의학석사 학위논문

Prognosis of colorectal cancer patients with diabetes according to medication adherence: A population-based cohort study

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Abstract

Prognosis of colorectal cancer patients with diabetes according to medication adherence: A population-based cohort study

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Diabetes mellitus (DM) is known to have negative effect on colorectal cancer (CRC) survival due to hyperinsulinemia, hyperglycemia or DM therapy. Diabetic medications such as metformin, which targets to lower insulin resistance and improve hyperinsulinemia, has preventive effect for the risk and death of CRC in diabetes patients. The aim of this study is to compare the risk of death in CRC patients with diabetes between different adherence levels to diabetic medications in a large size database.

We used National Health Information Database (NHID), which has the entire claims data for whom are registered in national

health insurance of Korea, from 2002 to 2016 for conducting a retrospective cohort study. Newly diagnosed CRC patient among diabetics were followed up from the date of diagnosis until death or Deccember 31st, 2016. The medication adherence was calculated with proportion of days covered (PDC) for oral diabetic agents with prescription data during CRC follow-up. Hazard ratios (HR) and 95% confidence interval (CI) for death were estimated using the low adherence diabetes patients as reference, and subgroup analyses were done by CRC sub sites.

A total of 33,841 diabetic patients were newly diagnosed with CRC whom were followed up for average 4.7 years. CRC patients with good adherence (PDC≥80%) showed reduced risk of death [HR (95% CI) 0.93 (0.89 - 0.97)] compared to poor adherence group (PDC<80%). CRC in distal colon showed protective effect with good adherence [HR (95% CI) 0.82 (0.76 - 0.91)] while CRC in proximal colon and rectum had no significant difference in risk of death [HR (95% CI) 0.96 (0.90 - 1.02) and 0.94 (0.86 - 1.03)].

Maintaining good medication adherence was related to favorable prognosis of CRC especially in distal colon.

Keywords: Colorectal Cancer, Diabetes Mellitus, Adherence, Cancer Prognosis

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Introduction

Colorectal Cancer in Korea

Colorectal cancer (CRC) is one of the most important diseases to Korean as it's age-standardized incidence rate (30.7/100,000) marks third and age-standardized mortality rate (8.2/100,000) marks fourth out of all types of cancer in both sex in 2016. After stratification by sex, age-standardized incidence and mortality rates were 40.4 and 11.1 per 100,000 in men, 22.4 and 5.9 per 100,000 in women (1). In spite of the fact that the trend of CRC incidence and mortality rates are declining since the year 2011, the seriousness of this disease affecting public health of Korea cannot be underestimated as in a single year of 2016, more than 28,000 people were diagnosed with it and more than 8,300 were dead (1).

Survival of the CRC patients has been dramatically improving in both sex, as 5-year relative survival was 77.8% and 73.2% from 2012 to 2016 in men and women respectively compared to 55.3% and 54.2% from 1993 to 1995 (1). Consequently, the

number of prevalent cases has been increased and as of January of 2017, 236,431 CRC patients diagnosed between 1999 and 2016 were alive (1). Therefore, management of CRC survivors such as coping with comorbidities should be prioritized in order to help the patients.

Diabetes Mellitus in Korea

Number of patients suffering from diabetes mellitus (DM) in Korea is increasing since 1998 (2). As of 2017 the prevalence of DM in adults aged 30 or more is up to 12.4% according to the data from the Korean National Health and Nutrition Examination Survey (KNHANES) (3). In one research done in Korea about the incidence trend of DM reported that age at DM diagnosis is getting younger every year since 2004. In 2012 more than 40% of newly diagnosed ones are in their 40s and 50s while it was not more than 30% in 2004, prolonging the period that DM is affecting each patient (4). This could be interpreted that, if this trend keeps in path, health effect directly or indirectly caused by DM will be catastrophic.

Colorectal Cancer & Diabetes Mellitus

Association between DM and cancer including CRC are widely accepted following a 2010 consensus report from American Diabetes Association (5), and many epidemiological studies are supporting that. Meta-analyses about DM and risk of CRC reported the increased relative risks of CRC of 1.30 (95% CI 1.20 – 1.40) and 1.37 (95% CI 1.30 – 1.45) (6, 7). Furthermore, there was a systematic review and meta-analysis done in 2008 reporting increased risk for long-term, all-cause mortality of CRC patients with preexisting DM [Pooled HR (95% CI), 1.32 (1.24 – 1.41)] (8).

Potential molecular mechanism explaining the linkage between CRC and DM are hyperinsulinemia, hyperglycemia or DM therapy. Medication for DM therapy such as insulin shows anti-apoptotic properties and tumor-enhancing effect in colon epithelium that are the results of working as growth factor through insulin receptor or insulin growth factor receptor while metformin is associated with decreased incidence and better survival via activation of AMP-activated protein kinase (AMPK).(5, 9, 10).

In spite of the fact that appropriate control of DM in CRC patient to cope with hyperglycemia or hyperglycemia is in importance, treatment rate and medication adherence of Korean population are far lower than expected. Treatment rate was 36.7 – 52.4% in 2012 depending the residential area of the patient (11), and calculated medication adherence by Medication possession ratio (MPR) was only 45% in 2013 (12). Consequently, proportion of DM patients achieving targeted HbA1C level is small as only 45.6% had its level controlled below 7.0% and 26% below 6.5% in 2014 (13).

Evaluation of medication adherence

Adherence to medication could be evaluated in either direct method, which includes observing the patient taking pills or measuring metabolite or biologic marker in blood sample, or indirect method such as patient questionnaires, assess rates of prescription refills or measuring physiologic markers (14). If one intends to estimate adherence in claims data when direct methods are not possible, two most commonly used approaches are available, the medication possession ratio (MPR) and the proportion of days covered (PDC) (14). MPR is calculated as

the days supplied or prescribed over the evaluation period divided by the duration from the first prescription to the end of the evaluation period (15). The PDC is calculated as the number of days with drug on hand divided by the number of days in the specified time interval (15). Although MPR has been used for over 2 decades and can produce results similar to other measures of adherence, PDC entails looking at each day in the designated time period as a simple binary measure indicating the presence or absence of a study drug, and is a more suitable method in clinical situations in which multiple medications within a class are often used concurrently (16).

Modification of prognosis of Colorectal Cancer

Even though probable causes influencing the risk of CRC is relatively well described and dealt with in many previous studies (17, 18), modifiable factors affecting prognosis is still not well recognized (19, 20). Prognosis, or survival, of a CRC patient is largely dependent on non-modifiable factors such as cancer staging, cancer treatment, or patient's basic characteristics like sex or age at diagnosis (21). That is in other words, once a patient is diagnosed with CRC, his/her

expected course of disease progression is roughly determined at that time.

However, according to one study summarizing prospective cohort studies emphasizing on modifiable factors that affects survival outcomes in CRC patients, there are a few yet limited evidence of possible modification done for better prognosis. This study describes that maintaining a normal weight, participating in regular physical activity, and avoiding unhealthy diet may be important preventive steps for improving survival outcomes (19).

Possibility of medication adherence as modifiable factor

Besides a few modifiable factors described above, medication lowering blood glucose and improving hyperinsulinemia such as metformin could be in effect when taken properly as directed (9, 10). Nonetheless, not every DM patients are taking only metformin, effect on prognosis of CRC of numerous other medication or combined effect of them are not well understood.

In a clinical point of view, if the relation between medication adherence of oral anti-diabetics combined and prognosis of CRC is identified, medical professionals could take advantage of it and spread direct and simple message for improving CRC outcome.

Purpose of this study

We aim to provide evidence to the thesis that CRC patients who were adherent to their diabetes medication will have better survival than patients who are not adherent. For that purpose, we tried to compare risk of death between CRC patients with different level of medication adherence for oral anti-diabetics.

Methods

Data Source

We used the National Health Information Database (NHID) of the National Health Insurance Service which is the entire claims data for who are registered in the insurance service (22). NHID provides data in two major forms. One is National Sample Cohort and the other one, which we acquired access and used for analyses, is Customized Database (DB). Customized DB consists of data which are collected, managed, and maintained by the NHIS and modified as requested by researchers in the purpose of policy or academic research, which includes basic demographics of every individual, records of inpatient and outpatient usage and related prescriptions, medical check-up results and date of death.

Identification of study subjects

First, we requested to gain access of all the patients who has three or more claims records of been diagnosed with 10^{th}

International Classification of Disease (ICD-10) codes C18 – C20 during the period 2002 and 2016 for the purpose of conducting a retrospective cohort study, tried to avoid overly approximating incidence rate of CRC than actual cancer registry data of Korea. Nevertheless, the acquired data showed higher incidence than the reported cancer incidence of Korea, since patients without CRC or at advanced-stage yet untreated patients could be included, we selected patients with certain claim code of treatment for CRC (Table 1) as CRC cases (23). In order to perform subgroup analyses by cancer subsite, patients who were diagnosed with ICD-10 codes C18.0 – C18.5, C18.6 – C18.7 and C19-C20 were classified as proximal colon cancer, distal colon cancer and rectal cancer, and all other codes such as C18.8, C18.9 or C18 were grouped into ETC.

Selection process for study population is depicted in figure 1. In order to identify medication adherence level for oral anti-diabetics, we excluded who has no history of being diagnosed with diabetes by ICD-10 code E10-E15 or being prescribed with medication from the date of CRC diagnosis. Codes used to

identify diabetes medication is listed in table 2. Individuals with only one prescription record were excluded since the adherence cannot be measured. Patients only who were already being prescribed with DM before the diagnosis of CRC were included.

Table 1. List of claims codes for treatment of colorectal cancer

Treatment type	Claims codes
Operation	
Rt. Or Lt. hemicolectomy	QA671, Q2671
Subtotal colectomy	Q1261, Q1262
Total colectomy	QA672, Q2672
Segmental resection	QA673, Q2673
Colectomy with proximal colostomy and distal stump	QA679, Q2679
Transanal Rectal tumor resection	Q2891
Transsacral or parasacral rectal tumor resection	Q2890
Abdominal approach rectal tumor resection	Q2892
Transanal endoscopic mmicrosurgery of rectal tumor resection	Q2893
Anterior resection	QA921, Q2921
Low anterior resection	Q2927, QA922, Q2922
Abdominoperineal resection	QA921, Q2923
Abdominal pull-through operation	QA924, Q2924
Total coloprotectomy with ileostomy	QA925, Q2925
Total coloprotectomy with ileal pouch-anal anastomosis	QA926, Q2926

Chemotherapy	
Capecitabine	122701ATB, 122702ATB
5-FU	161430BIJ, 161431BIJ, 161432BIJ
Leucovorin	566132BIJ, 566134BIJ, 622630BIJ, 622631BIJ, 622632BIJ, 521001BIJ, 521002BIJ
Irinotecan	177430BIJ, 177431BIJ, 177432BIJ, 177433BIJ, 177434BIJ, 177435BIJ, 177436BIJ, 177437BIJ
Bevacizumab	554330BIJ, 554331BIJ
Cetuximab	556430BIJ
Oxaliplatin	205830BIJ, 205834BIJ
Radiotherapy	HD051, HD054, HD052, HD055, HD053, HD056, HD057, HD058, HD059, HD061, HD071, HD072, HD073, HD080, HD081, HD082, HD083, HD084, HD085, HD086, HD087, HD088, HD089, HD111, HD112, HZ271

Table 2. List of codes for diabetes mellitus medication

Drug Class	Codes
Metformin	191501ATB 191502AGR 191502ATB 191502ATR 191503ATB 191504ATB 191504ATR 191505ATR 421100ATB 443400ATB 443500ATB 452700ATB 452900ATB 461200ATB 469100ATB 471800ATB 471900ATB 474200ATB 474300ATB 474300ATR 497200ATB 498100ATB 498600ATB 502200ATB 502300ATB 502300ATR 502900ATB 507000ATB 507100ATB 513700ATB 513700ATR 518500ATR 518600ATR 518800ATB 519600ATB 520500ATB 520600ATB 520700ATB 523600ATB 523700ATB 523800ATR 524700ATR 632000ATR 635600ATB 635700ATB 639800ATR 641400ATR 64160036J 641800ATR 641900ATR 642000ATR 64350084J 645000ATR 64810032J 648400ATB 648500ATB 648600ATB 649900ATR 650000ATR 650100ATR 653800ATR 653900ATR 654000ATR 66170011J 66890002J 639800ATR 641400ATR
Sulfonylurea	132001ATB 165401ATB 165402ATB 165501ATB 165601ACS 165602ACS 165602ATB 165603ATR 165604ATR 165701ATB 165702ATB 165703ATB 165704ATB 165801ATB 165901ATB 421100ATB 443400ATB 443500ATB 471900ATB 474200ATB 474300ATB 474300ATR 488800ATB 488900ATB 489000ATB 497200ATB 498600ATB 525500ATB 525600ATB A0096801

Thiazolidinedione	348001ATB 348002ATB 348003ATB 431901ATB 431902ATB 452700ATB 452900ATB 461200ATB 469100ATB 471800ATB 488800ATB 488900ATB 489000ATB 498100ATB 525500ATB 525600ATB 525901ATB 630500ATB 630600ATB 653800ATR 653900ATR 654000ATR
Alpha-glucosidase inhibitor	100601ATB 100602ATB 249001ATB 249001ATD 249002ATB 249002ATD 406201ATB 523600ATB 523700ATB A0237501 A0237601 A13800941
Dipeptidyl peptidase-4 inhibitor	500801ATB 501101ATB 501102ATB 501103ATB 502200ATB 502300ATB 502300ATR 502900ATB 507000ATB 507100ATB 513700ATB 513700ATR 518500ATR 518600ATR 519600ATB 520500ATB 520600ATB 520700ATB 523800ATR 524700ATR 613301ATB 613302ATB 616401ATB 619101ATB 624202ATB 624203ATB 627301ATB 630500ATB 630600ATB 632000ATR 635600ATB 635700ATB 639601ATB 641800ATR 641900ATR 642000ATR 645000ATR 645301ATB 648400ATB 648500ATB 648600ATB 649900ATR 650000ATR 650100ATR
Insulin	170101BIJ 170102BIJ 170103BIJ 170130BIJ 170131BIJ 170201BIJ 170401BIJ 170402BIJ 170403BIJ 170430BIJ 170431BIJ 170501BIJ 170502BIJ 170602BIJ 175301BIJ 175302BIJ 175303BIJ 175304BIJ 175330BIJ 175331BIJ 175332BIJ 175333BIJ 215701BIJ 327800BIJ 441301BIJ 441302BIJ 441303BIJ 441305BIJ 441330BIJ 441331BIJ 441332BIJ 441333BIJ 461801BIJ 461802BIJ 461804BIJ 461830BIJ 461831BIJ 461832BIJ 484901BIJ 484902BIJ 484930BIJ 484931BIJ 488701BIJ 488730BIJ 507401BIJ 626801BIJ 626830BIJ

Glucagon-like peptide-1 receptor agonist	512101BIJ 512102BIJ 512130BIJ 512131BIJ 626601BIJ 626602BIJ 626630BIJ 626631BIJ 639701BIJ 639702BIJ
Meglitinide	379501ATB 379502ATB 379503ATB 430201ATB 430202ATB 430203ATB 486101ATB 518800ATB
Sodium-glucose Cotransporter-2 Inhibitors	527302ATB 628201ATB 628202ATB 636101ATB

Evaluation of medication adherence

We used PDC, which is one of the most common methods used, to assess medication adherence in each CRC patients for oral anti-diabetics. Furthermore, we also assessed the adherence with MPR in order to compare the results with different measures. Adherence on prescribed injectable medications such as insulin or glucagon-like peptide-1 (GLP-1) receptor agonist were not measured. The data used to calculate PDC included prescriptions after the date of CRC diagnosis until the last prescription between 2002 and 2016. When multiple medications concurrently prescribed in a patient have different prescription duration, the shorter one is used to calculate PDC. Figure 3 shows the equations for calculating PDC and MPR. We categorized medication adherence into 2 groups: <80 and ≥80 for comparison.

Figure 1. Equations for calculating proportion of days covered (PDC) and medication possession ratio (MPR)

$$\text{PDC} = \frac{\text{Number of days in period "covered"}}{\text{Number of days in period}} \times 100$$

$$\text{MPR} = \frac{\text{Sum of days'supply for all fills in period}}{\text{Number of days in period}} \times 100$$

Covariates

We extracted a few factors widely accepted to be related with CRC besides age and sex such as insulin, metformin and aspirin usage. Individuals whomever received prescription during the period between 2002 and 2016 were categorized as ever user and was considered in analyses. Since our source data is derived from claims data, it lacks information of cancer staging data which is a critical element in comparing prognosis between different groups. Therefore, we categorized the study population into different cancer treatment they've received and regarded those as each different cancer staging considering the fact early stage patients usually are treated with surgery only while the most advanced staged ones typically receive palliative therapy with chemotherapy or radiotherapy without operation (24). Moreover, smoking and drinking status, which could be responsible to differ the patients' survival were analyzed. These behavioral variables were extracted from data of first health check-up available after CRC diagnosis.

Statistical Analyses

For basic characteristics, we used chi-square or t-test to compare between patients with different adherent level. Univariate regression analyses were done with basic characteristics which were possibly related with risk of death of CRC patients. Cox proportional hazard regression model was used to estimate risk of death of CRC patients as Hazard Ratios (HR) and 95% Confidence Interval (CI) using the non-adherent CRC patients as reference. Subgroup analyses were done by CRC subsites. Moreover, we performed same analyses after excluding patients with extremely low PDC (PDC lower than 5^{th} percentile) in order to eliminate the effect of outliers.

Results

Comparison of basic characteristics and survival probability curve between individuals included and excluded in this study are shown in table 4 and figure 3. Higher proportion of male, older patients were included as well as those diagnosed with proximal and distal colon cancer. Regarding the received cancer treatment, more patients received OP only or OP with CTx were included. Shorter follow-up period was observed in study population. According to survival curves, study population showed significantly worse survival throughout follow-up period compared to the patients excluded. Numbers of CRC patients diagnosed by age group at diagnosis from 2003 to 2016 are shown in table 3

Basic characteristics of CRC patients with diabetes by medication adherence are shown in table 5. Among 13,797 adherent patients (PDC $\geq$80), 62.5% were male and 37.5% were female, while 63.7% were male and 36.3% were female in 20,044 nonadherent patients (PDC <80). Mean age at diagnosis of CRC was higher in adherent patients. In terms of subsites of

CRC, adherent patients were diagnosed with proximal and distal cancer more frequently than nonadherent patients while proportion of rectal cancer was higher in nonadherent patients. Proportion of other CRC cancer (C18.8, C18.9 or individuals with code C18 which could be either proximal or distal colon cancer) were slightly higher in adherent patients. When we label the patients with the treatment they've taken by operation (OP), radiotherapy (RTx) or chemotherapy (CTx), more of the adherent patients received operative treatment only. Meanwhile, other treatment regimens such as OP with RTx, OP with both RTx and CTx and RTx or CTx without OP were higher in nonadherent patients. Mean follow-up were slightly longer in nonadherent ones. Calculated mean PDC was 87.4 and 64.7 in adherent and nonadherent patients respectively. Insulin, and aspirin usage were different between two groups of patients as proportion of insulin ever user were higher in nonadherent patients while proportion of aspirin usage was higher in adherent patients. No difference was found in metformin usage between both groups. There were 3,595 (26.1%) and 6,439 (32.1%) deaths in adherent and nonadherent patients respectively.

Table 6, table 7 and table 8 shows basic characteristics of patients diagnosed with proximal colon cancer, distal colon cancer and rectal cancer. In proximal colon cancer patients, percentage of male and female by adherence were 51.5, 48.5 and 54.5, 45.5, which were different from distal colon cancer and rectal cancer patients as higher proportion of female was included. Received cancer treatment and insulin usage were statistically different between adherence and there were smaller proportion received only OP and larger proportion received RTx or CTx in rectal cancer patients. Aspirin usage were different between adherence in all cancer patients, while insulin usage in proximal colon cancer patients and metformin usage in all cancer patients showed no difference between adherence.

We performed univariate regression analyses of patients' basic characteristics and risk of death (Table 9). Patients with higher PDC, female, younger age, earlier disease stage assumed by received cancer treatment, and ever user of metformin and

aspirin showed reduced risk of death while Insulin usage showed no relation to risk of death of CRC patients.

Results of the multivariate regression analyses of medication adherence and risk of death are shown in Table 10. Regardless of adjustments made on analyses, adherent CRC patients with high adherence to DM medication showed reduced risk of death than nonadherent patients. When we stratify the patients by CRC subsites, having higher adherent level for diabetes medication showed significantly protective effect on death in distal colon cancer patients while there was no change in risk of death in proximal colon and rectal cancer patients.

Table 11 shows the results of multivariate regression analyses after excluding patients with PDC lower than 5^{th} percentile. In both models, adherent CRC patients showed reduced risk of death than nonadherent patients by 4−5%, despite only the model one adjusted for sex, age at diagnosis and received treatment was statistically significant. In stratified analyses by CRC subsites, similar patterns were observed as table 9, the

relation between medication adherence and risk of death were observed only in distal colon but not in proximal colon cancer or rectal cancer.

For comparison, we also estimated the medication adherence by MPR and compared the results including basic characteristics of the cancer patients with those estimated by PDC. Characteristics shown in table 12 exhibits nearly the same pattern between adherence compared to table 4 except for little difference in number of patients, which is mainly caused by limiting cancer patients with MPR higher than 120. Multivariate regression analyses of medication adherence estimated by MPR and risk of death among colorectal cancer patients with diabetes mellitus are shown in table 13 and practically the same results as estimated by PDC which were shown in table 9. In other words, there are no noticeable difference in study results whether PDC or MPR is used for estimate patients' medication adherence.

We stratified CRC patients according to metformin or insulin

usage and performed multivariate regression analyses of medication adherence and risk of death in table 14 and table 15. Adherent metformin users showed reduced risk of death than nonadherent ones by 8% (distal colon cancer 19%), while metformin non-users' adherence showed no relation with risk of death. When stratified by insulin, only insulin non-users' adherence was related with lowered risk of death. We also stratified CRC patients by sex and received cancer treatment, since both variables showed significantly different distribution between subsites, and performed multivariate regression analyses, which is shown in table 16. Adherent patients for both sex showed reduced risk of death by 7-8%, while this risk reduction were shown only in patients received OP [HR (95% CI), 0.92 (0.87 – 0.98)] and OP with CTx [HR (95% CI), 0.85 (0.78 – 0.93)].

Table 17 shows the multivariate regression analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus according to different combinations of metformin, insulin or aspirin usage in order to

clarify that on which type of combination the drug adherence affects more on the risk of death. There are a total of 8 different combination groups and among them, only one group showed correlation of reduced risk of death by good drug adherence, which is metformin and aspirin user/ insulin non-user group [HR (95% CI), 0.89 (0.83 – 0.94)].

Smoking and drinking status of CRC patients, which could possibly exhibit certain behavioral patterns affecting their cancer survival, were shown according to medication adherence in table 18. There were more current smoker in nonadherent patients (12.0%) than adherent patients (8.8%) and among them, no statistically distinct daily cigarette consumption was observed. As for alcohol consumption, there were more proportion of patients who consumes no alcoholic drinks in adherent ones (83.5%) than nonadherent ones (81.3%). In terms of alcohol consumption amount, there was no statistical difference between adherence.

Table 3. Number of colorectal cancer (CRC) patients diagnosed by age group at diagnosis (2003 - 2016)

Age at diagnosis (Years)	N of CRC patients diagnosed													
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
20 - 24	0	0	0	0	0	0	0	1	0	0	0	0	0	0
25 - 29	0	0	0	0	0	1	0	0	1	0	0	1	0	0
30 - 34	2	0	0	1	1	2	1	0	2	0	2	1	2	2
35 - 39	5	2	2	6	5	9	9	10	5	2	5	4	10	9
40 - 44	17	15	22	23	19	23	15	22	30	19	29	34	23	26
45 - 49	38	46	51	67	50	73	79	73	64	75	69	74	63	93
50 - 54	75	96	114	136	145	158	208	191	205	236	223	206	240	164
55 - 59	120	168	214	240	283	286	317	364	404	402	418	414	399	474
60 - 64	249	290	313	331	390	413	498	552	599	588	571	548	512	635
65 - 69	283	317	388	491	577	540	655	709	688	670	693	638	687	749

70 - 74	206	261	323	434	516	576	661	708	824	908	853	883	784	793
75 - 79	89	125	176	228	290	315	426	476	556	620	677	700	735	834
80 - 84	39	58	58	74	115	125	170	194	229	298	345	342	367	484
85+	12	3	13	20	27	33	48	56	81	104	111	141	149	162
total	1,135	1,381	1,674	2,051	2,418	2,554	3,087	3,356	3,688	3,922	3,996	3,986	3,971	4,425

Figure 2. Selection process for study population

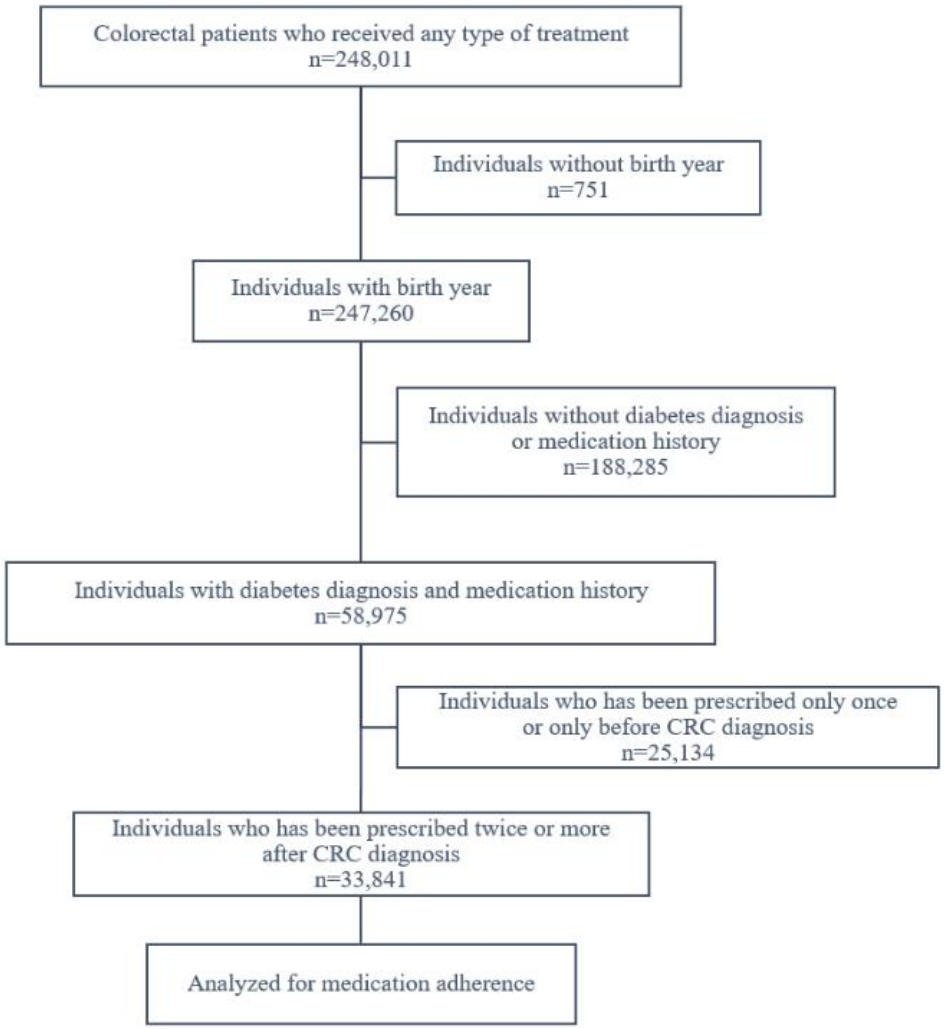

Table 4. Characteristics of colorectal cancer patients by study inclusion

	Included in study		Excluded in study		p-value
	N=33,841		N=213,419		
Sex, n(%)					
Male	21,397	(62.2)	126,250	(59.2)	<.0001
Female	12,444	(36.8)	87,169	(40.8)	
Age at diagnosis of CRC					
Mean±sd	67.2	±9.1	63.0	±12.2	<.0001
Cancer Subsite, n(%)					
Proximal colon	6,368	(18.8)	38,223	(17.9)	<.0001
Distal colon	7,870	(23.3)	47,529	(22.3)	
Rectum	13,100	(38.7)	87,047	(40.8)	
ETC	6,503	(19.2)	40,620	(19.0)	
Received cancer treatment, n(%)					
Op only	19,975	(59.0)	118,915	(55.7)	<.0001
Op with RTx	3,206	(9.5)	21,337	(10.0)	
Op with CTx	6,245	(18.5)	36,914	(17.3)	
Op with both RTx and CTx	1,795	(5.3)	13,112	(6.1)	
RTx or CTx without Op	2,620	(7.7)	23,141	(10.8)	
Follow-up period, years					
Mean±sd	4.7	±3.4	4.8	±3.8	<.0001

Deaths, n(%)	10,034	(29.7)	66,426	(31.1)	<.0001

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy

Figure 3. Survival probability of colorectal cancer patients by study inclusion

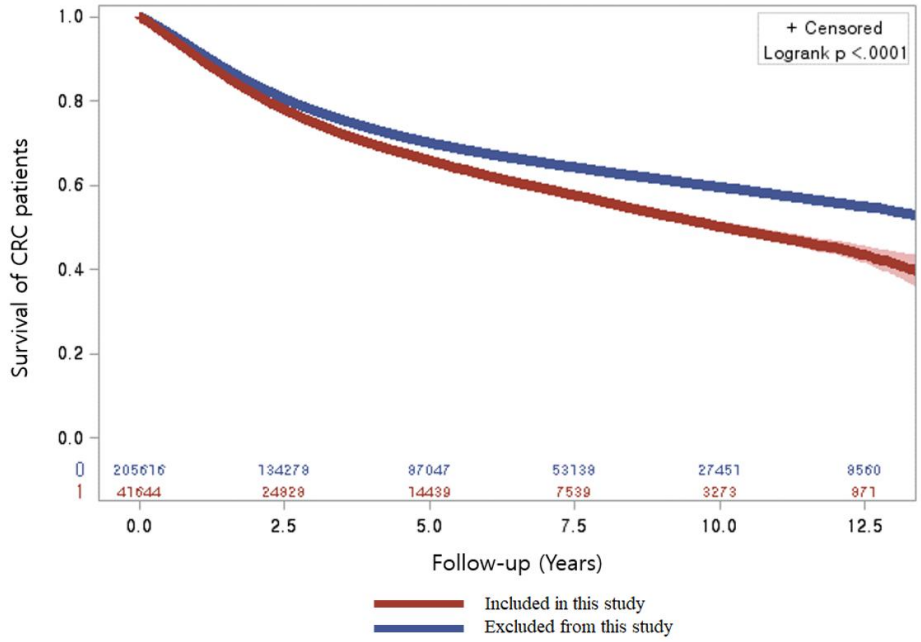

Table 5. Characteristics of colorectal cancer patients with diabetes mellitus by medication adherence

	PDC≥80		PDC<80		p-value
N(%)	13,797	(40.8)	20,044	(59.2)	
Sex, n(%)					
Male	8,625	(62.5)	12,772	(63.7)	0.0237
Female	5,175	(37.5)	7,272	(36.3)	
Age at diagnosis of crc					
Mean±sd	68.3	±8.8	66.5	±9.3	<.0001
Cancer Subsite, n(%)					
Proximal colon	2,790	(20.2)	3,578	(17.9)	<.0001
Distal colon	3,282	(23.8)	4,588	(22.9)	
Rectum	4,915	(35.6)	8,185	(40.8)	
ETC	2,810	(20.4)	3,693	(18.4)	
Received cancer treatment, n(%)					
Op only	8,466	(60.0)	11,509	(57.7)	<.0001
Op with RTx	1,150	(8.3)	2,056	(9.1)	
Op with CTx	2,613	(17.9)	3,632	(18.0)	
Op with both RTx and CTx	580	(4.1)	1,215	(5.4)	
RTx or CTx without Op	988	(9.7)	1,632	(9.9)	
Follow-up period, years					
Mean±sd	4.3	±3.4	4.9	±3.4	0.0003

PDC					
Mean±sd	87.4	±6.5	64.7	±15.6	<.0001
Q3	91.8		76.2		
Q2	84.9		70.2		
Q1	82.2		58.5		
Insulin ever user, n(%)					
Yes	1,812	(13.1)	2,886	(14.4)	0.0009
No	11,985	(86.9)	17,158	(85.6)	
Metformin ever use, n(%)					
Yes	13,073	(94.8)	18,947	(94.5)	0.3664
No	724	(5.3)	1,097	(5.5)	
Aspirin ever use, n(%)					
Yes	9,412	(68.2)	12,767	(63.7)	<.0001
No	4,385	(31.8)	7,277	(36.3)	
Deaths, n(%)	3,595	(26.1)	6,439	(32.1)	<.0001

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 6. Characteristics of proximal colon cancer patients with diabetes mellitus by medication adherence

	PDC≥80		PDC<80		p-value
N(%)	2,790	(43.8)	3,578	(56.2)	
Sex, n(%)					
Male	1,437	(51.5)	1,949	(54.5)	0.0186
Female	1,353	(48.5)	1,629	(45.5)	
Age at diagnosis of crc					
Mean±sd	69.7	±8.9	68.0	±9.4	<.0001
Received cancer treatment, n(%)					
Op only	1,904	(68.2)	2,439	(68.2)	0.0054
Op with RTx	84	(3.0)	104	(2.9)	
Op with CTx	685	(24.6)	835	(23.3)	
Op with both RTx and CTx	35	(1.3)	92	(2.6)	
RTx or CTx without Op	82	(2.9)	108	(3.0)	
Follow-up period, years					
Mean±sd	4.0	±3.1	4.6	±3.3	<.0001
PDC					
Mean±sd	87.6	±6.6	65.0	±15.5	<.0001
Q3	92.3		76.3		
Q2	85.2		70.3		

Q1	82.2		58.7		
Insulin ever user, n(%)					
Yes	357	(12.8)	498	(13.9)	0.1923
No	2,433	(87.2)	3,080	(86.1)	
Metformin ever use, n(%)					
Yes	2,642	(94.7)	3,374	(94.3)	0.4917
No	148	(5.3)	204	(5.7)	
Aspirin ever use, n(%)					
Yes	1,935	(69.4)	2,333	(65.2)	0.0005
No	855	(30.7)	1,245	(34.8)	
Deaths, n(%)	738	(26.5)	1,074	(30.0)	0.0018

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 7. Characteristics of distal colon cancer patients with diabetes mellitus by medication adherence

	PDC≥80		PDC<80		p-value
N(%)	3,282	(41.7)	4,588	(58.3)	
Sex, n(%)					
Male	2,196	(66.9)	3,084	(67.2)	0.7740
Female	1,086	(33.1)	1,504	(32.8)	
Age at diagnosis of crc					
Mean±sd	68.0	±8.5	66.6	±9.2	<.0001
Received cancer treatment, n(%)					
Op only	2,174	(66.2)	2,977	(64.9)	<.0001
Op with RTx	124	(3.8)	148	(3.2)	
Op with CTx	827	(25.2)	1,121	(24.4)	
Op with both RTx and CTx	71	(2.2)	175	(3.8)	
RTx or CTx without Op	86	(2.6)	167	(3.6)	
Follow-up period, years					
Mean±sd	4.3	±3.2	4.8	±3.3	<.0001
PDC					
Mean±sd	87.2	±6.3	65.0	±15.4	<.0001
Q3	91.2		76.3		

Q2	84.8		70.7		
Q1	82.2		59.1		
Insulin ever user, n(%)					
Yes	406	(12.4)	649	(14.2)	0.0227
No	2,876	(87.6)	3,939	(85.9)	
Metformin ever use, n(%)					
Yes	3,112	(94.8)	4,354	(94.9)	0.8748
No	170	(5.2)	234	(5.1)	
Aspirin ever use, n(%)					
Yes	2,282	(69.5)	2,964	(64.6)	<.0001
No	1,000	(30.5)	1,624	(35.4)	
Deaths, n(%)	730	(22.2)	1,389	(30.3)	<.0001

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 8. Characteristics of rectal cancer patients with diabetes mellitus by medication adherence

	PDC≥80		PDC<80		p-value
N(%)	4,915	(37.5)	8,185	(62.5)	
Sex, n(%)					
Male	3,222	(65.6)	5,396	(65.9)	0.6647
Female	1,693	(37.4)	2,789	(34.1)	
Age at diagnosis of crc					
Mean±sd	67.5	±8.8	65.5	±9.2	<.0001
Received cancer treatment, n(%)					
Op only	2,516	(51.2)	3,762	(46.0)	<.0001
Op with RTx	789	(16.1)	1,581	(19.3)	
Op with CTx	571	(11.6)	941	(11.5)	
Op with both RTx and CTx	410	(8.3)	835	(10.2)	
RTx or CTx without Op	629	(12.8)	1,066	(13.0)	
Follow-up period, years					
Mean±sd	4.4	±3.3	5.0	±3.5	<.0001
PDC					
Mean±sd	87.3	±5.4	64.6	±15.5	<.0001
Q3	91.6		76.1		
Q2	84.8		69.9		

Q1	82.1		58.8		
Insulin ever user, n(%)					
Yes	654	(13.3)	1,190	(14.5)	0.0495
No	4,261	(86.7)	695	(85.5)	
Metformin ever use, n(%)					
Yes	4,660	(94.8)	7,740	(94.6)	0.5402
No	25	(5.2)	445	(5.4)	
Aspirin ever use, n(%)					
Yes	3,258	(66.3)	5,076	(62.0)	<.0001
No	1,657	(33.7)	3,109	(38.0)	
Deaths, n(%)	1,377	(28.0)	2,799	(34.0)	<.0001

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 9. Univariate regression analyses of basic characteristics and risk of death among colorectal cancer patients with diabetes mellitus

Variables	Person Years	No. of event	HR	95% CI
PDC				
<80	98,755.4	6,439	Ref.	
>=80	59,633.7	3,595	0.93	0.89 – 0.96
Sex				
Men	99,307.6	6,417	Ref.	
Women	59,081.5	3,617	0.95	0.91 – 0.99
Age (years)	158,389.1	10,034	1.05	1.04 – 1.05
Received cancer treatment, n(%)				
Op only	103,838.1	4,460	0.21	0.20 – 0.22
Op with RTx	18,146.8	1,038	0.28	0.26 – 0.30
Op with CTx	22,043.1	2,075	0.47	0.44 – 0.50
Op with both RTx and CTx	6,309.5	871	0.68	0.63 – 0.74
RTx or CTx without Op	8,051.7	1,590	Ref.	
Metformin usage				
Never	7,885.1	939	Ref.	
Ever	150,504.0	9,095	0.51	0.47 – 0.54

Insulin usage				
Never	134,368.5	8,460	0.96	0.91 – 1.01
Ever	24,020.7	1,574	Ref.	
Aspirin				
Never	50,301.6	3,755	Ref.	
Ever	108,087.5	6,279	0.78	0.75 – 0.81

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 10. Multivariate regression analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus

	Person Years	No. of event	Crude		Model 1†		Model 2‡	
			HR and 95% CI					
PDC<80	98,755.4	6,439	1.00		1.00		1.00	
PDC≥80	59,633.7	3,595	0.93	0.89 – 0.96	0.91	0.88 – 0.95	0.93	0.89 – 0.97
Proximal colon cancer								
PDC<80	16,459.8	1,074	1.00		1.00		1.00	
PDC≥80	11,275.4	738	1.00	0.91 – 1.09	0.94	0.85 – 1.03	0.95	0.86 – 1.04
Distal colon cancer								
PDC<80	22,031.1	1,389	1.00		1.00		1.00	
PDC≥80	14,143.0	730	0.82	0.75 – 0.90	0.82	0.75 – 0.90	0.83	0.76 – 0.91

Rectal cancer								
PDC<80	41,117.0	2,779	1.00		1.00		1.00	
PDC≥80	21,608.9	1,377	0.95	0.89 – 1.01	0.94	0.88 – 1.00	0.96	0.90 – 1.02

†model 1 is adjusted for age at CRC diagnosis, sex and defined cancer staging.

‡model 2 is further adjusted for metformin usage and aspirin usage.

Table 11. Multivariate regression analyses of medication adherence and risk of death after exclusion of individuals with proportion of days covered (PDC) lower than 5th percentile.

	Person Years	No. of event	Crude		Model 1†		Model 2‡	
			HR and 95% CI					
PDC<80	90,237.31	5,664	1.00		1.00		1.00	
PDC≥80	59,633.71	3,595	0.96	0.92 - 1.00	0.95	0.91 - 0.99	0.96	0.92 – 1.00
Proximal colon cancer								
PDC<80	15,033.9	950	1.00		1.00		1.00	
PDC≥80	11,275.4	738	1.03	0.94 - 1.13	0.97	0.88 - 1.07	0.98	0.89 - 1.08
Distal colon cancer								
PDC<80	20,186.5	1,223	1.00		1.00		1.00	
PDC≥80	14,143.0	730	0.85	0.78 – 0.94	0.85	0.78 - 0.93	0.86	0.78 - 0.94

Rectal cancer								
PDC<80	37,701.5	2,459	1.00		1.00		1.00	
PDC≥80	21,608.9	1,377	0.98	0.92 - 1.05	0.97	0.91 – 1.04	0.99	0.92 – 1.05

†model 1 is adjusted for age at CRC diagnosis, sex and defined cancer staging.

‡model 2 is further adjusted for metformin usage and aspirin usage

Table 12. Characteristics of colorectal cancer patients with diabetes mellitus by medication adherence estimated with medication possession ratio (MPR).

	MPR≥80		MPR<80		p-value
N(%)	9,851	(23.7)	31,793	(76.3)	
Sex, n(%)					
Male	6,082	(61.7)	20,397	(64.2)	<.0001
Female	3,769	(38.3)	11,396	(35.8)	
Age at diagnosis of crc					
Mean±sd	69.0	±8.7	67.2	±9.5	<.0001
Cancer Subsite, n(%)					
Proximal colon	1,948	(19.8)	6,013	(18.9)	<.0001
Distal colon	2,383	(24.2)	7,203	(22.7)	
Rectum	3,471	(35.2)	12,436	(39.1)	
ETC	2,049	(20.8)	6,141	(19.3)	
Received cancer treatment, n(%)					
Op only	5,911	(60.0)	18,339	(57.7)	<.0001
Op with RTx	811	(8.2)	2,884	(9.1)	
Op with CTx	1,770	(18.0)	5,711	(18.0)	
Op with both RTx and CTx	405	(4.1)	1,723	(5.4)	
RTx or CTx without Op	954	(9.7)	3,136	(9.9)	

Follow-up period, years					
Mean±sd	4.1	±3.4	4.2	±3.4	0.0002
MPR					
Mean±sd	85.6	±5.4	59.0	±19.3	<.0001
Q3	87.7		74.1		
Q2	83.7		65.4		
Q1	81.6		49.3		
Insulin ever user, n(%)					
Yes	1,177	(12.0)	4,440	(14.0)	<.0001
No	8,674	(88.1)	27,353	(86.0)	
Metformin ever use, n(%)					
Yes	8,823	(89.6)	29,443	(92.6)	<.0001
No	1,028	(10.4)	2,350	(7.4)	
Aspirin ever use, n(%)					
Yes	6,699	(68.0)	20,096	(63.2)	<.0001
No	3,152	(32.0)	11,697	(36.8)	
Deaths, n(%)	3,052	(31.0)	10,884	(34.2)	<.0001

*abbreviations: CRC=Colorectal cancer, Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, MPR=medication possession ratio

Table 13. Multivariate regression analyses of medication adherence estimated by medication possession ratio (MPR) and risk of death among colorectal cancer patients with diabetes mellitus

	Person Years	No. of event	Crude		Model 1†		Model 2‡	
			HR and 95% CI					
MPR<80	97,400.2	6,439	1.00		1.00		1.00	
MPR≥80	60,633.3	3,595	0.93	0.89 - 0.97	0.91	0.88 - 0.95	0.93	0.89 - 0.97
Proximal colon cancer								
MPR<80	16,273.9	1,058	1.00		1.00		1.00	
MPR≥80	11,389.4	723	0.97	0.88 - 1.07	0.91	0.83 - 1.01	0.92	0.84 - 1.01
Distal colon cancer								
MPR<80	21,787.6	1,357	1.00		1.00		1.00	
MPR≥80	14,303.1	747	0.84	0.77 – 0.92	0.84	0.76 - 0.91	0.84	0.77 - 0.92

Rectal cancer								
MPR<80	40,499.6	2,717	1.00		1.00		1.00	
MPR≥80	22,159.4	1,406	0.85	0.89 – 1.01	0.94	0.88 – 1.00	0.96	0.90 – 1.02

Table 14. Multivariate regression analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus according to metformin

	Metformin non-users				Metformin users			
	Person Years	No. of event	†HR and 95% CI		Person Years	No. of event	†HR and 95% CI	
PDC<80	4,939.8	588	1.00		93,815.6	5,851	1.00	
PDC≥80	2,945.3	351	1.05	0.92 – 1.20	56,688.4	3,244	0.92	0.88 – 0.96
Proximal colon cancer								
PDC<80	870.1	93	1.00		15,589.7	981	1.00	
PDC≥80	608.6	62	0.97	0.70 – 1.40	10,666.8	676	0.95	0.86 – 1.05
Distal colon cancer								
PDC<80	1031.0	117	1.00		21,000.1	1,272	1.00	
PDC≥80	708.2	79	1.02	0.77 – 1.37	13,434.8	654	0.81	0.74 – 0.89

Rectal cancer								
PDC<80	2,057.2	256	1.00		39,059.8	2,523	1.00	
PDC≥80	1,042.5	123	1.06	0.86 – 1.32	20,566.4	1,254	0.95	0.88 – 1.01

Table 15. Multivariate regression analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus according to insulin.

	Insulin non-users				Insulin users			
	Person Years	No. of event	†HR and 95% CI		Person Years	No. of event	†HR and 95% CI	
PDC<80	82,929.1	5,386	1.00		15,826.3	1,053	1.00	
PDC≥80	51,439.4	3,074	0.92	0.88 – 0.96	8,194.3	521	0.97	0.88 – 1.08
Proximal colon cancer								
PDC<80	13,843.4	895	1.00		2,626.4	179	1.00	
PDC≥80	9,715.8	642	0.97	0.88 – 0.96	1,559.6	96	0.87	0.67 – 1.12
Distal colon cancer								
PDC<80	18,563.3	1,158	1.00		3,467.8	231	1.00	
PDC≥80	12,345.5	623	0.82	0.74 – 0.91	1,797.5	107	0.93	0.74 – 1.17

Rectal cancer								
PDC<80	34,496.6	2,332	1.00		6,620.5	447	1.00	
PDC≥80	18,517.5	1,190	0.96	0.90 – 1.03	3,091.4	187	0.93	0.78 – 1.10

Table 16. Multivariate analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus according to sex or received cancer treatment.

		Person Years	No. of event	HR and 95% CI	
Sex	Men				
	PDC<80	62,364.1	4,147	1.00	
	PDC≥80	36,943.5	2,270	0.92	0.88 – 0.97
	Women				
	PDC<80	36,391.3	2,292	1.00	
	PDC≥80	22,690.2	1,325	0.93	0.87 – 1.00
Received Cancer Treatment	OP				
	PDC<80	63,268.4	2,755	1.00	
	PDC≥80	40,569.7	1,705	0.92	0.87 – 0.98
	OP with RTx				
	PDC<80	12,014.8	695	1.00	
	PDC≥80	6,132.0	343	0.92	0.80 – 1.04
	OP with CTx				
	PDC<80	13,517.4	1,341	1.00	
	PDC≥80	8,525.7	734	0.85	0.78 – 0.93

OP with both RTx and CTx				
PDC<80	4,465.9	640	1.00	
PDC≥80	1,843.6	231	0.89	0.77 – 1.04
RTx or CTx without Op				
PDC<80	5,488.9	1,008	1.00	
PDC≥80	2,562.8	582	1.15	1.04 – 1.28

*abbreviations: Op=Operation, RTx=Radiotherapy, CTx=Chemotherapy, PDC=proportion of days covered

Table 17. Multivariate regression analyses of medication adherence and risk of death among colorectal cancer patients with diabetes mellitus according to different combinations of drug usage

Medication usage				Person Years	No. of event	†HR and 95% CI	
Metformin	Insulin	Aspirin					
No	No	No	PDC<80	2,020.2	280	1.00	
			PDC≥80	1,124.1	149	0.99	0.81 – 1.21
No	No	Yes	PDC<80	2,520.1	268	1.00	
			PDC≥80	1,602.9	176	1.10	0.91 – 1.34
No	Yes	No	PDC<80	122.6	14	1.00	
			PDC≥80	49.1	8	3.50	1.15 – 10.90
Yes	No	No	PDC<80	27,172.6	1,890	1.00	
			PDC≥80	14,321.2	969	0.95	0.88 – 1.03

Yes	Yes	No	PDC<80	3,809.7	325	1.00	
			PDC≥80	1,682.0	120	0.85	0.69 – 1.05
Yes	No	Yes	PDC<80	51,216.1	2,948	1.00	
			PDC≥80	34,391.1	1780	0.89	0.83 – 0.94
No	Yes	Yes	PDC<80	276.9	26	1.00	
			PDC≥80	169.2	18	1.12	0.59 – 2.12
Yes	Yes	Yes	PDC<80	11,617.1	688	1.00	
			PDC≥80	6,294.1	375	1.02	0.90 – 1.16

Table 18. Smoking and drinking status of colorectal cancer patients according to medication adherence

	PDC≥80		PDC<80		P-value
N	5,637		8,486		
Smoking					
Current	494	(8.8)	1,017	(12.0)	<.0001
Former	1,657	(29.4)	2,243	(26.5)	
Never	3,480	(61.8)	5,203	(61.5)	
Daily cigarette comsumption, cigarette	n=492		n=1,012		
<10	106	(21.5)	224	(22.0)	0.3871
10 – 19	213	(43.3)	393	(38.8)	
20 - 39	160	(32.5)	367	(36.3)	
<40	13	(2.6)	28	(2.8)	
Weekly alcohol consumption frequency	n=5,630		n=11,812		
0	4,699	(83.5)	8,474	(81.3)	0.0002
1 – 2	574	(10.2)	926	(10.9)	
3 – 4	213	(3.8)	373	(4.4)	
5 - 7	144	(2.6)	289	(3.4)	

Alcohol					
consumption, drinks	n=1,058		n=3,816		
3 or less	1,195	(70.1)	1,840	(66.7)	0.1268
4 - 7	391	(22.9)	692	(25.1)	
8 – 10	74	(4.3)	138	(5.0)	
11 or more	45	(2.6)	87	(3.2)	

Discussion

We found association between medication adherence for oral anti-diabetics and risk of death in CRC patients. In our crude and adjusted models maintaining good adherence to medication showed 7 – 9% lowered risk of death. In stratified analyses for cancer subsites, distal colon patients with good adherence had 17 – 18% lowered risk of death, yet prognosis of proximal colon and rectal cancer patients was not related. Similar yet marginally significant results were observed in analyses of adjusted models after exclusion of extremely low PDC, 4 – 5% lowered risk of death. After stratification by metformin and insulin, similar pattern of results were shown in metformin users and insulin non-users while metformin non-users showed and insulin users showed no noticeable relationship between risk of death and drug adherence. Stratification by different combination of metformin, insulin or aspirin usage depicted in which combination group the drug adherence associated with risk of death, which was metformin, aspirin user/insulin non-user.

This study's results showing adherent metformin users with lower risk of death stays in line with many epidemiologic studies done in the past (9, 10, 25-28). However not all metformin users showed reduced risk of death, as only metformin and insulin users were significantly related in table 17, indicating a possible interaction between the drugs patients are taking. On the other hand, distinctive results were shown compared to other studies showing insulin's adverse effect on CRC survival (25), as the observed reduced risk of death in adherent patients still remained effective even in insulin non-users in table 15.

The potential for enhancing survival of colorectal cancer patients of oral anti-diabetics are not fully understood. One possible explanation is that since these medications are mainly focused on improving hyperglycemia or hyperinsulinemia, which are the acknowledged mechanisms DM is contributing to cancer progression, and the better the adherence the stronger the effect of improving the survival of cancer patients (5, 9, 10).

Another explanation is that these effects are mainly caused by the anti-cancer effect of metformin which are well elucidated in many other studies (10, 25, 27, 28) including the effect of metformin associated with abundance of *Akkermasia muciniphila* in colon that directly enhances metabolism and improves insulin resistence in its host(29). In our study population, proportion of patients whoever have history of using metformin is up to 95% (table 5), and in multivariate regression analysis stratified by metformin usage, metformin non-users showed no relation between adherence and survival change (table 14). However, taking metformin as directed could not be the sole answer for better survival as patients who use metformin without aspirin showed no significant relation between adherence and survival (Table 17).

Difference in Insulin-like growth factor 1 (IGF-1) susceptibility in different colon parts may be responsible for different risk reduction for death of CRC patients in different cancer subsite. Patients who received operative treatment in our study population is up to 92.3% (table 4) which are

resection of the affected part of colon. High level of IGF-1 is thought to promote cancer development, which could be caused by hyperinsulinemia (30), and some studies shows that IGF-1 sensitivity is higher in distal colon than proximal colon (31). Therefore, patients with proximal colon cancer who haven't got their distal colon removed are still prone to the cancer promoting effect of insulin after treatment, and this effect might have counteracted to the anti-cancer effect of metformin. In an another effort to explain the different risk reduction for death of CRC patients in different cancer subsite, stratified multivariate regression were performed by sex and received cancer treatment, since distribution of both variables were different in proximal colon cancer patients compared to others. Both men and women with good adherence showed reduced risk of death while only the patients received OP, OP with RTx and OP with CTx showed risk reduction. In regard of the fact that proportion of patients received OP, OP with RTx and OP with CTx were relatively low in proximal cancer patients, this results indicate the difference were not derived by the distinct distribution of these variables.

Most of the epidemiologic studies explored relationship between specific type of medication and outcomes of interest such as metformin usage and survival of CRC patients (10, 28). However, the medication regimen to use in CRC patients with DM is mainly decided by the current status of DM, thus the role of such favorable outcome of metformin in CRC patients is limited in patients on other DM medication or on multiple medication regimen. In real world situation, more than 60% of DM patients were being prescribed with dual or triple therapy in 2013 (12), the association of different adherence on such complex regimen and CRC survival can only be grasped by measuring adherence and analyzing the risk on the total regimen of DM medication. To that extent, we could explain the patients and physicians the importance of persisting to the prescription received.

Strength of this study lies in the fact that we used the largest sized database that could be used, albeit not precisely a duplicate of national cancer registry. The source data of our study, NHID, covers 97% of the entire population, and our

study population included more than 40,000 CRC patients, incomparably higher than any other cohort studies done for modifiable factors. Additionally, even though large numbers of study are done with metformin or insulin, to our knowledge, this is the first study demonstrated the relation between medication adherence of oral anti-diabetics and prognosis of CRC.

Potential limitations of this study is as follows. First, we used claims data to estimate patients' medication adherence by calculating PDC and MPR. PDC and MPR are the most frequently used method evaluating adherence, yet it's adoption in a research relies on the premise that patients are ingesting the drug as prescribed, which is often not perfectly accurate. Direct methods such as directly observed therapy or measurement of the biologic markers in blood are surely the most accurate and objective way to evaluate adherence (32). However, these are not always viable nor efficient in retrospective cohort studies especially when the claims data is used. Hence, using indirect method was our preferred alternative approach for analyses.

Second, our source data has several weakness as clinical information relevant to CRC and DM such as cancer staging and HbA1c were unavailable and the proportions of the patients classified as ETC in cancer subsite (20.4% and 19.4% for adherent and nonadherent group) were considerably higher than Korean national cancer registry (5.1% in 2016), which could result in selection bias. Cancer staging is one of the most determining factors for patients' prognosis, and the information is covered in national cancer registry. Unfortunately, linkage of cancer registry data to other types of data is very limited due to the concern of privacy issue in Korea. Therefore, we had to undertake some other alternate measure, which is to utilize the data of treatments patients received. According to the European Society for Medical Oncology's consensus guidelines for CRC, deciding what treatment course a patient will receive is very complicated since numerous factors should be considered such as location or size of tumor, number of lymph nodes involved, or whether one experienced complication like perforation (24). Nevertheless, the treatment plan is typically composed with operation, radiotherapy and chemotherapy, patients with

different cancer staging usually have different combination of treatment modalities. In our own analysis, the survival and estimated risk of death was different by received cancer treatment, we used it as an adjustment variable, by assumption of it as the closest substitute of cancer staging.

Conclusion

Maintaining good medication adherence was related to favorable prognosis of CRC especially in distal colon.

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국문초록

대장암과 당뇨병은 한국인에게 가장 큰 영향을 미치는 질환이며, 당뇨병은 고인슐린혈증, 고혈당 및 당뇨병 치료 방법에 의해 대장암에 부정적 영향을 끼친다고 알려져 있다. 메트포민과 같은 경구 혈당강하제는 인슐린 저항성을 개선해줌에 따라 고인슐린혈증을 해결하고, 이에 따른 대장암 발생과 사망의 위험을 낮춘다고 알려져있다. 본 연구의 목적은 대장암을 진단받은 당뇨병 환자에 있어, 경구혈당강하제에 대한 복약순응도가 사망위험도에 어떠한 영향을 미치는지 대규모 코호트에서 비교하고자 함이다.

우리는 국민건강보험에 등록된 모든 청구자료를 포함하고 있는 국민건강정보자료를 활용하여 후향적 코호트 연구를 설계하였다. 2002-2016년 사이에 새롭게 대장암으로 진단받은 사람들을 사망시점 또는 2016년 12월 31일 까지 추적조사 하였다. 경구 당뇨병 용제의 복약순응도는 추적조사기간 내의 처방자료를 Proportion of Days Covered (PDC) 방법을 사용하여 계산하여 파악하였다. 복약순응도가 좋지 않은 사람들을 비교군으로 하여 대장암 환자의 사망위험을 비례위험도 및 95% 신뢰구간을 계산하여 분석하였고, 이를 다시 대장암의 세부 부위에 따라 층화분석을 하였다.

총 33,841명의 당뇨병 환자가 대장암으로 새롭게 진단받았고, 이들의 평균추적기간은 4.7년이었다. 복약순응도가 좋은 대장암 환자들 (PDC≥80%)은 그렇지 않은 환자들(PDC<80%)에 비해 사망위험이 낮은 것으로 나타났다 [HR (95% CI) 0.93 (0.89 – 0.97)]. 세부부위로 나눠 보았을 때에는 원위부결장암은 전체환자들과 일관되게 위험도가 낮게 나타났지만 [HR (95% CI) 0.83 (0.76 – 0.91)], 근위부결장암과 직장암의 경우에는 유의한 연관성이 나타나지 않았다 [HR (95% CI) 0.95 (0.86 – 1.04), HR (95% CI) 0.96 (0.90 – 1.02)].

경구혈당강하제의 복약 순응도가 좋은 것은 좋은 원위부결장암의 예후와 관련이 있다.