Prognostic and/or Predictive Factors in Biliary Tract Cancer: A Systematic Literature Review

C049

John A. Bridgewater,[1] Juan W. Valle,[2] Wayne Su,[3] Javier Sabater,[4] Sam Mettam,[4] Lin Fan,[3] Sally Bowditch,[4] Amit Ahuja,[5] Vijay Sharma,[5] Suzy Paisley,[6] Ankit Rohilla,[5] Aikyadeep Mandal,[5] Andrea Garcia,[7] Farshid Dayyani,[8] Richard Kim[9]

[1]UCL Cancer Institute, University College London, London, UK; [2]Cholangiocarcinoma Foundation, Herriman, UT, USA, and Division of Cancer Sciences, University of Manchester, Manchester, UK; [3]Jazz Pharmaceuticals, Philadelphia, PA, USA; [4]Jazz Pharmaceuticals, London, UK; [5]Lumanity, Gurugram, India; [6]Lumanity, London, UK; [7]Lumanity, Utrecht, The Netherlands; [8]UCI Health Chao Family Comprehensive Cancer Center, Orange, CA, USA; [9]Moffitt Cancer Center, Tampa, FL, USA

Introduction

- Biliary tract cancer (BTC) is a heterogeneous and rare group of malignancies that includes gallbladder cancer (GBC), intrahepatic, and extrahepatic cholangiocarcinoma (iCCA and eCCA, respectively).[1,2] BTC accounts for less than 1% of all cancers[3]
- Countries in the Asia-Pacific region and South America reported generally higher incidence rates (per 100,000) of BTC (Asia-Pacific: 1.12-9.00; South America: 2.73-12.42) compared to those in Europe (2.00-3.59) and North America (2.33-2.35)[4]
- Identifying prognostic and predictive factors is crucial for optimizing cancer management and guiding comparative effectiveness research, such as indirect treatment comparisons and external control arm analyses
  - Prognostic factors predict the outcomes of a disease regardless of treatment, such as survival based on a patient's performance status
  - Predictive factors indicate the likelihood of benefit from treatment, such as the presence of actionable biomarkers
  - Some factors may be both prognostic and predictive, depending on context and endpoint[5]
- Validation of prognostic and predictive factors can enhance clinical trial design, improve patient stratification, facilitate comparative effectiveness research, and minimize unnecessary treatment and associated toxicity, ultimately leading to better treatment outcomes and reduced healthcare costs[6]

Objectives

- A systematic literature review (SLR) was conducted to synthesize available evidence regarding the prognostic and predictive factors that may be associated with overall survival (OS) and/or progression-free survival (PFS) in patients with advanced or metastatic BTC

Methods

- The SLR followed the Cochrane and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards
- A comprehensive literature search was conducted covering the *Excerpta Medica* database (Embase®), Medical Literature Analysis and Retrieval System Online (MEDLINE®), MEDLINE® In-Process, and the Cochrane Library from database start to September 24, 2023
- Literature search results published from 2013 to 2023 were screened according to the pre-defined inclusion criteria (**Table 1**), first by title and abstract review, and then by full-text review
- Screening (both title/abstract and full text) was performed by 2 independent reviewers and any discrepancies were resolved by a third independent reviewer
- Studies identified for inclusion based on full-text screening were subjected to data extraction
- Data were extracted into pre-defined extraction grids by a single reviewer, with all extractions independently verified against the original source documents by a second reviewer
- The quality of the included studies was assessed using the Quality in Prognostic Studies (QUIPS) checklist, recommended by the National Institute for Health and Care Excellence[7]

Table 1: Study Selection Inclusion Criteria

Category	Inclusion/Exclusion Criteria
Population	Adults (≥18 years) with unresectable, locally advanced, or metastatic BTC Studies evaluating overall BTC; ie, combined populations of GBC and CCA were included Studies of GBC alone or CCA alone were deprioritized
Intervention/comparator	No restrictions
Outcomes	Prognostic or predictive factors (eg, age, sex, biomarker type, tumor response, BTC anatomical subtypes, etc.) and their statistical relationship[a] with PFS and OS
Study type	Full-text articles reporting prospective and retrospective observational studies, cohort studies, case-control studies, RCTs, systematic reviews, and meta-analyses[b]
Other restrictions	Articles published in the English language
Timeframe	Articles published from 2013 to 2023

[a]Statistical relationship was analyzed by univariate and multivariate analyses. Variables were categorized as prognostic or predictive if they had a statistically significant association with OS and/or PFS using multivariate analysis; [b]Relevant systematic literature reviews and meta-analyses were included at the title/abstract review stage to identify any additional studies not found in database searches.

BTC, biliary tract cancer; CCA, cholangiocarcinoma; GBC, gallbladder cancer; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trial.

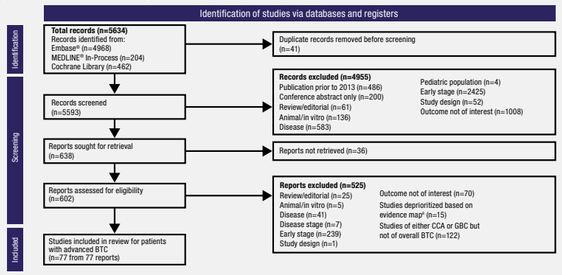
Evidence Mapping of Reported Prognostic and Predictive Factors

- Factors that were identified as statistically significant by individual studies were summarized in an evidence map that highlighted their distribution across univariate and multivariate analyses. This mapping resulted in a comprehensive compilation of all factors that had been assessed for their statistical association with OS and/or PFS outcomes
- Based on this evidence map, studies reporting statistically analyzed factors (based on univariate analyses) and reported across >3 studies were prioritized for data extraction

Results

- The PRISMA diagram for flow of citations from identification to inclusion in the SLR is presented in **Figure 1**
- Primary database searches yielded 5634 records
  - Duplicate screening excluded 41 records
  - Primary abstract screening excluded 4991 records
- 602 records underwent full-text screening, with 525 records excluded
- Based on the evidence map, 77 studies on overall BTC that reported statistically significant analyses of factors associated with OS and/or PFS across ≥3 studies were included for data extraction

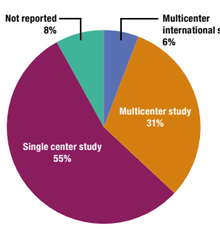
Figure 1: PRISMA Flow Diagram



*Studies of variables reported across less than 3 studies.

BTC, biliary tract cancer; CCA, cholangiocarcinoma; Embase®, *Excerpta Medica* database; GBC, gallbladder cancer; MEDLINE®, Medical Literature Analysis and Retrieval System Online.

Figure 2: Study Settings



Study and Patient Characteristics

- Of the studies identified for data extraction, 75 were observational studies, 1 was a randomized controlled trial, and 1 was a single-arm trial
- The majority of these studies were single center or multicenter studies conducted within a single country (**Figure 2**)
  - The geographic distribution of these studies, primarily conducted in South Korea, Japan, and Italy, is presented in **Figure 3**
- Study sample sizes ranged from 19 to 1333 patients (**Figure 4**)
- Median study follow-up duration ranged from 6.4 to 95.3 months (**Figure 5**), where reported
- Median patient age ranged from 53 to 75 years
- The proportion of female patients varied from 22.7% to 62.5%
- The proportion of patients with BTC subtypes ranged from 16% to 89% for iCCA, 6.6% to 52.1% for eCCA, and 5% to 47.1% for GBC
- Forty-eight (62%) studies enrolled patients who were receiving first-line chemotherapy

Figure 3: Study Geographical Distribution

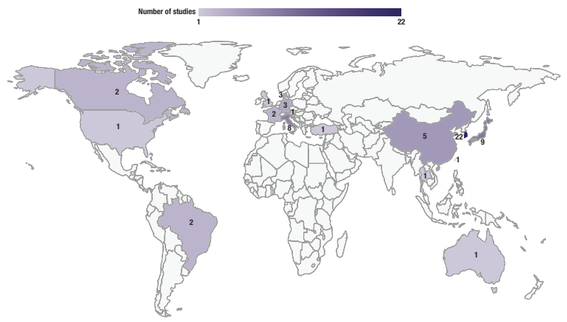


Figure 4: Study Population Sizes

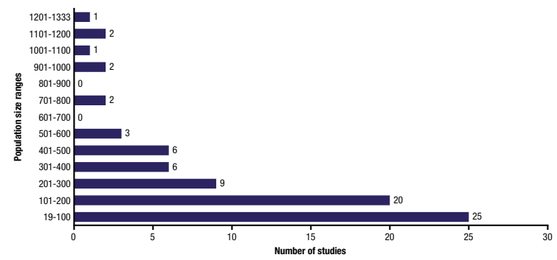


Figure 5: Study Median Follow-Up Duration

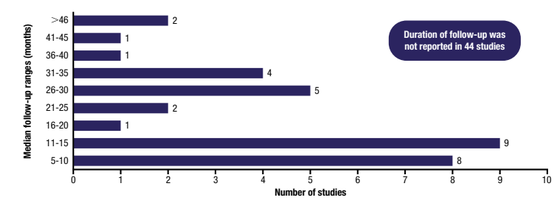


Table 2: Identified Prognostic and Predictive Factors

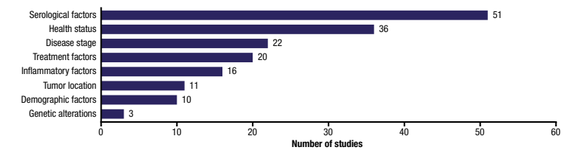
Category	Prognostic Factors	Predictive Factors
Demographics or clinical characteristic	Sex, age, BMI, ECOG PS	ECOG PS
Tumor stage	UICC scale, tumor grade, TNM stage, tumor size, tumor stage	–
Serological factor	Hemoglobin, albumin, CA 19-9, LDH, alkaline phosphatase, bilirubin, CEA, WBC count	Albumin, alkaline phosphatase, CA 19-9, CEA
Inflammatory factor	NLR, PLR, PNI	
Disease stage	Locally advanced or metastatic disease, site of metastasis, number of metastatic sites, differentiation of disease, recurrence status	–
Tumor location	iCCA, eCCA, GBC	
Treatment factor	Surgical intervention, outcome/response of treatment, line of therapy	Type of intervention
Genetic alteration	HER2/ERBB2	ARID1A alterations, PRGN overexpression

ARID1A, AT-Rich Interaction Domain 1A; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ERBB2, Erb-B2 receptor tyrosine kinase 2; GBC, gallbladder cancer; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PRGN, progranulin; TNM, Tumor, Node, Metastasis; UICC, Union for International Cancer Control; WBC, white blood cell.

Overview of Identified Factors

- Among the 77 studies identified for data extraction, 54 studies reported prognostic factors, 10 reported predictive factors, and 13 reported both predictive and prognostic factors for OS and/or PFS (**Table 2**)
- For prognostic factors predictive of overall BTC progression, a significant relationship was reported between demographic and clinical parameters, tumor stage and location, serological and inflammatory factors, disease stage, treatment factors, and genetic alterations with OS and/or PFS
- Significant relationships were also reported between certain predictive factors associated with inflammation, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio, carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), prognostic nutritional index, albumin, alkaline phosphatase, and OS and/or PFS
  - Other factors such as Eastern Cooperative Oncology Group performance status (ECOG PS), tumor location, genetic factors, and tumor response were also considered predictive of OS and/or PFS

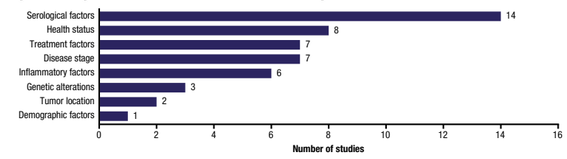
Figure 6: Prognostic and/or Predictive Factors for Overall Survival



Frequency of Prognostic and/or Predictive Factors Reported for OS and PFS

- The most commonly reported prognostic and/or predictive factors for OS were ECOG PS (n=34), CA 19-9 (n=16), CEA (n=15), NLR (n=12), disease extent (n=12), tumor location (n=11), and albumin (n=11), identified as statistically significant in multivariable analyses across multiple studies (**Figure 6**)

Figure 7: Prognostic and/or Predictive Factors for Progression-Free Survival



- The most commonly reported prognostic and/or predictive factors for PFS were ECOG PS (n=7), CA 19-9 (n=6), NLR (n=4), prior line of therapy (n=4), and metastatic disease (n=4), identified as statistically significant in multivariable analyses across multiple studies (**Figure 7**)

Table 3: Direction of Correlation Between Prognostic/Predictive Factors and Overall Survival and/or Progression-Free Survival

Variable	OS	PFS
ECOG PS[a]	ECOG PS >1 had worse OS	ECOG PS >1 had worse PFS
CA 19-9[a]	Elevated CA 19-9 had worse OS	Elevated CA 19-9 had worse PFS
CEA[a]	Elevated CEA levels had worse OS	Elevated CEA levels had worse PFS
Extent of disease	Metastatic disease had worse OS	Metastatic disease had worse PFS
NLR[a]	↓ (<3)	↓ (<3)
Albumin	↑ (>3 g/dL)	↑ (>3 g/dL)
Tumor location[a]	GBC<eCCA<iCCA	GBC<eCCA<iCCA
LOT	Patients at <2 LOT had worse OS	Patients at <2 LOT had worse PFS
Metastatic disease	Presence of metastasis and >1 sites had worse OS	Presence of metastasis and >1 sites had worse PFS
Presence of chemotherapy	Gem-based combination therapies had better OS	Gem-based combination therapies had better PFS
Chemotherapy response	Progressive disease had worse OS	Progressive disease had worse PFS
Sex	Males had worse OS	Females had worse PFS
ALP[a]	Higher ALP had worse OS	Higher ALP had worse PFS
Age	Older age was associated with worse OS	NR
Bilirubin	Higher bilirubin had worse OS	Higher bilirubin had worse PFS
Hemoglobin	Lower hemoglobin had worse OS	Lower hemoglobin had worse PFS
PLR[a]	Non-maintained PLR had worse OS	Non-maintained PLR had worse PFS
PNI[a]	<36.7 had worse OS	<44.30 had worse PFS
Prior resection	Absence of prior resection/surgery had worse OS	NR
Recurrent/relapsed	Recurrent/relapsed had better OS compared to inoperable disease	NR
BMI	Obese patients have worse OS	NR
Genetic factors[a]	Presence of HER2 and ARID1A alterations had worse OS	Presence of HER2, ARID1A alterations, and PRGN overexpression had worse PFS
LDH	Higher LDH had worse OS	NR
TNM stage	Stage III and above had worse OS	Stage III and above had worse PFS
Tumor grade	Grade 2 and above had worse OS	NR

≥10 studies reporting evidence; 6-10 studies reporting evidence; ≤5 studies reporting evidence; ↑ Positive correlation: the higher the value, the better the outcome; ↓ Inverse correlation: the higher the value, the poorer the outcome

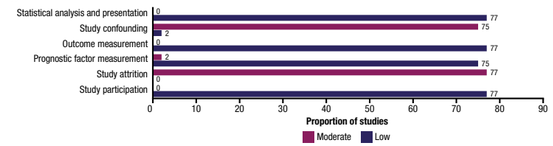
[a]Reported as a prognostic and predictive factor.

ALP, alkaline phosphatase; ARID1A, AT-Rich Interaction Domain 1A; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GBC, gallbladder cancer; Gem, gemcitabine; HER2, human epidermal growth factor receptor 2; iCCA, intrahepatic cholangiocarcinoma; LDH, lactate dehydrogenase; LOT, line of therapy; NLR, neutrophil-to-lymphocyte ratio; NR, not reported; OS, overall survival; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PR, partial response; PRGN, progranulin; TNM, Tumor, Node, Metastasis.

Direction of Correlation

- **Table 3** summarizes the direction of correlation of prognostic/predictive variables for OS and PFS, along with the frequency with which they were reported
- The prognostic and/or predictive factors associated with worse OS were ECOG PS >1, elevated CA 19-9 and CEA levels, metastatic disease, lower albumin level, GBC<eCCA<iCCA, uncontrolled disease, high metastatic burden, presence of distant metastasis, and male sex
- A high CA 19-9 level and ECOG PS >1 were associated with poor PFS. Additionally, high NLR, high CEA level, uncontrolled disease, and presence of distant metastasis were identified as prognostic/predictive factors for worse PFS

Figure 8: Risk of Bias Assessment



Quality Assessment of Included Studies

- The QUIPS checklist revealed low risk of bias (RoB) for the majority of studies across RoB domains, including (a) assessment of how participants were recruited/enrolled in the study (ie, study participation), (b) how prognostic factors were measured, (c) how outcomes were measured, and (d) robustness of statistical analyses used
- However, RoB was considered moderate across 2 domains; (a) study attrition as participant dropout details were not adequately reported in all studies, and (b) confounding summary score (**Figure 8**)

Conclusions

- To the best of our knowledge, this SLR is the first to systematically assess prognostic and predictive factors of OS and PFS in patients with advanced or metastatic BTC based on the published scientific literature
- Twenty-five clinical, disease, and treatment characteristics were identified as important prognostic and/or predictive factors of OS and/or PFS for patients with advanced or metastatic BTC
- Key prognostic and/or predictive factors of OS, with each reported in >10 studies, were ECOG PS, CA 19-9 level, CEA, NLR, disease stage, and albumin level
- Key prognostic and/or predictive factors of PFS, with support from ≥4 studies, were ECOG PS, CA 19-9 level, and NLR
- The prognostic value of genetic alterations (eg, human epidermal growth factor receptor 2, AT-Rich Interaction Domain 1A, and progranulin) was rarely assessed and correlation results for these factors were inconclusive
- Further studies and expert consensus are needed to refine the framework of these prognostic factors to optimize cancer management for patients with BTC and to guide comparative effectiveness research

References: 1. Valle JW, et al. *Lancet.* 2021;397(10272):428-444. **2.** Vogel A, et al. *Ann Oncol.* 2023;34(2):127-140. **3.** Siegel RL, et al. *CA Cancer J Clin.* 2022;72(1):7-33. **4.** Baria K, et al. *Gastro Hep Adv.* 2022;1(4):618-626. **5.** Simms L, et al. *J Thorac Oncol.* 2013;8(8):808-813. **6.** Duffy MJ, Crown J. *Crit Rev Clin Lab Sci.* 2024;51(1):30-45. **7.** Hayden JA, et al. *Ann Intern Med.* 2013;158(4):280-286.

Support and Acknowledgments: This study was supported by Jazz Pharmaceuticals. Medical writing support was provided by Rishabh Verma, an employee of Lumanity, India. Editorial and production support were provided by Brandon Samson, PharmD, of CMC Connect, a division of IPG Health Medical Communications, with funding from Jazz Pharmaceuticals, in accordance with Good Publication Practice (GPP 2022) guidelines.

Disclosures: JA Bridgewater has consulted for Bristol Myers Squibb, Incyte, Servier, and Taiho; received funding from Incyte; and received honoraria from Incyte and Servier. **JW Valle** reports consulting or advisory roles with AstraZeneca, Cogent Biosciences, Incyte, Jazz Pharmaceuticals, Oncosil, Owkin, Redx Pharma, Servier, and Taiho Oncology. **W Su**, **J Sabater**, **S Mettam**, and **S Bowditch** are current employees of, and own stock or stock options in, Jazz Pharmaceuticals. At the time of development for this abstract, **Lin Fan** was an employee of, and owned stock or stock options in, Jazz Pharmaceuticals. **A Ahuja**, **V Sharma**, **S Paisley**, **A Rohilla**, **A Mandal**, and **A Garcia** are employed by Lumanity which was reimbursed by Jazz Pharmaceuticals as a consultancy for time spent undertaking the systematic literature review. **F Dayyani** has served as a consultant or advisor for AstraZeneca and Eisai; participated in speaker bureaus for Astellas Pharma, Exelixis, Ipsen, Servier, and Sirtex Medical; and reports research funding from AstraZeneca, Bristol Myers Squibb, Exelixis, Genentech, Ipsen, Merck, and Taiho Pharmaceutical. **R Kim** reports advisory and consulting roles with AbbVie, AstraZeneca, Bayer, Eisai, Exelixis, Jazz Pharmaceuticals, Pfizer, Roche/Genentech, Servier, and Taiho Oncology; speaker bureau participation for AstraZeneca and Incyte; and honoraria from Natera.

Poster presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 2025, May 13-16, 2025, Montreal, Quebec, Canada