

The Effect of Type 2 Diabetes Mellitus on the Short-Term Outcomes and Prognosis of Stage I–III Colorectal Cancer: A Propensity Score Matching Analysis

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Purpose: The purpose of the current study was to analyze the effect of type 2 diabetes mellitus (T2DM) on the short-term outcomes and prognosis of stage I–III colorectal cancer (CRC) undergoing primary surgery.

Methods: Patients who underwent primary CRC surgery were retrospectively collected from Jan 2011 to Jan 2020 in a single clinical center. The short-term outcomes and prognosis were compared between T2DM group and non-T2DM group using propensity score matching (PSM) analysis.

Results: A total of 4250 patients were included in this study. There were 521 patients with T2DM and 3729 patients without T2DM. After 1:1 ratio PSM, there were 519 T2DM patients and 519 non-T2DM patients left in this study. No significant difference was found in baseline information after PSM ($p>0.05$). T2DM had higher overall complications ($p=0.033$) after PSM in terms of short-term outcomes. As for prognosis, T2DM group had worse overall survival (OS) in all stages ($p=0.044$), stage I ($p=0.009$) and stage II ($p=0.021$) of CRC and T2DM group had worse disease-free survival (DFS) than non-T2DM group in stage I ($p=0.008$) of CRC before PSM. However, T2DM did not affect the overall survival (OS) or disease-free survival (DFS) on different stages of CRC after PSM ($p>0.05$). Moreover, T2DM was not an independent predictor of OS or DFS ($p>0.05$).

Conclusion: T2DM increased overall complications after primary CRC surgery. However, T2DM might not affect OS and DFS of stage I–III CRC patients.

Keywords: colorectal cancer, type 2 diabetes mellitus, outcomes, prognosis

Introduction

Colorectal cancer (CRC) is the third leading cause of death and the fourth most common cancer in the world.¹ More than 900,000 people die every year because of CRC.² In addition, the number of CRC patients is expected to increase in the future,³ and surgery is still the main treatment for CRC.^{4,5}

Type 2 diabetes mellitus (T2DM) causes a significant burden on patients and society globally,⁶ and T2DM accounts for increased morbidity and mortality.⁷ The number of T2DM patients is expected to reach 700 million in 2045.⁸

Cancer and T2DM are two global public health problems and are also regarded as the world's major lethal and disabling diseases.⁹ They share various common risk factors (high blood pressure, obesity, hyperlipidemia) and have a similar etiological mechanism.^{10,11}

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As previous studies reported, T2DM could increase the incidence of CRC.¹² However, the effect of T2DM on CRC remains controversial.^{13,14} Furthermore, there have been no propensity score matching (PSM) studies concerning the relationship between CRC and T2DM. Therefore, the purpose of the current study was to analyze the effect of T2DM on the short-term outcomes and prognosis of CRC patients undergoing primary surgery using PSM analysis.

Methods

Patients

Patients who underwent primary CRC surgery were retrospectively collected from Jan 2011 to Jan 2020 in a single clinical center. This study was conducted in accordance with the World Medical Association Declaration of Helsinki. Ethical approval from the First Affiliated Hospital of Chongqing Medical University board was obtained (2021-336) and all the patients signed informed consent.

Inclusion and Exclusion Criteria

We included the patients who underwent primary CRC surgery and the pathology diagnosed CRC from a database of a single clinical center (n=5473). The exclusion criteria were as follows: 1) stage IV CRC (n=875); 2) incomplete medical records (n=323); and 3) non-R0 resection (n=25). Finally, a total of 4250 patients were included in the current study.

Surgery Management

All patients underwent radical resection according to the clinical guideline and total mesorectal excision or complete mesocolic excision was performed, and the pathology confirmed R0 resection. Patients were regularly followed up every 3 months for the first 3 years and every 6 months for the following 2 years.

Definitions

The tumor node metastasis (TNM) stage was diagnosed according to the AJCC eighth edition.¹⁵ Overall survival (OS) was defined as the time from primary CRC surgery to the last follow-up (when patients were alive) or death. Disease-free survival (DFS) was defined as the time from primary CRC surgery to recurrence, death or last follow-up (when patients were alive). The complications were defined according to the Clavien–Dindo classification,¹⁶ and major

complications were defined as \geq III classification complications.

Data Collection

Patient information was retrospectively collected from inpatient and outpatient system, and the follow-up information was collected from the outpatient system and telephone interviews. The peri-operative information included age, sex, body mass index (BMI), smoking, drinking, family history, hypertension, coronary heart disease (CHD), adjuvant therapy, tumor stage and tumor location. The short-term outcomes included operation time, blood loss, retrieved lymph nodes, hospital stay, overall complications, major complications, postoperative 30-day death, reoperation and anastomotic leakage. The prognosis included OS and DFS.

PSM

To minimize the bias of baseline information, PSM was conducted between T2DM group and non-T2DM group. Nearest neighbor matching was performed without replacement at a 1:1 ratio and a caliper width with a 0.01 standard deviation was specified. The baseline information was matched including age, sex, BMI, smoking, drinking, family history, hypertension, CHD, adjuvant therapy, tumor location and tumor stage.

Statistical Analysis

Continuous variables are expressed as the mean \pm SD, and independent-sample *t*-test was used to compare the difference between T2DM group and non-T2DM group. Frequency variables are expressed as n (%), and Chi-square test or Fisher's exact test was used. The Kaplan–Meier curve was conducted to compare T2DM on different pathological stages, and Cox regression analyses were performed to identify independent predictive factors for OS and DFS. Data were analyzed using SPSS (version 22.0) statistical software. A bilateral *p* value <0.05 was considered statistically significant.

Results

Patients

A total of 4250 patients were included in this study according to the inclusion and exclusion criteria. There were 521 patients with T2DM and 3729 patients without T2DM. After 1:1 ratio PSM, there were 519 T2DM patients and 519 non-

T2DM patients left in this study. The flow chart of inclusion, exclusion and PSM is shown in [Figure 1](#).

Baseline Information

Baseline information was compared between T2DM and non-T2DM groups, and T2DM group had an older age ($p=0.000$), higher BMI ($p=0.000$), higher portion of hypertension ($p=0.000$), higher portion of CHD ($p=0.000$) and lower portion of adjuvant therapy ($p=0.011$) before PSM. However, no significant difference was found after PSM in terms of age, sex, BMI, smoking, drinking, family history,

hypertension, CHD, adjuvant therapy, tumor location or tumor stage ($p>0.05$) ([Table 1](#)).

Short-Term Outcomes

The short-term outcomes including operation time, blood loss, retrieved lymph nodes, hospital stay, overall complications, major complications, postoperative 30-day death, reoperation and anastomotic leakage were compared between T2DM and non-T2DM group. T2DM group had longer hospital stay ($p=0.002$), higher overall complications ($p=0.000$) and higher anastomotic leakage ($p=0.022$) before PSM. After PSM, T2DM had higher overall complications ($p=0.033$) ([Table 2](#)).

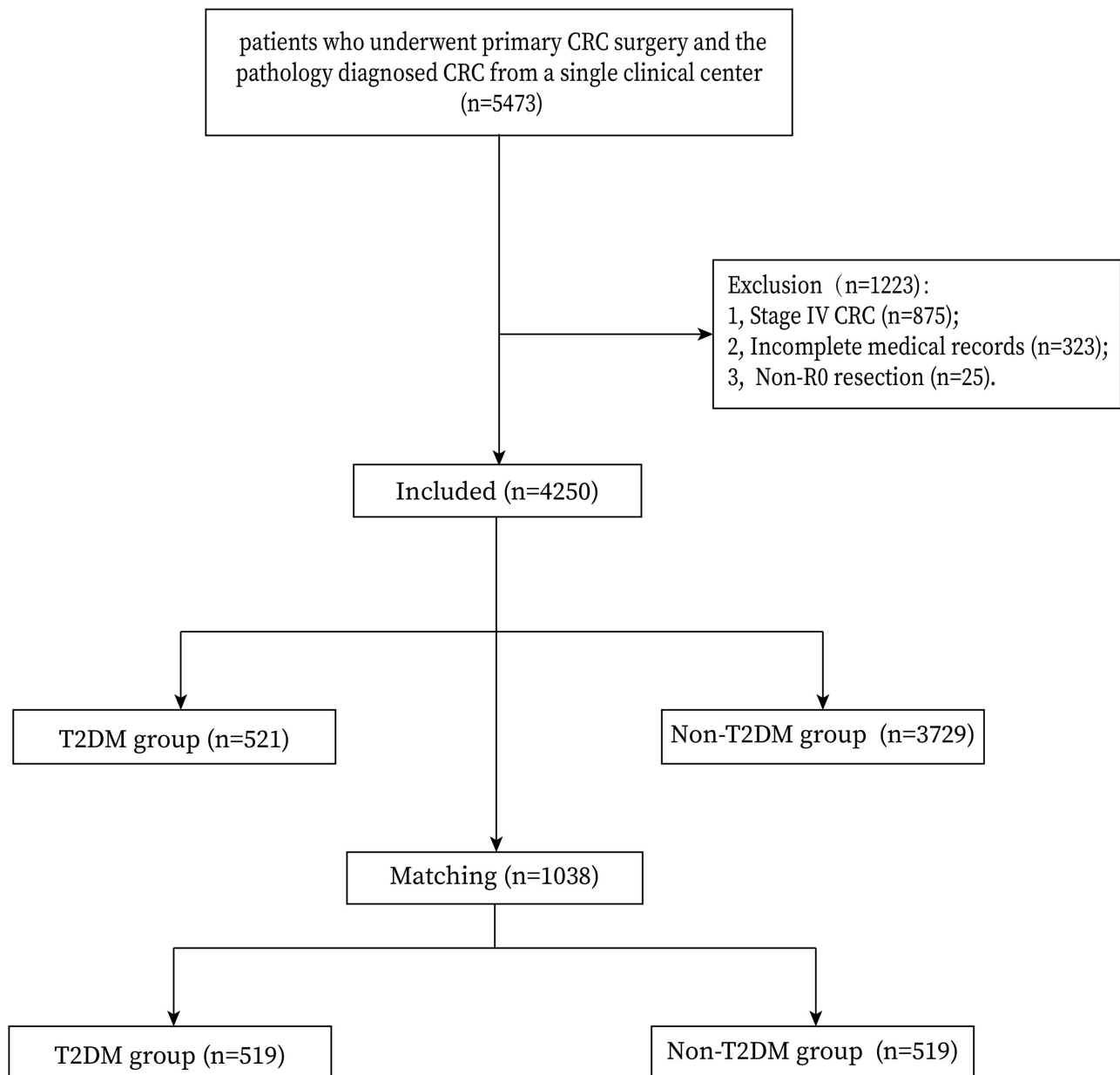


Figure 1 Flow chart of patient selection.

Table 1 Baseline Characteristics Before and After PSM

Characteristics	Before PSM			After PSM		
	T2DM (521)	Non-T2DM (3729)	P value	T2DM (519)	Non-T2DM (519)	P value
Age (years)	68.2 ± 9.7	62.2 ± 12.3	0.000*	68.2 ± 9.7	67.9 ± 11.1	0.662
Sex			0.448			0.572
Male	298 (57.2%)	2198 (58.9%)		296 (57.0%)	305 (58.8%)	
Female	223 (42.8%)	1531 (41.1%)		223 (43.0%)	214 (41.2%)	
BMI (kg/m ²)	23.6 ± 3.3	22.6 ± 3.2	0.000*	23.5 ± 3.3	23.4 ± 3.3	0.485
Smoking	181 (34.7%)	1426 (38.2%)	0.123	180 (34.7%)	181 (34.9%)	0.948
Drinking	151 (29.0%)	1150 (30.8%)	0.398	150 (28.9%)	148 (28.5%)	0.891
Family history	18 (3.5%)	109 (2.9%)	0.504	18 (3.5%)	17 (3.3%)	0.863
Hypertension	296 (56.8%)	812 (21.8%)	0.000*	294 (56.6%)	309 (59.5%)	0.345
CHD	56 (10.7%)	123 (3.3%)	0.000*	54 (10.4%)	52 (10.0%)	0.838
Tumor location			0.325			0.495
Colon	251 (48.2%)	1711 (45.9%)		250 (48.2%)	261 (50.3%)	
Rectum	270 (51.8%)	2018 (54.1%)		269 (51.8%)	258 (49.7%)	
Adjuvant therapy	41 (7.9%)	192 (5.1%)	0.011*	40 (7.7%)	32 (6.2%)	0.499
Tumor stage			0.482			0.894
I	96 (18.4%)	754 (20.2%)		96 (18.5%)	102 (19.7%)	
II	222 (42.6%)	1610 (43.2%)		220 (42.4%)	217 (41.8%)	
III	203 (39.0%)	1365 (36.6%)		203 (39.1%)	200 (38.5%)	

Notes: Variables are expressed as the mean ± SD, n (%), *P-value <0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; BMI, body mass index; PSM, propensity score matching; CHD, coronary heart disease; PSM, propensity score matching.

Table 2 Short-Term Outcomes Before and After PSM

Characteristics	Before PSM			After PSM		
	T2DM (521)	Non-T2DM (3729)	P value	T2DM (519)	Non-T2DM (519)	P value
Operation time (min)	225.1 ± 77.5	222.4 ± 76.1	0.463	224.6 ± 77.3	227.0 ± 82.1	0.640
Blood loss (mL)	97.4 ± 107.6	100.8 ± 128.0	0.560	95.6 ± 103.0	104.7 ± 143.1	0.240
Retrieved lymph nodes	14.6 ± 9.3	14.7 ± 7.2	0.793	14.7 ± 9.3	14.2 ± 7.0	0.389
Hospital stay (days)	12.5 ± 11.2	11.2 ± 8.4	0.002*	12.5 ± 11.2	11.6 ± 7.7	0.139
Overall complications	149 (28.6%)	778 (20.9%)	0.000*	148 (28.5%)	118 (22.7%)	0.033*
Major complications	17 (3.3%)	82 (2.2%)	0.132	17 (3.3%)	10 (1.9%)	0.172
Postoperative 30-day death	3 (0.6%)	9 (0.2%)	0.174	3 (0.6%)	0 (0.0%)	0.249
Re-operation	12 (2.3%)	59 (1.6%)	0.229	12 (2.3%)	10 (1.9%)	0.666
Anastomotic leakage	20 (3.8%)	82 (2.2%)	0.022*	20 (3.8%)	10 (1.9%)	0.064

Notes: Variables are expressed as the mean ± SD, n (%), *P-value <0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; PSM, propensity score matching.

Univariate and Multivariate Analyses of OS

The median follow-up time was 37 (1–114) months, univariate and multivariate analyses were conducted to find the predictors for OS of the 1038 patients after PSM. In univariate analysis, age ($p=0.000$, HR=2.007, 95% CI=1.486–2.710), BMI ($p=0.008$, HR=0.658, 95% CI=0.484–0.895), tumor stage ($p=0.000$, HR=1.556, 95% CI=1.253–1.931), overall complications ($p=0.000$, HR=1.898, 95% CI=1.407–2.561), major complications ($p=0.000$, HR=2.940, 95% CI=1.635–

5.287) and anastomotic leakage ($p=0.007$, HR=2.542, 95% CI=1.298–4.979) were predictors; however, T2DM was not a predictor ($p=0.764$, HR=0.956, 95% CI=0.712–1.283). In multivariate analysis, age ($p=0.000$, HR=1.843, 95% CI=1.350–2.515), BMI ($p=0.029$, HR=0.706, 95% CI=0.516–0.965), tumor stage ($p=0.000$, HR=1.587, 95% CI=1.273–1.979), overall complications ($p=0.016$, HR=1.496, 95% CI=1.077–2.077) and major complications ($p=0.010$, HR=2.767, 95% CI=1.270–6.029) were independent predictors for OS (Table 3).

Table 3 Univariate and Multivariate Analyses of Overall Survival (After PSM)

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>/≤69 years)	2.007 (1.486–2.710)	0.000*	1.843 (1.350–2.515)	0.000*
Sex (male/female)	0.891 (0.660–1.202)	0.449		
BMI (>/≤23.4 kg/m ²)	0.658 (0.484–0.895)	0.008*	0.706 (0.516–0.965)	0.029*
Hypertension (yes/no)	1.032 (0.767–1.390)	0.834		
T2DM (yes/no)	0.956 (0.712–1.283)	0.764		
Tumor site (colon/rectum)	1.193 (0.889–1.601)	0.240		
Tumor stage (III/II/I)	1.556 (1.253–1.931)	0.000*	1.587 (1.273–1.979)	0.000*
Smoking (yes/no)	0.884 (0.646–1.208)	0.438		
Drinking (yes/no)	0.775 (0.551–1.089)	0.142		
Family history (yes/no)	0.863 (0.382–1.948)	0.723		
CHD (yes/no)	1.086 (0.658–1.791)	0.747		
Adjuvant therapy (yes/no)	0.799 (0.354–1.806)	0.590		
Overall complications (yes/no)	1.898 (1.407–2.561)	0.000*	1.496 (1.077–2.077)	0.016*
Major complications (yes/no)	2.940 (1.635–5.287)	0.000*	2.767 (1.270–6.029)	0.010*
Anastomotic leakage (yes/no)	2.542 (1.298–4.979)	0.007*	1.225 (0.513–2.929)	0.648

Note: *P-value <0.05.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; PSM, propensity score matching.

Univariate and Multivariate Analyses of DFS

As for DFS, in univariate analysis, age ($p=0.000$, HR=1.747, 95% CI=1.325–2.303), BMI ($p=0.019$, HR=0.714, 95% CI=0.538–0.947), tumor stage ($p=0.000$, HR=1.796, 95% CI=1.447–2.229), overall complications ($p=0.001$,

HR=1.622, 95% CI=1.221–2.155), major complications ($p=0.002$, HR=2.506, 95% CI=1.398–4.494) and anastomotic leakage ($p=0.025$, HR=2.154, 95% CI=1.103–4.208) were predictors; however, T2DM was not a predictor ($p=0.353$, HR=0.878, 95% CI=0.667–1.155). In multivariate analysis, age ($p=0.001$, HR=1.656, 95% CI=1.245–2.204), tumor

Table 4 Univariate and Multivariate Analyses of Disease-Free Survival (After PSM)

Risk Factors	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (>/≤69 years)	1.747 (1.325–2.303)	0.000*	1.656 (1.245–2.204)	0.001*
Sex (male/female)	0.894 (0.676–1.181)	0.430		
BMI (>/≤23.4 kg/m ²)	0.714 (0.538–0.947)	0.019*	0.754 (0.566–1.004)	0.053
Hypertension (yes/no)	1.039 (0.788–1.370)	0.786		
T2DM (yes/no)	0.878 (0.667–1.155)	0.353		
Tumor site (colon/ rectum)	1.094 (0.833–1.438)	0.518		
Tumor stage (III/II/I)	1.796 (1.447–2.229)	0.000*	1.541 (1.258–1.888)	0.000*
Smoking (yes/no)	0.836 (0.623–1.121)	0.230		
Drinking (yes/no)	0.777 (0.566–1.066)	0.118		
Family history (yes/no)	0.737 (0.327–1.660)	0.461		
CHD (yes/no)	1.011 (0.631–1.622)	0.962		
Adjuvant therapy (yes/no)	0.996 (0.510–1.945)	0.991		
Overall complications (yes/no)	1.622 (1.221–2.155)	0.001*	1.325 (0.971–1.809)	0.076
Major complications (yes/no)	2.506 (1.398–4.494)	0.002*	2.551 (1.198–5.431)	0.015*
Anastomotic leakage (yes/no)	2.154 (1.103–4.208)	0.025*	1.217 (0.522–2.837)	0.649

Note: *P-value <0.05.

Abbreviations: HR, hazard ratio; CI, confidence interval; BMI, body mass index; T2DM, type 2 diabetes mellitus; CHD, coronary heart disease; PSM, propensity score matching.

stage ($p=0.000$, $HR=1.541$, 95% $CI=1.258-1.888$) and major complications ($p=0.015$, $HR=2.551$, 95% $CI=1.198-5.431$) were independent predictors for DFS (Table 4).

Prognosis in Different Tumor Stages

To analyze the effect of T2DM on prognosis on different stages of CRC, the Kaplan–Meier curve was conducted before and after PSM. Before PSM, T2DM group had worse OS in all stages ($p=0.044$), stage I ($p=0.009$) and stage II ($p=0.021$) (Figure 2), and in terms of DFS, T2DM group had worse DFS than non-T2DM group in stage I ($p=0.008$) (Figure 3). However, there were no difference in all stages, stage I, stage II and stage III in terms of OS or DFS after PSM ($p>0.05$) (Figures 4 and 5).

Discussion

In this study, T2DM had higher overall complications after PSM. As for prognosis, T2DM did not affect the OS or DFS on different stages of CRC after PSM, furthermore, T2DM was not an independent predictor of OS or DFS.

T2DM increased the global medical burden and economic burden,^{6,7} and furthermore, T2DM could increase the incidence of digestive cancers including esophageal cancer,¹⁷ gastric cancer¹⁸ and CRC.¹² However, there remained controversial about the outcomes of T2DM on CRC. Some studies reported that T2DM affected OS or DFS,^{13,14} a meta-analysis also reported that CRC patients with concurrent T2DM had worse DFS.¹⁹ However, other studies reported its negative influence.^{20–22}

OS before PSM

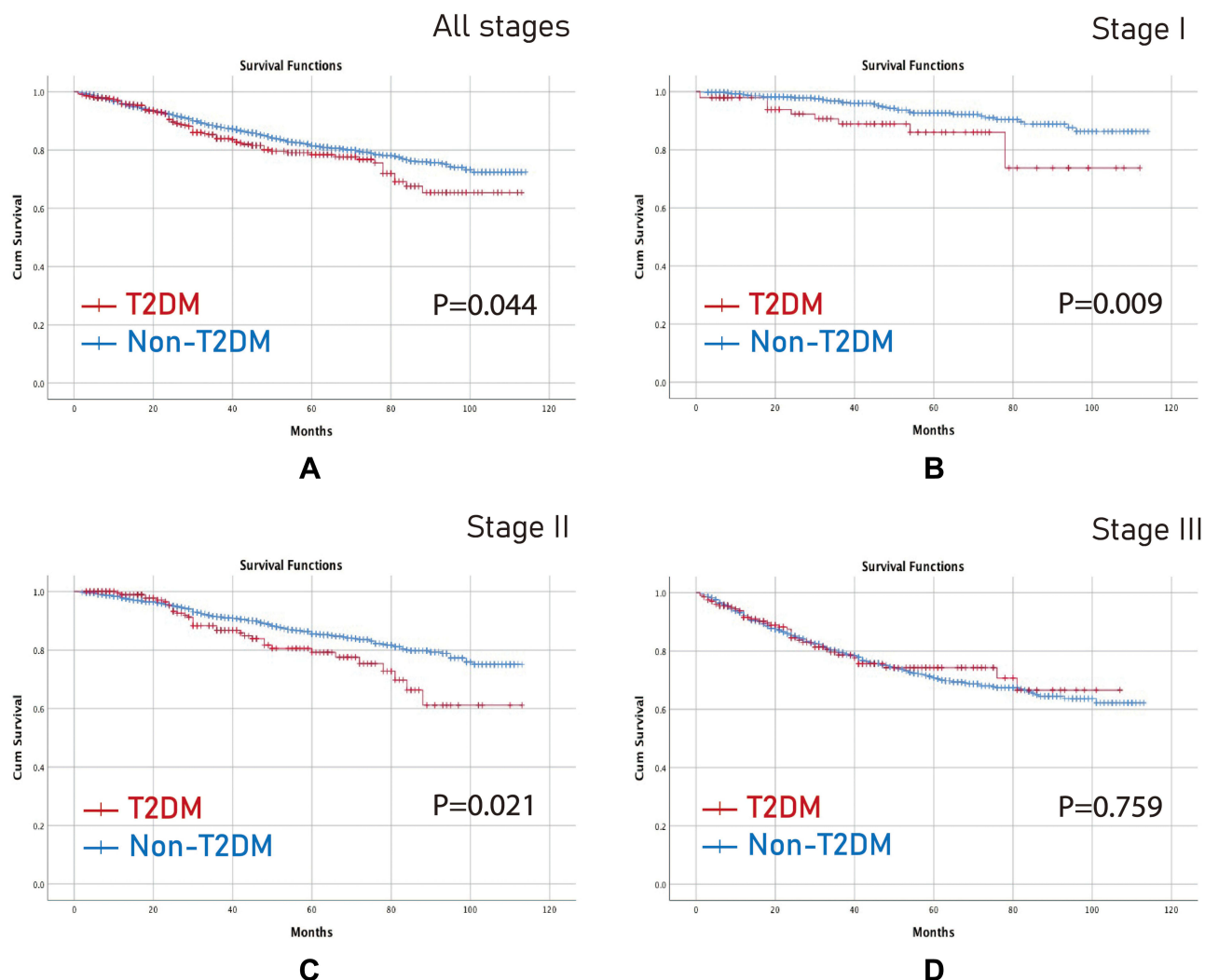


Figure 2 OS before PSM. (A) All stages; (B) Stage I; (C) Stage II; (D) Stage III.

Abbreviations: OS, overall survival; T2DM, type 2 diabetes mellitus; PSM, propensity score matching.

DFS before PSM

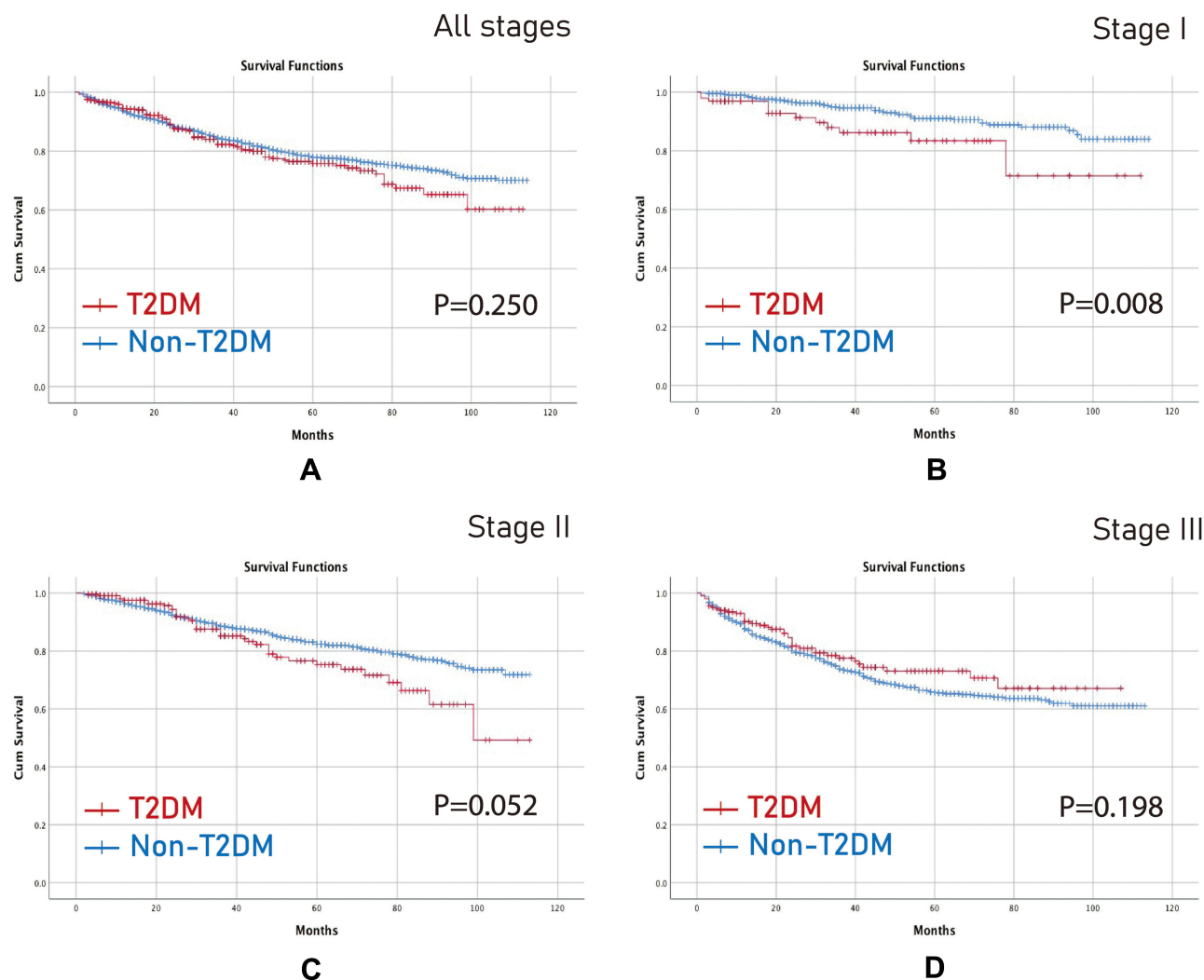


Figure 3 DFS before PSM. (A) All stages; (B) Stage I; (C) Stage II; (D) Stage III.

Abbreviations: DFS, disease-free survival; T2DM, type 2 diabetes mellitus; PSM, propensity score matching.

The mechanism of the outcomes between CRC and T2DM remained unclear, but some hypotheses have been reported. T2DM might enhance the chemo-resistance of CRC and hyperglycemic status affected the sensitivity to chemotherapy through multiple regulatory routes.^{23,24} Epidemiological studies reported metformin improved OS and DFS. Metformin enhanced response to radiotherapy and chemotherapy through synergistic interactions, indicating that it might help induce tumor regression.^{25,26}

PSM analysis is a statistical technique, which can deal with confounding bias and mimic a randomized clinical trial, improving the level of evidence in studies.²⁷ As far as we know, there were no related PSM studies about

T2DM and CRC, and this is the first study to analyze the potential effect of T2DM on CRC using PSM.

In this study, we analyzed the differences in surgical outcomes between T2DM group and non-T2DM group. It was found that the T2DM group had higher overall complications before and after PSM. Yap et al²⁸ reported higher overall complications and longer hospital stay in patients with T2DM, and higher complications were reported in another study as well.²⁹ The probable reason was that T2DM had poorer healing or comorbid with cardiovascular diseases.²⁸ Therefore, for surgeons, adequate perioperative management should be done for patients with concurrent CRC and T2DM.

OS after PSM

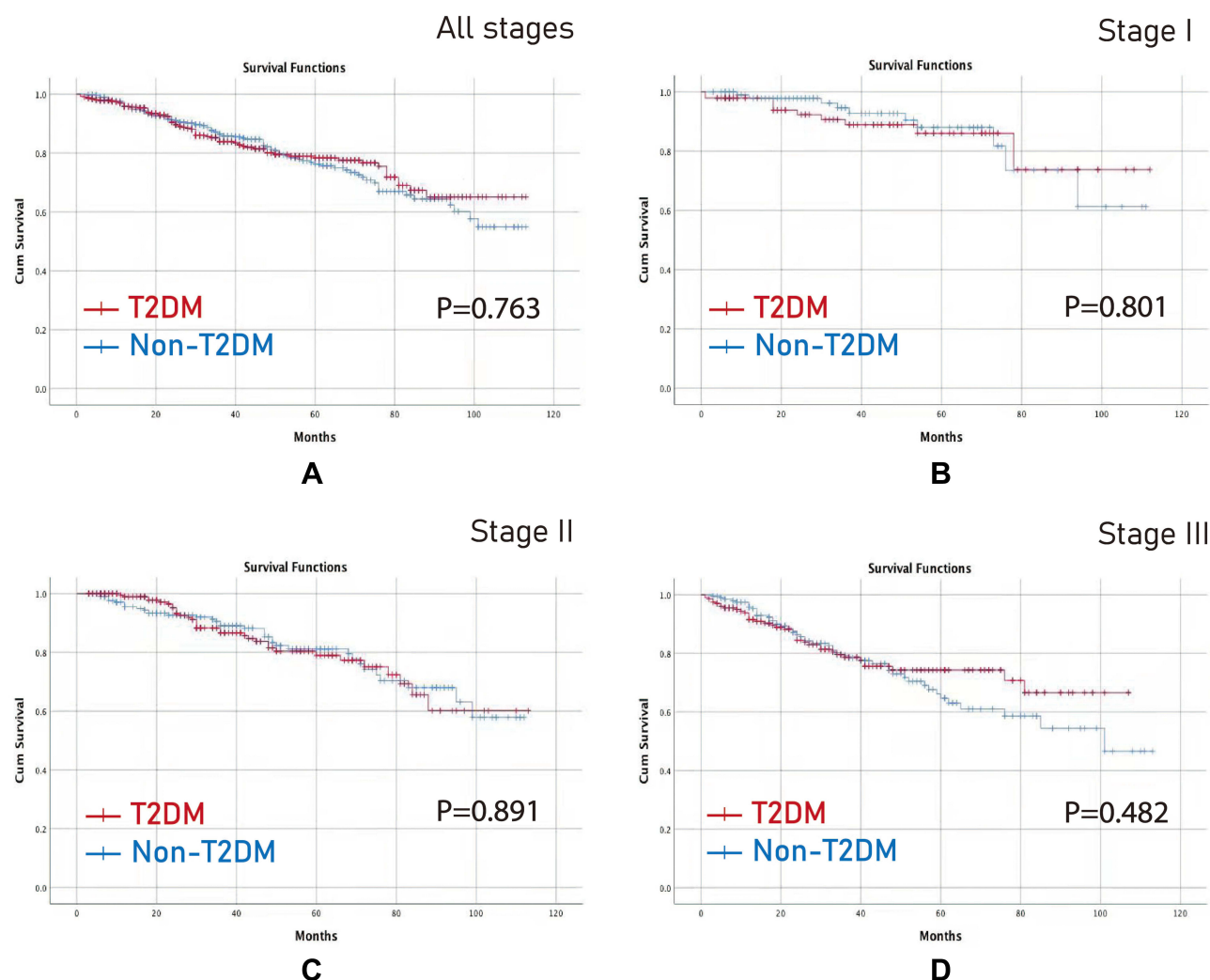


Figure 4 OS after PSM. (A) All stages; (B) Stage I; (C) Stage II; (D) Stage III.

Abbreviations: OS, overall survival; T2DM, type 2 diabetes mellitus; PSM, propensity score matching.

There were many factors that affected the prognosis of CRC, including age, tumor stage, and complications.^{30–32} In this study, we had the similar findings consistent with previous studies. In this study, T2DM was not a predictive factor in multivariate analysis. Furthermore, we examined T2DM at different stages of CRC to explore the exact impact of T2DM on OS and DFS. T2DM group had worse OS in all stages, stage I and stage II CRC and T2DM group had worse DFS than non-T2DM group in stage I CRC before PSM. We speculated that the possible reason was that patients had a longer OS in early tumor stage, T2DM and its related comorbidities might affect the prognosis. However, in advanced tumor stage, the tumor itself might affect the prognosis.

However, T2DM did not affect the OS or DFS at different stages of CRC after PSM, which represented that T2DM might not affect the prognosis of stage I–III CRC. Possible reasons for the null relationship between T2DM and CRC included duration and severity of T2DM, the type of T2DM medication used might be another reason.²¹ Further studies are needed in the future.

There were some limitations in this study. First, this was a retrospective single-center study; Second, the course and severity of T2DM were lacking, which might affect the outcome of CRC; Third, metformin use was another factor for T2DM, which needed to be analyzed in the future; Fourth, the follow-up time was relatively short. Therefore, larger sample size and multicenter prospective randomized controlled trials should be conducted in the following experiments.

DFS after PSM

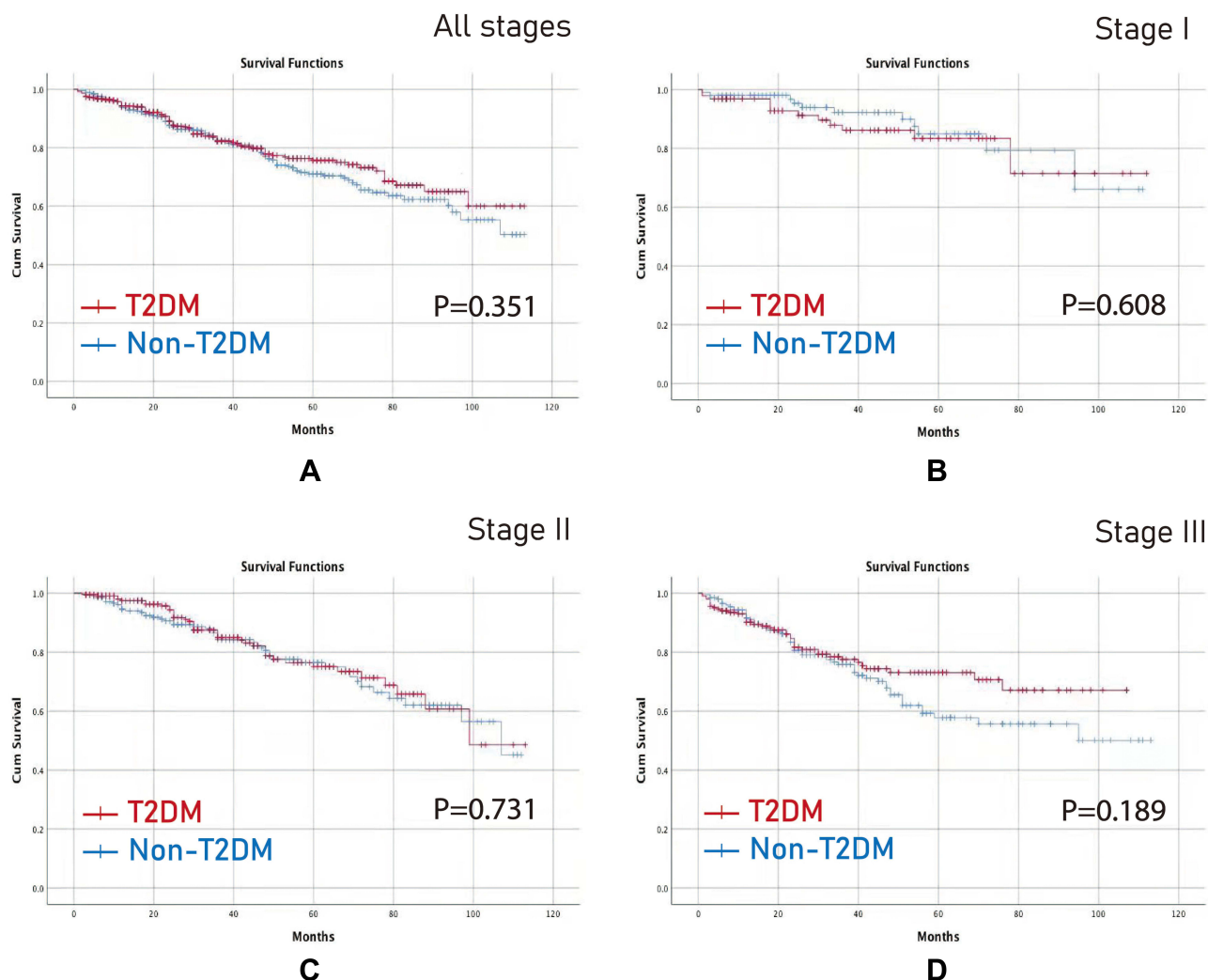


Figure 5 DFS after PSM. (A) All stages; (B) Stage I; (C) Stage II; (D) Stage III.

Abbreviations: DFS, disease-free survival; T2DM, type 2 diabetes mellitus; PSM, propensity score matching.

Conclusion

T2DM increased overall complications after primary CRC surgery. However, T2DM might not affect OS or DFS of CRC patients. Furthermore, T2DM did not affect the prognosis at different stages of CRC after PSM. Therefore, surgeons should be cautious when patients were with concurrent CRC and T2DM.

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Disclosure

The authors report no conflicts of interest in this work.

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