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Postdiagnosis aspirin use associated with decreased biliary tract cancer–specific mortality in a large nationwide cohort

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Abstract

Background & Aims

Biliary tract cancer (BTC) is rare and has limited treatment options. We aimed to examine aspirin use on cancer–specific survival in various biliary tract cancer (BTC) subtypes, including gallbladder cancer, ampulla of Vater cancer, and cholangiocarcinoma.

Approach & Results

Nationwide prospective cohort of newly diagnosed BTC between 2007 and 2015 were included and followed until December 31, 2017. Three nationwide databases, namely the Cancer Registration, National Health Insurance, and Death Certification System, were used for computerized data linkage. Aspirin use was defined as one or more prescriptions, and the maximum defined daily dose (DDD) was used to evaluate the dose–response relationship. Cox's proportional hazards models were applied for estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Analyses accounted for competing risk of cardiovascular deaths, landmark analyses to avoid immortal time bias were performed. In total, 2,519 of patients with BTC were exposed to aspirin after their diagnosis (15.7%). After a mean follow-up of 1.59 years, the 5-year survival rate was 27.4%. The multivariate-adjusted HR for postdiagnosis aspirin users, as compared with nonusers, was 0.55 (95% CI, 0.51 to 0.58) for BTC-specific death. Adjusted HRs for BTC-specific death were 0.53 (95% CI, 0.48 to 0.59) and 0.42 (95% CI, 0.31 to 0.58) for ≤1 and >1 maximum DDD, respectively, and showed a dose–response trend ($p < 0.001$; nonusers as a reference). Cancer–specific mortality was lower with postdiagnosis aspirin use in patients with all major BTC subtypes.

Conclusions

The nationwide study revealed that postdiagnosis aspirin use was associated with improved BTC-specific mortality of various subtypes. The findings suggest that additional randomized trials are required to investigate aspirin's efficacy in BTC.

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Introduction

Biliary tract cancers (BTCs), malignancies involving the biliary drainage system, are rare but lethal. BTCs include gallbladder cancer (GBC), ampulla of Vater cancer (AVC), and cholangiocarcinoma (CC), of which GBC is the most common BTC (1). These cancers are generally diagnosed at a late stage with few treatment options. The 5-year survival is usually 5%–15% (2). The absolute years of life lost due to BTCs has been constant in the past 10 years, suggesting limited progress in treating these cancers effectively (3). Although surgery and chemotherapy remain standard treatments, innovative regimens to improve cancer-specific survival are crucial.

Aspirin is a nonsteroidal anti-inflammatory drug commonly used for analgesic purposes and preventing cardiovascular diseases. Observational studies and clinical trials have indicated that the antitumor activity of aspirin may reduce cancer risk (4, 5). Regular aspirin has been associated with a significant reduction (63%) in GBC risk but nonsignificant reductions in the risk of bile duct cancer and AVC (6). A recent retrospective cohort study analyzed the overall survival of patients with an aspirin prescription and found that aspirin may improve the overall survival of patients with BTC (7). The survival benefits were significant for all BTC subtypes, with adjusted mortality hazard ratios (HRs) ranging from 0.44 to 0.71 (7). However, the aspirin dose use, chemotherapy, or surgical status of these patients with BTC was not considered. The benefits of aspirin in cancer-specific mortality, which is a measure of death due to only the target cancer, must be evaluated.

Thus, we conducted a nationwide cohort study of 16,057 patients with BTC to examine the effect of aspirin use on cancer-specific survival in various BTC subtypes. Furthermore, we evaluated the dose–response relationship of aspirin use on BTC-specific survival.

Materials and Methods

Study Design

We conducted a nationwide cohort study to investigate the cancer-specific mortality of patients with BTC diagnosed during 2007–2015. The study integrated three major nationwide health information profiles, provided by Health and Welfare Data Science Center, Ministry of Health and Welfare, in Taiwan. We used the National Cancer Registration database to identify patients with a primary diagnosis of BTC and obtained their detailed treatment information through computerized linkage to the National Health Insurance (NHI) database. The death

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certification system was used to prospectively follow-up the vital status of patients with BTC from 2007 to December 31, 2017. All these national registration profiles are complete, accurate, and updated, making them unique resources for academic research (8).

Study cohort and follow-up

In total, 16,057 patients with BTC were included (International Classification of Diseases, Ninth Revision [ICD-9] codes), comprising 2,422 GBC (156.0), 2,745 AVC (156.2), and 10,890 CC (156.1 and 155.1) cases. Intrahepatic (155.1) and extrahepatic (156.1) CC were pooled for analyses in order to increase the number of events. However, we separated intrahepatic and extrahepatic CC for additionally analyses to examine the associations of postdiagnosis aspirin use on each cancer-specific survivals. The cancer type, diagnostic age, sex, grade, and treatment regimens were collected in the cancer registration profiles. The date and cause of death were obtained through linkage with the death certification system by citizenship identification number and birthdate.

Assessment of aspirin use and covariates

The NHI reimburses a wide spectrum of health care services for >99% of residents in Taiwan (9) and is a compulsory program launched by the government. The claims data set has detailed information on drug prescriptions, medical procedures, outpatient visits, inpatient hospitalizations, and dates. The database was used to define aspirin use and identify comorbidities of the study patients.

We defined prediagnosis and postdiagnosis aspirin use as one or more prescriptions (Anatomical Therapeutic Chemical code: B01AC06 and N02BA01) recorded before and after the diagnostic date of any BTC, respectively. Any prescription before or after cancer diagnosis was defined as use in one's lifetime. More detailed information on medication use, including prescribing dose, frequency of drug use, and total number of prescriptions, was additionally collected in the NHI database from 2011, which facilitated the subsequent dose–response relationship analyses among the patients diagnosed after 2011. The maximum prescribed dose for an individual was used and expressed through defined daily dose (DDD) as recommended by the World Health Organization to measure the prescribed amount of aspirin. The DDD is the assumed average maintenance dose per day of aspirin used for its main indication. The maximum daily prescription dose was used to define the exposure levels of aspirin.

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The comorbidities (ICD-9 codes in Supplementary Table 1) including diabetes, hypertension, liver cirrhosis, chronic pancreatitis, gastric disease, inflammatory bowel disease, biliary tract disease, alcohol-related disease, gallstones, angina, myocardial infarction, and ischemic stroke were considered based on the diagnostic codes from at least two outpatient visits or at least one hospital admission code before the specific cancer diagnosis. The Charlson comorbidity index (CCI) 1 year before BTC diagnosis was applied to evaluate general health conditions. The CCI is a composite measure frequently used to control for the overall burden of comorbidities in administrative health data and demonstrates validity in predicting mortality (10).

Statistical analyses

We evaluated the effect of aspirin use on BTC and its subtypes, namely GBC, AVC, and CC. The subtypes of CC, including intrahepatic and extrahepatic CC, were also analyzed. The person-years of follow-up were calculated for each patient as the BTC diagnostic date to the date of death, or December 31, 2017, whichever came first. Cancer-specific mortality for BTC was calculated by dividing the number of cancer-specific deaths by the follow-up person-years, and differences in mortality rates by aspirin use were calculated using log-rank test. Cox's proportional hazards models with the time (in years) after the cancer diagnosis as the time scale were used to estimate the adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for aspirin use and cancer-specific mortality. Proportional hazards assumptions were evaluated before the Cox models were used and the assumptions were not violated. Baseline characteristics and comorbidities significantly associated with cancer-specific mortality in the univariate analyses were considered potential confounders and adjusted in multiple regressions. The additional analyses were repeated by adjustment of all putative confounders even they were non-significantly associated with cancer-specific mortality. To avoid immortal time bias, landmark analyses were performed repeatedly to examine the associations between aspirin use and cancer-specific mortality with the landmark times set to 0.25, 0.5, 1.0, and 1.5 years after cancer diagnosis. For each landmark analysis, aspirin use was assessed prior to the landmark time to avoid immortal time bias. Stratification analyses were additionally performed to evaluate the associations between postdiagnosis aspirin use and cancer-specific mortality based on baseline characteristics. The dose–response relationships between aspirin use and specific BTC death were examined through comparison of nonuse (reference), ≤1.0 DDD, and >1.0 DDD with a Cochran–Armitage test of trend among patients diagnosed after 2011.

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In order to avoid potential bias and competing risks of death, we repeated the analyses by excluding patients who died within 1 year after cancer diagnosis. Separate repeated analyses were performed by excluding patients with prediagnosis aspirin use to evaluate the effects of postdiagnosis aspirin use. To verify the analyses, we estimated propensity scores for aspirin use to approximate the findings from a randomized trial. The covariates (age at diagnosis, sex, CCI, surgery status, and prediagnosis aspirin use) were related to both cancer-specific deaths and aspirin use or to deaths based on the methods for creating propensity scores (11). We created two pseudo-populations with aspirin use and nonuse with balanced characteristics. Cox regression models were used to compare the risk of cancer-specific deaths based on aspirin use. Aspirin is frequently prescribed for patients with underlying cardiovascular diseases. We considered deaths from cardiovascular diseases (Supplementary Table 2) as a competing risk (12) to repeatedly evaluate aspirin effects.

The statistical analyses were two-sided, and $p < 0.05$ was considered significant. All statistical analyses were performed using SAS software (version 9.4; SAS institute, Cary, NC).

Results

Study Patients

Among the 16,057 BTC patients in this cohort, 2,422 (15.1%), 2745 (17.1%), and 10,890 (67.8%) had GBC, AVC, and CC, respectively. After a mean follow-up of 1.24–2.74 years, 42.33%–61.57% died from their specific cancers. The 5-year survival rates for BTC, GBC, AVC, and CC were 27.4%, 32.1%, 47.0%, and 20.3%, respectively. Men had a slightly higher incidence of AVC and CC than women. Almost half of the patients with BTC were diagnosed after age 70 years (Table 1). Thus, a substantial proportion of the patients had comorbidities, including diabetes, hypertension, biliary tract disease, and liver cirrhosis (Supplementary Table 3). Among patients with BTC, 8,323 (51.8%) had ever used aspirin in their lifetime. In total, 2,519 (15.7%) and 7,791 (48.5%) patients were postdiagnosis and prediagnosis aspirin users, respectively.

Aspirin Use and Cancer-Specific Mortality for BTC Subtypes

The mortality rates were 30.8, 15.5, and 49.7 per 100 person-years for GBC, AVC, and CC, respectively (Table 2). Postdiagnosis aspirin users had lower cancer-specific mortality rates than nonusers ($p < 0.0001$ for all cancers subtypes). Conversely, those who used aspirin before cancer diagnosis generally had increased mortality rates ($p < 0.0001$ for AVC and CC). We evaluated aspirin use status and cancer-specific deaths taking factors associated with cancer-specific

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mortality into account. Generally, nonsignificant associations were noted between prediagnosis aspirin use and cancer-specific mortality, except in patients with GBC (HR = 0.88, 95% CI = 0.79–0.99). The multivariable-adjusted HRs for postdiagnosis aspirin use according to BTC subtypes, as compared with aspirin nonuse, were 0.48 (0.41–0.56), 0.61 (0.52–0.72), and 0.55 (0.51–0.60) for GBC, AVC, and CC, respectively (Table 2). The associations between postdiagnosis aspirin use and improved biliary tract cancer–specific mortality remained significant when considered for treatment modalities (either surgery or chemotherapy) ($p<0.0001$), or after additional adjustment of the history of cardiovascular diseases before cancer diagnosis ($p<0.0001$), and all putative confounders ($p<0.0001$) (Supplementary Table 4).

In order to examine the relationships between postdiagnosis aspirin use and cancer–specific survival and avoid the bias introduced by immortal time, landmark analyses were performed extensively. A significantly decreased risk of each BTC-specific death related to postdiagnosis aspirin use was still observed even after various years were used in landmark analyses ($p<0.05$ for each BTC subtype, Supplementary Table 5). The improved BTC-specific survival by postdiagnosis aspirin use remained significant ($p<0.05$ for each BTC subtype by various landmark time) even considering competing risk of cardiovascular deaths.

Analyses stratified according to age, sex, grade, diabetes, hypertension, biliary tract disease, liver cirrhosis, treatment, and CCI showed an increased risk associated with each BTC subtype, and cancer-specific mortality was significantly lower among postdiagnosis aspirin users compared with nonusers ($p < 0.05$) in all strata except patients with well-differentiated cancer (GBC and AVC), poor or undifferentiated cancer (AVC), CCI ≥ 5 (AVC), or those undergoing chemotherapy (AVC; Figure 1).

The multiple adjusted HR (95% CI) for death from BTC for postdiagnosis aspirin users according to the maximum daily dose, as compared with aspirin nonuse, were 0.53 (0.48–0.59) for ≤1.0 DDD and 0.42 (0.31–0.58) for >1.0 DDD (Table 3). For GBC, AVC, and CC, significant trends showed that an increased dose of aspirin may decrease risk of death from specific cancers (p for trend < 0.05). The dose–response relationship between aspirin use and cancer-specific deaths for each BTC subtype remained the same after the competing risk of death from cardiovascular diseases was accounted for.

Aspirin Use and Cancer-Specific Mortality for Intrahepatic and Extrahepatic CC

The CC were additionally separated into intrahepatic and extrahepatic subtypes to evaluate the benefit effects of aspirin use. Among 10,890 CC patients, there were 8,124 (74.6%)

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intrahepatic CC and 2,766 (25.4%) extrahepatic CC patients. The mortality rates were 54.4, and 39.1 per 100 person-years for intrahepatic and extrahepatic CC, respectively The post-cancer diagnosis use of aspirin remained significantly improved the cancer-specific survival for intrahepatic and extrahepatic CC, with the adjusted HR of 0.57, 95% CI = 0.52–0.62 and 0.52, 95% CI = 0.45–0.60, respectively (Supplementary Table 6). We performed landmark analyses by various years to evaluate postdiagnosis aspirin use on intrahepatic or extrahepatic CC-specific deaths. The protective estimates of postdiagnosis aspirin use on intrahepatic and extrahepatic CC consistently remained (supplementary table 7) by various landmark time ($p<0.05$). We additionally performed stratification analyses for CC patients with intrahepatic and extrahepatic subtypes. Generally, patients with postdiagnosis aspirin use had improved cancer-specific survivals compared to non-users (supplementary figure 1). The dose-response relationships for postdiagnosis aspirin use was consistently found for the patients with intrahepatic or extrahepatic CC (p for trend<0.0001), even considering for competing risks of cardiovascular deaths (supplementary table 8). Compared to nonusers, the HR_{adj} for those who used aspirin ≤1.0 DDD and >1.0 DDD was 0.50 (0.44-0.58) and 0.39 (0.25-0.61) for intrahepatic CC; and 0.50 (0.40-0.62) and 0.28 (0.12-0.68) for extrahepatic CC, in correspondingly.

Sensitivity Analysis

Analyses excluding patients who died within 1 year after cancer diagnosis revealed similar results. In addition, the results were similar to those for patients without prediagnosis aspirin use (Supplementary Table 9). The reduced cancer-specific mortality among patients who only used aspirin postdiagnosis compared with patients who had never used aspirin was observed for all BTC subtypes: the multivariate-adjusted HRs for death from BTC subtypes among aspirin postdiagnosis users ranged from 0.36 (95% CI, 0.25–0.51) for GBC to 0.61 (95% CI, 0.52–0.73) for CC. To adjust for the differences in postdiagnosis aspirin use, we repeated the analyses with the inverse probability treatment weights. The propensity score results were similar to those of the main analyses and showed that postdiagnosis aspirin use lowered the mortality of patients with BTC subtypes ($p < 0.05$; Supplementary Table 9). Among CC patients, the sensitivity analyses were performed for the intrahepatic and extrahepatic subtypes. It showed that patients with postdiagnosis aspirin use had improved cancer-specific survivals compared to non-users after diagnosis ($p<0.05$, Supplementary Table 10).

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Discussion

This nationwide study showed the advantages of aspirin use for the survival of patients with BTC. Patients with postdiagnosis aspirin use exhibited at least a 45% reduction in BTC cancer-specific mortality. In addition, postdiagnosis aspirin use exhibited a dose–response relationship with survival for each BTC subtype. The findings could not be accounted for by competing risks due to cardiovascular deaths, grade or treatment status.

The United States Preventive Services Task Force (USPSTF) recommended low-dose aspirin use for chronic disease prophylaxis, including colorectal cancer prevention among adults aged 50–59 years with specific cardiovascular risk profiles (13). The USPSTF Recommendation Statement indicates that the net benefit of aspirin use is moderate to substantial. Retrospective long-term analyses in randomized trials have shown at least a 20% reduction in cancer incidence and mortality among patients using aspirin (14-16). The effects were seen across cancer types but were most marked in gastrointestinal tract malignancies (5, 17). Large-scale prospective studies have suggested that aspirin use may prevent incident hepatocellular carcinoma (18, 19). In addition, a significant inverse association of aspirin use was observed for various CC subtypes, with a 65%–70% decreased risk for intrahepatic, perihilar, and distal CC (20). The evidence for the association between aspirin use and BTC risk was limited because of the relatively low incidence of BTC compared with other cancers. However, a population-based case–control study suggested that regular aspirin user was negatively associated with GBC risk (6). Although the prevalence of aspirin use was low, with 5.7% of regular users in unaffected controls, the inverse relationship was evident with respect to frequency, early initiation, and use duration (6).

Aspirin use has been shown to reduce cancer metastasis in various primary tumor types (17, 21), with a more predominant effect on adenocarcinoma (21). In addition to the primary prevention of cancer risk, aspirin use was associated with favorable cancer-specific and overall mortality among patients already diagnosed as having cancers (22-27), particularly those in an advanced stage (26). However, the evidence was generated from data on colon, breast, and prostate cancers (28). Significant advantages of aspirin use on cancer-specific survival among patients with gastrointestinal cancers has also been observed (25). At the fifth year after diagnosis, aspirin users were found to have 20% decreased overall mortality rates compared with nonusers (25). The decreased mortality could be a result of prolonged time to tumor metastasis and recurrence, which have been reported in clinical studies and murine models (28, 29). Our findings

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showed that postdiagnosis aspirin users had a decreased risk of BTC-specific mortality, which was in line with studies conducted for other cancers (23, 25-27).

A recent study conducted using the United Kingdom's Clinical Practice Research Datalink showed that aspirin prescriptions significantly decreased overall mortality within each BTC subtype (7). Notably, postdiagnosis aspirin use was associated with greater benefits among patients with no history of aspirin use compared with those with prediagnosis use. In line with their findings, we found that patients with aspirin use after their cancer diagnosis showed a greater reduction in their risk of cancer-specific deaths than prediagnosis users. In addition, our findings showed a favorable dose–response relationship between aspirin DDD and decreased mortality. In our study, the most common BTC subtype was CC (68%), followed by AVC (17%) and GBC (15%). Conversely, the British cohort had different subtype proportions (23% GBC, 53% CC, and 8% AVC) (7), indicating uneven distributions of BTC subtypes in the two studies with different ethnicities. The etiology, treatment responses, and prognosis might vary based on ethnicity. Although it is broadly consistent with previous findings, our study has novel contributions. With the advantage of a nationwide computerized data linkage, we could ascertain cancer-specific deaths of patients with various subtypes instead of analyzing overall survival. Overall survival measures time from treatment to death due to any cause, whereas cancer-specific mortality measures only death due to the target cancer. Our study strengthened the evidence that aspirin use improved the survival of patients with target cancers. The consistency of the findings from these studies conducted in Taiwan and Britain (7) suggest that international multicenter trials to evaluate the efficacy of aspirin on the survival of patients with BTCs might be worthwhile.

It is possible that BTCs that progress rapidly have molecular characteristics that make them more susceptible to inhibition by aspirin (22). However, biological evidence is still required to support this hypothesis. Notably, prediagnosis use was associated with slightly decreased GBC-specific deaths but not AVC- and CC-specific deaths. Thus, the effectiveness of aspirin in reducing cancer mortality depended on the anatomic site within the biliary tract. The dose of aspirin that provides the optimal efficacy for each subtype is worthy of investigation. In studies of other cancers, long-term follow-up or randomized trials of aspirin users versus nonusers for a duration of at least 5 years revealed a reduced risk of cancer incidence (5, 14, 19), suggesting that a longer duration of aspirin use may be required for primary prevention than for secondary prevention, particularly for high-fatality and progressive cancers.

The mechanisms responsible for improved BTC survival from aspirin use remains unclear.

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The proposed mechanism for the biological activity of aspirin against cancers has traditionally been the suppression of proinflammatory mediators, including cytokines, which increase GBC risk (30). Cyclooxgenase (COX)-1 and COX-2 are the key targets of aspirin and are involved in prostaglandin biosynthesis. Specifically, COX-2 overexpression was noted in bile duct cancer cells (31). Aspirin may alter the enzymatic substrate specificity and activity of COX. In addition, aspirin-triggered lipid autacoids that stimulate endogenous inflammation resolution mechanisms were found to inhibit primary tumor growth through enhancing macrophage phagocytosis of tumor cell debris (32). Through inhibiting platelet-derived COX-1/thromboxane A2, aspirin may block the formation of metastatic intravascular niches (33). It is possible that aspirin improves survival because it reduces platelets and slows metastasis. Aspirin has been reported to modulate Wnt signaling, nuclear factor kappa B signaling, polyamine metabolism, and DNA repair (34, 35).

The large-scale, nationwide, population-based cohort had several strengths. We followed newly diagnosed patients with BTC from 2007 to 2015. All the patients had accurate and updated records in an unselected and consecutive manner regarding their BTC subtypes and treatment. Recall and selection bias is low in record linkage studies. The NHI system provides health care for almost 100% of Taiwan's residents, allowing the detailed assessment of the benefits of aspirin at a range of doses over time after surgical status is considered. Through integration of the national database, patients could be followed up for their cause and date of death. To date, this is the largest BTC-related study, consisting of 16,057 patients with BTC. Moreover, we conducted several sensitivity analyses, and all results showed consistency, suggesting the findings were reliable. To minimize immortal time bias, we performed landmark analyses. Furthermore, we considered competing risks of cardiovascular deaths, which could be possibly associated with aspirin prescriptions. Even after considering these factors, aspirin was consistently associated with reduced risk of BTC death.

Despite the detailed information on medical diagnoses and clinical treatment ascertained from NHI database, the claims database lacked clinical information on blood tests. Thus, we were unable to investigate the correlations between aspirin use and changes in seromarkers that might provide insights into the mechanism of aspirin benefits. Recording of data on the characteristics of BTC (stage, size, presence of metastasis during diagnosis) was not compulsory, and thus, the information was not available for most of the patients. Notable limitations included the absence of information on some nutritional or lifestyle habits. However, these factors might be not associated with aspirin prescriptions. This study was observational, and thus, we could not rule out that the

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associations due to confounders associated with both aspirin use and cancer prognosis. The indication for aspirin use was uncertain, and prescription bias may have occurred. However, we used propensity score analyses to ascertain that the beneficial effects of aspirin remained significant after accounting for comorbidities of the patients. Lack of adherence and over-the-counter use, primarily use for analgesia, was likely nondifferential, leading to misclassification that would attenuate the beneficial effects of aspirin (36). In Taiwan, over-the-counter use of aspirin without prescriptions is rare.

Before aspirin is introduced as standard treatment, randomized trials are required to evaluate whether postdiagnosis aspirin use reduces cancer-specific mortality among patients with BTC. The potential preventive effects of aspirin may influence the initiation, growth, and spread of cancers, but time of initiation and dose optimization for each BTC subtype must be determined. An ongoing Add-Aspirin randomized trial is examining the effect of daily aspirin use on recurrence and survival after radical cancer therapy in patients with several cancers (37). Gastrointestinal bleeding attributable to aspirin was not significantly increased in previous reports (38, 39), suggesting that aspirin is well tolerated. In the future, identifying patients with specific molecular profiles (22, 27) that are more responsive to aspirin use are required to further investigate improved survival.

In conclusion, we observed a 45% reduced risk of BTC-specific mortality with postdiagnosis aspirin use. Aspirin use was associated with decreased mortality at every anatomic site in the biliary tract. Prospective evaluations of aspirin use through observational studies or, ideally, clinical trials are required to confirm the effects of aspirin use on BTC subtypes.

List of abbreviations

ampulla of Vater cancer (AVC); Biliary tract cancers (BTCs); cholangiocarcinoma (CC); Charlson comorbidity index (CCI); confidence intervals (CIs); Cyclooxgenase (COX); defined daily dose (DDD); gallbladder cancer (GBC); hazard ratios (HRs); adjusted hazard ratio (HR_{adj}); International Classification of Diseases, Ninth Revision (ICD-9); National Health Insurance (NHI); person-year (PY); United States Preventive Services Task Force (USPSTF)

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Figure Legend

Fig. 1. Stratified analyses of cancer-specific mortality for postdiagnosis aspirin use among patients with (A) biliary tract cancer[a]; (B) gallbladder cancer[b]; (C) ampulla of Vater cancer[c]; (D) cholangiocarcinoma[d]

Adjustment for confounders depended on various biliary tract cancer subtypes:
[a]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, biliary tract disease, liver cirrhosis, Charlson comorbidity index, and cholecystectomy; [b]adjusted for age at diagnosis, sex, grade, surgery, hypertension, biliary tract disease, liver cirrhosis, gallstones, and cholecystectomy; [c]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gastric disease, and Charlson comorbidity index; [d]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gallstones, biliary tract disease, liver cirrhosis, alcohol-related disease, and cholecystectomy. The stratification variable was omitted from each model.
Abbreviation: HR_{adj}, adjusted hazard ratio

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Table 1. Baseline characteristics and aspirin use status of patients with biliary tract cancer based on cancer subtype

	Biliary tract cancer (N=16,057)	**Gallbladder cancer (N=2,422)**	**Ampulla of Vater cancer (N=2,745)**	**Cholangiocarcinoma (N=10,890)**
No. of deaths, No. (%)	9,274 (57.8)	1,407 (58.1)	1,162 (42.3)	6,705 (61.6)
Age at diagnosis (years), mean (SD)	68.16 (12.7)	70.67 (13.2)	68.22 (12.2)	67.58 (12.6)
Age at diagnosis (years), No. (%)				
<60	4,118 (25.7)	509 (21.0)	689 (25.1)	2,920 (26.8)
60-69	4,039 (25.2)	474 (19.6)	707 (25.8)	2,858 (26.2)
70-79	4,659 (29.0)	754 (31.1)	809 (29.5)	3,096 (28.4)
80+	3,241 (20.2)	685 (28.3)	540 (19.7)	2,016 (18.5)
Sex, No. (%)				
Male	8,518 (53.1)	1,045 (43.2)	1,500 (54.6)	5,973 (54.9)
Female	7,539 (47.0)	1,377 (56.9)	1,245 (45.4)	4,917 (45.2)
Grade, No. (%)				
I (well-differentiated)	1,044 (6.5)	199 (8.2)	350 (12.8)	495 (4.6)
II (moderately-differentiated)	4,205 (26.2)	655 (27.0)	1,338 (48.7)	2,212 (20.3)
III, IV (poorly or undifferentiated)	2,500 (15.6)	406 (16.8)	380 (13.8)	1,714 (15.7)
Not determined or stated	8,308 (51.7)	1,162 (48.0)	677 (24.7)	6,469 (59.4)
Surgery, No. (%)				
No	9,628 (60.0)	1,017 (42.0)	888 (32.4)	7,723 (70.9)
Yes	6,429 (40.0)	1,405 (58.0)	1,857 (67.7)	3,167 (29.1)

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Aspirin use after cancer diagnosis, No. (%)				
No	13,538 (84.3)	1,965 (81.1)	2,224 (81.0)	9,349 (85.9)
Yes	2,519 (15.7)	457 (18.9)	521 (19.0)	1,541 (14.2)
Aspirin use before cancer diagnosis, No. (%)				
No	8,266 (51.5)	1,206 (49.8)	1,426 (52.0)	5,634 (51.7)
Yes	7,791 (48.5)	1,216 (50.2)	1,319 (48.1)	5,256 (48.3)
Aspirin use lifetime, No. (%)				
No	7,734 (48.2)	1,111 (45.9)	1,283 (46.7)	5,340 (49.0)
Yes	8,323 (51.8)	1,311 (54.1)	1,462 (53.3)	5,550 (51.0)

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Table 2. Associations of aspirin use with decreased cancer-specific mortality among patients with biliary tract cancer based on cancer subtype *

	Biliary tract cancer (N=16,057)				Gallbladder cancer (N=2,422)				Ampulla of Vater cancer (N=2,745)				Cholangiocarcinoma (N=10,890)			
	No of Death	**PY**	**Mortality (%)**	**HR_{adj} (95% CI) [a]**	**No of Death**	**PY**	**Mortality (%)**	**HR_{adj} (95% CI) [b]**	**No of Death**	**PY**	**Mortality (%)**	**HR_{adj} (95% CI) [c]**	**No of Death**	**PY**	**Mortality (%)**	**HR_{adj} (95% CI) [d]**
Total																
	9,274	25,593	36.2		1,407	4,570	30.8		1,162	7,522	15.5		6,705	13,501	49.7	
Aspirin use																
Post-cancer diagnosis																
No	8,073	19,253	41.9	1.00	1,209	3,133	38.6	1.00	975	5,641	17.3	1.00	5,889	10,479	56.2	1.00
Yes	1,201	6,340	19.0	0.55 (0.51-0.58)	198	1,437	13.8	0.48 (0.41-0.56)	187	1,881	9.9	0.61 (0.52-0.72)	816	3,022	27.0	0.55 (0.51-0.60)
p-value			<0.0001	<0.0001			<0.0001	<0.0001			<0.0001	<0.0001			<0.0001	<0.0001
Pre-cancer diagnosis																
No	4,770	14,459	33.0	1.00	714	2,475	28.9	1.00	578	4,352	13.3	1.00	3,478	7,632	45.6	1.00
Yes	4,504	11,134	40.5	0.98 (0.94-1.03)	693	2,095	33.1	0.88 (0.79-0.99)	584	3,170	18.4	1.07 (0.94-1.22)	3,227	5,868	55.0	0.98 (0.93-1.04)
p-value			<0.0001	0.3629			0.2795	0.0376			<0.0001	0.2782			<0.0001	0.5476
Lifetime																
No	4,547	12,570	36.2	1.00	683	2,020	33.8	1.00	533	3,714	14.4	1.00	3,331	6,836	48.7	1.00
Yes	4,727	13,02	36.3	0.90	724	2,550	28.4	0.77	629	3,808	16.5	0.95	3,374	6,665	50.6	0.93

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	3		(0.86-0.94)			(0.68-0.86)			(0.83-1.08)			(0.88-0.98)
p-value		0.3123	<0.0001		0.0729	<0.0001		0.0194	0.3992		0.0848	0.0048

Abbreviations: PY, person-year; HR_{adj}, adjusted hazard ratio; CI, confidence interval.

Adjustment for confounders depended on various biliary tract cancer subtypes:

[a]Adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, biliary tract disease, liver cirrhosis, Charlson comorbidity index, and cholecystectomy.

[b]Adjusted for age at diagnosis, sex, grade, surgery, hypertension, biliary tract disease, liver cirrhosis, gallstones, and cholecystectomy.

[c]Adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gastric disease, and Charlson comorbidity index.

[d]Adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gallstones, biliary tract disease, liver cirrhosis, alcohol-related disease, and cholecystectomy.

*all of the adjusted confounders significantly associated with cancer-specific survival for each BTC subtype in various models

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Table 3. Dose–response relationship of postdiagnosis aspirin use on cancer-specific survival among patients with biliary tract cancer

Maximum dose per day (DDD)	No of cancer/ No of death	Full Model: HR_{adj} (95% CI)	p-value	Full Model after considering competing risks of cardiovascular deaths: HR_{adj} (95% CI)	p-value
Biliary tract cancer[a]					
No use	8,185/4,791	1.00		1.00	
≤1.0	1,021/479	0.53 (0.48-0.59)	<0.0001	0.53 (0.48-0.58)	<0.0001
>1.0	114/40	0.42 (0.31-0.58)	<0.0001	0.40 (0.29-0.55)	<0.0001
P for trend			<0.0001		<0.0001
Gallbladder cancer[b]					
No use	1,154/691	1.00		1.00	
≤1.0	178/82	0.57 (0.45-0.72)	<0.0001	0.58 (0.45-0.74)	<0.0001
>1.0	22/9	0.61 (0.31-1.18)	0.1405	0.46 (0.22-0.97)	0.0416
P for trend			<0.0001		<0.0001
Ampulla of Vater cancer[c]					
No use	1,289/526	1.00		1.00	
≤1.0	198/70	0.69 (0.54-0.90)	0.0052	0.69 (0.54-0.88)	0.0029

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>1.0	24/7	0.48 (0.23-1.02)	0.0557	0.43 (0.23-0.79)	0.0071
P for trend			0.0009		<0.0001
Cholangiocarcinoma[d]					
No use	5,742/3,574	1.00		1.00	
≤1.0	645/327	0.50 (0.44-0.56)	<0.0001	0.49 (0.44-0.55)	<0.0001
>1.0	68/24	0.37 (0.24-0.55)	<0.0001	0.36 (0.23-0.54)	<0.0001
P for trend			<0.0001		<0.0001

Abbreviations: HR_{adj}, adjusted hazard ratio; DDD, defined daily dose; CI, confidence interval.

Adjustment for confounders depended on various biliary tract cancer subtypes:

[a]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, biliary tract disease, liver cirrhosis, Charlson comorbidity index, and cholecystectomy.

[b]adjusted for age at diagnosis, sex, grade, surgery, hypertension, biliary tract disease, liver cirrhosis, gallstones, and cholecystectomy.

[c]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gastric disease, and Charlson comorbidity index.

[d]adjusted for age at diagnosis, sex, grade, surgery, diabetes, hypertension, gallstones, biliary tract disease, liver cirrhosis, alcohol-related disease, and cholecystectomy.

* all of the adjusted confounders significantly associated with cancer-specific survival for each BTC subtype in various models

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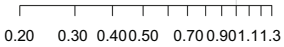
(A) Biliary tract cancer

	No of cancer	No of death	HR_{adj} (95% CI)	p-value
Age at diagnosis (years)				
<70	8157	4564	0.56 (0.51-0.62)	<0.0001
70+	7900	4710	0.55 (0.51-0.59)	<0.0001
Sex				
Male	8518	4795	0.55 (0.51-0.60)	<0.0001
Female	7539	4479	0.55 (0.50-0.60)	<0.0001
Grade				
I (well-differentiated)	1044	386	0.56 (0.43-0.74)	<0.0001
II (moderately-differentiated)	4205	2174	0.60 (0.53-0.67)	<0.0001
III, IV (poorly or undifferentiated)	2500	1459	0.66 (0.56-0.78)	<0.0001
Not determined or stated	8308	5255	0.51 (0.47-0.56)	<0.0001
Diabetes				
No	10120	5846	0.55 (0.51-0.60)	<0.0001
Yes	5937	3428	0.55 (0.50-0.60)	<0.0001
Hypertension				
No	5387	3095	0.56 (0.47-0.66)	<0.0001
Yes	10670	6179	0.55 (0.52-0.59)	<0.0001
Biliary tract disease				
No	10348	5947	0.57 (0.53-0.62)	<0.0001
Yes	5709	3327	0.52 (0.47-0.57)	<0.0001
Liver cirrhosis				
No	9154	5423	0.54 (0.50-0.59)	<0.0001
Yes	6903	3851	0.56 (0.51-0.62)	<0.0001
Charlson comorbidity index				
0-4	14957	8690	0.56 (0.52-0.59)	<0.0001
5+	1100	584	0.52 (0.42-0.65)	<0.0001
Surgery				
No	9628	6380	0.57 (0.52-0.61)	<0.0001
Yes	6429	2894	0.54 (0.49-0.60)	<0.0001
Chemotherapy				
No	11539	6268	0.48 (0.44-0.52)	<0.0001
Yes	4518	3006	0.71 (0.63-0.79)	<0.0001



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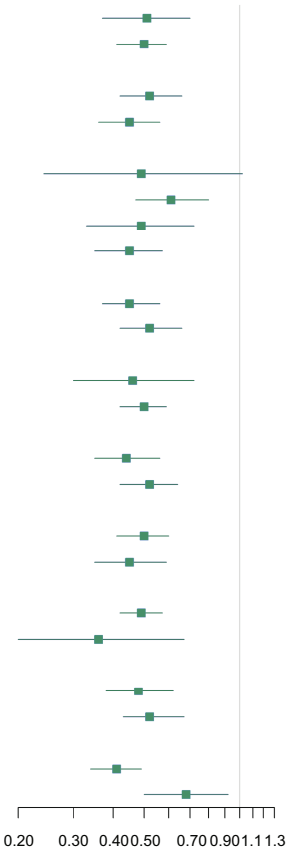
(B) Gallbladder cancer

	No of cancer	No of death	HR_{adj} (95% CI)	p-value
Age at diagnosis (years)				
<70	983	514	0.51 (0.37-0.70)	<0.0001
70+	1439	893	0.50 (0.41-0.59)	<0.0001
Sex				
Male	1045	615	0.53 (0.42-0.66)	<0.0001
Female	1377	792	0.45 (0.36-0.56)	<0.0001
Grade				
I (well-differentiated)	199	57	0.49 (0.24-1.02)	0.0568
II (moderately-differentiated)	655	348	0.61 (0.47-0.80)	0.0003
III, IV (poorly or undifferentiated)	406	275	0.49 (0.33-0.72)	0.0003
Not determined or stated	1162	727	0.45 (0.35-0.57)	<0.0001
Diabetes				
No	1522	887	0.45 (0.37-0.56)	<0.0001
Yes	900	520	0.52 (0.42-0.66)	<0.0001
Hypertension				
No	747	420	0.46 (0.30-0.72)	0.0007
Yes	1675	987	0.50 (0.42-0.59)	<0.0001
Biliary tract disease				
No	1132	691	0.44 (0.35-0.56)	<0.0001
Yes	1290	716	0.52 (0.42-0.64)	<0.0001
Liver cirrhosis				
No	1600	965	0.50 (0.41-0.60)	<0.0001
Yes	822	442	0.45 (0.35-0.59)	<0.0001
Charlson comorbidity index				
0-4	2249	1312	0.49 (0.42-0.57)	<0.0001
5+	173	95	0.36 (0.20-0.67)	0.0012
Surgery				
No	1017	728	0.48 (0.38-0.62)	<0.0001
Yes	1405	679	0.52 (0.43-0.64)	<0.0001
Chemotherapy				
No	1788	962	0.41 (0.34-0.49)	<0.0001
Yes	634	445	0.68 (0.50-0.92)	0.0132



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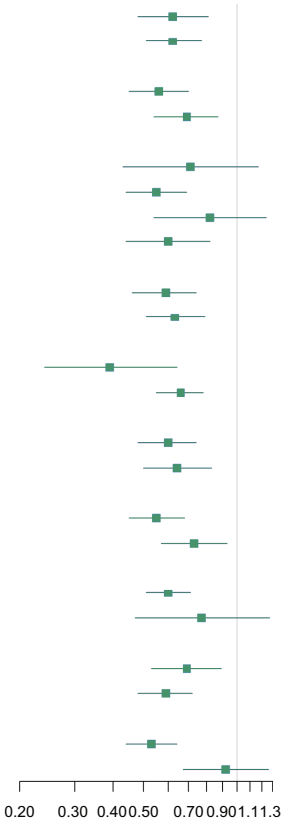
(C) Ampulla of Vater cancer

	No of cancer	No of death	HR_{adj} (95% CI)	p-value
Age at diagnosis (years)				
<70	1396	554	0.62 (0.48-0.81)	0.0003
70+	1349	608	0.62 (0.51-0.77)	<0.0001
Sex				
Male	1500	651	0.56 (0.45-0.70)	<0.0001
Female	1245	511	0.69 (0.54-0.87)	0.0016
Grade				
I (well-differentiated)	350	88	0.71 (0.43-1.17)	0.1788
II (moderately-differentiated)	1338	559	0.55 (0.44-0.69)	<0.0001
III, IV (poorly or undifferentiated)	380	205	0.82 (0.54-1.24)	0.3454
Not determined or stated	677	310	0.60 (0.44-0.82)	0.0015
Diabetes				
No	1687	689	0.59 (0.46-0.74)	<0.0001
Yes	1058	473	0.63 (0.51-0.79)	<0.0001
Hypertension				
No	943	381	0.39 (0.24-0.64)	0.0001
Yes	1802	781	0.66 (0.55-0.78)	<0.0001
Biliary tract disease				
No	1755	738	0.60 (0.48-0.74)	<0.0001
Yes	990	424	0.64 (0.50-0.83)	0.0005
Liver cirrhosis				
No	1677	724	0.55 (0.45-0.68)	<0.0001
Yes	1068	438	0.73 (0.57-0.93)	0.0115
Charlson comorbidity index				
0-4	2550	1070	0.60 (0.51-0.71)	<0.0001
5+	195	92	0.77 (0.47-1.27)	0.3084
Surgery				
No	888	453	0.69 (0.53-0.89)	0.0037
Yes	1857	709	0.59 (0.48-0.72)	<0.0001
Chemotherapy				
No	2114	841	0.53 (0.44-0.64)	<0.0001
Yes	631	321	0.92 (0.67-1.26)	0.5883



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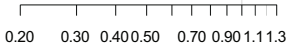
(D) Cholangiocarcinoma

	No of cancer	No of death	HR adj (95% CI)	p-value
Age at diagnosis (years)				
<70	5778	3496	0.58 (0.51-0.65)	<0.0001
70+	5112	3209	0.55 (0.50-0.61)	<0.0001
Sex				
Male	5973	3529	0.57 (0.51-0.63)	<0.0001
Female	4917	3176	0.55 (0.49-0.61)	<0.0001
Grade				
I (well-differentiated)	495	241	0.57 (0.39-0.84)	0.0039
II (moderately-differentiated)	2212	1267	0.63 (0.54-0.74)	<0.0001
III, IV (poorly or undifferentiated)	1714	979	0.69 (0.56-0.84)	0.0002
Not determined or stated	6469	4218	0.52 (0.47-0.57)	<0.0001
Diabetes				
No	6911	4270	0.58 (0.52-0.64)	<0.0001
Yes	3979	2435	0.54 (0.48-0.60)	<0.0001
Hypertension				
No	3697	2294	0.64 (0.53-0.77)	<0.0001
Yes	7193	4411	0.55 (0.50-0.59)	<0.0001
Biliary tract disease				
No	7461	4518	0.59 (0.54-0.65)	<0.0001
Yes	3429	2187	0.50 (0.44-0.57)	<0.0001
Liver cirrhosis				
No	5877	3734	0.55 (0.50-0.62)	<0.0001
Yes	5013	2971	0.56 (0.50-0.63)	<0.0001
Charlson comorbidity index				
0-4	10158	6308	0.56 (0.52-0.61)	<0.0001
5+	732	397	0.48 (0.36-0.62)	<0.0001
Surgery				
No	7723	5199	0.57 (0.52-0.62)	<0.0001
Yes	3167	1506	0.53 (0.46-0.62)	<0.0001
Chemotherapy				
No	7637	4465	0.50 (0.45-0.54)	<0.0001
Yes	3253	2240	0.68 (0.60-0.78)	<0.0001



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Accepted Article

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