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ORIGINAL ARTICLE

Role of cyclooxygenase-2 inhibitors in the survival outcome of colorectal cancer patients: A population-based cohort study

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Abstract The aim of this study is to investigate whether use of cyclooxygenase-2 (COX-2) inhibitors as auxiliary drug in colorectal cancer (CRC) patients will lead to better survival outcome. This population-based retrospective cohort study was conducted using the Taiwan National Health Insurance Research Database. The cohort consisted of newly diagnosed CRC adult patients during 2003–2010 with at least one prescription of nonsteroidal anti-inflammation drugs. Analysis groups were defined as users or nonusers of COX-2 inhibitors based on their usage prior to or 1 year after diagnosis of CRC. The outcome measurement was overall survival. The application of propensity scores through the inverse probability of treatment weighting (IPTW) was applied to the study groups. Subgroup analyses included stratification of different cancer site, treatment modalities, and first chemotherapy regimens. Kaplan–Meier estimates and Cox regressions were used to compare survival outcome. We identified 14,688 patients with newly diagnosed CRC. The adjusted hazard ratio (HR) with IPTW was 0.91 [95% confidence interval (CI), 0.86–0.96] in patients using COX-2 inhibitors in before and after diagnosis groups, and statistical significance was not reached for usages at only prior to or only after diagnosis. In subgroup analyses, patients with rectal cancer (adjusted HR with IPTW = 0.86; 95% CI, 0.79–0.94) who received surgery followed by chemoradiation (adjusted HR with IPTW = 0.57; 95% CI, 0.47–0.77) and with adjuvant chemotherapy of FOLFOX regimen (adjusted HR with IPTW = 0.81; 95% CI, 0.67–0.99) had survival benefits in using COX-2 inhibitors both prior to and after diagnosis. Use of COX-2 inhibitors was found to

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be associated with reduction in mortality for CRC patients when taken both prior to and after cancer diagnosis.

Introduction

Colorectal cancer (CRC) is the third leading cause of morbidity and mortality in Taiwan, and the 5-year survival rate is approximately 62.7% worldwide [1]. Although the treatment strategies for CRC have been well developed, researchers still attempt to add auxiliary agents to create a synergistic effect on standard treatment regimens in CRC to prolong survival time. It has been suggested that higher cyclooxygenase-2 (COX-2) expression may be associated with tumor metastasis and poor prognosis; therefore, using nonsteroidal anti-inflammatory drugs (NSAIDs) may induce tumor cell apoptosis and inhibit proliferation [2,3]. Studies on the association between use of NSAIDs and overall cancer survival rates have previously been reported. Coghill et al [4] proposed that using NSAIDs prior to diagnosis may lead to less aggressive tumors with an improved survival rate and 24% less chance [hazard ratio (HR) = 0.76; 95% confidence interval (CI), 0.62—0.93] of CRC-specific mortality. Zell et al [5] also reported that regular prediagnosis NSAID use was independently associated with a significant decrease in mortality compared with nonregular use of NSAIDs (HR = 0.71; 95% CI, 0.53—0.95). The effect of using NSAIDs after diagnosis on survival rates has also been investigated. However, the results revealed an increase in mortality in CRC patients within subgroup analyses [6,7]. Walker et al [7] reported an HR of 0.95 (95% CI, 0.87—1.03) with inclusion of using NSAIDs both prior to and after diagnosis of CRC [7]. Although our previous report supports the chemoprevention role of COX-2 inhibitors to CRC in the general population [8], its effect on the prognosis of CRC patients has not yet been discussed. Therefore, the purpose of this study was to investigate the association between COX-2 inhibitors and mortality among CRC patients. In addition, subgroup analyses were conducted to ascertain which subpopulation showed a higher reduction of mortality risk.

Methods

Data source

This retrospective cohort study used the Taiwan National Health Insurance Research Database (NHIRD) as a population-based reimbursement dataset from 2002 to 2011. The National Health Insurance (NHI) program in Taiwan has been the national, single, and compulsory health insurance program since March 1, 1995, and nearly 99.9% of Taiwan's population had been enrolled in the program by 2014. The Bureau of National Health Insurance collects monthly claims data from all medical care units in Taiwan and provides the claims data to the National Health Research Institutes for academic research. Data in the NHIRD have been encrypted to preserve anonymity. The NHIRD is updated yearly, and it includes registration files and original claims data. This study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital (KMUH-IRB-EXEMPT-20140054).

Study cohort

Patients with CRC were identified by screening NHIRD and the Registry for Catastrophic Illness via CRC-related International Classification of Diseases Revision 9 (ICD-9) codes (153, 154 for CRC). The inclusion criteria included being newly diagnosed with CRC in 2003—2010, age of 18—100 years to allow for at least 1 year of prior medication history taken, and at least 1 year of follow-up time for patients responding to their primary cancer treatment. The reason for further extracted patients who had at least one prescription of NSAIDs prior to their CRC diagnosis date was to ensure that our study participants all had the same indication of using COX-2 inhibitors, as NSAIDs (including traditional NSAIDs and COX-2 inhibitors) are primarily used for anti-inflammation. Those patients who had less than 1 year of follow-up time from the date of cancer diagnosis were excluded from the study cohort to ensure that only patients who responded to their primary cancer treatment were included.

Drug categories and analysis groups

COX-2 inhibitors included celecoxib (M01AH01), rofecoxib (M01AH02), and etoricoxib (M01AH05), and preferential selective COX-2 inhibitors included nabumetone (M01AX01), meloxicam (M01AC06), etodolac (M01AB08), and nimesulide (M01AX17) according to the Anatomical Therapeutic Chemical classification system. Rofecoxib was no longer available after it was withdrawn in 2004 because of an increased risk of cardiovascular diseases. Based on the use of COX-2 inhibitors prior to or after diagnosis of CRC within a 1-year period, four exposure patterns were defined in this study, including: (1) use prior to and after diagnosis, (2) use only prior to diagnosis, (3) use only after diagnosis, (4) nonusers.

Outcome measurement and confounding factors

The outcome measurement was overall survival (OS) in this study. Each patient was followed from the index date to death date or from the index date to the censor date (December 31, 2011). The index date was defined as the

first date in the first appearance of two consecutive diagnoses of CRC within 30 days to avoid prior screening purpose. The relevant confounding factors were as follows: age, sex, comorbidities, treatment modalities, and use of comedications. Patient comorbidities recorded at the year prior to CRC diagnosis were identified (including myocardial infarction, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, diabetes with end organ damage, hemiplegia, moderate or severe renal disease, moderate or severe liver disease). Treatment modalities within 180 days after diagnosis with CRC were only operation (OP), OP plus radiation (RT), OP plus chemotherapy (CT), and OP plus chemoradiation therapy (CRT). To allow comparison of the effect of doses across study drugs (COX-2 inhibitor), we use defined daily dose for comparison. Moreover, use of comedications 1 year prior to or 1 year after diagnosis with CRC included aspirin (N02BA01), traditional NSAIDs (M01AB01-15, M01AC01, M01AE01-03, M01AG01), angiotensin-converting enzyme inhibitors (C09AA01-09), angiotensin receptor blockers (C09CA01-08), statins (C10AA01-08), sulfonylureas (A10BB01-12, A10BB31), and metformin (A10BA02). Comorbidities, treatment modalities, and comedications were all considered dichotomous variables (yes/no).

Statistical analyses

Descriptive statistics were initially used to characterize the cohort by chi-square for categorical variables and analysis of variance for continuous variables. Propensity scores were generated between users and nonusers of COX-2 inhibitors at 1 year prior to diagnosis. A logistic regression with covariates of age (years), sex, comorbidities (myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, diabetes, hemiplegia, moderate/severe renal disease, diabetes with end organ damage) at the prior year, and comedication (traditional NSAIDs, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statin, metformin, sulfonylurea) was used to compute the propensity scores. The application of propensity score through the inverse probability of treatment weighting (IPTW) [8] was applied to Kaplan–Meier estimates, log-rank test, and COX regression for estimating the mortality risk. Subgroup analyses included stratification of diverse anatomical site of cancer (colon or rectal), treatment modalities, and initially received CT regimen [5-fluorouracil (5-FU)/leucovorin or FOLFOX]. All statistical tests were two-sided with a level of significance at 0.05. Data management and statistical analyses were conducted using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

Results

During the period between January 1, 2003 and December 31, 2010, a total of 24,970 newly diagnosed CRC patients were initially identified. Among them, 14,688 patients were included in the analysis after excluding those who were <18 years and more than 100 years ($N = 6$), who were followed less than 1 year ($N = 4542$); who had no prescription of NSAIDs ($N = 5701$); or had missing data on ID, sex, birthday, or index date during processing ($N = 31$). The mean and median follow-up time was 3.96 ± 2.26 and 3.46 years, respectively. One-half of the patients had not used COX-2 inhibitors, 14.4% patients were users both prior to and after diagnosis of CRC, 15.5% patients were users only prior to diagnosis of CRC, and 13.7% patients were users only at after diagnosis of CRC. The vast majority in each group was the elderly population (age older than 65 years). Users of COX-2 inhibitors 1 year before diagnosis seemed to be more likely to suffer from diseases such as congestive heart failure, cerebrovascular disease, chronic pulmonary disease, or ulcer disease. More patients were diagnosed with colon cancer compared to patients diagnosed with rectal cancer (61.1% vs. 38.9%, respectively). Nearly 60% of patients had OP, only 3% received OP and RT, 21% had OP and CT, and 4.5% received OP followed by CRT. Patients who used COX-2 inhibitors both prior to and after diagnosis of CRC took more dosages of COX-2 inhibitors than those who were using them only prior to or only after diagnosis of CRC (Table 1). After IPTW weighting, we could observe that there were similarly equal distributions in different age stratification and comorbidities between patients with or without COX-2 inhibitors prior to cancer diagnosis (Appendix 1).

In Table 2, there are significant differences in the OS according to the Kaplan–Meier estimates. After weighting with IPTW, patients using COX-2 inhibitors both prior to and after diagnosis had the best 5-year OS ($p < 0.001$) at a significant level. Table 3 indicates that patients who used COX-2 inhibitors both prior to and after diagnosis had a 10% decreased risk of all-cause mortality than patients in the nonuser group (adjusted HR with IPTW = 0.91; 95% CI, 0.86–0.96; $p = 0.001$).

As shown in Table 3, in the subgroup analysis among different cancer sites, patients with colon cancer diagnosis who used COX-2 inhibitors both prior to and after diagnosis had a slightly decreased risk of mortality (adjusted HR with IPTW = 0.93; 95% CI, 0.87–1.00; $p = 0.064$). Among those with diagnosis of rectal cancer, patients who used COX-2 inhibitors both prior to and after diagnosis had significantly decreased (14%) risk of mortality (adjusted HR with IPTW = 0.86; 95% CI, 0.79–0.94; $p = 0.001$). In addition, there was significant reduction in mortality among patients using COX-2 inhibitors both prior to and after diagnosis who received OP followed by CRT (adjusted HR with IPTW = 0.57; 95% CI, 0.43–0.77; $p < 0.001$). Furthermore, patients receiving FOLFOX CT regimen were significantly associated with decreasing mortality risk in after diagnosis groups compared with the nonusers group (adjusted HR with IPTW = 0.81, $p = 0.038$ in before and after diagnosis groups; 0.77, $p = 0.032$ in use only after diagnosis group). After conducting subgroup analysis by different severity of comorbidities (Appendix 2), only CCI score = 0 and use COX-2 inhibitors before and after CRC diagnosis groups were significantly associated with increasing survival outcome (adjusted HR with IPTW = 0.79, $p = 0.0006$).

Table 1 Baseline characteristics of patients in different groups of cyclooxygenase-2 inhibitors.

	No. of patients	Use B & A diagnosis	Use only B diagnosis	Use only A diagnosis	Nonusers	*p*
		N (%)	*N* (%)	*N* (%)	*N* (%)	
Total	14,688	2114	2270	2011	8293	
Sex						
Male	7914	927 (43.9)	1093 (48.1)	998 (49.6)	4896 (59.0)	<0.001*
Female	6774	1187 (56.1)	1177 (51.9)	1013 (50.4)	3397 (41.0)	<0.001*
Age at cancer diagnosis (y)						
Mean ± SD	70.18	74.47 ± 8.04	73.28 ± 8.65	71.27 ± 9.55	67.98 ± 10.49	<0.001*
18–49	472	15 (0.7)	27 (1.2)	44 (2.2)	386 (4.7)	<0.001*
50–64	3695	223 (10.5)	330 (14.5)	436 (21.7)	2706 (32.6)	
65–74	5396	794 (37.6)	920 (40.5)	774 (38.5)	2908 (35.1)	
≥75	5125	1082 (51.2)	993 (43.7)	757 (37.6)	2293 (27.6)	
Comorbidity (yes)						
Myocardial infarct	260	41 (1.9)	45 (2.0)	36 (1.8)	138 (1.7)	0.687
Congestive heart failure	1133	223 (10.5)	240 (10.6)	177 (8.8)	493 (5.9)	<0.001*
Peripheral vascular disease	365	76 (3.6)	71 (3.1)	46 (2.3)	172 (2.1)	<0.001*
Cerebrovascular disease	2418	467 (22.1)	448 (19.7)	330 (16.4)	1173 (14.1)	<0.001*
Dementia	369	76 (3.6)	81 (3.6)	42 (2.1)	170 (2.0)	<0.001*
Chronic pulmonary disease	3222	587 (27.8)	576 (25.4)	481 (23.9)	1578 (19.0)	<0.001*
Connective tissue disease	238	108 (5.1)	53 (2.3)	24 (1.2)	53 (0.6)	<0.001*
Ulcer disease	4319	834 (39.5)	820 (36.1)	542 (27.0)	2123 (25.6)	<0.001*
Mild liver disease	1528	240 (11.4)	245 (10.8)	195 (9.7)	848 (10.2)	0.287
Diabetes	4428	646 (30.6)	727 (32.0)	621 (30.9)	2434 (29.4)	0.072
Hemiplegia	160	37 (1.8)	27 (1.2)	11 (0.5)	85 (1.0)	0.002*
Moderate/severe renal disease	1089	191 (9.0)	157 (6.9)	160 (8.0)	581 (7.0)	0.008*
DM with end organ damage	1155	197 (9.3)	206 (9.1)	172 (8.6)	580 (7.0)	<0.001*
Cancer site						
Colon	8979	1294 (61.2)	1417 (62.4)	1229 (61.1)	5639 (60.8)	0.557
Rectum	5709	820 (38.8)	853 (37.6)	782 (38.9)	3254 (39.2)	
Treatment modalities within 180 d						
OP only	8796	1370 (64.8)	1451 (63.9)	1187 (59.0)	4788 (57.4)	<0.001*
OP plus RT	415	61 (2.9)	64 (2.8)	57 (2.8)	233 (2.8)	
OP plus CT	3092	344 (16.3)	415 (18.3)	418 (20.8)	1915 (23.0)	
OP and CRT	658	72 (3.4)	77 (3.4)	117 (5.8)	392 (4.7)	
Usage of COX-2 inhibitor						
Preuser	4384					
DDD		88.44 ± 113.41	43.51 ± 65.30	—	—	<0.001*
Postuser	4125					
DDD		90.15 ± 116.71	—	51.85 ± 81.11	—	<0.001*

A = after; B = before; CT = hemotherapy; DDD = defined daily dose; DM = diabetes mellitus; OP = operation; RT = radiation therapy; SD = standard deviation.

* Significant difference, $p < 0.05$.

Discussion

This large population-based cohort study found that only use of COX-2 inhibitors both prior to and after diagnosis of CRC was associated with reduced mortality. The result was not completely consistent with other studies showing that use of NSAIDs regularly or over a prolonged duration prior to CRC was associated with decreased mortality among CRC patients [4,5]. However, in this study use of COX-2 inhibitors only prior to diagnosis of CRC did not show this protective effect. The distribution of age could be the cause of the differences when compared to previous studies. This study had an enrolled population that was older than those in previous studies, with a mean age of 70 years, and the majority was older than 65 years. The mean age was 65 years in Zell et al's [5] study, and the majority of the population was younger than 70 years in Coghill et al's [4] study. Although Yang et al [9] presented a trend that patients taking selective COX-2 inhibitors over 6 months had a significant reduction in risk of CRC (odds ratio = 0.72; 95% CI, 0.56–0.93), the tumor characteristics may be more aggressive in the use only before diagnosis group, even using COX-2 inhibitors prior to diagnosis of CRC. Different exposure patterns of COX-2 inhibitors play different roles in CRC survival. Using them before diagnosis may lead to less aggressive tumors, and using them after diagnosis may contribute to slower disease progress [4].

Table 2 Overall survival rates in analysis groups.

	No.	Survival rate after diagnosis (%)			
		Weighted with IPTW			
		3 y	5 y	7 y	Log rank
					p
Group	14,688				<0.001*
Use B & A diagnosis	2114	79.5	68.9	59.3	
Use only B diagnosis	2270	79.0	67.0	58.8	
Use only A diagnosis	2011	76.0	61.1	52.2	
Nonusers	8293	78.9	67.1	59.4	

A = after; B = before; IPTW = inverse probability of treatment weighting.
* Significant difference, $p < 0.05$.

Regarding cancer site, patients with rectal cancer diagnosis who used COX-2 inhibitors both prior to and after diagnosis of CRC had significant reduction in mortality risk; however, a slight survival benefit was observed in patients diagnosed with colon cancer. Although it has been suggested that there was no significant correlation between COX-2 expression and clinicopathological status [10], in previous studies different results have been witnessed on this issue. In the aspect of using NSAIDs prior to diagnosis of CRC, significant differences in colon cancer OS are revealed but not seen in rectal cancer OS (colon cancer HR = 0.68; 95% CI, 0.48—0.97) [4,5]. In another aspect of using NSAIDs after diagnosis of CRC, it seemed that there was no substantial difference between cancer sites (HR = 0.89; 95% CI, 0.79—1.01 for colon cancer; HR = 0.90; 95% CI, 0.59—1.38). However, all of these studies mentioned that there might be a different mechanism of carcinogenesis at different anatomic subsites consequently affecting CRC treatment. Further research is necessary to clarify the effects of using COX-2 inhibitors prior to and after diagnosis of CRC at different subsites.

In general, the duration of adjuvant therapy after first surgery was within 2 to 3 months, and it was consistent with the principle that adjuvant therapy should be administered as soon as the patient is medically able. A systemic review demonstrated that each 4 weeks of delay in CT resulted in a 14% decrease in OS [11]. We demonstrated treatment modalities within 180 days after diagnosis of CRC in Table 3; however, statistical significance was only shown in the OP with any combination therapy and was not present in only RT, only CT, or CRT modalities because of the small number of patient. After adjusting relevant covariates, patients receiving OP followed by CRT who were using COX-2 inhibitors had greater association with CRC survival. However, patients receiving OP plus CT or OP plus RT did not show significant survival benefits. Our result was consistent with previous studies. Nakata et al [12] conducted a laboratory murine model study and revealed that selective COX-2 inhibitors greatly enhanced the tumor response to CRT, by assessment of tumor growth delay and enhancement factor. However, the mechanisms by which COX-2 inhibitors enhance tumor response to RT or CT agents are not entirely understood [12]. The mechanisms of using COX-2 inhibitors related to radiosensitivity are multiple and complex, although the concept of radiation-induced apoptosis is the most adopted. It has been suggested that addition of celecoxib to preoperative CRT tended to induce a better response [13]. One recent phase II trial study that included 53 patients used the combination of celecoxib and preoperative CRT for locally advanced rectal cancer, and demonstrated that this combination was well tolerated. Pathological complete response was seen in six patients (13%), whereas T or N down-staging was found in 38 (81%). Sphincter preservation was achieved in 77% of low-positioned tumors [14].

5-FU/leucovorin and FOLFOX regimens are the most common adjuvant therapies in CRC. The 5-FU/leucovorin regimen is generally used for lower risk patients with stage II colon cancer, which could be considered as early stage (without regional lymph nodes, N0). The FOLFOX regimen is generally for higher-risk stage II patients and patients with positive regional lymph nodes (any N). In this study, patients who received FOLFOX regimen using COX-2 inhibitors both prior to and after diagnosis or only after diagnosis had reduced risk of mortality. This result was similar to a study conducted by Jin et al [15], who enrolled 90 patients and randomly divided them into two groups: a group that received the combination of celecoxib with FOLFOX4 regimen, and another group that received the FOLFOX4 regimen alone. It was concluded that the combined approach (celecoxib with FOLFOX4) increased the short-term efficacy and the 3-year survival rate, and improved the quality of life of patients with advanced CRC [15]. It was suggested that the combined use of oxaliplatin and celecoxib could cause tumor inhibition and suppress the expression levels of COX-2 enzyme, a vascular endothelial growth factor [16]. We did not further analyze the association between the patterns of exposure to COX-2 inhibitors and other adjuvant regimens because of the small number of populations receiving adjuvant therapy in the form of capecitabine and FOLFIRI. More clinical trials would be needed to determine whether COX-2 inhibitors are able to improve patient outcome with a reasonable safety profile prior to addition of COX-2 inhibitors to the standard CT regimens.

Strengths and limitations

Our study has several important strengths. To our knowledge, this study is the first population-based study to evaluate COX-2 inhibitors use and CRC survival and included cases diagnosed at all stages of the disease in Asia. We further conducted subgroup analysis to ascertain which population group had been substantially influenced by using COX-2 inhibitors. This is the first observation study simultaneously taking different exposure patterns of COX-2 inhibitors into consideration. The study cohort was drawn from the National Health Insurance Registers of Taiwan, which covers almost all CRC cases in Taiwan, suggesting good internal generalizability. Furthermore, this is the largest scale study including the most extensive amount of study information (14,688 patients). Patient comorbidity and the use of other comedications were all recorded in the database in detail without raising concerns of recall bias.

Table 3 Multivariable analysis and subgroup analysis in colorectal cancer patients.

	Adjusted HR with IPTW[a]	*p*
Total population		
Groups		
Use B & A diagnosis	0.91 (0.86–0.96)	0.001*
Use only B diagnosis	1.03 (0.97–1.08)	0.344
Use only A diagnosis	1.07 (1.00–1.15)	0.061
Nonusers	Ref	—
Subgroup analysis		
Cancer site		
Colon cancer		
Use B & A diagnosis	0.93 (0.87–1.00)	0.064
Use only B diagnosis	0.98 (0.92–1.06)	0.655
Use only A diagnosis	1.10 (1.01–1.21)	0.033*
Nonusers	Ref	—
Rectum cancer		
Use B & A diagnosis	0.86 (0.79–0.94)	0.001*
Use only B diagnosis	1.10 (1.02–1.19)	0.019*
Use only A diagnosis	0.99 (0.89–1.11)	0.888
Nonusers	Ref	—
Treatment modalities		
Only OP		
Use B & A diagnosis	1.02 (0.94–1.10)	0.643
Use only B diagnosis	1.00 (0.93–1.07)	0.939
Use only A diagnosis	1.04 (0.95–1.15)	0.377
Nonusers	Ref	—
OP and RT		
Use B & A diagnosis	0.88 (0.59–1.30)	0.509
Use only B diagnosis	1.52 (1.07–2.16)	0.019*
Use only A diagnosis	2.21 (1.47–3.31)	<0.001*
Nonusers	Ref	—
OP and CT		
Use B & A diagnosis	0.96 (0.85–1.08)	0.473
Use only B diagnosis	1.15 (1.04–1.27)	0.008*
Use only A diagnosis	1.04 (0.90–1.20)	0.598
Nonusers	Ref	—
OP and CRT		
Use B & A diagnosis	0.57 (0.43–0.77)	<0.001*
Use only B diagnosis	0.93 (0.73–1.20)	0.583
Use only A diagnosis	0.93 (0.69–1.26)	0.635
Nonusers	Ref	—
First chemotherapy regimen		
5-FU/leucovorin		
Use B & A diagnosis	0.99 (0.84–1.16)	0.869
Use only B diagnosis	1.32 (1.14–1.52)	<0.001*
Use only A diagnosis	1.17 (0.96–1.42)	0.118
Nonusers	Ref	—
FOLFOX		
Use B & A diagnosis	0.81 (0.67–0.99)	0.038*
Use only B diagnosis	0.98 (0.83–1.16)	0.813
Use only A diagnosis	0.77 (0.61–0.98)	0.032*
Nonusers	Ref	—

5-FU = 5-fluorouracil; A = after; ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; B = before; CT = chemotherapy; DDD = defined daily dose; HR = hazard ratio; NSAID = nonsteroidal anti-inflammatory drug; OP = operation; RT = radiation therapy.

[a] Computed by multivariable Cox regression and adjusted variables include sex, index age, comorbidities, rectal cancer, treatment modalities within 180 days after diagnosis of colorectal cancer (only OP, OP plus CT, OP plus RT, OP plus CT/RT), comedication (traditional NSAID usage cumulative DDD, aspirin, ACEI, ARB, statin, metformin, sulfonylurea).

* Significant difference, $p < 0.05$.

However, several limitations of this study should also be considered in interpreting our results. First, the database is for reimbursement; so, there is a lack of information regarding some important tumor characteristics that may influence cancer prognosis, such as body mass index, weight, smoking, dietary habit, and cancer stage. Although cancer stage is an important factor for cancer prognosis, the use of COX-2 inhibitors in cancer patients may be largely attributable to their comorbidities, and is not part of cancer treatment management for different cancer stages. Therefore, we speculate that after considering comorbidities in the statistical analysis, the effect by cancer stages may be limited. Second, our ability to investigate the relation of specific CRC survival was limited because the vast majority of death reasons in the database were not clearly recorded. Third, our study focused on COX-2 inhibitors, which are not long-term prescriptions that patients take from hospitals or pharmacies. We were unable to distinguish between the differences in COX-2 inhibitors' effect between before first half-year of diagnosis and before last half-year of diagnosis, as well as after half-year of diagnosis and after last half-year of diagnosis. We also could not calculate the drug effect for drugs purchased over the counter. Finally, the majority of the cohort race in this study was Chinese, which might limit the generalizability of these findings to other ethnicities.

Conclusions

In summary, we observed that the use of selective COX-2 inhibitors both prior to and after diagnosis of CRC seemed to be mildly associated with the reduction in mortality of CRC patients. This survival benefit was also shown in patients diagnosed with rectal cancer or those receiving OP followed by CRT within 180 days after diagnosis. Moreover, we also observed that COX-2 inhibitors might play a synergistic role in adjuvant CT of FOLFOX regimen. All of these results point out the rationality of use in patients who had used COX-2 inhibitors 1 year prior to diagnosis of CRC, where patients could continuously receive these types of drugs after diagnosis of CRC if clinically necessary. However, future studies would need to focus on the application of the appropriateness of "adding COX-2 inhibitors as auxiliary agents into standard CRC treatment strategies" prior to making any clinical recommendations.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.kjms.2017.03.004.