.6%) is significantly worse than that in non-T2DM group (56.3%) (HR=1.516, 95% CI: 1.004−2.290, P=0.045). Univariate and multivariate analyses showed that T2DM was an independent risk factor for PFS but not for CSS. In T2DM group, metformin use subgroup was associated with superior 5-year CSS and PFS in compared with non-metformin use subgroup, although the difference was not statistically significant (5-year CSS: 48.0% *vs*. 45.4%, HR=0.680, 95% CI: 0.352−1.313, P=0.246; 5-year PFS: 43.5% *vs*. 35.7%, HR=0.763, 95% CI: 0.400−1.454, P=0.406). The 5-year CSS rate was 47.5% in good glycemic control subgroup and 44.1% in poor glycemic control subgroup (HR=0.826, 95% CI: 0.398−1.713, P=0.605). And both two subgroups yielded a similar 5-year PFS rate (42.2% *vs*. 36.3%, HR=0.908, 95% CI: 0.441−1.871, P=0.792).

Conclusions: DM promoted disease progress of GC after gastrectomy but had not yet led to the significant discrepancy of CSS. For GC patients with T2DM, metformin use was associated with superior survival but without statistical significance, while better glycemic control could not improve the prognosis.

Keywords: Gastric cancer; diabetes mellitus; prognosis; metformin; glycemic; gastrectomy

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Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related deaths worldwide and a substantial global health burden (1-3). Although the cornerstone treatment, gastrectomy and lymphadenectomy, has reached the

maturity level (4-6), locally advanced GC still has a high risk of recurrence (7,8). While diabetes mellitus (DM) also is a major cause of morbidity and death worldwide (9,10). It is worth noting that DM has been closely linked to cancer epidemiologically and biologically (11,12). The underlying mechanisms for higher risk of cancer in patients with DM including insulin resistance, inadequate glycemic control, oxidative stress etc. have been revealed (11,13). It has been demonstrated that breast cancer patients with DM are at increased risk of all-cause mortality compared with non-DM subgroup (14). Also, the systematic review and meta-analysis confirmed that compared with the non-DM counterparts, breast cancer patients with pre-existing diabetes have a greater risk of death (15). It also has been suggested stage II/III colon cancer (CRC) patients with DM experience a significantly higher rate of overall mortality and cancer recurrence (16). Similar phenomenon has also been observed in pancreatic cancer (17) and prostate cancer (18). However, there are discrepant reports about the relationship between DM and the risk or prognosis of GC (19-24), which still await to be further investigated.

More interestingly, some population studies have indicated that metformin, the most widely used oral hypoglycemic agent in the biguanide class for the treatment of type 2 DM (T2DM), could reduce the risk of cancer and cancer mortality in patients with T2DM (25-30). It's remarkable that Lee *et al*. (31) retrospectively analyzed data from 1,974 GC patients performed with gastrectomy (326 DM and 1,648 non-DM patients), and found those treated with metformin (n=132) had a significantly superior prognosis than those who were not (n=194) after a median follow-up of 6.2 years. And multivariable analysis further showed that each cumulative 6 months of metformin use was significantly related to a decreased risk of recurrence, cancer-specific mortality, and all-cause mortality.

Therefore, we aimed to investigate the long-term oncologic outcomes of GC patients with T2DM *vs.* without T2DM, and assess the impact of metformin use and glycemic control on the survival of T2DM subgroup based on Chinese population which account for 41% of the newly diagnosed GC worldwide (32).

Materials and methods

Patients

A total of 1,909 consecutive patients were diagnosed with GC and underwent surgery at Nanfang Hospital, Southern Medical University between October 2004 and December 2015. The analyses were based on the prospective database which was specifically designed for GC and has been serviced in Nanfang Hospital since 2004 (33). Data monitoring was always conducted by experienced medical recorders. The patient selection standard contains: 1) confirmed by pathological examination; 2) performed with laparoscopy; 3) with active follow-up; and 4) with exact survival months and definite endpoint. Two independent surgical oncologists retrospectively reviewed the pathological reports and medical records of patients, and patients who met the following criteria were excluded: 1) did not receive gastrectomy; 2) aged <18 years; or 3) combined with type 1 DM. After the above inclusion and exclusion criteria were applied, 1,692 patients were enrolled. According to the concomitant T2DM, patients were classified into two groups: GC with T2DM (n=71) and GC without T2DM (n=1,621). After generating propensity score matching (PSM) with five covariates (age, sex, pT status, pN status, pM status) by parameters of "method='nearest', ratio=2, caliper=0.01", 139 GC patients without T2DM (non-T2DM group) were matched to 71 GC patients with T2DM (T2DM group) (*Figure 1*).

The cancer stage was determined or recorded based on the 7th edition of the AJCC TNM staging system (34). The gastrectomy reconstruction and methods of lymph node examination followed standard guidelines and the experiences we reported (6,35-37). The good glycemic control subgroup was defined as patients maintained blood glucose not higher than 11.1 mmol/L most time in T2DM group. The poor glycemic control subgroup was defined as patients often presenting with random plasma glucose higher than 11.1 mmol/L. The status of glycemic control was depended on the status of blood glucose monitored by patients or their families. The metformin use subgroup was defined as patients use metformin as the main approach to control T2DM. The non-metformin use subgroup was defined as patients did not use metformin as the approach to control T2DM.

The study complied with the principles set forth in the Declaration of Helsinki. The data collection protocol was approved by the Ethics Committee of Nanfang Hospital, Southern Medical University. Written informed consent was obtained from all the patients in the study.

Diagnosis of DM

Diagnosis of DM was based on the record of the

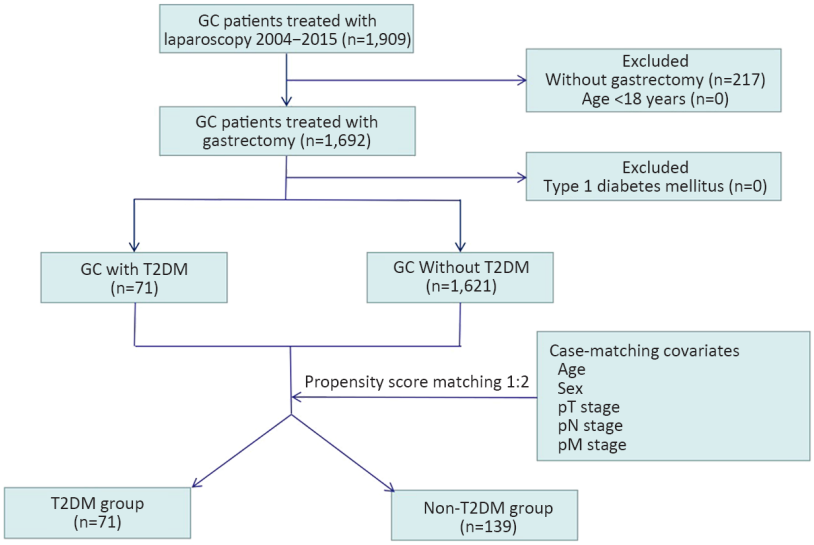

Figure 1 Study flow diagram. GC gastric cancer; T2DM, type 2 diabetes mellitus.

prospective GC database (33), which defined DM according to the following criteria: 1) HbA1c ≥6.5%; or 2) fasting plasma glucose (FGP) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h; or 3) 2 h plasma glucose 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT); 4) patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose 200 mg/dL (11.1 mm/L); or 5) patients do not meet above conditions, but have a specific history of DM with well-controlled medication. The exact time of receiving the test of DM was during preparation process of undergoing surgery in Nanfang Hospital.

Follow-up

All patients were followed up until death or last follow-up in January 2019. The follow-up scheme was 3-month interval during the first 2 years after surgery, and 6-month interval in the next 3 years, and annually afterwards. The follow-up duration was measured from the time of surgery to the last follow-up date. Cancer-specific survival (CSS) was measured from the date of surgery to the date of cancer-specific death. Progress-free survival (PFS) after surgery was defined as the time from surgery to recurrence or disease progression.

Statistical analysis

Data are presented as number (%) for categorical variables for which χ^2 test and Fisher's exact test were used to compare as appropriate. PSM with five covariates (age, sex, pT status, pN status, pM status) by the parameter of "method='nearest', ratio=2, caliper=0.01" was performed using R software (Version 3.6.1, https://www.r-project.org/) with the matchit package. Survival probability was estimated with Kaplan-Meier method and compared by log-rank test with the ggplot2, survminer and survival packages. Risk factors for survival were evaluated by univariate and multivariate analyses using Cox regression models. Hazard ratio (HR) is presented with 95% confidence interval (95% CI). Variables with statistical P<0.10 in univariate analysis as well as the critical factor in present analysis, DM (i.e., T2DM or non-T2DM) were entered into the multivariable model and were analyzed by using an "Enter" method. P<0.05 (two-tailed) was considered statistically significant. The statistical software SPSS for Windows (Version 25.0; IBM Corp., New York, USA) was used for all statistical analyses.

Results

Patient characteristics

Clinical and pathological characteristics of 1,692 eligible patients are shown in *Table 1*. By PSM, non-T2DM group (n=139) and T2DM group (n=71) were more balanced in baseline variables. Notably, the unbalance of age was redressed and the most important variables that were considered as the most important factors to assess the disease status and affect prognosis (i.e. pT, pN, pM) were more comparable between two groups.

Table 1 Patient characteristics

Variable	Before PSM				After PSM			
	Non-T2DM group (n=1,621)	T2DM group (n=71)	Statistic	P	Non-T2DM group (n=139)	T2DM group (n=71)	Statistic	P
Sex				0.407				0.899
Male	1,088 (67.1)	51 (71.8)	0.686		101 (72.7)	51 (71.8)	0.016	
Female	533 (32.9)	20 (28.2)			38 (27.3)	20 (28.2)		
Age (year)				0.001				0.767
<40	187 (11.5)	1 (1.4)	−0.318		2 (1.4)	1 (1.4)	−0.296	
40−69	1,249 (77.1)	56 (78.9)			112 (80.6)	56 (78.9)		
≥70	185 (11.4)	14 (19.7)			25 (18.0)	14 (19.7)		
Hepatitis				0.904				0.672
No	1,535 (94.7)	67 (94.4)	0.015		133 (95.7)	67 (94.4)	0.180	
Yes	86 (5.3)	4 (5.6)			6 (4.3)	4 (5.6)		
HBsAg (+)				0.792				0.491
No	1,517 (93.6)	67 (94.4)	0.070		134 (96.4)	67 (94.4)	0.475	
Yes	104 (6.4)	4 (5.6)			5 (3.6)	4 (5.6)		
Tumor location				0.187				0.487
Upper	275 (17.0)	18 (25.4)	3.357		30 (21.6)	18 (25.4)	1.437	
Middle	345 (21.3)	14 (19.7)			21 (15.1)	14 (19.7)		
Lower	1,001 (61.8)	39 (54.9)			88 (63.3)	39 (54.9)		
Ascites				0.977				0.324
No	1,531 (94.4)	67 (94.4)	0.001		135 (97.1)	67 (94.4)	0.974	
Yes	90 (5.6)	4 (5.6)			4 (2.9)	4 (5.6)		
Gastrectomy				0.861				0.905
Total	500 (30.8)	24 (33.8)	0.298		43 (30.9)	24 (33.8)	0.199	
Proximal	112 (6.9)	5 (7.0)			11 (7.9)	5 (7.0)		
Distal	1,009 (62.2)	42 (59.2)			85 (61.2)	42 (59.2)		
Reconstruction				0.391				0.470
Roux-en-Y	515 (31.8)	26 (36.6)	0.735		44 (31.7)	26 (36.6)	0.521	
Others	1,106 (68.2)	45 (63.4)			95 (68.3)	45 (63.4)		
Lymphadenectomy				0.689				0.917
Non-D2/D2+	233 (14.4)	9 (12.7)	0.160		15 (10.8)	8 (11.3)	0.011	
D2/D2+	1,388 (85.6)	62 (87.3)			124 (89.2)	63 (88.7)		
Radical resection				0.516				0.842
Yes	1,296 (80.0)	59 (83.1)	0.423		117 (84.2)	59 (83.1)	0.040	
No	325 (20.0)	12 (16.9)			22 (15.8)	12 (16.9)		
Approach				0.300				0.922
Open/Conversion	671 (41.4)	25 (35.2)	1.074		48 (34.5)	25 (35.2)	0.010	
Laparoscopy	950 (58.6)	46 (64.8)			91 (65.5)	46 (64.8)		
Receiv adjuvant chemotherapy				0.720				0.824
No	924 (57.0)	42 (59.2)	0.129		80 (57.6)	42 (59.2)	0.049	

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Before PSM				After PSM			
	Non-T2DM group (n=1,621)	T2DM group (n=71)	Statistic	P	Non-T2DM group (n=139)	T2DM group (n=71)	Statistic	P
Yes	697 (43.0)	29 (40.8)			59 (42.4)	29 (40.8)		
Histology				0.058				0.010
Signet-ring cell	332 (20.5)	8 (11.3)	3.596		37 (26.6)	8 (11.3)	6.578	
Others	1,289 (79.5)	63 (88.7)			102 (73.4)	63 (88.7)		
Grade				0.938				0.639
G1–G2	340 (21.0)	15 (21.1)	0.127		29 (20.9)	15 (21.1)	0.896	
G3–G4	1,097 (67.7)	47 (66.2)			98 (70.5)	47 (66.2)		
Unknown	184 (11.4)	9 (12.7)			12 (8.6)	9 (12.7)		
Vascular invasion				0.454				0.321
No	1,356 (83.7)	57 (80.3)	0.561		119 (85.6)	57 (80.3)	0.984	
Yes	265 (16.3)	14 (19.7)			20 (14.4)	14 (19.7)		
Neural invasion				0.217				0.422
No	1,245 (76.8)	59 (83.1)	1.525		109 (78.4)	59 (83.1)	0.644	
Yes	376 (23.2)	12 (16.9)			30 (21.6)	12 (16.9)		
Lymphatic vessel invasion				0.503				0.721
No	1,414 (87.2)	60 (84.5)	0.449		120 (86.3)	60 (84.5)	0.128	
Yes	207 (12.8)	11 (15.5)			19 (13.7)	11 (15.5)		
Primary tumor invasion				0.860				0.814
T1	287 (17.7)	16 (22.5)	−0.176		32 (23.0)	16 (22.5)	−0.236	
T2	138 (8.5)	4 (5.6)			7 (5.0)	4 (5.6)		
T3	112 (6.9)	3 (4.2)			9 (6.5)	3 (4.2)		
T4	1,084 (66.9)	48 (67.6)			91 (65.5)	48 (67.6)		
Lymph node status				0.571				0.667
N0	609 (37.6)	24 (33.8)	−0.566		50 (36.0)	24 (33.8)	−0.430	
N1	260 (16.0)	13 (18.3)			26 (18.7)	13 (18.3)		
N2	316 (19.5)	13 (18.3)			26 (18.7)	13 (18.3)		
N3	436 (26.9)	21 (29.6)			37 (26.6)	21 (29.6)		
Metastasis				0.550				0.662
No	1,398 (86.2)	63 (88.7)	0.358		126 (90.6)	63 (88.7)	0.192	
Yes	223 (13.8)	8 (11.3)			13 (9.4)	8 (11.3)		
Tumor size (cm)				0.481				0.568
<5	981 (60.5)	40 (56.3)	0.497		84 (60.4)	40 (56.3)	0.326	
≥5	640 (39.5)	31 (43.7)			55 (39.6)	31 (43.7)		

HBsAg, hepatitis B surface antigen; PSM, propensity score matching; T2DM, type 2 diabetes mellitus.

Long-term oncologic outcomes of T2DM group and non-T2DM group

Patients were followed up for a median of 70 (range, 1–168) months and a mean of 72.9 months. The 5-year CSS rate was 47.0% (95% CI: 34.26%–59.74%) in T2DM group and 58.0% (95% CI: 49.18%–66.82%) in non-T2DM group, with no significant difference between two groups (HR=1.319, 95% CI: 0.868–2.005, P=0.192) (*Figure 2A*). However, the 5-year PFS in T2DM group [40.6% (95% CI: 27.86%–53.34%)] is significantly worse than that in non-T2DM group [56.3% (95% CI: 47.28%–65.31%)]

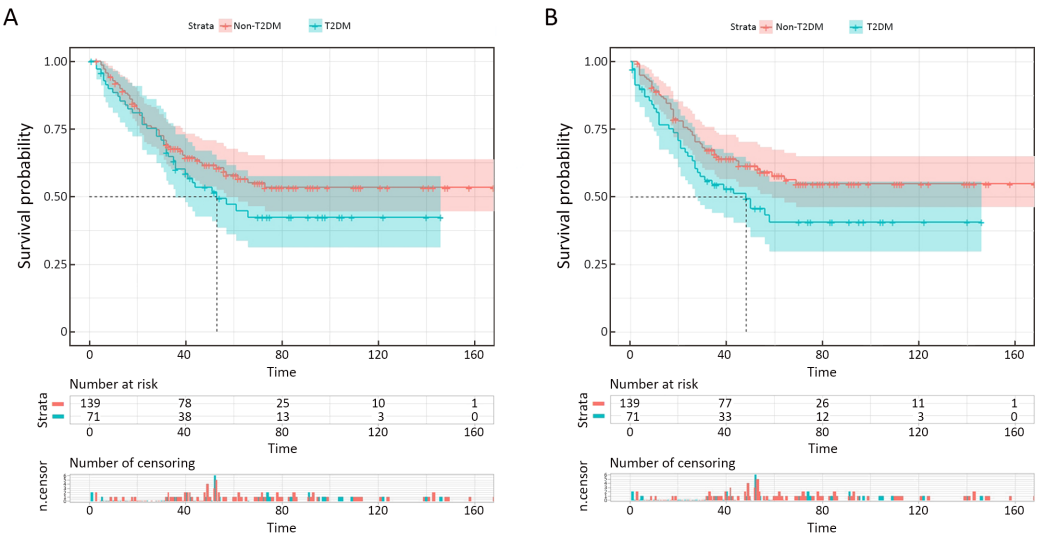

Figure 2 Long-term oncologic outcomes of T2DM group and non-T2DM group of GC patients after gastrectomy. (A) 5-year CSS rate between T2DM group and non-T2DM group [47.0% *vs.* 58.0%, HR=1.319 (95% CI: 0.868–2.005), P=0.192]; (B) 5-year PFS rate between T2DM group and non-T2DM group [40.6% *vs.* 56.3%, HR=1.516 (95% CI: 1.004–2.290), P=0.045]. T2DM, type 2 diabetes mellitus; GC, gastric cancer; CSS, cancer-specific survival; HR, hazard ratio; 95% CI, 95% confidence interval; PFS, progress-free survival.

(HR=1.516, 95% CI: 1.004–2.290, P=0.045) (*Figure 2B*).

Risk factors for survival

Univariate and multivariate analyses of risk factors for CSS and PFS are presented in *Table 2*,*3*, respectively. Univariate analyses revealed that the extent of lymphadenectomy less than D2, unradical resection, the open/conversion surgical approaches, without receiving adjuvant chemotherapy, advanced primary tumor invasion, lymph node metastasis, distant organ(s) metastasis and larger (≥5 cm) tumor size were risk factors for CSS. Multivariate analyses further indicated that without receiving adjuvant chemotherapy, advanced primary tumor invasion, lymph node metastasis were independent risk factors for CSS. Notably, T2DM was not identified as a risk factor for CSS. Univariate analyses revealed that T2DM, ascites, proximal or total gastrectomy, the extent of lymphadenectomy less than D2, unradical resection, the open/conversion surgical approaches, without receiving adjuvant chemotherapy, advanced primary tumor invasion, lymph node metastasis, distant organ(s) metastasis were risk factors for PFS. Multivariate analyses further indicated that T2DM, without receiving adjuvant chemotherapy, advanced primary tumor invasion, lymph node metastasis were independent risk factors for PFS. The sensitive analysis by multivariable analysis without PSM was supplied in *Supplementary Table S1*,*S2* and showed satisfied results.

Impact of metformin use and blood glucose control on survival for T2DM group

In T2DM group, metformin use subgroup was associated with superior 5-year CSS and PFS compared with non-metformin use subgroup, although the difference was not statistically significant [5-year CSS: 48.0% (95% CI: 32.60%–62.10%) *vs.* 45.4% (95% CI: 25.02%–65.78%), HR=0.680, 95% CI: 0.352–1.313, P=0.246; 5-year PFS: 43.5% (95% CI: 27.23%–59.77%) *vs.* 35.7% (95% CI: 15.12%–56.28%), HR=0.763, 95% CI: 0.400–1.454; P=0.406] (*Figure 3*). The 5-year CSS rate was 47.5% (95% CI: 32.60%–62.10%) in good glycemic control subgroup and 44.1% (95% CI: 19.21%–68.99%) in poor glycemic control subgroup, with no significant difference between the groups (HR=0.826, 95% CI: 0.398–1.713, P=0.605) (*Figure 4A*). And both two subgroups yielded a similar 5-year PFS rate [42.2% (95% CI: 27.70%–56.70%) *vs.* 36.3% (95% CI: 11.02%–61.58%), HR=0.908, 95% CI: 0.441–1.871, P=0.792] (*Figure 4B*).

Discussion

Our study investigated the impact of T2DM on long-term oncologic outcomes of GC patients after gastrectomy and found that T2DM is an independent adverse factor of PFS. However, further analysis showed that for GC patients in T2DM group, metformin use was associated with superior

Table 2 Univariate and multivariate Cox regression analyses of risk factors for CSS

Variables	Univariate analysis		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
T2DM (Yes *vs*. No)	1.319 (0.868–2.005)	0.192	1.153 (0.745–1.786)	0.523
Sex (Female *vs*. Male)	1.422 (0.919–2.199)	0.110		
Age (year)		0.451		
40–69 *vs*. <40	0.909 (0.126–6.572)	0.925		
≥70 *vs*. <40	1.248 (0.167–9.334)	0.829		
Hepatitis (Yes *vs*. No)	1.003 (0.407–2.471)	0.995		
HBsAg (+) (Yes *vs*. No)	1.379 (0.559–3.401)	0.481		
Tumor location		0.547		
Middle *vs*. Upper	0.871 (0.450–1.683)	0.680		
Lower *vs*. Upper	0.767 (0.477–1.241)	0.281		
Ascites (Yes *vs*. No)	2.428 (0.984–5.988)	0.054	1.491 (0.473–4.702)	0.495
Gastrectomy		0.051		0.346
Proximal *vs*. Total	1.003 (0.480–2.098)	0.993	0.756 (0.327–1.746)	0.512
Distal *vs*. Total	0.605 (0.390–0.938)	0.025	0.668 (0.387–1.151)	0.146
Reconstruction (Roux-en-Y *vs*. Others)	1.238 (0.804–1.906)	0.329		
Lymphadenectomy (D2/D2+ *vs*. Others)	0.367 (0.216–0.622)	<0.001	0.338 (0.067–1.699)	0.188
Radical resection (Yes *vs*. No)	0.300 (0.190–0.474)	<0.001	0.998 (0.435–2.289)	0.995
Approach (Laparoscopy *vs*. Open/conversion)	0.596 (0.394–0.902)	0.013	0.674 (0.397–1.146)	0.145
Received adjuvant chemotherapy (Yes *vs*. No)	0.587 (0.382–0.903)	0.014	0.341 (0.203–0.571)	<0.001
Histology (signet-ring *vs*. Others)	1.311 (0.812–2.117)	0.265		
Grade		0.160		0.442
G3–4 *vs*. G1–2	1.697 (0.954–3.020)	0.072	1.425 (0.741–2.741)	0.288
Unknown *vs*. G1–2	1.850 (0.839–4.079)	0.127	1.014 (0.395–2.607)	0.977
Vascular invasion (Yes *vs*. No)	1.563 (0.931–2.623)	0.087	1.210 (0.651–2.250)	0.546
Neural invasion (Yes *vs*. No)	1.356 (0.822–2.237)	0.230		
Lymphatic vessel invasion (Yes *vs*. No)	1.268 (0.716–2.243)	0.412		
Primary tumor invasion		<0.001		0.001
T2 *vs*. T1	2.971 (0.709–12.450)	0.136	6.086 (1.288–28.749)	0.023
T3 *vs*. T1	6.637 (2.023–21.775)	0.002	14.013 (3.457–56.806)	<0.001
T4 *vs*. T1	7.962 (3.220–19.686)	<0.001	9.108 (2.863–28.971)	<0.001
Lymph node status		<0.001		0.028
N1 *vs*. N0	1.811 (0.895–3.665)	0.099	0.750 (0.329–1.705)	0.492
N2 *vs*. N0	2.730 (1.392–5.355)	0.003	0.990 (0.444–2.206)	0.980
N3 *vs*. N0	6.340 (3.551–11.318)	<0.001	1.886 (0.908–3.917)	0.089
Metastasis (M1 *vs*. M0)	3.482 (2.052–5.908)	<0.001	0.359 (0.060–2.157)	0.263
Tumor size (cm) (≥5 *vs*. <5)	2.524 (1.679–3.814)	<0.001	1.131 (0.684–1.869)	0.631

CSS, cancer-specific survival; T2DM, type 2 diabetes mellitus; HBsAg, hepatitis B surface antigen; HR, hazard ratio; 95% CI, 95% confidence interval.

survival but without statistical significance, while good control of blood glucose could not improve their prognosis.

Similar to our finding that T2DM had an adverse effect on disease PFS, some other studies have also indicated that T2DM is related to an increased risk and inferior prognosis in many other cancer types (12,19,29,38). And consistent with the clinical consequences, preclinical data have shown that multiple metabolic changes factors, including

Table 3 Univariate and multivariate Cox regression analyses of risk factors for PFS

Variables	Univariate analysis		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
T2DM (Yes *vs*. No)	1.516 (1.004–2.290)	0.045	1.567 (1.021–2.404)	0.040
Sex (Female *vs*. Male)	1.385 (0.897–2.137)	0.137		
Age (year)		0.297		
40–69 *vs*. <40	1.044 (0.145–7.537)	0.966		
≥70 *vs*. <40	1.528 (0.205–11.384)	0.679		
Hepatitis (Yes *vs*. No)	0.983 (0.399–2.420)	0.970		
HBsAg (+) (Yes *vs*. No)	1.396 (0.567–3.441)	0.463		
Tumor location		0.505		
Middle *vs*. Upper	0.913 (0.479–1.741)	0.783		
Lower *vs*. Upper	0.763 (0.472–1.232)	0.269		
Ascites (Yes *vs*. No)	2.516 (1.021–6.204)	0.037	1.595 (0.510–4.991)	0.422
Gastrectomy		0.040		0.265
Proximal *vs*. Total	1.013 (0.486–2.112)	0.972	0.803 (0.347–1.857)	0.609
Distal *vs*. Total	0.598 (0.388–0.923)	0.020	0.638 (0.371–1.097)	0.104
Reconstruction (Roux-en-Y *vs*. others)	1.250 (0.817–1.912)	0.300		
Lymphadenectomy (D2/D2+ *vs*. others)	0.339 (0.203–0.568)	<0.001	0.337 (0.072–1.580)	0.168
Radical resection (Yes *vs*. No)	0.284 (0.181–0.445)	<0.001	1.009 (0.439–2.320)	0.983
Approach (Laparoscopy *vs*. Open/conversion)	0.638 (0.423–0.961)	0.029	0.787 (0.464–1.334)	0.374
Received adjuvant chemotherapy (Yes *vs*. No)	0.558 (0.364–0.856)	0.006	0.309 (0.184–0.520)	<0.001
Histology (Signet-ring *vs*. Others)	1.256 (0.779–2.025)	0.346		
Grade		0.130		0.309
G3–4 *vs*. G1–2	1.742 (0.980–3.094)	0.059	1.601 (0.833–3.080)	0.158
Unknown *vs*. G1–2	1.917 (0.870–4.226)	0.106	1.178 (0.458–3.029)	0.734
Vascular invasion (Yes *vs*. No)	1.632 (0.984–2.708)	0.054	1.178 (0.644–2.157)	0.594
Neural invasion (Yes *vs*. No)	1.273 (0.773–2.095)	0.338		
Lymphatic vessel invasion (Yes *vs*. No)	1.349 (0.775–2.347)	0.285		
Primary tumor invasion		<0.001		<0.001
T2 *vs*. T1	2.566 (0.641–10.275)	0.183	5.545 (1.212–25.364)	0.027
T3 *vs*. T1	5.469 (1.761–16.980)	0.003	12.519 (3.242–48.342)	<0.001
T4 *vs*. T1	6.841 (2.979–15.709)	<0.001	8.102 (2.728–24.060)	<0.001
Lymph node status		<0.001		0.013
N1 *vs*. N0	1.748 (0.872–3.501)	0.115	0.773 (0.340–1.754)	0.538
N2 *vs*. N0	2.521 (1.299–4.893)	0.006	0.937 (0.423–2.078)	0.873
N3 *vs*. N0	6.551 (3.711–11.562)	<0.001	2.039 (0.988–4.209)	0.054
Metastasis (M1 *vs*. M0)	3.819 (2.275–6.411)	<0.001	0.381 (0.068–2.147)	0.274
Tumor size (cm) (≥5 *vs*. <5)	2.606 (1.731–3.923)	<0.001	1.136 (0.689–1.874)	0.617

PFS, progress-free survival; T2DM, type 2 diabetes mellitus; HBsAg, hepatitis B surface antigen; HR, hazard ratio; 95% CI, 95% confidence interval.

hyperinsulinemia and insulin-like growth factor I, hyperglycemia, dyslipidemia, adipokines and cytokines, and the gut microbiome (39), potentially contributed to the progression of cancer in T2DM patients. Not only metabolic changes factors that may play a role in promoting tumor growth were discovered, some researchers even further revealed its detailed mechanisms. For example, the dysregulation of the 5'-AMP-activated

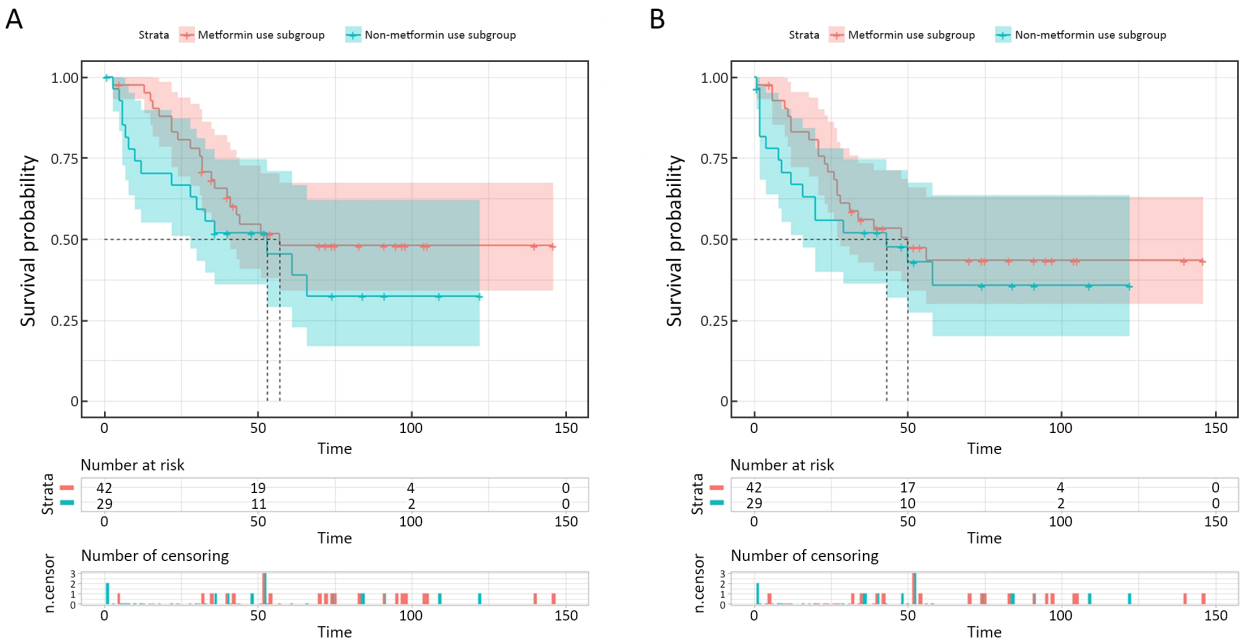

Figure 3 Long-term oncologic outcomes of metformin use subgroup and non-metformin use subgroup of GC patients after gastrectomy in T2DM group. (A) 5-year CSS rate between metformin use subgroup and non-metformin use subgroup [48.0% *vs*. 45.4%, HR=0.680 (95% CI: 0.352−1.313), P=0.246]; (B) 5-year PFS rate between metformin use subgroup and non-metformin use subgroup [43.5% *vs*. 35.7%, HR=0.763 (95% CI: 0.400−1.454), P=0.406]. GC, gastric cancer; T2DM, type 2 diabetes mellitus; CSS, cancer-specific survival; HR, hazard ratio; 95% CI, 95% confidence interval; PFS, progress-free survival.

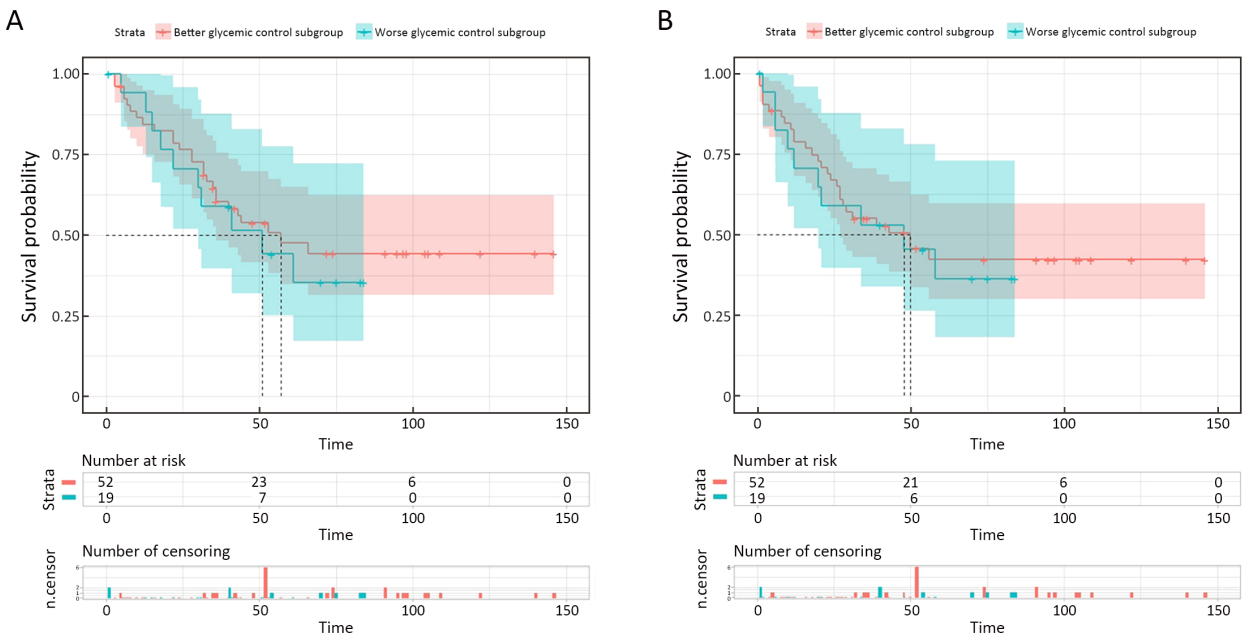

Figure 4 Long-term oncologic outcomes of good glycemic control subgroup and poor glycemic control subgroup of GC patients after gastrectomy in T2DM group. (A) 5-year CSS rate between good glycemic control subgroup and poor glycemic control subgroup [47.5% *vs*. 44.1%, HR=0.826 (95% CI: 0.398−1.713), P=0.605]; (B) 5-year PFS rate between good glycemic control subgroup and poor glycemic control subgroup. [42.2% *vs*. 36.3%, HR=0.908 (95% CI: 0.441−1.871), P=0.792]. GC, gastric cancer; T2DM, type 2 diabetes mellitus; CSS, cancer-specific survival; HR, hazard ratio; 95% CI, 95% confidence interval; PFS, progress-free survival.

protein kinase pathway and crosstalk between RAS and insulin-like growth factor 1-cholesterol pathways give rise to a cancer-promoting milieu (40). Also, Wu *et al*. (41) found hyperglycemic conditions have an adverse effect on the DNA 5-hydroxymethylome, which activate the subsequent molecular pathway and reprogram the epigenome towards an oncogenic state. Their findings indicated that sustained hyperglycemia destabilizes tumor suppressor TET2 and deregulates levels of 5hmC, and glucose-AMPK-TET2-5hmC axis links the level of extracellular glucose to the dynamic regulation of 5hmC, which connects DM to cancer.

However, there are also studies that reported the negative relationship between DM and the prognosis of GC (21,24). In a large cohort of US adults, diabetes was not associated with fatal GC in males or females after 16 years of mortality follow-up. A systematic analysis even showed that overall risk estimates do not present an association between DM and GC (24). Many reasons may result in the inconclusive evidence of the association between DM and risk and cancer prognosis of GC. The heterogeneity of clinical characteristics and biological characteristics, such as the difference of studying population (i.e. East population *vs*. Western population), the *H. pylori* infection, TMN stage, treatment strategies and molecular subtypes, usually cannot be comprehensively balanced in the previous studies (24). Further, GC is relatively less common in Western countries, studies in these countries evaluating the association between GC and DM were not powered to evaluate the risk of GC in detail. Besides, the gastrectomy and digestive tract reconstruction could also obviously change the dietary habit, calorie intake, and exercises of patients who had DM, while gastrectomy and digestive tract reconstruction differed in each center.

Metformin is a commonly used oral diabetic agent that reduces hyperinsulinemia and has been reported to be linked to decreased cancer incidence and mortality (30,42-44). Specifically, there was an investigation suggested that metformin may favorably affect the outcome in patients with DM and GC (45). Likewise, recently, research based on East cohort reveals that metformin use was associated with a lower GC risk among *H. pylori*-eradicated DM patients in duration- and dose-response way (46). Further, preclinical data have provided evidence for the mechanism that may contribute to antineoplastic effects of metformin. Kato *et al*. (47) showed that metformin inhibits GC cell proliferation and blocks cell cycle in G(0)-G(1) *in vitro* and *in vivo*. Specifically, Wu *et al*. unravelled metformin mediates epigenetic pathway to suppression tumor (41). The metformin use protects AMP-activated protein kinase (AMPK)-mediated phosphorylation of serine 99, thereby increasing TET2 stability and 5hmC levels. This finding indicated that epigenetic regulation by glucose-AMPK-TET2-5hmC axis has a direct effect on the efficacy of metformin in preventing cancer. Consistently, Zakikhani *et al*. also demonstrated metformin is an AMPK-dependent growth inhibitor for tumor (48). More interesting, a recent study revealed that AMPK activates Krüppel-like factor 4 in progenitors to decrease self-renewal and promote acid-secreting parietal cells fate, while AMPK-PGC1α activation within the acid-secreting parietal cells lineage promotes maturation. The finding explained the potential mechanism that metformin increases acid secretion and lowers the risk of suffering GC in humans (49). Encouragingly, the specific mechanisms of metformin's role in cancer immunity have also been uncovered recently. Cha *et al*. (50,51) showed that metformin increases T lymphocyte activity by reducing the stability and membrane localization of programmed death ligand-1 (PD-L1) with AMPK pathway activation, while the hindering of the inhibitory signal of PD-L1 boosts cytotoxic T lymphocyte activity against cancer cells. The revealing of these biological mechanisms provides novel avenues for future clinical investigation about the anti-cancer effect of metformin use and make clinical research more reasonable. However, taking into consideration of the conflicting relationship between T2DM and GC prognosis (19-24) and the complexity that gastrectomy may lead to reliving of hyperglycemia in some T2DM patients with GC (52,53), the association between metformin use and prognosis after radical surgery for GC remains uncertain. Notably, both metformin use and good control of blood glucose cannot confer significantly better prognosis in our research. However, as the complexity of preventing cancer mechanism and effect of metformin, a simple analysis by dichotomizing based on metformin use in our study to determine the anti-GC effect of metformin is not adequate. Thus, subsequent studies are necessary to investigate if some dose of metformin can cause anti-GC effects. And from the perspective of clinical data, TOSCA study sub-analysis indicated there is no association between metformin use or dosages and patient survival on resected CRC patients (54). But on the contrary, Cheung *et al*. recently showed that metformin use was linked to a lower GC risk among *H. pylori*-eradicated DM patients in

duration- and dose-response mode (46). Hence, although metformin use could not result in statistically significant superior survival, we still could not deny anti-GC effects of metformin in the result of our study. Whether cumulative use could reverse the impact of T2DM on clinical outcomes of patients with GC after gastrectomy might require further study.

Remarkably, the metastasis stage was not an independent prognostic factor for CSS and PFS in our research. However, it has been demonstrated that metastasis stage was associated with a dismal prognosis (55-57). Reviewing the analysis process, we found the following reasons may be attributed to the abnormal result: 1) Patients with metastasis present a lower percentage (10%, 21/210), and the limited number of metastasis status impaired the ability to detect its impact; 2) Patients with metastasis status enrolled in our study were those underwent gastrectomy, and some of them achieved good survival with multi-model treatment. One of the patients with metastasis in this study survived 143 months after surgical treatment. Some patients with metastasis achieved satisfied survival have been reported by our team and other centers (57,58). Thus, some of patients with metastasis status achieved satisfied survival further impaired the survival distinction between M0 and M1 subgroup in our study.

Another point that attracts our attention is that T2DM was only showed statistically significant for PFS of GC patients' cohort, but not for CSS. It seemed that the reasons may be attributed as follows: 1) After recurring, management of GC patients will be intensified, which will dilute the oncological effect of DM on GC, leading to negative results of CSS; 2) Recurrence and metastasis are very complex multistep processes which are affected by many factors, thus the impact of DM on recurrence and prognosis may fluctuate as time went on; 3) CSS was more prone to be affected by variables of socioeconomic status or performance status (59-61).

There are some limitations in our study. Since the cumulative duration and dose of metformin might affect its anti-cancer effect, this factor had better be taken into considerations in our study. Nevertheless, as the retrospective characteristics of our study, we could not exactly identify the duration of metformin use. But it did not deny the value of this retrospective research. The subsequent well-designed, prospective controlled trials should be designed on the basis of reliable retrospective studies. Also, because of inherent limitations of retrospective studies, some clinical characteristics, such as age, was unbalanced between T2DM and non-T2DM group. Hence, PSM was conducted to avoid potential confounding effects. Along with most basic variables (age, sex), the pT stage, N stage and M stage which were considered as the most important factors to assess the disease status, were included as the covariates of PSM. To make the important variables comparable further, we set caliper of matching as 0.01; and to make the oncologic effect to be assessed adequately in retrospective study, we only enrolled patients who underwent gastrectomy before the year of 2016 and conducted last follow-up in January 2019. Also, the gastrectomy and digestive tract reconstruction could also obviously change the dietary habit, calorie intake, and exercises of patients, which make assessment of DM effect on GC more complicated. But luckily, after PSM, the variables of gastrectomy and digestive tract reconstruction were well balanced. Besides, nearby 15% of the majority of advanced tumors were not radically resected. However, these data characteristics accorded with the epidemiologic features of GC in China and Western countries where advanced GC accounts for far larger proportion. To emphasize experience and evidence focused on the real world, we did not exclude these advanced tumors.

Conclusions

T2DM promoted disease progress of GC after gastrectomy but did not lead to the significant prognosis discrepancy of CSS in the cohort of Nanfang Hospital. The anticancer effect of metformin needs to be further confirmed by well-designed, prospective controlled trials on GC patients with T2DM and with the exact information of cumulative duration of metformin and dynamic monitoring the control of blood glucose. Also, as the adjuvant treatment strategies based on GC subgroups of specific pathological stages have achieved great progress, treatment tactics according to specific biological characteristics are moving forward (62-64). Thus, researches to explore the biological behavior of GC with DM and the mechanism of the impact of DM on GC are necessary for GC to make adjuvant treatments more tailored and individualized.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Multivariate Cox regression analyses of risk factors for CSS before PSM

Variables	HR (95% CI)	P
T2DM (Yes *vs*. No)	1.070 (0.685–1.482)	0.685
Ascites (Yes *vs*. No)	1.760 (1.365–2.267)	<0.001
Gastrectomy		0.136
Proximal *vs*. Total	0.909 (0.677–1.222)	0.528
Distal *vs*. Total	0.850 (0.724–0.997)	0.046
Lymphadenectomy (D2/D2+ *vs*. others)	0.728 (0.500–1.059)	0.097
Radical Resection (Yes *vs*. No)	0.525 (0.361–0.764)	0.001
Grade		0.172
G3–4 *vs*. G1–2	1.059 (0.867–1.293)	0.574
Unknown *vs*. G1–2	1.263 (0.973–1.639)	0.079
Vascular invasion (Yes *vs*. No)	1.112 (0.925–1.336)	0.258
Primary tumor invasion		<0.001
T2 *vs*. T1	2.083 (1.282–3.385)	0.003
T3 *vs*. T1	2.686 (1.661–4.342)	<0.001
T4 *vs*. T1	3.503 (2.385–5.146)	<0.001
Lymph node status		<0.001
N1 *vs*. N0	1.555 (1.194–2.024)	0.001
N2 *vs.* N0	2.266 (1.785–2.876)	<0.001
N3 *vs.* N0	3.751 (2.982–4.718)	<0.001
Metastasis (M1 *vs*. M0)	0.997 (0.681–1.461)	0.989
Tumor size (cm) (≥5 *vs*. <5)	1.098 (0.933–1.293)	0.261

CSS, cancer-specific survival; PSM, propensity score matching; T2DM, type 2 diabetes mellitus; HR, hazard ratio; 95% CI, 95% confidence interval.

Table S2 Multivariate Cox regression analyses of risk factors for PFS before PSM

Variables	HR (95% CI)	P
T2DM (Yes *vs*. No)	1.396 (1.001–1.945)	0.049
Ascites (Yes *vs*. No)	1.590 (1.233–2.050)	<0.001
Gastrectomy		0.148
Proximal *vs*. Total	0.845 (0.588–1.214)	0.362
Distal *vs*. Total	0.769 (0.586–1.008)	0.057
Lymphadenectomy (D2/D2+ *vs*. others)	0.522 (0.368–0.740)	<0.001
Radical resection (Yes *vs*. No)	0.473 (0.334–0.670)	<0.001
Grade		0.069
G3–4 *vs*. G1–2	0.990 (0.813–1.204)	0.918
Unknown *vs*. G1–2	1.271 (0.979–1.649)	0.071
Vascular invasion (Yes *vs*. No)	1.078 (0.894–1.301)	0.431
Primary tumor invasion		0.001
T2 *vs*. T1	2.123 (1.316–3.424)	0.002
T3 *vs*. T1	2.720 (1.699–4.354)	<0.001
T4 *vs*. T1	3.332 (2.285–4.858)	<0.001
Lymph node status		<0.001
N1 *vs*. N0	1.667 (1.284–2.164)	<0.001
N2 *vs.* N0	2.434 (1.917–3.091)	<0.001
N3 *vs.* N0	3.669 (2.914–4.619)	<0.001
Metastasis (M1 *vs*. M0)	0.938 (0.642–1.371)	0.742
Tumor size (cm) (≥5 *vs*. <5)	0.834 (0.638–1.091)	0.072

PFS, progress-free survival; PSM, propensity score matching; T2DM, type 2 diabetes mellitus; HR, hazard ratio; 95% CI, 95% confidence interval.