Prognosis of Patients with Colorectal Cancer with Diabetes According to Medication Adherence: A Population-Based Cohort Study

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ABSTRACT

Background: Diabetes mellitus is known to have a negative effect on colorectal cancer survival due to hyperinsulinemia or hyperglycemia, and medications such as metformin, which targets insulin resistance and hyperinsulinemia, have a preventive effect on the risk of death. The aim of this study was to compare the risk of death among patients with colorectal cancer with diabetes with different levels of adherence to oral antidiabetics.

Methods: National Health Information Database was used, which has all claims data for those who are registered for national health insurance in Korea, from 2002 to 2016, for conducting a retrospective cohort study. Newly diagnosed patients with colorectal cancer among diabetics were followed up from the date of diagnosis until death or December 31, 2016. The medication adherence was calculated as the proportion of days covered (PDC). The HR and 95% confidence interval (CI) for death were estimated using the low-adherence patients as a reference.

Results: A total of 33,841 diabetic patients with newly diagnosed colorectal cancer were followed for an average of 4.7 years. Patients with colorectal cancer with good adherence (PDC ≥ 80%) showed a reduced risk of death [HR (95% CI), 0.82 (0.78–0.86)] compared with those with poor adherence (PDC < 80%). A reduced risk of death was observed for all cancer subsites.

Conclusions: The maintenance of good medication adherence for diabetes mellitus was related to a favorable prognosis of colorectal cancer.

Impact: This study provides evidence that patients with colorectal cancer who are adherent to their diabetes medication will have better survival than patients who are not adherent.

Introduction

Colorectal cancer is one of the major cancers globally; as of 2018, its incidence marks third and mortality marks second out of all types of cancer in both sexes worldwide (1). The age-standardized incidence and mortality rates of colorectal cancer were third and fourth in South Korea in 2016 (2). Trends of the survival of patients with colorectal cancer differ widely around the world, as countries with higher a human development index (HDI) tend to show decreasing mortality over the most recent 10-year period, while countries with a lower HDI show increasing mortality (3). In South Korea, the survival has been dramatically improving in both sexes, as the 5-year relative survival was 77.8% and 73.2% from 2012 to 2016 in men and women, respectively, compared with 55.3% and 54.2% from 1993 to 1995 (2). Consequently, the number of prevalent cases has greatly increased, which makes the management of colorectal cancer survivors, including help coping with comorbidities, a priority to help the patients.

According to the World Health Organization global report on diabetes, the age-standardized prevalence in adults 18 years old and above has almost doubled, from 4.7% in 1980 to 8.5% in 2014 (4). In addition, a study that estimated projections of global diabetes mellitus prevalence reported that prevalence will rise to 9.9% by 2045 (5). As the number of people suffering from diabetes grows, controlling the concomitant health effect will become more urgent than ever.

The association between diabetes mellitus and cancer, including colorectal cancer, is widely accepted following a 2010 consensus report from the American Diabetes Association (6), and many epidemiologic studies support this hypothesis. Two meta-analyses of diabetes mellitus and the risk of colorectal cancer reported increased the RRs of colorectal cancer of 1.30 and 1.37, respectively, according to studies in different languages included (7, 8). Furthermore, there was a systematic review and meta-analysis performed in 2008 reporting an increased risk for long-term, all-cause mortality of patients with colorectal cancer with preexisting diabetes mellitus [pooled HR (95% CI), 1.32 (1.24–1.41); ref. 9].

Potential molecular mechanisms explaining the linkage between colorectal cancer and diabetes mellitus are hyperinsulinemia, hyperglycemia, or diabetes mellitus therapy. Medication for diabetes mellitus therapy, such as insulin, shows antiapoptotic properties and tumor-enhancing effects in colon epithelium that are the result of working as a growth factor through the insulin receptor or insulin growth factor receptor, while metformin is associated with decreased incidence and better survival through the activation of AMP-activated protein kinase (6, 10, 11).

Although appropriate control in diabetes mellitus in patients with colorectal cancer to cope with hyperglycemia or hyperglycemia is important, the level of diabetes control and medication adherence in many countries is far lower than expected. According to the National

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Diabetes Statistics Report of Centers for Disease Control and Prevention of the United States, 23.8% of total estimated patients with diabetes were left undiagnosed in 2015 (4), and a study reported that medication adherence among those diagnosed was only 60% (12). In addition, the percentage of patients achieving HbA1c less than 7% was 50.9% in the period of 2011–2014, which was 56.8% in 2003–2006 (12). In Korea, the treatment rate was 36.7%–52.4% in 2012 depending on the residential area of the patient (13), and the calculated medication adherence by the medication possession ratio was only 45% in 2013 (14). Consequently, the proportion of patients with diabetes mellitus achieving the targeted HbA1c level is small, as only 45.6% had its level controlled below 7.0% and 26% below 6.5% in 2014 (15).

According to a study summarizing prospective cohort studies emphasizing modifiable factors that affect survival outcomes in patients with colorectal cancer, there are a few studies of possible modifications to better prognosis, although the evidence is limited. This study describes that maintaining a normal weight, participating in regular physical activity, and avoiding an unhealthy diet may be important preventive steps for improving survival outcomes (16).

In addition to a few modifiable factors described above, medication lowering blood glucose and improving hyperinsulinemia such as metformin could have an effect on colorectal cancer survival outcomes when taken as directed (10, 11). Nonetheless, a study reported that only approximately 23% of the total patients received metformin monotherapy, while 21% received dual or more therapy with other medications (17), and the effect on the prognosis of colorectal cancer of other medications or the combined effect of these medications is not well understood.

We aim to provide evidence to the thesis that patients with colorectal cancer who are adherent to their diabetes medication will have better survival than patients who are not adherent. For that purpose, we tried to compare the risk of death between patients with colorectal cancer with different levels of medication adherence to oral antidiabetics.

Materials and Methods

We used the customized database of the National Health Information Database (NHID) of the National Health Insurance Service (NHIS), which includes all of the claims data for those who are registered in the insurance service (18). The customized database consists of data that are collected, managed, and maintained by the NHIS and modified as requested by researchers in the purpose of policy or academic research, and it includes basic demographics of every individual, records of inpatient and outpatient usage and related prescriptions, medical check-up results, and date of death from 2002 to 2016.

We selected patients who had three or more claims records of being diagnosed with codes C18–C20 from the 10th revision of the International Classification of Disease (ICD-10) and received any treatment such as operation, chemotherapy, or radiotherapy as patients with colorectal cancer (19). Patients with claims records before 2003 were excluded to identify newly diagnosed patients with cancer. 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 having proximal colon cancer, distal colon cancer, or rectal cancer, and all other codes such as C18.8, C18.9, or C18 were grouped into undefined colon cancer.

To identify medication adherence levels for oral antidiabetics, we included those who had a history of being diagnosed with diabetes by ICD-10 code E10-E15 with a record of being prescribed medication from the date of colorectal cancer diagnosis. Individuals with only one prescription record were excluded because the adherence cannot be measured. Only patients who were already being prescribed antidiabetics before the diagnosis of colorectal cancer were included. The selection process for the study population is depicted in **Fig. 1**.

We used the proportion of days covered (PDC), which is one of the most common methods used to assess medication adherence, in each patient with colorectal cancer for oral antidiabetics. The PDC is calculated as the number of days with drug on hand divided by the number of days in the specified time interval (20). Adherence to prescribed injectable medications such as insulin or glucagon-like peptide-1 receptor agonist was not measured. The data used to calculate the PDC included prescriptions from the first observed prescription until the last prescription between 2002 and 2016. In addition, we performed a sensitivity analysis calculating the PDC with prescriptions before or after the date of colorectal cancer diagnosis to reflect the effect of the oral antidiabetics ingested after colorectal cancer diagnosis. When multiple medications concurrently prescribed in a patient had different prescription durations, the shorter one was used to calculate the PDC to produce more conservative results. We categorized medication adherence into two groups: <80% and ≥80% for comparison.

Information on age at cancer diagnosis, sex, insulin, and metformin and aspirin usage was extracted. Ever user was defined as an individual who received prescriptions during the follow-up period for calculating the PDC. Because our source data lack information on cancer staging data, and cancer staging is a critical element in comparing prognosis between different groups, we categorized the study population into different cancer treatments that they received and regarded each different cancer staging considering that early-stage patients are usually treated with surgery only, while the most advanced-stage patients typically receive palliative therapy with chemotherapy or radiotherapy without operation (21). Moreover, smoking and drinking status, which could be responsible for differing patient survival, were analyzed. These behavioral variables were extracted from data from the first health check-up available after colorectal cancer diagnosis.

For basic characteristics, we used the χ^2 or t test to compare patients with different adherence levels. Univariate regression analyses were performed with basic characteristics that were possibly related to the risk of death of patients with colorectal cancer. A Cox proportional hazard regression model was used to estimate the risk of death of patients with colorectal cancer as the HR and 95% confidence interval (CI) using nonadherent colorectal cancer patients as a reference. Subgroup analyses were performed using colorectal cancer subsites. The Kaplan–Meier method and log-rank test were used to compare cumulative survival between different adherence in total and stratified groups for metformin or insulin usage.

Results

The basic characteristics of patients with colorectal cancer with diabetes by medication adherence are shown in **Table 1**. Among 7,615 adherent patients (PDC ≥ 80%) and 26,226 nonadherent patients (PDC < 80%), the mean age at diagnosis of colorectal cancer was higher in adherent patients. In terms of the subsites of colorectal cancer, adherent patients were diagnosed with colon cancer more than nonadherent patients. When we categorized the patients by the treatment they received, more of the adherent patients received operative treatment only, while operation with radiotherapy, operation with both radiotherapy and chemotherapy, and radiotherapy or chemotherapy

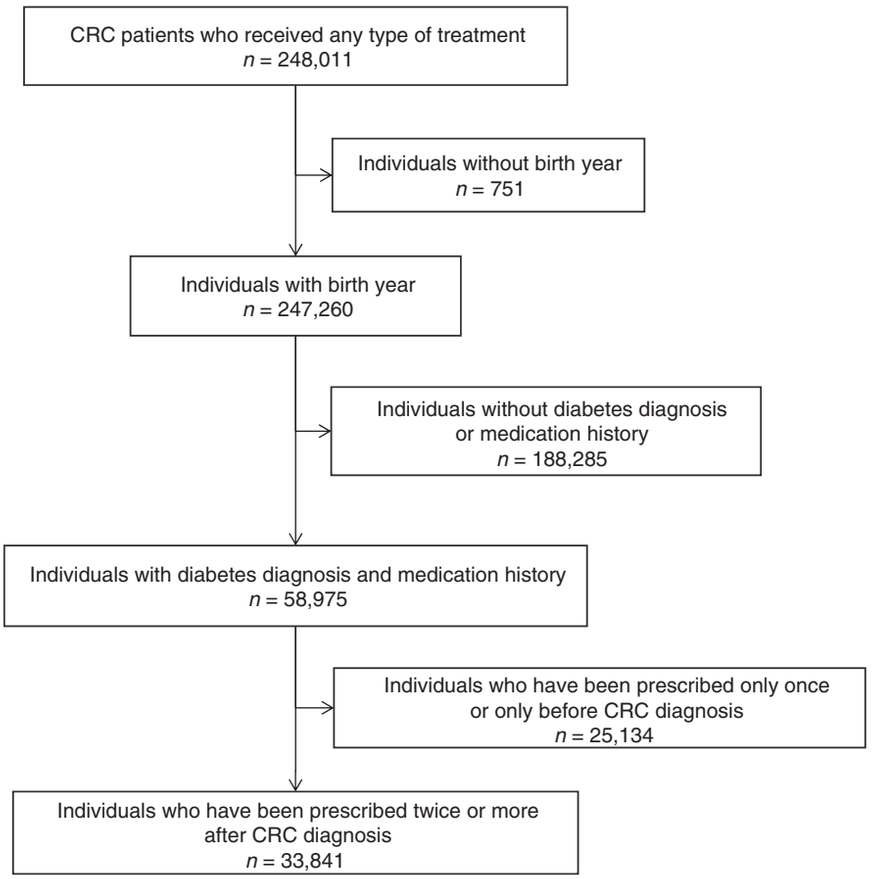

Figure 1.
Selection process for study population. CRC, colorectal cancer.

without operation were higher in nonadherent patients. The number of concurrent oral antidiabetics used was higher in nonadherent patients. The proportion of insulin and metformin ever users was higher in nonadherent patients, while the proportion of aspirin usage was higher in adherent patients. Information on smoking and alcohol consumption was available for 3,167 adherent and 10,927 and 10,937 nonadherent patients. There were more current smokers among the nonadherent patients (11.5%) than among the adherent patients (7.9%). Regarding alcohol consumption, there was a greater proportion of patients who consumed no alcoholic drinks among the adherent patients (84.0%) than among the nonadherent patients (81.6%). There were 1,958 (25.7%) and 8,076 (30.8%) deaths among the adherent and nonadherent patients, respectively.

In the univariate regression analyses, patients with a higher PDC, female sex, younger age, earlier disease stage assumed by the cancer treatment received, and ever user status of metformin and aspirin showed a reduced risk of death, while insulin usage showed no relation to the risk of death of patients with colorectal cancer (Supplementary Table S1).

The results of the multivariate regression analyses of medication adherence and risk of death are shown in **Table 2**. Regardless of the adjustments made in the analyses, adherent patients with colorectal cancer with high adherence to diabetes mellitus medication showed a reduced risk of death by 16%–19% compared with nonadherent patients. When we stratified the patients by colorectal cancer subsites, having a higher adherence level for diabetes medication showed a significant protective effect on death in every subsite. A sensitivity analysis with the PDC calculated with prescriptions before and after colorectal cancer diagnosis is shown in Supplementary Tables S2 and S3. Similar results were shown, as adherent patients with colorectal cancer with high adherence to diabetes mellitus medication showed a reduced risk of death by 7%–10% compared with nonadherent patients. However, in subgroup analysis by cancer subsites, the statistically significant correlation was shown for proximal colon and rectal cancer when prescriptions before cancer diagnosis were used and only for distal colon cancer when prescriptions after cancer diagnosis were used.

Figure 2 shows the cumulative survival of patients with colorectal cancer with diabetes according to medication adherence. As shown in **Fig. 2A**, adherent patients in total showed better survival than nonadherent patients. After stratifying the patients with metformin or insulin usage, only the metformin users and insulin nonusers showed significantly better survival in adherent patients (**Fig. 2B** and **E**).

In terms of HRs, adherent metformin users showed a reduced risk of death compared with nonadherent users by 19%, while other drug users' adherence showed no relation with risk of death. When stratified by insulin, both insulin users' and nonusers' adherence was related to a lowered risk of death by 17% and 21%, respectively (**Table 3**). We also stratified patients with colorectal cancer by sex and cancer treatment received and performed multivariate regression analyses, which are shown in **Table 4**. Adherent patients for both sexes showed a reduced risk of death by 17%–19%, while this risk reduction was shown only in patients who received surgery [HR (95% CI), 0.77 (0.71–0.82)], operation with radiotherapy [HR (95% CI), 0.76 (0.65–0.89)], and operation with chemotherapy [HR (95% CI), 0.84 (0.75–0.94)].

Table 1. Characteristics of patients with colorectal cancer with diabetes mellitus by medication adherence.

	PDC (%) ≥80	PDC (%) <80	*P*
N (%)	7,615 (22.5)	26,226 (77.5)	
Sex, *n* (%)			
Male	4,648 (61.0)	16,749 (63.9)	<0.0001
Female	2,967 (39.0)	9,477 (36.1)	
Age at diagnosis of colorectal cancer, years			
Mean ± SD	68.7 ± 8.4	66.8 ± 9.3	<0.0001
Cancer subsite, *n* (%)			
Proximal colon	1,467 (19.3)	4,901 (18.7)	<0.0001
Distal colon	1,879 (24.7)	5,991 (22.8)	
Rectum	2,701 (35.5)	10,399 (39.7)	
Unspecified colon cancer	1,567 (20.6)	4,935 (18.8)	
Received cancer treatment, *n* (%)			
Operation only	4,684 (61.5)	15,291 (58.3)	<0.0001
Operation with radiotherapy	663 (8.7)	2,543 (9.7)	
Operation with chemotherapy	1,422 (18.7)	4,823 (18.4)	
Operation with both radiotherapy and chemotherapy	307 (4.0)	1,488 (5.7)	
Radiotherapy or chemotherapy without operation	539 (7.1)	2,081 (7.9)	
Follow-up period, years			
Mean ± SD	4.7 ± 3.4	4.7 ± 3.3	0.703
PDC (%)			
Mean ± SD	84.5 ± 4.3	60.7 ± 17.9	
75%	86.0	74.5	
50%	83.2	66.4	
25%	81.4	52.2	
Insulin ever use, *n* (%)			
Yes	975 (12.8)	3,723 (14.2)	0.002
No	6,640 (87.2)	22,503 (85.8)	
Metformin ever use, *n* (%)			
Yes	7.153 (93.9)	24,867 (94.8)	0.003
No	462 (6.1)	1,359 (5.2)	
Aspirin ever use, *n* (%)			
Yes	5,378 (70.6)	16,801 (64.1)	<0.0001
No	2,237 (29.4)	9,425 (35.9)	
Number of oral antidiabetics used			
1	1,231 (16.2)	4,695 (17.9)	<0.0001
<2	3,460 (45.4)	12,575 (48.0)	
<3	2,613 (34.3)	8,088 (30.8)	
≥3	311 (4.1)	868 (3.3)	
Smoking status	*n* = 3,167	*n* = 10,927	
Current	250 (7.9)	1,261 (11.5)	<0.0001
Former	938 (29.6)	2,962 (27.1)	
Never	1,979 (62.5)	6,704 (61.4)	
Daily cigarette consumption, cigarettes	*n* = 250	*n* = 1,254	
<10	42 (16.8)	288 (23.0)	0.013
10–19	123 (49.2)	483 (38.5)	
20–39	78 (31.2)	449 (35.8)	
<40	7 (2.8)	34 (2.7)	
Weekly alcohol consumption frequency, days	*n* = 3,167	*n* = 10,937	
0	2,660 (84.0)	8,925 (81.6)	0.002
1–2	309 (9.8)	1,191 (10.9)	
3–4	129 (4.1)	457 (4.2)	
5–7	69 (2.2)	364 (3.3)	
Deaths, *n* (%)	1,958 (25.7)	8,076 (30.8)	

Discussion

We found an association between medication adherence for oral antidiabetics and the risk of death in patients with colorectal cancer. In our crude and adjusted models, maintaining good adherence to medication showed a 16%–19% lowered risk of death. In stratified analyses for cancer subsites, a lowered risk of death was observed for every cancer subsite, and patients with distal colon cancer showed the most prominent results, with a 21%–24% lowered risk. After stratification by metformin and insulin, similar patterns of results were shown, except for the metformin nonusers.

This study's results showing adherent metformin users with lower risk of death are in-line with those of many epidemiologic studies done in the past (10, 11, 22–25). On the other hand, distinctive results were

Table 2. Multivariate regression analyses of medication adherence and risk of death among patients with colorectal cancer with diabetes mellitus.

	Patients, *n*	Person-years	Events, *n*	Crude HR (95% CI)	Model 1[a] HR (95% CI)	Model 2[b] HR (95% CI)
PDC (%) <80	26,226	122,846.0	8,076	1.00	1.00	1.00
PDC (%) ≥80	7,615	35,543.1	1,958	0.84 (0.80–0.88)	0.81 (0.77–0.85)	0.82 (0.78–0.86)
Proximal colon cancer						
PDC (%) <80	4,901	21,472.7	1,431	1.00	1.00	1.00
PDC (%) ≥80	1,467	6,262.5	381	0.92 (0.82–1.03)	0.88 (0.78–0.98)	0.88 (0.79–0.99)
Distal colon cancer						
PDC (%) <80	5,991	27,481.0	1,697	1.00	1.00	1.00
PDC (%) ≥80	1,879	8,693.0	422	0.79 (0.71–0.88)	0.76 (0.68–0.84)	0.76 (0.68–0.84)
Rectal cancer						
PDC (%) <80	10,399	49,607.9	3,409	1.00	1.00	1.00
PDC (%) ≥80	2,701	13,118.1	747	0.83 (0.77–0.90)	0.80 (0.74–0.87)	0.82 (0.75–0.88)

[a]Model 1 is adjusted for age at colorectal cancer diagnosis, sex, and received cancer treatment.
[b]Model 2 is further adjusted for metformin usage and aspirin usage.

shown compared with other studies showing insulin's adverse effect on colorectal cancer survival (25), as the observed better survival and reduced risk of death in adherent patients still remained even in insulin nonusers, as shown in **Fig. 2** and **Table 3**.

The potential for enhancing the survival of patients with colorectal cancer with oral antidiabetics is not fully understood. One possible explanation is that because these medications are mainly focused on improving hyperglycemia or hyperinsulinemia, which are the acknowledged mechanisms by which diabetes mellitus contributes to cancer progression, the better the adherence, the stronger the effect of improving the survival of patients with cancer (6, 10, 11). Another explanation is that these effects are mainly caused by the anticancer effect of metformin, which has been well elucidated in many other studies (11, 22, 23, 25), including the effect of metformin associated with the abundance of *Akkermansia muciniphila* in the colon that directly enhances metabolism and improves insulin resistance in its host (26). In our study population, the proportion of patients with a history of metformin use was up to 95% (**Table 1**), and in a multivariate regression analysis stratified by metformin usage, metformin nonusers showed no relation between adherence and survival change (**Table 3**).

Most epidemiologic studies have explored the relationship between specific types of medication and outcomes of interest, such as metformin usage and the survival of patients with colorectal cancer (11, 22). However, the medication regimen used in patients with colorectal cancer with diabetes mellitus is mainly decided by the current status of diabetes mellitus; thus, the role of such a favorable outcome of metformin in patients with colorectal cancer is limited in patients on other diabetes mellitus medications or on multiple medication regimens. In a real-world situation, more than 60% of patients with diabetes mellitus were prescribed dual or triple therapy in

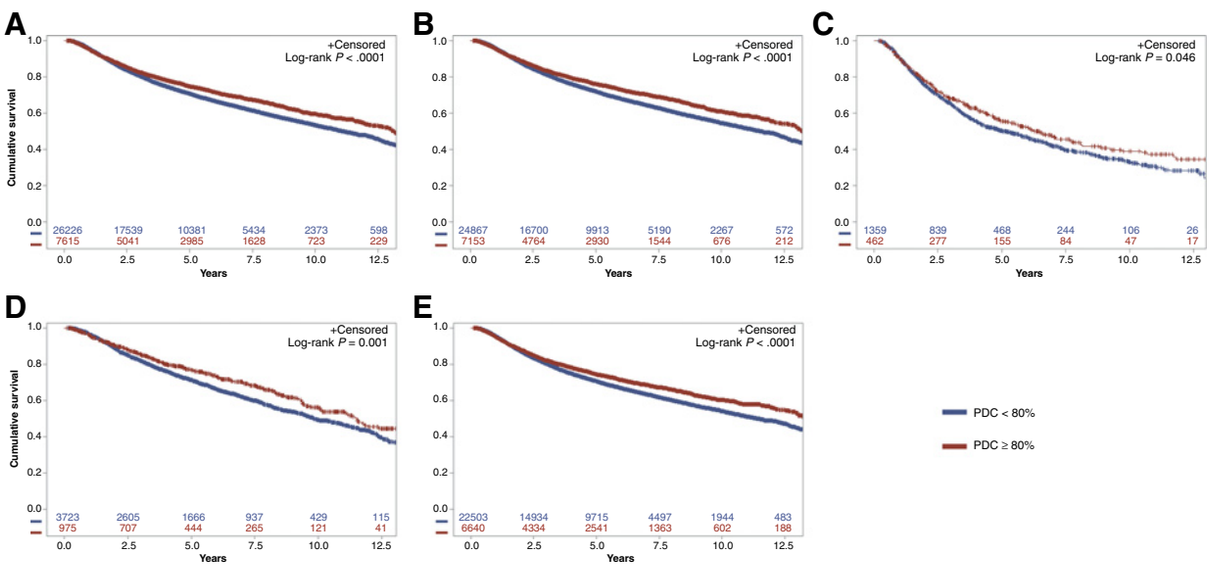

Figure 2.
Cumulative survival of patients with colorectal cancer with diabetes according to medication adherence. **A,** Total patients. **B,** Patients who ever used metformin. **C,** Patients who never used metformin. **D,** Patients who ever used insulin. **E,** Patients who never used insulin.

Table 3. Multivariate regression analyses of medication adherence and risk of death among patients with colorectal cancer with diabetes mellitus according to metformin or insulin use.

	Metformin nonusers			Metformin users		
	Person-years	**Events, *n***	**HR (95% CI)**	**Person-years**	**Events, *n***	**HR (95% CI)**
PDC (%) <80	5,870.0	728	1.00	116,975.8	7,348	1.00
PDC (%) ≥80	2,014.9	211	0.89 (0.76–1.04)	33,528.2	1,747	0.81 (0.77–0.86)
Proximal colon cancer						
PDC (%) <80	1,095.5	114	1.00	20,377.2	1,317	1.00
PDC (%) ≥80	383.2	41	1.08 (0.74–1.57)	5,879.4	340	0.86 (0.77–0.97)
Distal colon cancer						
PDC (%) <80	1,231.5	148	1.00	26,249.5	1,549	1.00
PDC (%) ≥80	507.7	48	0.78 (0.56–1.09)	8,185.4	374	0.76 (0.67–0.85)
Rectal cancer						
PDC (%) <80	2,320.5	303	1.00	47,287.3	3,106	1.00
PDC (%) ≥80	779.2	76	0.84 (0.65–1.08)	12,338.9	1,861	0.81 (0.75–0.88)
	Insulin nonusers			**Insulin users**		
	Person-years	**Events, *n***	**HR (95% CI)**	**Person-years**	**Events, *n***	**HR (95% CI)**
PDC (%) <80	103,896.4	6,782	1.00	18,949.6	1,294	1.00
PDC (%) ≥80	30,472.1	1,678	0.83 (0.78–0.87)	5,071.0	280	0.79 (0.69–0.90)
Proximal colon cancer						
PDC (%) <80	18,304.1	1,208	1.00	3,268.6	223	1.00
PDC (%) ≥80	5,355.2	329	0.90 (0.79–1.01)	907.4	52	0.84 (0.61–1.14)
Distal colon cancer						
PDC (%) <80	23,395.3	1,421	1.00	4,085.7	276	1.00
PDC (%) ≥80	7,513.5	360	0.77 (0.68–0.86)	1,179.5	62	0.72 (0.55–0.95)
Rectal cancer						
PDC (%) <80	41,836.3	2,876	1.00	7,771.5	533	1.00
PDC (%) ≥80	11,177.8	646	0.83 (0.76–0.90)	1,940.3	101	0.75 (0.60–0.93)

2013 (14), and the association of different adherence to such a complex regimen and colorectal cancer survival can be grasped only by measuring adherence and analyzing the risk on the total regimen of diabetes mellitus medication. To that extent, we should explain to patients and physicians the importance of adhering to the prescription received.

The number of patients suffering from diabetes mellitus in Korea has increased since 1998 (27). As of 2017, the prevalence of diabetes mellitus in adults aged 30 or more is up to 12.4% according to the data from the Korean National Health and Nutrition Examination Survey (28). In one study, conducted in Korea, about the incidence trend of diabetes mellitus, the age at diabetes mellitus diagnosis has become younger every year since 2004. In 2012, more than 40% of newly diagnosed patients were in their 40s and 50s, while this number was not more than 30% in 2004, and diagnosis earlier in life prolongs the period that diabetes mellitus affects each patient (29). This finding could suggest that, if this trend continues, the health effects directly or indirectly caused by diabetes mellitus will be catastrophic.

The strength of this study lies in the fact that we used the largest database that could be used, albeit not precisely a duplicate of the national cancer registry. The source data of our study, the NHID, covers 97% of the entire population, and our study population included more than 40,000 patients with colorectal cancer, incomparably higher than any other cohort studies done for modifiable factors. In addition, although a large number of studies have been performed with metformin or insulin, to our knowledge, this is the first study to demonstrate the relationship between medication adherence to oral antidiabetics and the prognosis of colorectal cancer.

The potential limitations of this study are as follows. First, we used claims data to estimate patients' medication adherence by calculating the PDC. The PDC is the one of the most frequently used methods for evaluating adherence, yet its adoption in research relies on the premise that patients ingest the drug as prescribed, which is often not perfectly accurate. Direct methods such as directly observed therapy or measurement of the biological markers in blood are surely the most accurate and objective way to evaluate adherence (30). However, these are not always viable or efficient in retrospective cohort studies, especially when claims data are used. Hence, using the indirect method was our preferred alternative approach for analyses.

Second, our source data have several weaknesses, as clinical information relevant to colorectal cancer and diabetes mellitus, such as cancer staging and HbA1c, were unavailable, and the proportions of the patients classified as having undefined colon cancer (20.6% and 18.8% for the adherent and nonadherent groups, respectively) were considerably higher than the Korean national cancer registry (5.1% in 2016), which could result in selection bias. Cancer staging is one of the most determining factors for patient prognosis, and the information is covered in the national cancer registry. Unfortunately, the linkage of cancer registry data to other types of data is very limited because of the concern of privacy issues in Korea. Therefore, we had to undertake an alternative measure, which was to utilize the data of the treatments that the patients received. According to the European Society for Medical Oncology's consensus guidelines for colorectal cancer, deciding what treatment course a patient will receive is very complicated because numerous factors should be considered, such as the location or size of the tumor, the number of lymph nodes involved, or whether one experienced complications, such as perforation (21). Nevertheless, the

Table 4. Multivariate analyses of medication adherence and risk of death among patients with colorectal cancer with diabetes mellitus according to sex or cancer treatment received.

	Patients, *n*	Person-years	Events, *n*	HR (95% CI)
Sex				
Men				
PDC(%) <80	16,749	77,570.2	5,184	1.00
PDC (%) ≥80	4,648	21,737.5	1,233	0.81 (0.76–0.87)
Women				
PDC (%) <80	9,477	45,275.9	2,892	1.00
PDC (%) ≥80	2,967	13,805.6	725	0.83 (0.77–0.90)
Received cancer treatment				
Operation				
PDC (%) <80	15,291	79,752.1	3,571	1.00
PDC (%) ≥80	4,684	24,086.0	889	0.77 (0.71–0.82)
Operation with radiotherapy				
PDC (%) <80	2,543	14,313.2	853	1.00
PDC (%) ≥80	663	3,833.6	185	0.76 (0.65–0.89)
Operation with chemotherapy				
PDC (%) <80	4,823	17,077.1	1,656	1.00
PDC (%) ≥80	1,422	4,966.0	419	0.84 (0.75–0.94)
Operation with both radiotherapy and chemotherapy				
PDC (%) <80	1,488	5,247.1	732	1.00
PDC (%) ≥80	307	1,062.4	139	0.94 (0.79–1.13)
Radiotherapy or chemotherapy without operation				
PDC (%) <80	2,081	6,456.5	1,264	1.00
PDC (%) ≥80	539	1,595.1	326	1.00 (0.89–1.13)

treatment plan is typically composed of operation, radiotherapy, and chemotherapy; patients with different cancer staging usually have different combination of these treatment modalities. In our own analysis, the survival and estimated risk of death were different by the cancer treatment received. For this reason, we used the cancer treatment received as an adjustment variable and assumed it was the closest substitute for cancer staging.

In conclusion, maintaining good medication adherence was related to favorable prognosis of patients with colorectal cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: S. Choe, S.-Y. Jeong, Y.M. Cho, B.-J. Park, A. Shin
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