EE431 The Economic Burden of Advanced/Metastatic Biliary Tract Cancer: A Systematic Literature Review

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Background

- Biliary tract cancer (BTC) encompasses a group of rare and aggressive malignancies, including cholangiocarcinoma (CCA) and gallbladder cancer[1]

Objective

- This systematic literature review (SLR) aimed to comprehensively explore the economic burden of BTC in terms of healthcare resource utilisation (HCRU) and costs in patients with advanced or metastatic BTC

Methods

- The SLR followed the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards.[2] A comprehensive literature search covering Embase®, MEDLINE®, MEDLINE In-Process, EconLit®, the International Network of Agencies for Health Technology Assessment and the Centre for Reviews and Dissemination at York University was conducted on 12 April 2024. Relevant conferences from 2021-2023 were hand-searched
- The search strategy and conduct of the SLR was aligned with the requirements of evidence reviews for the National Institute for Health and Care Excellence (NICE) and other global health technology assessment agencies[3]
- Inclusion and exclusion criteria can be found in **Table 1**

Table 1. PICOS Table for HCRU Review

Category	Inclusion Criteria	Exclusion Criteria
Population	Adults (⩾18 years) with advanced or metastatic BTC, including BTC subtypes	Disease other than BTC
Intervention(s)	No restrictions	Non-pharmacological interventions
Comparator(s)	No restrictions	No exclusion on comparator
Outcome(s)	Direct medical costs Direct non-medical costs Indirect costs Unit costs HCRU Budget impact	Studies assessing outcomes not relevant to the review
Study design(s)	Cost studies	Case series and case reports
	Resource use studies	Reviews
	Cost and resource use studies	Animal/in vitro studies
	Economic evaluations reporting costs or resource use	Studies not reporting cost-effectiveness or cost-utility data
	Systematic reviews conducted on relevant population	
Language	Any article published in languages other than English and meeting the review inclusion criteria will be flagged and shared with Jazz Pharmaceuticals for review to determine their inclusion	
Country	US, Canada, EU5, Japan	
Time limit	Last 10 years (2013-2023)	

BTC, biliary tract cancer; EU5, France, Germany, Italy, Spain, the UK; HCRU, healthcare resource utilisation; PICOS, population, intervention(s), comparator(s), outcome(s), study design(s).

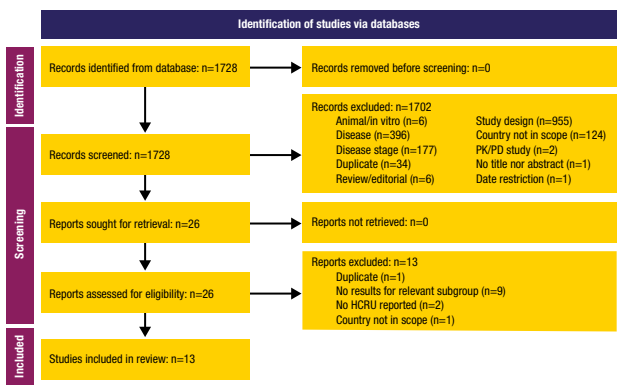
- Screening was conducted according to the pre-defined inclusion criteria. Records were screened first by title and abstract, then by full text
- Two independent reviewers performed the title/abstract and full-text screening, a third independent reviewer resolved discrepancies
- Studies included from the full-text screening stage were included for data extraction and reporting
- Data were extracted into pre-defined extraction grids by a single reviewer; all extractions were verified against original sources by a second reviewer

Results

Overview of included studies

- A total of 1728 potentially relevant records were identified for review and screened based on the information reported within their titles and/or abstracts. Full-text screening and assessment against the inclusion and exclusion criteria was conducted for 26 records. Of these, 13 studies were identified that captured the economic burden of BTC in the countries of interest (**Figure 1**)
- Studies were primarily conducted within the US and Japan, but also included analyses from the UK, Canada, China and Spain. Eight studies included patients with BTC, and 5 focussed specifically on patients with CCA. Of these, 1 study focused on intrahepatic CCA (iCCA) only. The other 4 studies considered both iCCA and extrahepatic CCA, either reporting on each group individually or collectively if it was not possible to distinguish between the two

Figure 1. PRISMA Flow Diagram for HCRU Studies



HCRU, healthcare resource utilisation; PD, pharmacodynamics; PK, pharmacokinetics; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

- The outcomes reported in the included studies are diverse, reflecting the different country perspectives and types of studies identified. As summarised in **Table 2**, there were 3 cost-effectiveness analyses[4-6] and 1 cost-consequence analysis[7] that reported direct cost and/or resource use estimates. Additionally, 7 were retrospective studies,[8-14] including retrospective analyses of medical records and/or claims databases. One SLR[15] was also included
- We have summarised some key findings by type of study: economic evaluations, retrospective studies and the SLR and budget impact analysis. We present further detail for the following key outcomes in **Table 3** (type and frequency of HCRU), **Figure 2** (per patient per month [PPPM] all-cause healthcare costs) and **Figure 3** (end-of-life care cost estimates)

Table 2. Characteristics of Studies

Publication Author, Year	Study Type	Population	HCRU	Cost Data	CEA	EoL Costs	Perspective	Currency, Year
Tsukiyama 2017[6]	CEA	BTC		✓	✓	✓	**Japan** - Hospital records	JPY, 2012
Wadhwa 2017[10]	RS	iCCA*		✓			**The US** - Insurance claims	USD, 1997-2012
Chamberlain 2021[12]	RS	CCA	✓	✓			**The US** - Insurance claims	USD, 2019
Darba 2021[13]	RS	iCCA	✓	✓			**Spain** - Hospital records	EUR, 2000-2017
Kim 2022[9]	RS	BTC		✓		✓	**Japan** - Payer	JPY, 2015-2020
Wang 2022[11]	RS	BTC	✓	✓			**The US** - Insurance claims	USD, 2020
Argoubi 2023[14]	RS	BTC	✓				**Japan** - Payer	NR
Hernando-Calvo 2023[7]	CC	BTC		✓	✓		**Canada** - Payer	CAD, 2019
Lee 2023[8]	RS	CCA	✓	✓			**The US** - Hospital records	USD, 2016-2019
Tang 2023[16]	BIA	BTC		✓			**Japan** - Payer	JPY, 2022-2026
Zhu 2023[4]	CEA	BTC		✓	✓	✓	**The US and China** - Hospital records, insurance claims	USD, 2023
Kamble 2024[15]	SLR	BTC	✓				NA	NA
McCarthy 2024[5]	CEA	CCA			✓	✓	**The UK** - Payer	GBP, 2021

In this poster results were converted to USD using the 2017 USD conversion rate and inflated to 2024 from country-specific data obtained from Federal Reserve Economic Data.[3] Cost data include DHC, TC and PPPM costs. *The study population comprised patients with discharge diagnoses corresponding to primary ICD-9-CM diagnosis codes 155.1 (malignant neoplasm of intrahepatic bile ducts) and 156 (malignant neoplasm of the gallbladder, including extrahepatic ducts, ampulla of Vater, and unspecified sites), which were collectively referred to as iCCA.
BIA, budget impact analysis; BTC, biliary tract cancer; CC, cost-consequence analysis; CCA, cholangiocarcinoma; CEA, cost-effectiveness analysis; DHC, direct hospital costs; EoL, end of life; HCRU, healthcare resource utilisation; iCCA, intrahepatic cholangiocarcinoma; ICD-9-CM, The International Classification of Diseases, Ninth Revision, Clinical Modification; NA, not applicable; NR, not reported; PPPM, per patient per month costs; RS, retrospective study; SLR, systematic literature review; TC, total costs.

Healthcare resource utilisation

- HCRU was identified in 4 retrospective studies, 1 budget impact and 1 SLR. Each study reported the percentage of patients with diagnosed BTC or CCA that incurred at least 1 healthcare resource event (eg, inpatient admission, outpatient admission, hospice visit) and are summarised in **Table 3**

Table 3. Characteristics of Studies

Publication Author, Year	Study Size	Resource Use	Percentage of Patients With the Resource Use
Japan			
Argoubi 2023[14]	325	Laboratory test Diagnostic imaging Outpatient visit Inpatient admission Home care visit Rehabilitation visit Radiotherapy Resection surgery	96.9 96.3 92.3 84.6 23.7 23.1 19.6 6.2
Tang 2023[16]	8600	Genomic testing	11.5-24.0
Spain			
Darba 2021[13]	23,315	Inpatient admission Diagnostic imaging (CT) Readmission	67.1 45.7 16.3
US			
Wang 2022[11]	300	Inpatient admission	67
Kamble 2024[15]	NR	Outpatient visit Inpatient admission ER visit	98 70-80 33-80
Chamberlain 2021[12]	1298	Outpatient visit Radiology visit Inpatient admission ICU admission ER visit Home care visit	59.9 44.1 38.7 14.3 11.0 8.6

All resource use percentages reported for Kamble 2024 pertain to patients receiving first-line therapy only.
Chamberlain 2021 reported CCA-related HCRU, which might reduce the values compared with other studies.
CCA, cholangiocarcinoma; CT, computed tomography; ER, emergency room; HCRU, healthcare resource utilisation; ICU, intensive care unit; NR, not reported.

Japan

- Reported HCRU frequencies in Argoubi 2023[14] show that 84.6% of patients had at least 1 hospital admission, averaging 3.2 hospitalisations, with a median stay of 70 days. Laboratory tests were conducted for 96.9% of patients (mean: 15.1 tests), and diagnostic imaging for 96.3% of patients (mean: 8.7). Resection surgeries were rare (6.2%; mean: 0.1 surgeries), whereas 19.6% underwent radiotherapy. Outpatient visits were very common, with 92.3% of patients having at least 1 visit and an average of 16 visits reported amongst all patients, varying slightly by treatment line. Home care visits and rehabilitation visits were noted in 23.7% and 23.1% of patients, respectively, with means of 3.4 and 2.6 visits reported and more visits in the third line compared with the first and second line. Mean and median follow-up time was not reported
- The expected number of patients in whom genomic tests were performed in Tang 2023[16] was reported to be 24.0% in the non-comprehensive genomic profiling group and 11.5% in the comprehensive genomic profiling group. Mean and median follow-up time was not reported

Spain

- As reported in Darba 2021,[13] HCRU data show that 67.1% of patients had urgent admissions, with an average hospital stay of 14.2 days and a median of 10 days (range: 0-331). Readmissions occurred in 16.3% of cases. Diagnostic procedures were common, including computed tomography scans (45.7%), ultrasounds (42.2%) and magnetic resonance imaging scans (15.3%). Mean and median follow-up time was not reported

The US

- In a retrospective study, Chamberlain 2021[12] reported the HCRU of patients with CCA-related HCRU with a mean follow-up of 229 days (median: 140 days). Amongst these patients, there were 38.7% inpatient admissions, 14.3% had been admitted to an intensive care unit (ICU), 59.9% had outpatient visits, 11.0% had emergency room (ER) visits, 8.6% had home health care/hospice visits and 44.1% had radiology visits. The mean number of medical services PPPM were reported as 0.2 inpatient admissions, with an average length of stay of 4.4 days; 0.1 ICU admissions, with an average stay of 3.6 days; 0.1 home health care/hospice visits; 1.0 outpatient visits; and 0.2 radiology visits
- In a second retrospective study, Wang 2022[11] reported that the number of hospitalisations was 201 (67.0%). The reported ER visits were virtually 0. The average length of hospitalisation stay was 7.0 days. The mean number of inpatient visits ranged from 1.5-1.8; ER visits from 1.1-1.4; and outpatient visits from 34.4-41.3, also across lines of treatment during a median follow-up of 7.6 months. As reported in the Kamble 2024[15] SLR, US HCRU in the first line was primarily driven by outpatient visits (98.0%), ER visits (33.0-80.0%) and hospitalisations (70.0-80.0%). The mean hospital stay ranged from 0.6-7 days PPPM. Mean and median follow-up time was not reported
- Reporting by HCRU was inconsistent by cost category, with gaps in reporting both by cost setting perspective (country and payer perspective) and by treatment line

Direct hospital costs, total costs and PPPM costs

- Six retrospective studies that reported HCRU costs, direct hospital costs or PPPM costs were identified across 3 separate country perspectives: 4 for the US (Wadhwa 2017,[10] Chamberlain 2021,[12] Wang 2022,[11] Lee 2023[8]), 1 for Spain (Darba 2021[13]) and 1 for Japan (Kim 2022[9]). In addition, the SLR identified the following non-retrospective studies that reported cost outcomes: a cost calculator for Canada (Hernando-Calvo 2023[7]); a budget impact analysis (Tang 2023[16]) and a cost-effectiveness model (Tsukiyama 2017[6]) for Japan; and a cost-effectiveness model that included both US and China perspectives (Zhu 2023[4])
- Results were converted to USD using the 2017 USD conversion rate and inflated to 2024 from country-specific data obtained from Federal Reserve Economic Data[17]

Japan

- A retrospective claims data analysis conducted by Kim[9] estimated the mean monthly all-cause healthcare costs for patients with metastatic BTC to be US$4089. In a secondary study conducted by Tsukiyama,[6] a monthly cost per patient of US$12,818 was reported. Tang 2023[16] evaluated the budget impact of comprehensive genomic profiling before standard of care for patients with BTC

Spain

- Darba 2021[13] is a retrospective multicentre study that utilised the Spain-based hospital database and Spanish national discharge database to collect data on iCCA cases between 1 January 2000 and 31 December 2018. The study estimated the mean monthly direct medical cost of secondary care of CCA (all stages) to be US$373 per admission and US$564 per patient

The US

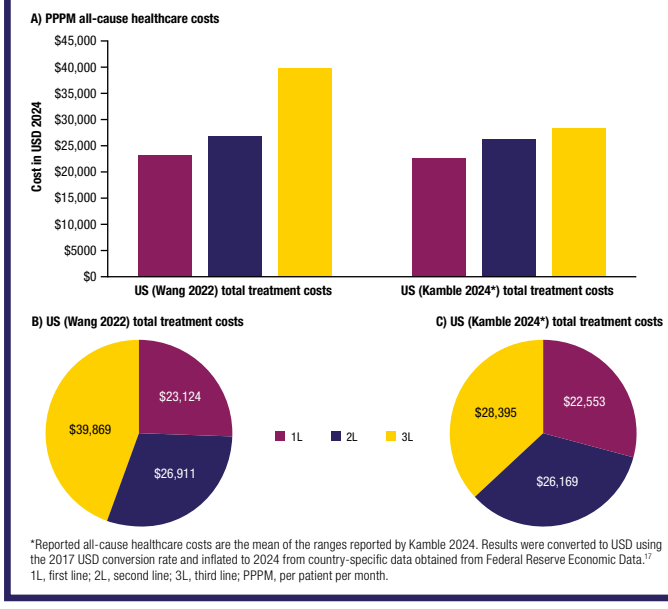
- A retrospective analysis of US claims conducted by Chamberlain[12] found that the average monthly direct healthcare cost for patients with CCA was US$9477 across all treatment lines. Mean medical service cost PPPM was US$8182, which could be further differentiated by cost setting: inpatient (US$4319), ICU (US$1799) and outpatient (US$2707). Additional HCRU costs were reported as US$97 for mean ER visit, US$53 for hospice care and US$786 for radiology
- In a study using the US National Inpatient Sample, Wadhwa[10] reported mean monthly hospital charges of US$10,564 for CCA admissions during hospitalisation
- Zhu 2023[4] conducted an economic evaluation of 2 interventions to treat BTC based on TOPAZ-1 and KEYNOTE-966 trial data. Cost of treatment and cost per cycle were based on Centers for Medicare & Medicaid Services data in 2023 USD. Monthly mean non-treatment healthcare costs were US$4916, of which US$3568 went to best supportive care and US$1347 to testing and imaging services

- Two studies from the US (Kamble 2024,[15] Wang 2022[11]) reported PPPM (including treatment costs) ranging from US$22,553-US$23,124 in first-line treatment; US$26,169-US$26,911 in second-line treatment; and US$28,395-US$39,869 in third-line treatment (**Figure 2A**). Both Wang (**Figure 2B**) and Kamble (**Figure 2C**) reported that subsequent treatment costs are higher than first-line treatment costs, suggesting that costs increase depending on the line of treatment
- Lee 2023[8] synthesised generalised state-independent data collected by the Agency for Healthcare Research and Quality via the Healthcare Cost and Utilization Project, reporting mean CCA-related hospital costs of US$23,141

Canada

- One study (Hernando-Calvo 2023[7]) reported data from a Canadian perspective. The study estimated a full breakdown of the total reimbursed anticancer cost associated with BTC to be $12,091, including: hospitalisations, $3771; hospital outpatient clinic costs, $1239; same-day surgery, $279; dialysis visit costs, $3827; and ER visits, $259

Figure 2. PPPM All-Cause Healthcare Costs

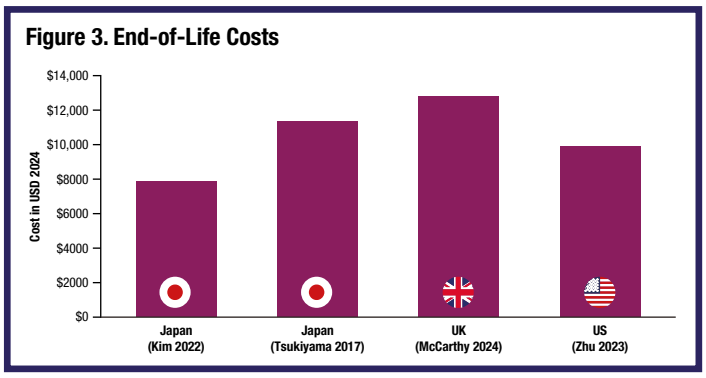


*Reported all-cause healthcare costs are the mean of the ranges reported by Kamble 2024. Results were converted to USD using the 2017 USD conversion rate and inflated to 2024 from country-specific data obtained from Federal Reserve Economic Data.[17]
1L, first line; 2L, second line; 3L, third line; PPPM, per patient per month.

End-of-life costs

- Four studies reported end-of-life costs within Japan,[6, 9] the UK[5] and the US.[4] End-of-life costs ranged from US$7863 in Japan to US$12,781 in the UK, as shown in **Figure 3**. These costs were likely included in the previously described direct healthcare costs. However, examining these costs separately permits a deeper investigation of the sources of cost discrepancies between country perspectives. Each study examines end-of-life costs from a different time period (eg, 30 days before death[6] or from the start of opioids to death[5]), echoing the heterogeneity within the studies

Figure 3. End-of-Life Costs



Conclusions

- BTC represents a major economic burden to health plans, institutions and payers worldwide, with considerable HCRU and cost across care settings
- Costs associated with treatment and diagnostics (ie, inpatient hospitalisation, diagnostic imaging) were identified as a major contributor to the overall burden of illness given the size of the patient population and the per patient cost. The per patient cost generally increases as patients progress to subsequent lines, eventually leading to an end-of-life cost of approximately US$7000-US$13,000. In the US, the cost of care was driven mostly by hospitalisation (including ICU), medical services and to a less extent, drug acquisition
- Approximately 60-80% of BTC patients had at least 1 hospitalisation due to any cause. Other common HCRU includes diagnostic imaging and laboratory tests, though the extent of these HCRUs varies considerably between countries. The difference in reporting standards and healthcare systems between countries made cross comparisons difficult
- HCRU patterns and costs of care may have shifted due to recent approvals of immunotherapies and targeted treatments for advanced and metastatic disease, which can be a topic for future research

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