



Real-World Analysis of Treatment Patterns, Healthcare Utilization, Costs, and Mortality Among People with Biliary Tract Cancers in the USA

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ABSTRACT

Introduction: People with advanced biliary tract cancers (BTCs) have a 5-year survival of approximately 2% in the USA. Most cases are inoperable or require systemic treatment following surgery. This study adds to current literature by describing treatment patterns, healthcare resource utilization (HCRU), costs, and mortality among people with BTCs.

Methods: Adults diagnosed with BTCs were identified in the Merative MarketScan administrative claims databases from 1 January 2016 to 30 June 2020. Descriptive analysis was used to measure treatment patterns (i.e., regimen types, therapy duration) during three lines of therapy (LOT). All-cause and disease-related HCRU and costs were measured per-patient-per-month

(PPPM) during the entire follow-up and in each LOT. Mortality was reported among the subset linked to the National Death Index (NDI).

Results: There were 2648 eligible people with BTCs [mean age 64.0 (standard deviation [SD] 12.4) years, 51.5% female, average follow-up 11.9 (SD 11.1) months]. Treatment was received by 56.3% ($n = 1490$), and 20.9% ($n = 5534$) and 7.1% ($n = 187$) moved on to a second and third LOT, respectively. The average treatment duration decreased across LOTs, from 3.8 (SD 3.1) months in LOT1 to 2.6 (SD 2.4) months in LOT3. Gemcitabine + cisplatin was the most common regimen in LOT1 (44.6%). Total all-cause mean healthcare costs PPPM increased after LOT1 (mean \$21,517, \$29,721, and \$28,557, for LOT1, LOT2, and LOT3, respectively) and the majority (71.2%) were related to BTCs. Of people with BTCs linked to the NDI ($n = 2168$), 66.1% died and average time to death was 11.3 (SD 11.2) months.

Conclusions: These findings, showing a high rate of mortality, a decrease in treatment duration, and an increase in costs as people progress after LOT1, add recent data to current literature highlighting the unmet need for more effective treatment options for people with BTCs.

Keywords: Biliary tract cancer; Cost of illness; Healthcare; USA

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Key Summary Points

Why carry out this study?

The incidence of cholangiocarcinoma, which is a rare and aggressive form of hepatobiliary cancer located in the bile ducts, has been reported as 1.26 per 100,000 from 2001 to 2015, and increasing in later years.

Most people with biliary tract cancers (BTCs) are already at an advanced disease stage upon diagnosis, leaving them ineligible for surgery and with limited options for systemic treatment.

This study adds to current literature by describing treatment patterns, healthcare resource utilization (HCRU), costs, and mortality among people with BTCs.

What was learned from the study?

This analysis of people with BTCs expands and strengthens prior literature showing high economic burden and high rate of mortality, thus underscoring the need for newer and more effective systemic treatment options, both in first-line and subsequent lines of therapy.

These findings highlight the unmet need for expanded treatment options that delay onset of metastasis and extend survival.

Findings from this analysis also support the importance of prioritizing treatment decisions to ensure the most effective treatment option is provided in the first line of therapy.

and the fourth highest among men in the USA between 2013 and 2017 [2]. It is the sixth deadliest cancer in the USA, and only 20.8% survive 5 years or more following their diagnosis [1, 3]. The incidence of cholangiocarcinoma (CCA), which is a rare and aggressive form of hepatobiliary cancer located in the bile ducts, has been reported as 1.26 per 100,000 from 2001 to 2015, and increasing in the later years [4].

Biliary tract cancers (BTCs) form in the gall bladder, intrahepatic, or extrahepatic bile ducts, with an average age at diagnosis of ~70 years [1, 5]. People with BTCs may be asymptomatic or present with nonspecific symptoms (e.g., loss of appetite, abdominal pain, fever, weight loss) leading to delays in accurate diagnosis. As a result, most people are already at an advanced disease stage upon diagnosis, leaving them ineligible for surgery and with limited options for systemic treatment [6]. Currently available systemic treatment options are largely ineffective, as people with advanced stage BTC have a 5-year survival rate of only 2% [7]. Given the poor prognosis for long-term survival among people with advanced BTCs, ongoing research for alternative treatment options to delay progression and extend survival is vital.

Historically, the first-line standard of care (SOC) listed as the preferred regimen by the National Comprehensive Cancer Network (NCCN) for unresectable BTCs is gemcitabine + cisplatin [8]. Other NCCN recommended options included monotherapies [5-fluorouracil (5-FU), capecitabine, and gemcitabine] or combination therapies (5-FU + oxaliplatin, 5-FU + cisplatin, gemcitabine + capecitabine, gemcitabine + cisplatin, and gemcitabine + oxaliplatin), as systemic therapy options are dependent on disease status [9]. Recently, the Phase 3 TOPAZ-1 trial demonstrated that people treated with durvalumab plus gemcitabine + cisplatin had a significantly and clinically meaningful improvement in overall survival (OS) and progression-free survival (PFS) compared with those treated with gemcitabine + cisplatin alone [10, 11] and this regimen has just been newly added as a preferred (Category 1) recommendation in the NCCN guidelines updated on 15 July 2022 [12].

INTRODUCTION

Hepatobiliary cancers include malignancies located in the liver, gall bladder, and bile ducts [1]. Hepatobiliary cancer had the highest incidence rate of new cancer cases among women

To date, there is no SOC treatment for people with BTCs that progress beyond first line, but there are ongoing clinical trials to expand options [13, 14].

Prior research has reported high rates of healthcare resource utilization (HCRU) and costs among people with BTCs [15]. More effective systemic treatment options that may reduce the need for high-cost urgent care admissions and emergency room (ER) visits are needed. However, gaps in recent literature remain, as a comprehensive understanding of a patient's progression through multiple treatment regimens (i.e., not just in the first-line setting, but as a patient moves through subsequent lines of therapy) and how this advancement impacts HCRU and costs is needed. This study was hypothesis generating, and aimed to augment prior literature and provide insight into real-world treatment patterns, HCRU, healthcare costs, and mortality among adults with BTCs.

METHODS

Study Design and Data Sources

This retrospective study utilized US administrative claims data from the Merative MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits (Medicare) Databases [16]. The databases include the inpatient, outpatient, and prescription drug experiences of employees, dependents, and retirees covered under a variety of fee-for-service and managed care health plans between 1995 and 2020. All database records are statistically de-identified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Additionally, the National Death Index (NDI) database from the National Center for Health Statistics was linked to approximately 80% of selected people from the MarketScan databases. The NDI data include all deaths in the USA from 1979 and provide dates and cause(s) of death for persons who have died. Institutional Review Board (IRB) waiver of

authorization approval was obtained from WCG IRB (IRB study: 1320660; IRB protocol: 20215641) on 27 October 2021. All variables were defined using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition (CPT-4) codes, Healthcare Common Procedure Coding System (HCPCS) codes, and National Drug Codes (NDCs).

Selection of People with BTCs

A cohort of people in the MarketScan databases with a diagnosis of BTCs identified by an ICD-10-CM code on any two non-diagnostic claims 1–90 days apart between 1 January 2016 and 30 June 2020, were initially selected. The earliest observed claim for BTCs in the selection window was the index date. Eligible individuals were aged 18 years or older on index date, had continuous enrollment for at least 6 months prior to the index date (baseline period), and for a minimum of 1 month following the index date. The follow-up period was variable in length until database disenrollment or study end (31 July 2020). Adults were excluded if they had evidence of other primary cancers (not including non-melanoma skin cancer or other liver cancers) during the study period, evidence of prior systemic treatment (to ensure a newly treated cohort), or evidence of clinical trial participation.

People with BTCs initiating systemic therapy (i.e., chemotherapy, targeted therapy, immunotherapy, or bevacizumab) during the follow-up period were identified and stratified into the following regimen cohorts of interest (selected based on recommendations in NCCN guidelines and after review of treatment patterns observed in the data used for this analysis) during a first, second, and third line of therapy (LOT): gemcitabine + cisplatin, FOLFIRINOX (fluorouracil, irinotecan, leucovorin, oxaliplatin), FOLFIRI (fluorouracil, irinotecan, leucovorin), FOLFOX (fluorouracil, leucovorin, oxaliplatin), gemcitabine monotherapy, and capecitabine monotherapy. Each LOT start was defined as the date of the first claim with an

NDC code or HCPCS code for systemic treatment (for LOT1) or date of first claim for systemic treatment following the earlier of treatment switch or discontinuation (gap of > 60 days of no treatment) of the previous LOT. The LOT regimen was defined by all treatments within the first 28 days of the initiation date. LOT end was defined as the earlier of a treatment switch, discontinuation, or censoring at end of follow-up.

Demographic characteristics were reported on the index date and included age, sex, geographic region of residence, payer, and index year. Characteristics reported during the 6-month baseline period included surgical procedures (tumor removal, liver transplant, cholecystectomy, lymphadenectomy), the National Cancer Institute (NCI) adapted Charlson Comorbidity Index (CCI) calculated as an aggregate measure of patient comorbidity, and baseline total healthcare costs. Cancer location (extrahepatic, intrahepatic, gall bladder) at index and the proportion of people with evidence of metastatic disease during follow-up was also reported.

Outcomes

Systemic treatment patterns were described over the full follow-up period and during each LOT (up to three) among people with systemic treatment for BTCs. For each LOT, the duration (defined as LOT start date to LOT end date) and end triggering event (defined as switching, discontinuation, or end of follow-up) were reported. All-cause and disease-related HCRU and expenditures were reported by type of service (inpatient, outpatient, outpatient pharmacy) during the full variable-length patient follow-up period and during each LOT. Intensive care unit (ICU) utilization and costs were reported as a subset of inpatient services. Outpatient services included ER visits, outpatient office visits, outpatient treatment for BTCs, and other outpatient services. Disease-related HCRU and costs were defined by medical claims with a diagnosis for BTCs, metastasis, sepsis, biliary obstruction, cholangitis, and medical/pharmacy claims for any systemic treatments for BTCs.

Healthcare costs were based on paid amounts of adjudicated claims, including insurer and health plan payments, as well as patient cost-sharing in the form of copayment, deductible, and coinsurance. Healthcare costs comprise inpatient admission expenditures, outpatient expenditures (which includes emergency room visits, outpatient office visits, and other outpatient service visits), and pharmacy expenditures. Each expenditure comprises the total gross payment to a provider for a specific service. Cost for services provided under capitated arrangements were estimated using payment proxies computed based on paid claims at the procedure level using the MarketScan Commercial and Medicare databases. All dollar estimates were inflated to 2019 dollars (which was the latest full year of data) using the Medical Care Component of the Consumer Price Index. Owing to the variable length of follow-up and duration of LOT, all continuous measures of all-cause and disease-related HCRU and costs measured during these time periods were reported in a per-patient-per-month (PPPM) format.

Mortality was reported for the subset of people with BTCs linked to the NDI. Cause of death was defined by ICD-10-CM codes and classified as all-cause, cancer-specific, or other causes of death. Survival time was calculated from index date and start of first line (among treated people with BTCs) to the earlier of death or censoring at the end of the study period.

Statistical Analysis

Descriptive analyses were conducted using the latest version of World Programming System, which is a software platform for working with data and statistics. Categorical variables were presented as the count and percentage of people in each category, and continuous variables were summarized by mean and standard deviation (SD). OS time was calculated using Kaplan–Meier analysis.

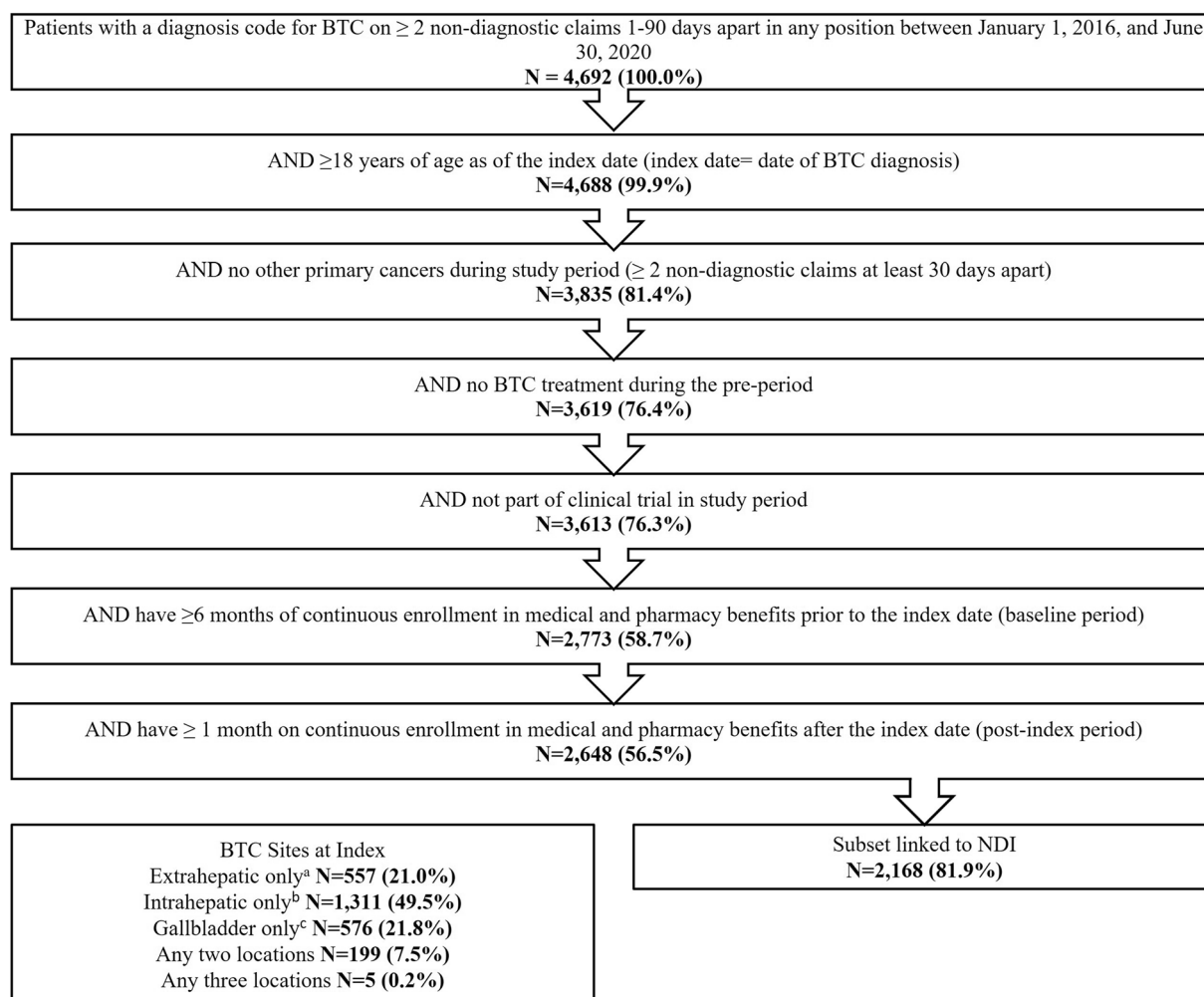


Fig. 1 Sample selection of people with BTCs. *BTC* biliary tract cancer, *N* number, *NDI* National Death Index. ^aExtrahepatic BTC site was defined using the following International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes C24.0, C24.8,

C24.9. ^bIntrahepatic BTC site was defined using the following ICD-10-CM codes: C22.1, C22.3. ^cGall bladder BTC site was defined using the following ICD-10-CM code: C23

RESULTS

Characteristics of People with BTCs

The total study population included 2648 people with BTCs meeting all eligibility criteria, of which at index diagnosis, 49.5% had intrahepatic CCA, 21.0% had extrahepatic CCA, 21.8% gall bladder CCA, and 7.7% had disease in more than one location (Fig. 1). The mean (SD) age of all people with BTCs was 64.0 years (SD 12.4 years) and most of the population was

between the age of 55 and 64 years (42.6%; 1128/2648). The average length of follow-up was approximately 1 year (mean 11.9 months; SD 11.1 months), during which 63.2% had evidence of metastatic disease. During baseline, the average NCI score was 1.3 (SD 1.5) with the most common NCI conditions including mild liver disease (35.0%), diabetes (mild to moderate; 25.7%), and chronic pulmonary disease (10.6%). Surgery was uncommon prior to index date (7.2% with tumor removal, 5.6% with

Table 1 Characteristics of people with BTCs

	All people with BTCs, N = 2648
Characteristics measured on index date	
Age; mean (SD)	64.0 (12.4)
Age group; n (%)	
18–34	32 (1.2%)
35–44	99 (3.7%)
45–54	373 (14.1%)
55–64	1128 (42.6%)
65–74	446 (16.8%)
≥ 75	570 (21.5%)
Female sex; n (%)	1364 (51.5%)
Payer; n (%)	
Commercial	1622 (61.3%)
Medicare	1026 (38.8%)
Index year; n (%)	
2016	532 (20.1%)
2017	611 (23.1%)
2018	456 (17.2%)
2019	583 (22.0%)
2020	466 (17.6%)
Characteristics measured during 6-month baseline period	
NCI modification of CCI; mean (SD)	1.3 (1.5)
NCI comorbidity categories; n (%)	
Myocardial infarction	51 (1.9%)
Congestive heart failure	139 (5.3%)
Peripheral vascular disease	184 (7.0%)
Cerebrovascular disease	127 (4.8%)
Dementia	43 (1.6%)
Chronic pulmonary disease	280 (10.6%)
Rheumatologic disease	60 (2.3%)
Peptic ulcer disease	79 (3.0%)
Mild liver disease	927 (35.0%)

Table 1 continued

	All people with BTCs, N = 2648
Diabetes (mild to moderate)	681 (25.7%)
Diabetes with chronic complications	231 (8.7%)
Hemiplegia/paraplegia	6 (0.2%)
Chronic renal disease	183 (6.9%)
Moderate or severe liver disease	96 (3.6%)
HIV	8 (0.3%)
Prior surgery; n (%)	
Tumor removal	190 (7.2%)
Liver transplant	2 (0.1%)
Cholecystectomy	147 (5.6%)
Lymphadenectomy	29 (1.1%)
Baseline healthcare costs; mean (SD)	\$27,126 (\$48,623)

BTC biliary tract cancer, CCI Charlson Comorbidity Index, HIV human immunodeficiency virus, NCI National Cancer Institute, SD standard deviation

cholecystectomy, and 1.2% with liver transplant or lymphadenectomy) (Table 1).

Treatment Patterns

Of the 2648 people with BTCs, 56.3% had at least one LOT (n = 1490), 554 (20.9%) received a second LOT, and 187 (7.1%) received a third LOT. Gemcitabine + cisplatin was the most common regimen during LOT1 (44.6%), although there was no predominant regimen in later lines, with 39.4% of people in LOT2 and 56.1% of people in LOT3 moving on to a regimen other than gemcitabine + cisplatin, FOL-FIRINOX, FOLFIRI, FOLFOX, gemcitabine monotherapy, or capecitabine monotherapy (Fig. 2, Table 2). The duration of each LOT decreased from LOT1 to LOT3 from 3.8 months

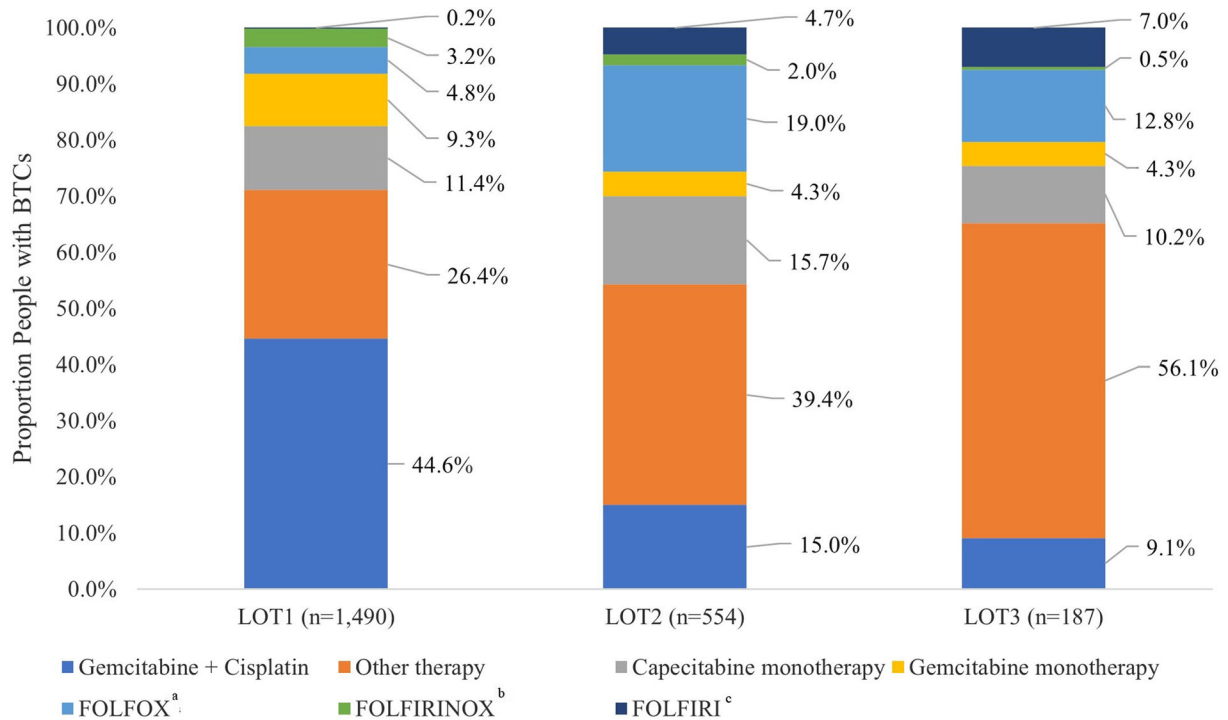


Fig. 2 Regimen distribution by LOT. Data expressed as percentages. *BTCs* biliary tract cancers, *LOT* line of therapy ^aFluorouracil, leucovorin, oxaliplatin. ^bFluorouracil, irinotecan, leucovorin, oxaliplatin. ^cFluorouracil, irinotecan, leucovorin

(SD 3.1) to 2.6 months (SD 2.4) and the LOT end triggering event was discontinuation (gap > 60 days) for the majority (63.9–65.0%) of people with BTCs, which was consistent across LOT1 through LOT3 (Table 2).

Healthcare Utilization and Costs

During the entire variable-length follow-up, people with BTCs who received treatment ($n = 1490$) extensively utilized healthcare resources. Nearly 80% of people in LOT1 had an inpatient admission related to BTCs, and one-third had an ICU admission (33.2%) or ER visit (33.1%) related to BTCs. Nearly all people had an outpatient physician office visit (98.1%) related to BTCs, with an average of 2.0 (SD 1.3) visits PPPM. Most people received outpatient systemic treatment (91.3%) for BTCs, with approximately 1.8 (SD 1.5) treatments PPPM (Table 3). During each LOT, the proportion of people with an inpatient admission and with a visit to the ICU related to BTCs increased from LOT1 to LOT3 (30.0% to 33.2% all inpatient

admissions and 8.5% to 13.4% ICU visits), despite a decrease in duration of each line (Table 3).

Total all-cause healthcare costs incurred by all treated people with BTCs ($n = 1490$) during the full variable-length follow-up period was \$20,696 PPPM (SD \$18,615; Fig. 3), of which 51.2% were for outpatient services, 44.8% were for inpatient admissions, and 4.0% were for outpatient pharmacy prescriptions. Total BTC-related healthcare costs during the full variable-length follow-up period were 75.9% of the total healthcare costs [mean \$15,698 PPPM (SD \$15,525)] and were driven by medical costs inclusive of inpatient and outpatient services [mean PPPM \$15,479 (SD \$15,500); Fig. 3]. The average (SD) total all-cause costs measured PPPM during each LOT were \$21,517 (SD \$26,164), \$29,721 (SD \$45,191), and \$28,954 (SD \$37,290) for LOT1, LOT2, and LOT3, respectively. Office-administered outpatient treatment costs for BTCs measured PPPM increased across LOTs, with \$1857 (SD \$4826)

Table 2 Treatment patterns

	People with LOT1, measured during LOT1, <i>n</i> = 1490	People with LOT2, measured during LOT2, <i>n</i> = 554	People with LOT3, measured during LOT3, <i>n</i> = 187
Average duration of LOT, in months; mean (SD)	3.8 (3.1)	3.1 (2.9)	2.6 (2.4)
LOT end triggering event; <i>n</i> (%)			
Discontinuation	952 (63.9%)	360 (65.0%)	121 (64.7%)
Switch	269 (18.1%)	90 (16.3%)	31 (16.6%)
End of follow-up	269 (18.1%)	104 (18.8%)	35 (18.7%)
Regimen cohorts of interest; <i>n</i> (%)			
FOLFIRINOX ^a	48 (3.2%)	11 (2.0%)	1 (0.5%)
Gemcitabine + cisplatin	665 (44.6%)	83 (15.0%)	17 (9.1%)
Gemcitabine monotherapy	138 (9.3%)	24 (4.3%)	8 (4.3%)
Capecitabine monotherapy	170 (11.4%)	87 (15.7%)	19 (10.2%)
FOLFIRI ^b	3 (0.2%)	26 (4.7%)	13 (7.0%)
FOLFOX ^c	72 (4.8%)	105 (19.0%)	24 (12.8%)
Other	394 (26.4%)	218 (39.4%)	105 (56.1%)
Observed treatments LOT; <i>n</i> (%)			
Bevacizumab	12 (0.8%)	9 (1.6%)	5 (2.7%)
Chemotherapy			
Capecitabine	266 (17.9%)	129 (23.3%)	35 (18.7%)
Carboplatin	45 (3.0%)	23 (4.2%)	5 (2.7%)
Cisplatin	717 (48.1%)	105 (19.0%)	27 (14.4%)
Erlotinib	0 (0.0%)	2 (0.4%)	1 (0.5%)
Fluorouracil	195 (13.1%)	192 (34.7%)	61 (32.6%)
Gemcitabine	1,067 (71.6%)	208 (37.6%)	63 (33.7%)
Nanoliposomal irinotecan	0 (0.0%)	2 (0.4%)	2 (1.1%)
Irinotecan	67 (4.5%)	61 (11.0%)	33 (17.7%)
Leucovorin	144 (9.7%)	163 (29.4%)	50 (26.7%)
Oxaliplatin	231 (15.5%)	173 (31.2%)	49 (26.2%)
Paclitaxel	65 (4.4%)	47 (8.5%)	24 (12.8%)
Immunotherapy			
Atezolizumab	1 (0.1%)	0 (0.0%)	1 (0.5%)
Durvalumab	0 (0.0%)	1 (0.2%)	0 (0.0%)

Table 2 continued

	People with LOT1, measured during LOT1, <i>n</i> = 1490	People with LOT2, measured during LOT2, <i>n</i> = 554	People with LOT3, measured during LOT3, <i>n</i> = 187
Ipilimumab	3 (0.2%)	0 (0.0%)	3 (1.6%)
Nivolumab	8 (0.5%)	8 (1.4%)	7 (3.7%)
Pembrolizumab	9 (0.6%)	17 (3.1%)	12 (6.4%)
Targeted therapy			
Cabozatinib	0 (0.0%)	0 (0.0%)	0 (0.0%)
Entrectinib	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ivosidenib	0 (0.0%)	1 (0.2%)	3 (1.6%)
Larotrectinib	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pemigatinib	0 (0.0%)	1 (0.2%)	0 (0.0%)
Regorafenib	0 (0.0%)	1 (0.2%)	0 (0.0%)
Sorafenib	9 (0.6%)	3 (0.5%)	0 (0.0%)
Days from index to first treatment; mean (SD)	64.2 (104.7)		

LOT line of therapy, SD standard deviation

^aFluorouracil, irinotecan, leucovorin, oxaliplatin

^bFluorouracil, irinotecan, leucovorin

^cFluorouracil, leucovorin, oxaliplatin

during LOT1, \$3708 (SD \$22,092) during LOT2, and \$5401 (SD \$27,219) during LOT3 (Fig. 3).

Survival Analyses

Among all people with BTCs, 81.9% (*n* = 2168) of the study population were eligible for analysis of mortality (i.e., linked to the NDI) and of these, 1434 (66.1%) died following diagnosis (among those, 95.2% had a cancer-related death). Among all people with BTC, median survival time from index diagnosis was 13.0 months (Fig. 4). Among people with BTCs eligible for analysis of mortality and with systemic treatment (*n* = 1179), 67.5% died following initiation of LOT1 and median survival time from LOT1 start was 12.7 months (Fig. 5).

DISCUSSION

This retrospective claims analysis of people with BTCs expands and strengthens prior literature, showing high economic burden and high rate of mortality, thus underscoring the need for newer and more effective systemic treatment options, both in first-line and in subsequent LOTs [15, 17]. Results from this analysis found that that average duration of each LOT decreases as people move from LOT1 to LOT3, that HCRU and costs increase after LOT1, and with 67.5% experiencing a death following initiation of first-line treatment.

The diagnosis of BTCs at advanced stages is well documented [17] and consistent with our study findings, as more than half of the cohort had BTCs in two or more locations during the

Table 3 BTC-related healthcare utilization, measured PPM during entire follow-up and during each LOT

	People with treatment measured during entire follow-up, <i>n</i> = 1490	People with LOT1, measured during LOT1, <i>n</i> = 1490	People with LOT2, measured during LOT2, <i>n</i> = 554	People with LOT3, measured during LOT3, <i>n</i> = 187
Inpatient admissions				
Have inpatient admission; <i>n</i> (%)	1169 (78.5%)	447 (30.0%)	177 (32.0%)	62 (33.2%)
Number of inpatient admissions; mean (SD)	0.2 (0.3)	0.2 (0.4)	0.3 (0.5)	0.3 (0.5)
Average length of stay ^a ; mean (SD)	0.6 (0.9)	0.8 (2.7)	1.6 (6.0)	1.1 (2.6)
In ICU; <i>n</i> (%)	494 (33.2%)	127 (8.5%)	59 (10.7%)	25 (13.4%)
Number of ICU days; mean (SD)	0.5 (1.6)	0.4 (2.1)	0.8 (4.4)	0.6 (3.0)
Outpatient services				
Have ER visit; <i>n</i> (%)	493 (33.1%)	215 (14.4%)	84 (15.2%)	26 (13.9%)
Number of ER visits; mean (SD)	0.3 (1.5)	0.3 (2.2)	0.3 (1.2)	0.2 (0.9)
People with a physician office visit; <i>n</i> (%)	1461 (98.1%)	1348 (90.5%)	489 (88.3%)	165 (88.2%)
Number of physician office visits; mean (SD)	2.0 (1.3)	2.4 (1.7)	2.5 (2.0)	2.4 (1.8)
People with an outpatient BTC treatment; <i>n</i> (%)	1361 (91.3%)	1322 (88.7%)	465 (83.9%)	167 (89.3%)
Number of outpatient BTC treatments; mean (SD)	1.8 (1.5)	3.5 (2.6)	3.6 (3.8)	3.3 (2.6)
People with other outpatient services; <i>n</i> (%)	1483 (99.5%)	1406 (94.4%)	526 (95.0%)	178 (95.2%)
Number of other outpatient services; mean (SD)	22.7 (15.7)	31.7 (20.5)	34.0 (33.0)	30.9 (17.8)

Table 3 continued

	People with treatment measured during entire follow-up, <i>n</i> = 1490	People with LOT1, measured during LOT1, <i>n</i> = 1490	People with LOT2, measured during LOT2, <i>n</i> = 554	People with LOT3, measured during LOT3, <i>n</i> = 187
Outpatient pharmacy				
Have pharmacy claims; <i>n</i> (%)	399 (26.8%)	255 (17.1%)	131 (23.7%)	39 (20.9%)
Number of pharmacy claims; mean (SD)	0.1 (0.2)	0.2 (0.5)	0.4 (1.4)	0.3 (0.5)

BTC biliary tract cancer, *ER* emergency room, *ICU* intensive care unit, *LOT* line of therapy, *PPPM* per-patient-per-month, *SD* standard deviation

^aAverage length of stay was measured in days, per-patient-per-month (PPPM)

follow-up period and two-thirds had evidence of metastatic disease. Historically, gemcitabine + cisplatin has been the first-line SOC for people with advanced or unresectable BTC [8, 18, 19]. In the current study, 45% initiated gemcitabine + cisplatin regimen in LOT1, which is lower than expected for the SOC given that the majority of patients were identified as having advanced disease. In addition, among all

people with BTCs treated with systemic therapy, the duration of treatment decreased from LOT1 to LOT3, suggesting limited effectiveness of treatment in later lines. These findings using real-world data are important and should be considered when prioritizing treatment decisions for people with BTCs. The ongoing Phase 3 clinical trial TOPAZ-1 is investigating the combination of the immunotherapy agent

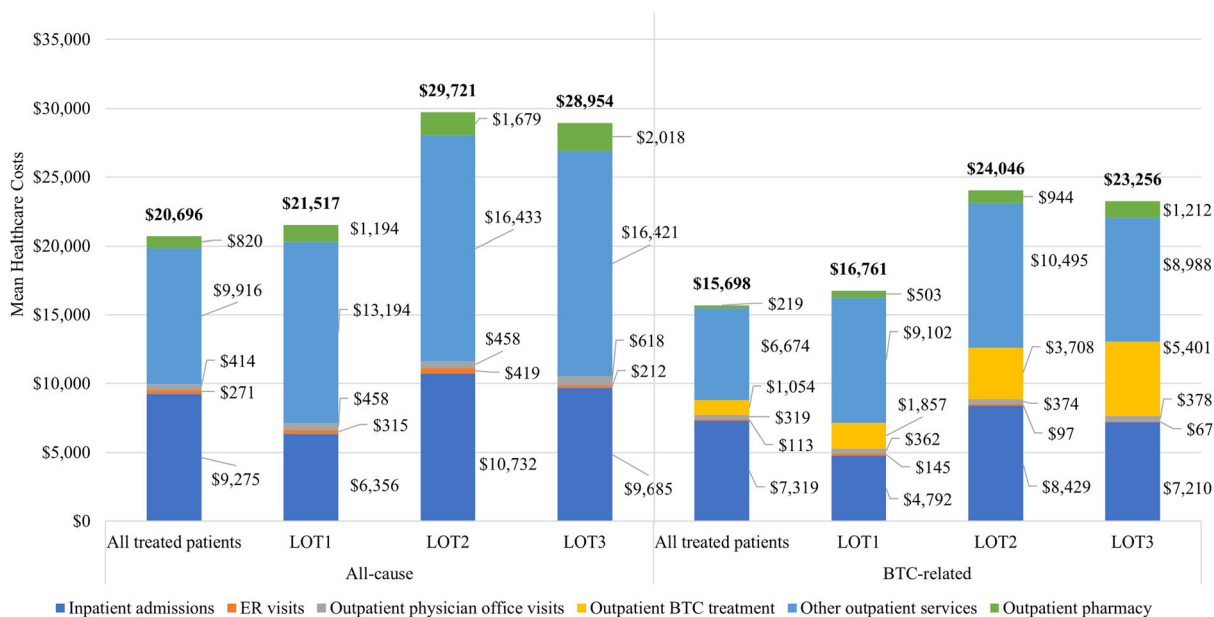


Fig. 3 All-cause and disease-related healthcare expenditures, PPPM. Costs were inflated to 2019 US dollars using the Medical Care Component of the Consumer Price

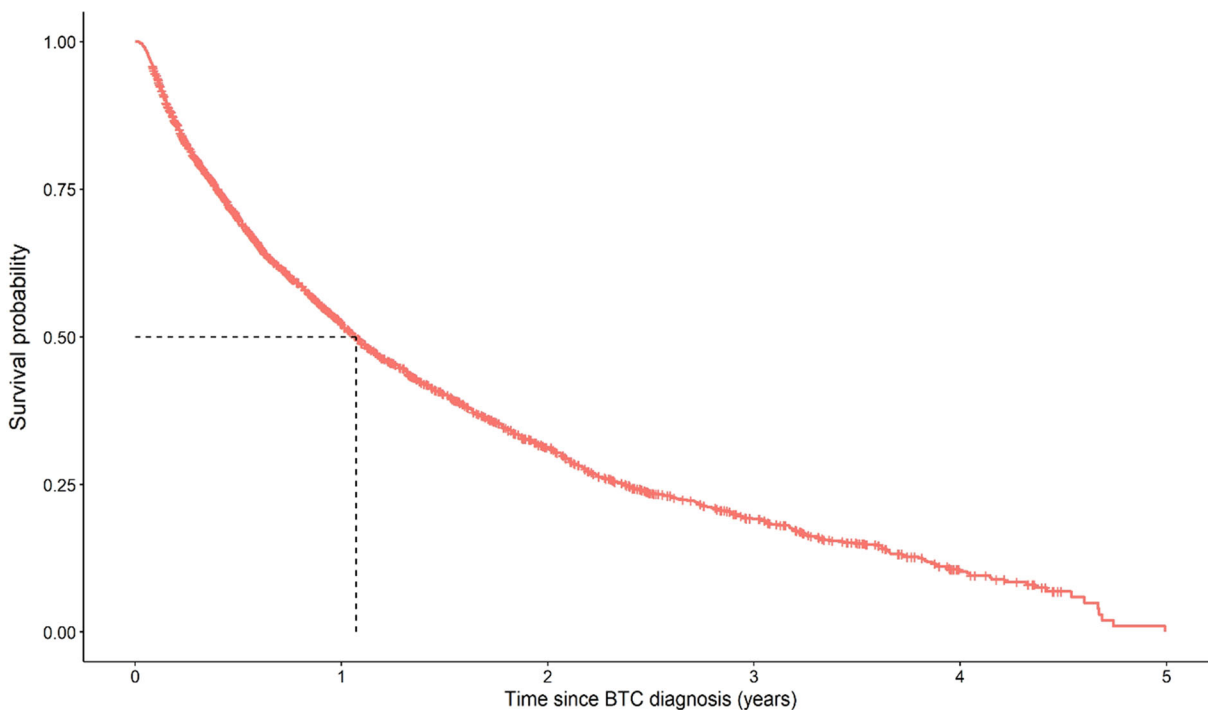
Index. *BTCs* biliary tract cancers, *ER* emergency room, *LOT* line of therapy, *PPPM* per-patient-per-month

durvalumab plus the SOC (gemcitabine + cisplatin) as a first-line treatment for advanced BTCs, potentially providing both improved OS and PFS with the addition of durvalumab [9]. It is the first trial in over a decade to report significant and clinically meaningful improved OS and PFS compared with people on a placebo + gemcitabine + cisplatin combination and could become a much needed new SOC for people with advanced BTCs [9].

In the current study, most healthcare costs were disease-related and increased after LOT1, driven by higher costs of inpatient admissions in later lines. Further research is needed to determine whether PFS on first line (delaying the need to move to a second or third line of therapy) may have cost benefits (in addition to the clinical benefit). Our study adds more recent data to prior literature evaluating healthcare costs associated with BTCs [15, 20–22]. Costs

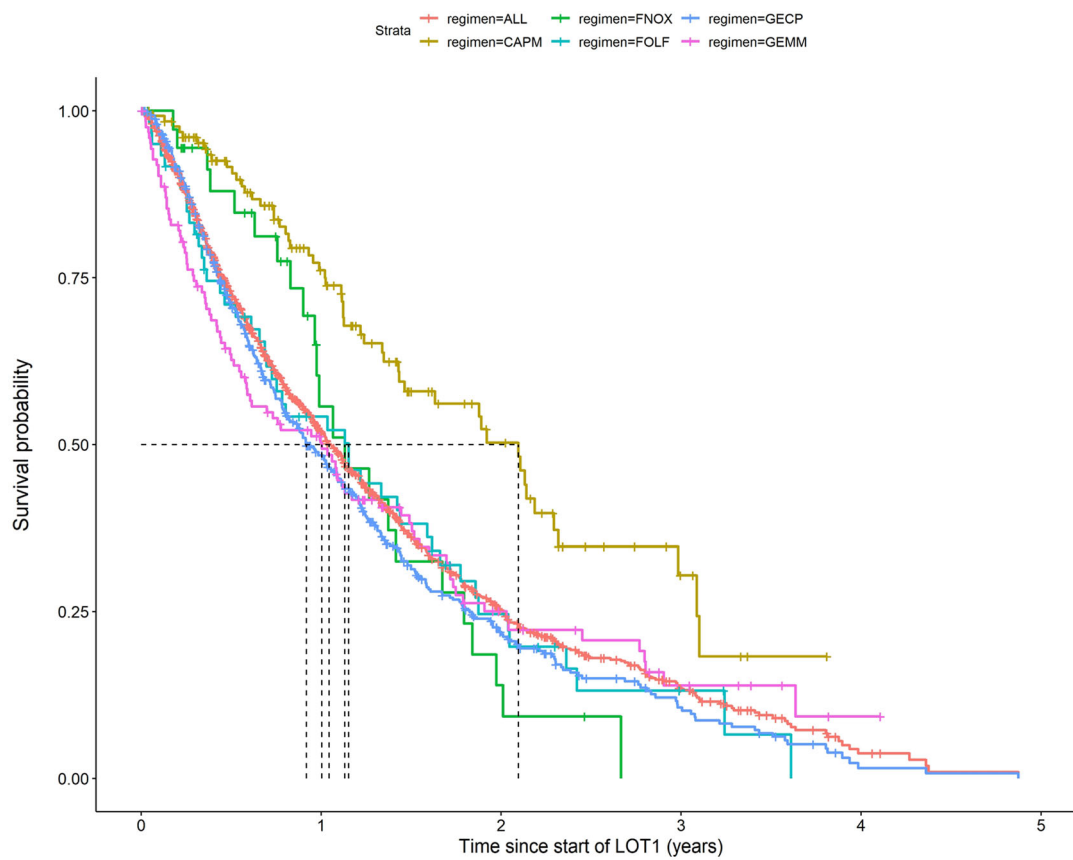
related to BTCs comprised most of the costs in a commercial and Medicare claims analysis conducted by Chamberlain et al. from 2007 to 2019 [15]. Consistent with our findings, cost drivers in Chamberlain et al. included inpatient admissions and a high proportion of ICU admissions related to BTCs. In the current analysis, the number of inpatient admissions and ICU stays increased progressively from the first to third LOT across the entire cohort. This provides further evidence that improved treatment options may reduce the need for inpatient admissions.

The 5-year survival rates are ~20% for people with BTCs with localized disease and only ~2% among those with advanced stage cancer [7]. The high mortality rate (67.5% following start of LOT1) and median survival time of 12.7 months reported in this study are consistent with US survival rates, median age of



	People with a Death	Median Survival time (Months)
All people with BTCs (n=2,168)	1,434	13.0

Fig. 4 Kaplan–Meier curve of overall survival measured from BTC index date. *BTCs*: biliary tract cancers, *n* number



LOT1 Regimen	Number of People	Number of People with a Death	Median Survival Time (months)
All regimens	1,179	796	12.7
Capecitabine monotherapy	131	53	25.5
FOLFIRI ^a	60	46	14.0
Gemcitabine monotherapy	124	90	12.2
FOLFIRINOX ^b	37	23	13.8
Gemcitabine + cisplatin	513	377	11.2

Fig. 5 Kaplan–Meier curve of overall survival measured from start of LOT1. *CAPM* capecitabine monotherapy, *GECP* gemcitabine + cisplatin, *GEMM* gemcitabine

monotherapy, *LOT* line of therapy, *n* number. ^aFluorouracil, irinotecan, leucovorin. ^bFluorouracil, irinotecan, leucovorin, oxaliplatin

diagnosis in the USA of 66 years, and median age of death in the USA at 68 years of age [23].

Limitations associated with this study include the Covid-19 pandemic, lack of clinical detail required to understand the reason a patient may stop treatment (i.e., toxicity or lack of effectiveness), cancer stage at BTC index date, and the reason for initial regimen (e.g.,

adjuvant setting or for palliative care) selection following BTC diagnosis. The study period in the current analysis used data through 30 June 2020, and while the last few months overlap with the start of the Covid-19 pandemic (approximately March 2020), most results are reported prior to the start, and therefore we do not expect these data would be impacted.

Additionally, historical information before enrollment in the MarketScan databases were not available, nor was access to medical charts or records other than administrative healthcare claims. Therefore, misclassification of people with BTCs or underestimates of baseline clinical conditions was possible. This study used a 6-month pre-index period, which may be insufficient to ensure people were initiating first-line therapy after diagnosis. Although MarketScan Commercial and Medicare databases are convenience samples of employees, retirees, and dependents with US commercial and Medicare supplemental health insurance coverage, results from these databases may not be generalizable to the wider population, particularly to those who receive other healthcare coverage (Medicaid) or who lack healthcare coverage. Lastly, reported HCRU are not stratified or adjusted for age or disease stage, which are important factors to consider that shape recommendations for subsequent LOTs and should be considered in future analyses.

CONCLUSION

This real-world analysis of people with BTCs found that treatment duration decreases as people move from first to subsequent LOTs, 67.5% experience a death following LOT1 start, and HCRU and costs increase after LOT1. These findings add more recent data to current literature highlighting the unmet need for more effective treatment options that delay onset of metastasis and extend survival. In addition, it supports the importance of prioritizing treatment decisions to ensure the most effective treatment option is provided in the first LOT.

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Author Contributions. The study conception and design were conducted by Nilofer Azad, Elisabetta Malangone-Monaco, Marcus Healey, Brian Seal, and Rory Smoot. Material preparation, data collection and analysis were performed by Danae Black, Elisabetta Malangone-Monaco, and Nicole Princic. The first draft of the manuscript was written by Danae Black and Nicole Princic and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Disclosures. Marcus Healey is employed by AstraZeneca Pharmaceuticals; Brian Seal was employed by AstraZeneca Pharmaceuticals at the time the study was conducted. Elisabetta Malangone-Monaco, Nicole Princic, and Danae Black are employed by Merative (previously IBM Watson Health) which received funding from AstraZeneca Pharmaceuticals to conduct this study. Rory Smoot and Nilofer Azad are paid consultants of AstraZeneca Pharmaceuticals. Danae Black is also affiliated with the University of Washington.

Compliance with Ethics Guidelines. All database records are statistically de-identified and certified to be fully compliant with US patient confidentiality requirements set forth in the Health Insurance Portability and Accountability Act of 1996. Additionally, the NDI database from the National Center for Health Statistics was linked to approximately 80% of selected people from the MarketScan databases. IRB waiver of authorization approval was

obtained from WCG IRB (IRB study #: 1320660; IRB protocol #: 20215641) on October 27, 2021.

Data Availability. The data that support the findings of this study are available from Merative (previously IBM Watson Health). Restrictions apply to the availability of these data, which were used under license for this study.

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