Original Article

Use of Metformin to Treat Type II Diabetes Mellitus Improved Colorectal Cancer Prognosis — A Retrospective Observational Study

Chia-Han Lee
Chung-Wei Fan
Wen-Ko Tseng
Yen-Lin Yu
Division of Colorectal Surgery, Department of Surgery, Chang Gung Memorial Hospital, Keelung, Taiwan

Key Words
Metformin;
Type II diabetes mellitus;
Colorectal cancer;
Prognosis

Purpose. There is conflicting evidence of the beneficial effect of metformin on survival in colorectal cancer (CRC) patients. We therefore performed a retrospective study to assess the association between use of metformin and outcomes of CRC patients with concomitant type 2 diabetes mellitus (T2DM).

Methods. Patients diagnosed with CRC with concomitant T2DM between January 1, 2006, and December 31, 2015, were identified in the Chang Gung Research Database. Overall survival and CRC-specific survival were estimated using the Kaplan-Meier method, and cumulative risks were compared between groups using the log-rank test.

Results. A total of 1673 T2DM patients with newly diagnosed CRC were included in this study. Overall survival was significantly higher in the metformin users than in the metformin non-users (hazard ratio [HR], 1.248; 95% CI, 1.1-1.415, $p < .001$). In subgroup analysis, post-diagnosis metformin users had better overall survival (HR, 1.718; 95% CI, 1.446-2.042, $p < .001$) and CRC-specific survival (HR, 1.489; 95% CI, 1.195-1.857, $p < .001$) than metformin non-users.

Conclusions. For T2DM patients with newly diagnosed CRC, the use of metformin had a protective effect on overall survival. Patients who began using metformin post-diagnosis also had significantly better overall survival and CRC-specific survival. These findings support the use of metformin as an adjuvant therapy for CRC.

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Colorectal cancer (CRC) is one of the most common cancers and a leading cause of mortality worldwide, accounting for approximately 935,000 deaths in 2020.[1] Epidemiologic studies have identified several risk factors for CRC,[2] including a high-fat diet, sedentary lifestyle, obesity, smoking, and alcoholic beverage consumption, which have been shown to be shared with type II diabetes mellitus (T2DM),[3-5] which is the most frequently occurring metabolic syndrome worldwide. Studies have shown that patients who suffer from T2DM have an approximately 21% to 36% higher incidence of CRC,[6,7] and that improving blood sugar control improved survival in patients with CRC.[8] These observational results have generated several hypotheses: (1) that decreasing high blood sugar associated complications, such as renal, retinal, and peripheral neuropathy, improved CRC patient survival; (2) amelioration of altered metabolism (Warburg ef-

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Correspondence to: Dr. Ling-Chiao Song, Division of Colon and Rectal Surgery, Department of Surgery, E-DA Hospital, No. 1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung 82445, Taiwan. Tel: 886-7-615-0011; Fax: 886-7-615-5352; E-mail: kulairumi@gmail.com

fect) by tumor, which further inhibits tumor growth; and (3) repurposing effect of hypoglycemic agents, which interfere tumor development and progression.

For decades, oral hypoglycemic agents have been used to control T2DM, markedly improving the convenience and compliance of patients' blood sugar control. Several groups of drugs are used today, including:

- Biguanides (metformin, buformin), which are insulin sensitizers;
- Thiazolidinediones (pioglitazone) and secretagogues (glipizide, gliclazide), which increase insulin secretion from the pancreas;
- Alfa-glucosidase inhibitors (acarbose), which slow down glucose absorption from the small intestine;
- Glycosurics (glifozins), which increase urine glucose secretion.

The choice of hypoglycemic agent depends on physician preference and patient factors. However, with the exception of metformin, most of these hypoglycemic agents have been found to be associated with poorer CRC survival and higher CRC incidence among T2DM patients.

Metformin is the most commonly used oral hypoglycemic drug because it is widely available and inexpensive and has a good safety profile.[9] A number of studies have reported its chemopreventive effect in several types of cancers, including CRC.[10-13] The mechanism underlying its chemopreventive effect is not well established, but most theories focus on suppression of cancer stem cells.[14] Recent advancements in molecular biology have seen a shift in our understanding of cancer-cell resistance from homogenous cancer cells in the entire bulk of tumor, to a heterogeneous, hierarchical distribution of cancer cells in the tumoral bulk that allows the cancer to evadecytotoxic, radiation, and immune-therapy treatments. One of the most important goals of research is therefore the identification of cancer stem cells responsible for cancer development, progression, metastasis, recurrence, and resistance to multiple therapeutic modalities.

According to previous cohort observational studies[15,16] of patients with T2DM, the incidences of CRC and rates of recurrence of large colon adenoma were lower in patients who took metformin for blood sugar control than in those who did not. These results further hinted at the possible role of the effect of T2DM on the initiation of CRC in terms of its responsibility for the existence of cancer stem cells. However, subsequent studies showed conflicting results regarding the effect of metformin on CRC survival.[17-21] Therefore, we performed a retrospective study, using the Chang Gung Research Database (CGRD), to assess the association between use of metformin and outcomes of CRC in CRC patients with concomitant T2DM.

Materials and Methods

The CGRD is derived from the electronic medical records of all patients from all Chang Gung Memorial Hospital departments. Patients' complete medical records, including medication history, imaging studies, biochemistry studies, surgery, and co-morbidities, were all collected. The study group comprised patients with a history of T2DM controlled by medication at least 6 months prior to the diagnosis of colorectal cancer and subdivided groups into metformin users before or after CRC diagnosis. All patients hospitalized between January 1, 2006, and December 31, 2015, were enrolled.

Patients were excluded who (1) had a history of another type of cancer or metachronous CRC; (2) had pathologic non-adenocarcinoma; (3) had American Joint Committee on Cancer Staging Manual, 8th Edition, stage 0 CRC; (4) were lost to follow-up within 3 months after diagnosis of CRC; or (5) died within 3 months after diagnosis of CRC. All included patients were followed until December 31, 2019. The primary endpoint was death from any cause during the study period. The secondary endpoint was tumor recurrence at any site during the study period. Metformin user was defined as a patient with two or more continuous prescriptions (> 6 months). International Classification of Diseases (ICD)-9 (153x or 154x) or ICD-10 (C18x~C20x) were used to screen for CRC-specific mortality.

Categorical variables were compared using the Chi-squared test and continuous variables using Stu-

dent's *t* test or Mann-Whitney *U* test. Overall survival and CRC-specific survival were estimated using the Kaplan-Meier method. The log-rank test was used to compare cumulative risks between groups. Differences with *p* values less than .05 were considered statistically significant. This study was approved by the Institutional Review Board of the Chang Gung Medical Foundation (202001537B0). All statistical analysis was conducted using SPSS Version 21.0 (IBM SPSS Statistics for Windows, Version 21.0; Armonk, NY, USA).

Results

A total 17,523 CRC patients diagnosed between January 1, 2006, and December 31, 2015, were identified, of whom 3977 were excluded by the study's exclusion criteria. After filtering those with concomitant T2DM, 3438 CRC patients were enrolled in our study. Excluding patients without newly diagnosed CRC with concomitant with T2DM, the final cohort was1673 T2DM patients with newly diagnosed CRC (Fig. 1). Patient demographic data, categorized by metformin use, are presented in Table 1. The two groups of patients were demographically similar, including sex, body mass index, smoking status, cancer staging, and Charlson Comorbidity Index (CCI) (Table 1).

During a median follow-up of 3.9 years (Q1-Q3, 0.9-6.1 years), 973 deaths (58.2%) occurred, including 579 CRC-specific deaths (34.6%). When grouped by metformin use, there were 485 deaths (54.9%) and 301 CRC-specific deaths (34.1%) in metformin users, compared with 488 total deaths (61.8%) and 278 CRC-specific deaths (35.2%) among metformin non-users. Overall survival was significantly higher in the metformin users than in metformin non-users (hazard ratio [HR], 1.248; 95% CI, 1.1-1.415, $p < .001$) (Fig. 2a). There were no significant differences in CRC-specific mortality within each groups (HR, 1.124; 95% CI, 0.955-1.323, $p = .16$) (Fig. 2b).

In subgroup analysis, we divided the metformin users into two groups by date of CRC diagnosis. There were no significant differences between pre-diagnosis metformin users and metformin non-users in overall survival (HR, 1.015; 95% CI, 0.874-1.178, $p = .846$) and CRC-specific survival (HR, 0.953; 95% CI, 0.785-1.156, $p = .623$) (Fig. 2c, d). In the post-diagnosis metformin-user group, overall survival (HR, 1.718; 95% CI, 1.446-2.042, $p < .001$) and CRC-specific survival (HR, 1.489; 95% CI, 1.195-1.857; $p < .001$) were significantly higher than in the metformin non-user group (Fig. 2e, 2f). The demographic data of the two groups are presented in Table 2. Metformin non-users were elderly and had a higher percentage of distant metastasis and more comorbidity. Multivariate analysis showed distant metastasis to be a confounding risk factor that decreased overall and cancer-specific survival (Table 3).

We extracted data for patients with stage II/III and stage IV for further analysis. Both groups were demographically similar to metformin non-users and users

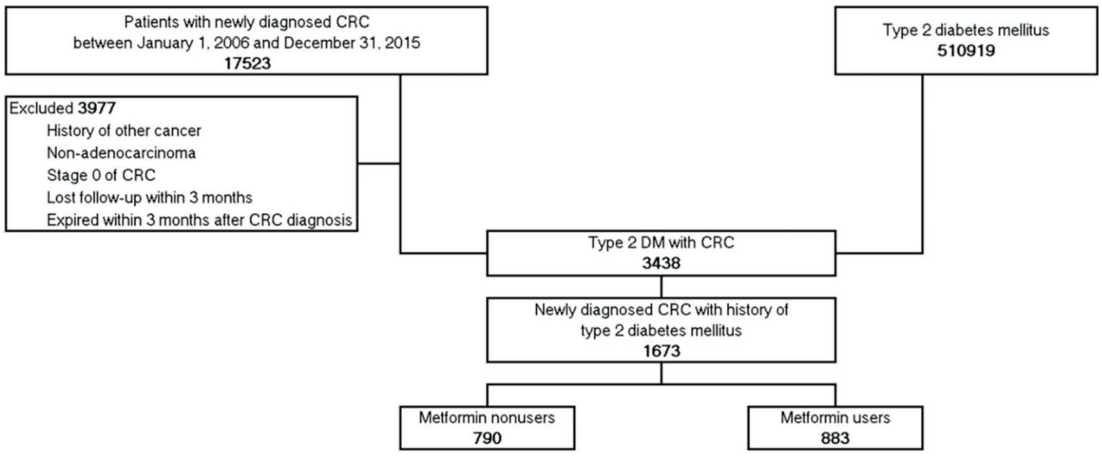

Fig. 1. Flow diagram of selection of T2DM patients with newly diagnosed colorectal cancer.

Table 1. Patient demographics and baseline clinical characteristics, metformin users vs. metformin non-users

	Nonusers (n = 790)	Metformin users (n = 883)	*p*
Age	71.8 ± 11.1	71.4 ± 10.1	0.394
Sex			0.155
Male	440 (55.7%)	461 (52.2%)	
Female	350 (44.3%)	422 (47.8%)	
BMI (kg/m^2)	24.9 ± 3.9	25.1 ± 4.4	0.392
NA	411 (52%)	427 (48.4%)	
Smoking			0.103
Yes	45 (5.7%)	65 (7.4%)	
No	300 (38%)	371 (42%)	
Quit	62 (7.8%)	58 (6.6%)	
NA	383 (48.5%)	389 (44.1%)	
T stage			0.072
1	55 (7%)	72 (8.2%)	
2	62 (7.8%)	68 (7.7%)	
3	418 (52.9%)	488 (55.3%)	
4	165 (20.9%)	190 (21.5%)	
NA	90 (11.4%)	65 (7.4%)	
Region lymph node metastasis			0.118
Yes	380 (48.1%)	425 (48.1%)	
No	327 (41.4%)	398 (45.1%)	
NA	83 (10.5%)	60 (6.8%)	
Distant metastasis			0.063
Yes	227 (28.7%)	228 (25.8%)	
No	474 (60%)	591 (66.9%)	
NA	89 (11.3%)	64 (7.2%)	
Charlson Comorbidity Index (CCI)	6.01 ± 2.2	6.16 ± 2.1	0.155

p value calculated using χ-squared test.
BMI, body mass index; CCI, Charlson Comorbidity Index; NA, not available.

(Table 4). Overall survival of post-diagnosis metformin users was significantly higher than for the metformin non-users (HR, 1.444; 95% CI, 1.116-1.869; $p < .005$ for stage II/III; HR, 1.607, 95% CI, 1.202-2.147, $p < .001$ for stage IV) (Fig. 3a, c). The CRC-specific survival of post-diagnosis metformin users with stage IV CRC was significantly higher than that of the metformin non-user group (HR, 1.373; 95% CI, 1.003-1.88, $p = .048$) (Fig. 3d).

Discussion

The similarity of risk factors such as sex, age, high-fat diet, obesity, and sedentary lifestyle between CRC and T2DM[22-24] led researchers to attempt to elucidate the possible shared mechanisms that promote the occurrence of CRC in T2DM patients. In several epidemiological studies, the use of hypoglycemic agents like insulin, sulfonylurea, dipeptidyl peptidase 4 (DPP-4) inhibitors, and glucose-dependent insulinotropic peptide (GLP-1) analogs have been reported to be associated with increased risk of several cancers, including CRC. In contrast to these findings, metformin, a biguanide widely used by patients with T2DM, was reported to decrease the incidence of, and improve survival in patients with, CRC and several other cancers. Reductions in the incidences of multiple cancers, including CRC, in T2DM patients who used metformin were demonstrated in a 2005 retrospective epidemiologic study conducted in Scotland[25] as well as in other studies, where it also played inhibitory roles in tumor progression; e.g., in angiogenesis, proliferation, metastasis, and radio-chemotherapy resistance.[26-30] Most recent meta-analysis[31] of 58 articles found that the use of metformin had reduced 23% of colon ad-

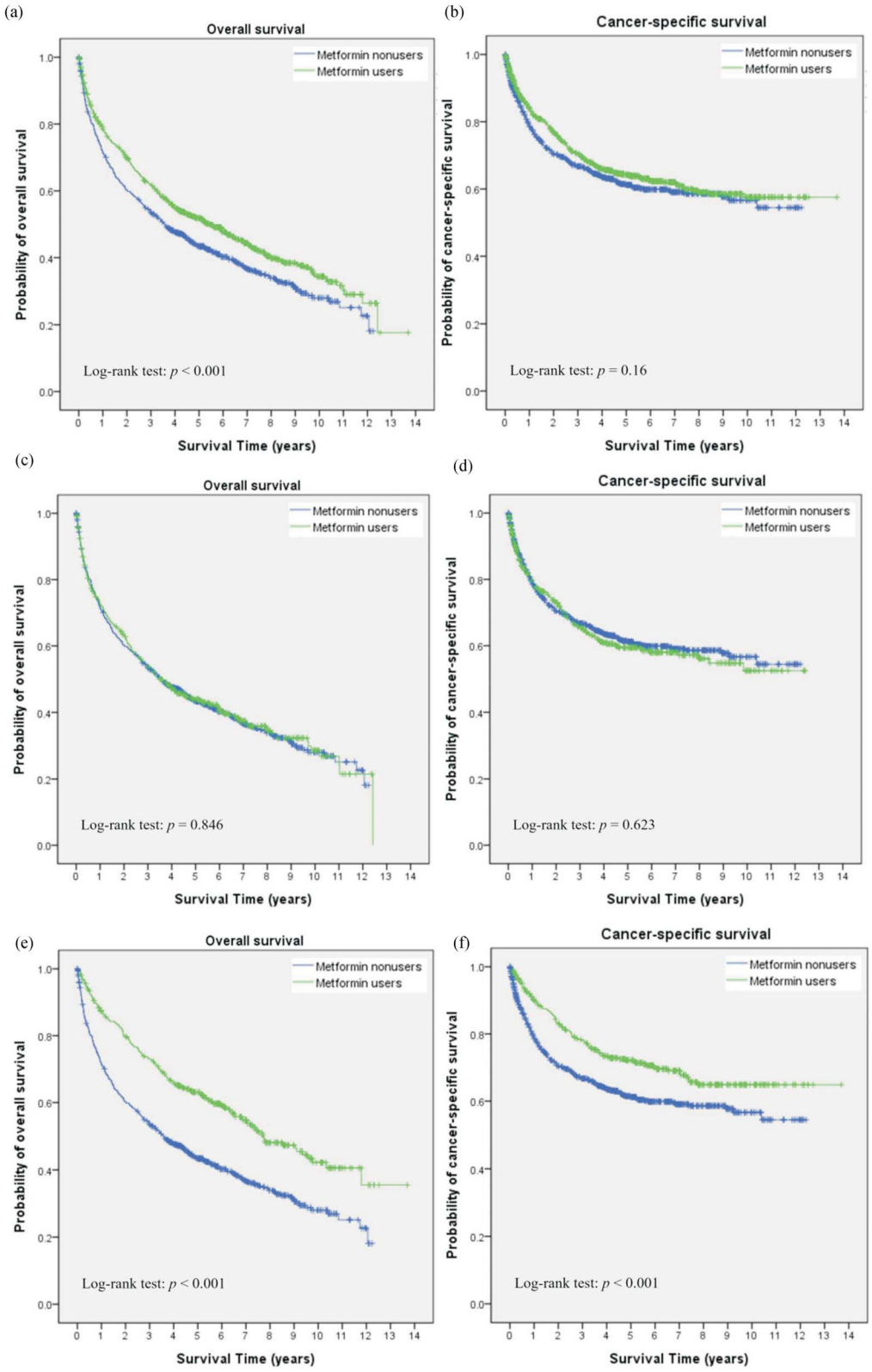

Fig. 2. Overall survival and cancer-specific survival assessed by Kaplan-Meier method. (a, b) overall, (c, d) pre-diagnosis metformin use, (e, f) post-diagnosis metformin use.

Table 2. Patient demographics and baseline clinical characteristics, non-users vs.post-diagnosismetformin users

	Nonusers (n = 790)	Metformin users (n = 381)	*p*
Age	71.8 ± 11.1	69.9 ± 9.8	0.003
Sex			0.211
Male	440 (55.7%)	197 (51.7%)	
Female	350 (44.3%)	184 (48.3%)	
BMI (kg/m^2)	24.9 ± 3.9	25.3 ± 4.4	0.214
NA	411 (52%)	177 (46.5%)	
Smoking			0.061
Yes	45 (5.7%)	25 (6.6%)	
No	300 (38%)	170 (44.6%)	
Quit	62 (7.8%)	19 (5%)	
NA	383 (48.5%)	167 (43.8%)	
T stage			0.086
1	55 (7%)	32 (8.4%)	
2	62 (7.8%)	38 (10%)	
3	418 (52.9%)	190 (49.9%)	
4	165 (20.9%)	93 (24.4%)	
NA	90 (11.4%)	28 (7.3%)	
Region lymph node metastasis			0.056
Yes	380 (48.1%)	168 (44.1%)	
No	327 (41.4%)	186 (48.8%)	
NA	83 (10.5%)	27 (7.1%)	
Distant metastasis			0.043
Yes	227 (28.7%)	78 (20.5%)	
No	474 (60%)	276 (72.4%)	
NA	89 (11.3%)	27 (7.1%)	
Charlson Comorbidity Index (CCI)	6.01 ± 2.2	5.47 ± 2	< 0.001

p value calculated using χ-squared test.

BMI, body mass index; CCI, Charlson Comorbidity Index; NA, not available.

Table 3. Overall survival and cancer-specific survival of post-diagnosis metformin users assessed by the Cox regression model

	Overall survival			Cancer-specific survival		
	Adjusted odds ratio	95% CI	*p*	Adjusted odds ratio	95% CI	*p*
Male	1.035	0.642-1.669	0.886	0.786	0.459-1.347	0.381
Age	0.945	0.893-1.13	0.11	0.961	0.923-1.061	0.053
BMI	1.01	0.951-1.073	0.742	1.001	0.938-1.068	0.973
Smoke	0.853	0.516-1.409	0.534	1.143	0.505-2.585	0.794
R	0.723	0.251-1.33	0.102	0.831	0.688-1.12	0.097
D	0.83	0.64-0.981	0.041	0.91	0.72-0.989	0.046
Charlson Comorbidity Index (CCI)	1.012	0.885-1.157	0.86	1.1	0.946-1.279	0.215
Post-diagnosis metformin use	1.882	1.47-2.41	< 0.001	1.321	1.013-1.721	0.034

BMI, body mass index; D, distant metastasis; R, regional lymph node.

enomas and 39% of advanced colon adenomas. The 24% decrease in the incidence of CRC in metformin users was statistically significant, as were increases in overall survival (40%) and CRC-specific survival (36%).

The underlying mechanisms associated with the beneficial effects of metformin include the activation of adenosine monophosphate (AMP) protein kinase (AMPK),[32] inhibition of phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of

Table 4. Patient demographics and baseline clinical characteristics of patients with stage II/III and stage IV CRC

	Stage 2/3			Stage 4		
	Nonusers (n = 369)	Metformin users (n = 472)	*p*	Nonusers (n = 227)	Metformin users (n = 228)	*p*
Age	70.9 ± 10.3	71.3 ± 10.2	0.633	74.1 ± 12.1	72.6 ± 10.5	0.156
Sex			0.627			0.05
Male	201 (54.5%)	249 (52.8%)		126 (55.5%)	108 (47.4%)	
Female	168 (45.5%)	223 (47.9%)		101 (44.5%)	120 (52.6%)	
BMI (kg/m^2)	24.7 ± 3.5	24.8 ± 4.3	0.684	24.9 ± 4.6	25.2 ± 4.5	0.557
NA	162 (43.9%)	195 (41.3%)		120 (52.9%)	122 (53.5%)	
Smoking			0.767			0.857
Yes	29 (7.9%)	41 (8.7%)		9 (4%)	13 (5.7%)	
No	161 (43.6%)	219 (46.4%)		93 (41%)	92 (40.4%)	
Quit	31 (8.4%)	35 (7.4%)		16 (7%)	15 (6.6%)	
NA	148 (40.1%)	177 (37.5%)		109 (48%)	108 (47.4%)	
T stage			0.56			0.378
1	2 (0.5%)	7 (1.5%)				
2	10 (2.7%)	11 (2.3%)		1 (0.4%)	4 (1.8%)	
3	251 (68%)	326 (69.1%)		167 (73.6%)	162 (71.1%)	
4	106 (28.7%)	128 (27.1%)		59 (26%)	62 (27.2%)	
Region lymph node metastasis			0.768			0.364
Yes	200 (54.2%)	251 (53.2%)		206 (90.7%)	200 (87.7%)	
No	169 (45.8%)	221 (46.8%)		21 (9.3%)	28 (12.3%)	
Charlson Comorbidity Index (CCI)	5.93 ± 2.2	6.15 ± 2.1	0.143	6.29 ± 2.4	6.3 ± 2.2	0.972

p value calculated using χ-squared test.
BMI, body mass index; CCI, Charlson Comorbidity Index; NA, not available.

rapamycin (mTOR)[33,34] and insulin-like growth factor (IGF)-1 signaling pathways.[35,36] AMPK is an energy-sensing kinase that is activated when intracellular AMP concentration increases. Metformin activates liver kinase B-1 (LKB-1), which directs phosphorylated AMPK to activate AMPK;[37] metformin also interacts with intracellular mitochondrial respiratory chain complex 1,[38,39] which interferes with the synthesis of ATP and further increases AMP concentration in cytoplasm. As the AMP/ATP ratio increases, AMPK is further activated. The activation of AMPK promotes a shift in cellular metabolism from anabolic to catabolic and further enhances cellular autophagy through activation of Unc-51-likeautophagy-activating kinase 1 (ULK1).[40] AMPK activation also inhibits protein synthesis through the activation of tuberous sclerosis protein complex 1/2 (TSC1/2), which inhibits them TOR signaling pathway and intracellular protein synthesis/translation and further arrests the cell cycle and proliferation.[41] Furthermore, AMPK activation also inhibits the insulin/ILGF-1 receptor pathway and further inhibits the PI3K/Akt/mTOR signaling pathways, which are crucial for CRC tumorigenesis and angiogenesis.[42,43] All these mechanisms may explain the inhibitory effects of metformin on CRC development and progression.

Characteristic of T2DM is the decreased sensitivity of insulin, compared with that of people without diabetes mellitus, in tissues in which serum insulin/glucose level is substantially elevated. The elevated serum insulin level/hyperglycemia further induces and increases the expression of ILGFs, which in turn promote tumorigenesis of epithelial cells, as in CRC,[44] and the higher incidence of cancer in T2DM patients maybe explained by this phenomenon. Becker et al. mention in their review that greatly reduced CRC survival in T2MD patients has also been observed,[45] and both all-cause mortality and CRC-specific mortality were significantly increased in CRC patients with T2DM.[46] In patients with advanced CRC, those with comorbid T2DM had poorer survival than non-diabetic CRC patients. These observational results re-

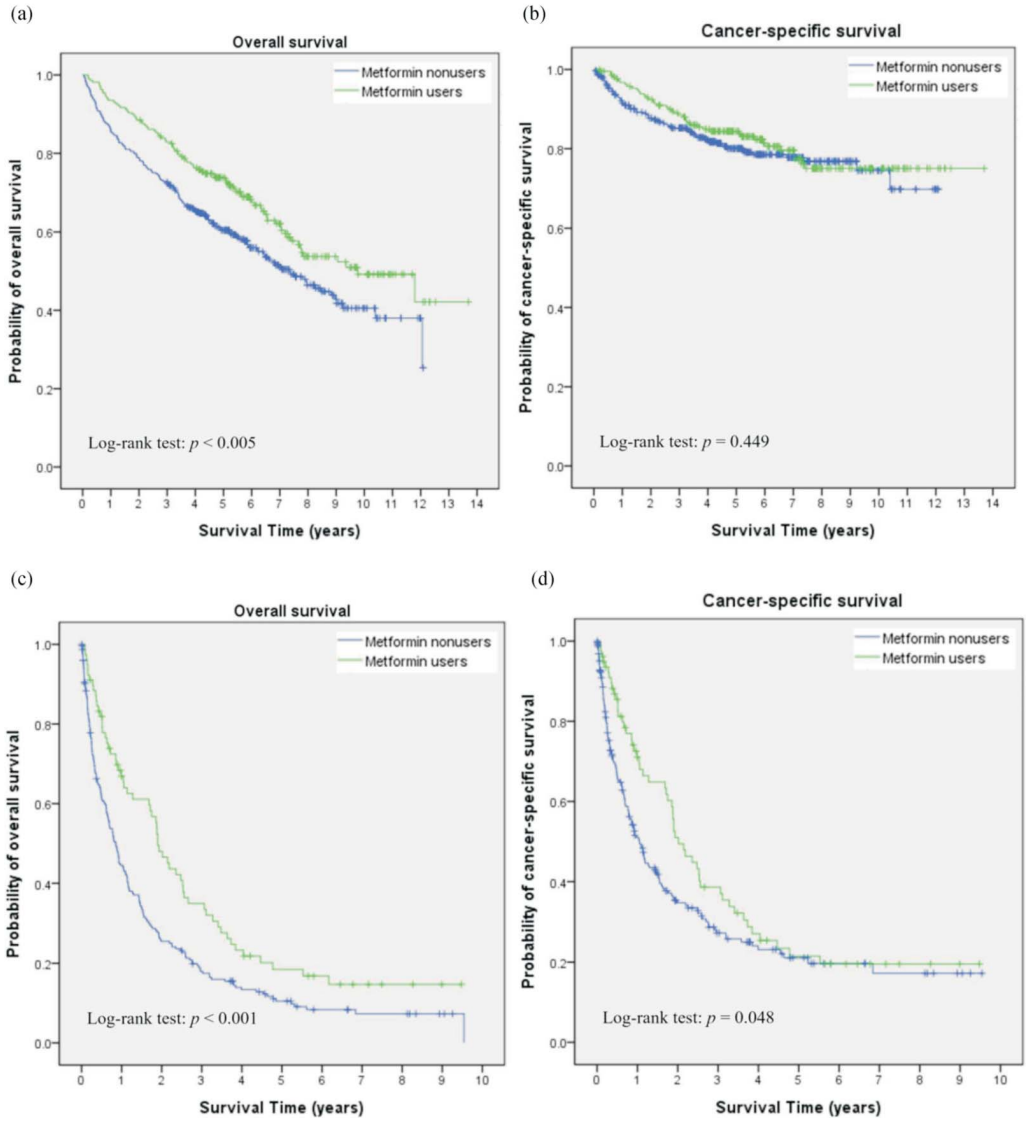

Fig. 3. Overall survival and cancer-specific survival assessed using Kaplan-Meier method. (a, b) Stage II/III, (c, d) stage IV.

vealed worse prognoses in patients who used insulin or insulin analogs for blood sugar control.[47]

These studies demonstrate that T2DM is a negative prognostic factor in CRC patients. Although using insulin can improve blood sugar control and lead to more stable HbA1C monitoring, insulin and its analogs may further erode CRC survival. In contrast, metformin had cancer-protective effects, even off setting the negative effects of other hypoglycemic agents. The chemoprotective effect of metformin in CRC patients is consistent with our results, which showed that T2DM patients who received metformin therapy had significantly better overall survival. This effect can also be seen in patients who use metformin after CRC diagnosis and treatment. The benefit CRC patients received from metformin maybe explained by the inhibitory effect on CRC stem cells. It is believed that CRC stem cells are responsible for cancer recurrence and metastasis, as well as for resistance to therapies. Our results showed that further improvement in CRC-specific survival after the introduction of metformin could be a manifestation of metformin's interference with the development of CRC stem cells.

This study has several limitations. First, this is a

non-randomized retrospective study. Second, we had a limited sample size in a single institution and presumably mostly non-heterogeneous population with regard to race/ethnicity, especially in subgroup analysis based on cancer stage and the timing of metformin use, which may have led to type I errors (false-positive results). Third, the absence of hemoglobin A1c surveillance might affect the assessment of diabetes severity. Fourth, metformin may have been prescribed before a patient's first visit to our hospital. Fifth, we could not know patients' medication compliance; in particular, gastrointestinal adverse effects related to metformin could have reduced compliance.

Conclusion

In the present study, metformin is associated with significant decrease in overall mortality in T2DM patients with newly diagnosed CRC. In subgroup analysis, post-diagnosis use of metformin was significantly associated with higher rates of both overall survival and CRC-specific survival. Further dividing CRC patients into stage II/III and stage IV groups showed that metformin users had significantly better overall survival than metformin non-users. In all comparisons, the beneficial effect of metformin as adjuvant for CRC in previous studies can also seen in our results. These findings support the use of metformin as an adjuvant treatment for T2DM patients with CRC. We would like to proceed the prospective randomized study to further validate these result in the future.

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原　著

雙胍類降血糖藥對於患有糖尿病的大腸直腸癌患者的預後有幫助 – 回顧性觀察研究

李佳翰　范仲維　曾文科　游彥麟

長庚紀念醫院　基隆分院　大腸直腸外科

目的　雙胍類降血糖藥在之前的文獻都有提到對於大腸直腸癌病人的存活率有改善，但有一些文獻則認為沒有幫助。因此我們想運用長庚研究資料庫來探討雙胍類降血糖藥對於患有糖尿病的大腸直腸癌患者的預後是否有所幫助。

方法　我們運用長庚研究資料庫，擷取從 2006 年 1 月 1 日到 2015 年 12 月 31 日診斷大腸直腸癌同時有第二型糖尿病的患者來進行分析。收集包含病患性別、年齡、身體質量指數、腫瘤期別、共病性。雙胍類降血糖藥使用定義為六個月內至少服用兩次以上的處方。最後分析有使用藥物和沒使用藥物兩組病患的整體存活率和癌症特異性存活率。

結果　研究結果顯示，我們收錄了 1673 名病患，有使用雙胍類降血糖藥的病患其整體存活率較沒使用的好。在分組分析之下，診斷大腸直腸癌之後才開始使用雙胍類降血糖藥的病患，其整體存活率和大腸直腸癌存活率都比沒使用的患者好。

結論　我們的研究證實雙胍類降血糖藥對於大腸直腸癌同時有第二型糖尿病的患者的存活率是有幫助的，尤其是大腸直腸癌診斷後的持續使用。

關鍵詞　雙胍類降血糖藥、第二型糖尿病、大腸直腸癌、預後。