Journal of Cancer Research and Clinical Oncology (2025) 151:95
https://doi.org/10.1007/s00432-025-06096-y

RESEARCH

Sex-related disparities in outcomes of survival in biliary tract cancer patients

Nadiye Sever[1] · Emil Yunusov[2] · Nargiz Majidova[1] · Erkam Kocaaslan[1] · Pınar Erel[1] · Yeşim Ağyol[1] · Ali Kaan Güren[1] · Abdussamet Çelebi[1] · Selver Işık[1] · İbrahim Vedat Bayoğlu[1] · Osman Köstek[3] · Murat Sarı[3]

Received: 10 November 2024 / Accepted: 14 January 2025 / Published online: 27 February 2025

Abstract

Introduction Biliary tract cancer (BTC) is a rare and aggressive cancer with a poor prognosis. Despite treatment, overall survival is less than 12 months. It is a proven fact that women have better chemotherapy responses and survival than men in almost all cancer types. We believe that gender is one of the important factors affecting the prognosis of BTC. In this study, we aimed to investigate the effect of gender on prognosis in this type of cancer.

Methods This study was designed as a single-centre retrospective analysis of patients with BTC. All patients, regardless of operability, were included in the study. Prognostic factors were analysed using univariate and multivariate analysis.

Results A total of 100 patients (48% female) were included in the study. The median follow-up time was 72.2 months (95% CI 39.3–105.0), and the median OS was 9.5 months (95% CI 5.3–13.8) for all study patients. The 72-month survival rate was 13.4%. The observed survival rates at 10.4% for male patients and 15.7% for female patients demonstrate the importance of considering gender as a prognostic factor. A multivariate analysis indicated a significant association between female gender and longer overall survival, with an adjusted hazard ratio of 0.59 (95% CI 0.38–0.92, $p=0.02$).

Conclusion It is clear that female gender is associated with a better response to chemotherapy and longer survival in BTCs. These findings should be taken into account in treatment selection and prognosis predictions. Further research may help elucidate the mechanisms underlying these sex differences and help develop more effective treatments.

Keywords Biliary cancers · Survival · Gender · Chemotherapy

✉ Murat Sarı
drmuratsari@gmail.com

Nadiye Sever
dr.nadya@hotmail.com

Emil Yunusov
emil.yunusov.1996@gmail.com

Nargiz Majidova
nergiz.mecidova1991@gmail.com

Erkam Kocaaslan
erkamkocaaslan@gmail.com

Pınar Erel
pnarerell@gmail.com

Yeşim Ağyol
yesimagyol@gmail.com

Ali Kaan Güren
alikaanguren@gmail.com

Abdussamet Çelebi
abdussametcelebi@gmail.com

Selver Işık
dr-selver83@hotmail.com

İbrahim Vedat Bayoğlu
dr.vebay@gmail.com

Osman Köstek
osmankostek@yahoo.com

[1] Division of Medical Oncology, Department of Internal Medicine, Marmara University Hospital, İstanbul, Turkey

[2] Department of Internal Medicine, Marmara University Hospital, İstanbul, Turkey

[3] Department of Medical Oncology, Medipol University Faculty of Medicine, Istanbul, Turkey

Introduction

Biliary tract tumors (BTC) is subclassified according to the location of the tumour as gallbladder (GB), intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (eCCA). In general, BTCs are rare in high-income countries, but incidence rates vary widely by sex, geographical region and anatomical subregion (Valle et al. 2021). Although systemic chemotherapy is among the first-line treatment options for patients with BTCs, systemic treatment approaches for these tumors have evolved significantly in recent years. Therapies such as immune checkpoint inhibitors (ICI) have shown promising results in the treatment of BTC. However, the side effects of these therapies are also noteworthy (Rizzo et al. 2021). For example, it has been reported that most cases of hearing loss associated with ICIs are reversible and usually occur in melanoma patients (Guven et al. 2023). In addition to ICIs, the identification of mutations, particularly in DNA damage repair (DDR) pathways, such as BRCA1/2 mutations, also affects treatment strategies for patients with BTC. The presence of these mutations is considered as potential biomarkers for targeted therapies (Ricci et al. 2020).

Although they have a similar anatomical origin in the biliary system, there are significant differences in clinicopathological features and prognostic factors in this group of diseases. As BTC is a rare and heterogeneous group of tumors with high mortality, there is an incomplete understanding of long-term outcomes that affect survival. However, according to the data we have obtained, there is a gender-related survival disparity in this tumor group and it is thought that the survival rate is better in the female gender. Many studies have shown that gender is associated with prognosis and survival in gallbladder cancer(He et al. 2010; Zhang et al. 2015). In primary liver cancers, prognosis differs according to gender and mortality rate is higher in males than females. One of the reasons for this may be the known differences in liver disease between men and women(Scaglione et al. 2015). The sex hormones estrogen and androgens are responsible for many physiological processes by signalling through their receptors (Kur et al. 2020). Estrogen receptors (ER) and androgen receptors (AR) are expressed in liver and bile duct cells in both men and women in normal and diseased states. The liver is therefore considered to be a sex hormone-sensitive organ. It is thought that this information may explain sex differences in the incidence of treatment response and survival in primary liver cancer (BTCs, including GBC, hepatocellular carcinoma and cholangiocarcinoma). In addition, this difference may be due to sex-related differences in metabolism, drug pharmacokinetics or pharmacodynamic activities between men and women(Desbois et al. 2020) Based on this information, we aimed to analyse the prognostic factors and the relationship between treatment response and gender in our patients diagnosed with BTC.

Material methods

We retrospectively analysed patients aged 18 years and older with histologically confirmed biliary adenocarcinoma (intrahepatic or extrahepatic cholangiocarcinoma and gallbladder) who were seen at the medical oncology outpatient clinic between January 2011 and December 2023. The study was approved by our hospital's local ethics committee, approval number [22.04.2024.502]. All patients who were operable or inoperable at diagnosis were included in the study. A total of 100 patients with available clinical data were analysed. Demographic and clinical information was obtained from patient records and an electronic database. Progression-free survival (PFS) was calculated as the time from treatment initiation to disease progression or death, and overall survival (OS) was calculated as the time from diagnosis to death. Factors included in the univariate analyses for PFS and OS were age, sex, ECOG performance status, tumor location, primary tumor surgery, presence of biliary drainage, disease stage and chemotherapy regimen used in treatment.

Statistical analysis

Data analysis was performed using SPSS 26.0 statistical software, with continuous data summarised as median and interquartile range. Categorical variables were analysed using chi-square or Fisher's exact test. Survival curves were constructed for each subgroup using the Kaplan-Meier method, with 95% confidence intervals (CIs). The log-rank test was used to compare differences in survival between groups. Prognostic factors were examined using univariate analysis, and factors with a p-value of less than 0.5 in multivariate analysis were then examined. Statistical significance was defined as $p < 0.05$. Cox regression backward LR model was calculated from sex, current lymph node dissection and lymph node metastasis, current CEA and Ca19.9 level, stage at diagnosis, grade and current primary surgery that were significant in univariable analysis. Hazard ratios (HRs) for these comparisons were calculated using a Cox proportional hazards model.

Results

Demographic and clinical characteristics of the Study population

A total of 100 patients were included in the study, with a median age of 61 years (interquartile range: 56–68). The gender distribution was 52% male and 48% female. The Eastern Cooperative Oncology Group (ECOG) performance score distribution revealed that 93% of patients had scores of 0–1. 28% of patients had intrahepatic cholangiocarcinoma, 43% had extrahepatic cholangiocarcinoma, and 29% had gallbladder carcinoma. The diameter of the primary tumor was greater than 30 mm in 48% of patients. While the tumor was solitary in 30% of patients, it was multiple in 70% of patients. At the time of diagnosis, 66% of patients had lymph node metastasis. At the initial diagnosis, 37% of patients were stage I-III, and 63% of patients were stage IV. 40% of patients had undergone surgical intervention at the time of diagnosis, while 30% had received adjuvant chemotherapy. The most commonly used systemic chemotherapy regimen in the first-line setting was cisplatin-gemcitabine. (Table 1).

Table 1 The clinical and demographic characteristics of the study patients

Age, year	
Median (Interquartile range)	61 (56–68)
Gender, n (%)	
Female	48 (48.0)
Male	52 (52.0)
ECOG-performance status, n (%)	
0–1	93 (93.0)
2 and above	7 (7.0)
Primary tumor location, n (%)	
Intrahepatic	28 (28.0)
Extrahepatic	43 (43.0)
Gall bladder	29 (29.0)
Tumor number, n (%)	
Solitary	30 (30.0)
Multiple	70 (70.0)
Largest tumor dimension (mm)	
<30	52 (52.0)
≥30	48 (48.0)
Lymph node dissection, present, n (%)	34 (34.0)
Lymph node metastasis, present, n (%)	66 (66.0)
Increased CA 19.9 level	
Absent	25 (25.0)
Present	75 (75.0)
Increased CEA level	
Absent	64 (64.0)
Present	36 (36.0)
Stage at initial diagnosis	
Stage I-III	37 (37.0)
Stage IV	63 (63.0)
Grade	
Grade 1	13 (13.0)
Grade 2	24 (24.0)
Grade 3	63 (63.0)
Primary surgery, present, n (%)	40 (40.0)
Adjuvant chemotherapy, present, n (%)	30 (30.0)
Systemic treatment in first line, n (%)	
Cisplatin – Gemcitabine	44 (50.0)
Other chemotherapy regimens	44 (50.0)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; CA 19−9, carbohydrate antigen 19−9; CEA, carcinoembryonic antigen

Survival analysis

The median follow-up time was 72.2 months (95% CI 39.3–105.0), and the median OS was 9.5 months (95% CI 5.3–13.8) for all study patients. For patients with stage 4 disease, the median progression-free survival (PFS) was 3.5 months (95% confidence interval (CI) 3.1–3.9 months). The median progression-free survival (PFS) for patients receiving gemcitabine and cisplatin as first-line therapy for metastatic disease was 5.4 months (95% confidence interval (CI) 2.9–8.1), while the median PFS for patients receiving other regimens was 3.1 months (95% CI 2.4–3.7) ($p=0.06$). At the 72-month follow-up, the survival rate was 13.4%. The respective survival rates at 10.4% for male and 15.7% for female patients (shown in Fig. 1) indicate that there is a significant difference in survival outcomes between male and female patients. The 72nd-month survival rate was 30.5% for patients diagnosed with stage I-III disease and 3.3% for those diagnosed with stage IV disease (shown in Fig. 2).

Univariable and multivariable cox proportional hazards models

Table 2 demonstrated the univariable factors associated with overall survival. The analysis demonstrated that age ($p=0.71$), ECOG performance score ($p=0.79$), tumor location ($p=0.44$), tumor number ($p=0.20$), tumor size ($p=0.62$) and systemic treatment ($p=0.23$) had no significant associations with survival outcomes. The results demonstrated that gender ($p=0.009$), the presence of lymph node dissection ($p=0.006$), the presence of lymph node metastasis ($p<0.001$), an increased Ca19-9 level at the diagnosis ($p=0.008$), an increased CEA level at the diagnosis ($p=0.002$), the stage at the initial diagnosis ($p<0.001$), the grade ($p<0.001$), and the primary surgery ($p<0.001$) were significantly associated with longer OS.

The patients were analyzed in two separate groups as male and female. There was no difference between the two groups in terms of age ($p=0.61$), tumor location ($p=0.17$), those with metastatic disease at diagnosis ($p=0.18$), those

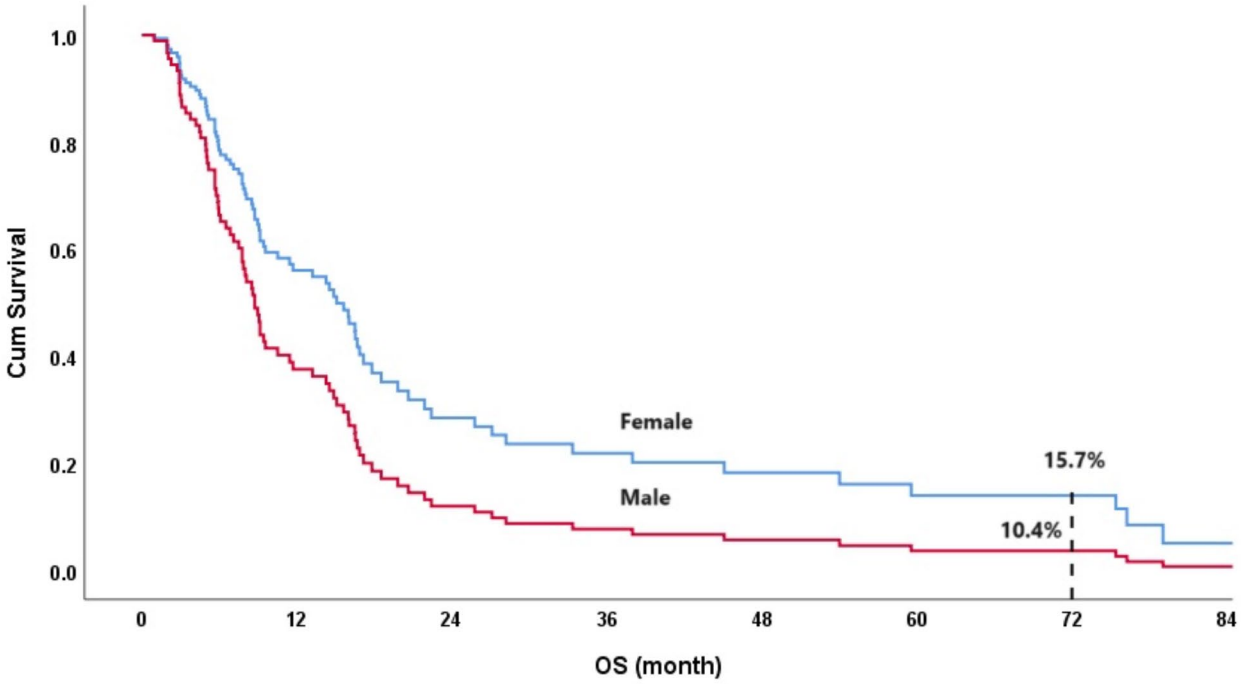

Fig. 1 Comparison of overall survival in female and male participants with BTC

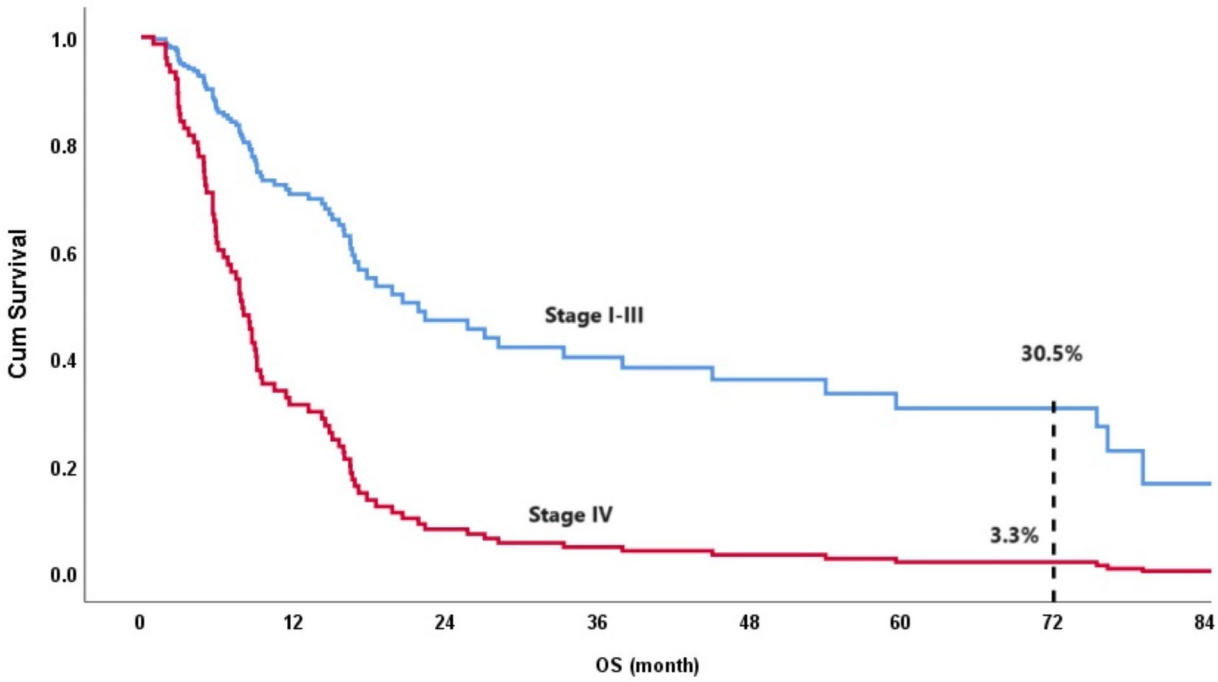

Fig. 2 The correlation between stage and OS

Table 2 Univariable analyses of prognostic factors for OS

	72-months (%)	Median OS (95%CI)	p
Age, year			
<65	12.5	9.0 (6.9–11.2)	0.71
≥65	15.4	13.2 (5.6–20.8)	
Gender			
Female	15.7	16.0 (13.8–18.1)	**0.009**
Male	10.4	7.8 (5.8–9.8)	
ECOG-performance status			
0–1	13.9	10.5 (5.4–15.5)	0.79
2 and above	0	6.0 (5.2–6.9)	
Primary tumor location			
Intrahepatic	0	10.5 (0.2–20.9)	0.44
Extrahepatic	11.1	8.7 (7.0-10.4)	
Gall bladder	17.9	15.0 (6.1–24.0)	
Tumor number			
Solitary	12.4	16.5 (13.9–19.1)	0.2
Multiple	13.5	8.7 (7.1–10.2)	
Primary tumor dimension			
<30	13.7	9.1 (5.4–12.8)	0.62
≥30	13.7	14.5 (5.9–23.1)	
Lymph node dissection			
Absent	10.3	8.5 (6.2–10.7)	**0.006**
Present	20.3	18.5 (11.9–25.1)	
Lymph node metastasis			
Absent	29.6	27.1 (8.3–45.8)	**<0.001**
Present	7.5	8.0 (6.3–9.8)	
Increased Ca19.9 level			
Absent	18.1	21.8 (0-48.9)	**0.008**
Present	10.5	8.5 (7.1–9.8)	
Increased CEA level			
Absent	17.5	15.0 (8.4–21.6)	**0.002**
Present	5.3	7.8 (4.5–11.2)	
Stage at initial diagnosis			
Stage I-III	30.5	22.4 (13.1–31.6)	**<0.001**
Stage IV	3.3	7.4 (4.7–10.1)	
Grade			
Grade 1	54.5	118.6 (NA-NA)	**<0.001**
Grade 2	13.4	19.8 (12.9–26.6)	
Grade 3	4.8	7.4 (5.2–9.7)	
Primary surgery			
Absent	6.7	7.1 (4.0-10.1)	**<0.001**
Present	24.9	21.8 (13.0-30.7)	
Systemic treatment			
Cisplatin-Gemcitabine	8.8	9.5 (7.0–12.0)	0.23
Others	7.2	7.0 (4.2–9.9)	

with recurrence during follow-up ($p=0.71$) and systemic treatment used in the first line ($p=0.58$). We also conducted a comparison between male and female patients regarding adjuvant therapy. In both groups, the most commonly used regimens were capecitabine or gemcitabine, either alone or in combination with other agents. There was no significant difference between the two groups in terms of the type of therapy received ($p=0.10$) (Table 3).

Table 3 Patient characteristics by gender

	Female	Male	p
Age, year, n (%)			
<65	30 (46.2)	35 (53.8)	0.61
≥65	18 (51.4)	17 (48.6)	
ECOG-performance status, n (%)			
0–1	43 (46.2)	50 (53.8)	0.2
≥2	5 (71.4)	2 (28.6)	
Primary tumor location, n (%)			
Gall bladder	17 (58.6)	12 (41.4)	0.17
Cholangiocellular (ICC, eCCA)	31 (43.7)	40 (56.3)	
Stage at initial diagnosis, n (%)			
Stage I-III	21 (56.7)	16 (43.3)	0.18
Stage IV	27 (42.8)	36 (57.2)	
Primary surgery, present, n (%)	21 (52.5)	19 (47.5)	0.46
Adjuvant chemotherapy, present, n (%)	18 (60.0)	12 (40.0)	0.11
Recurrence/metastasis during follow-up, n (%)	13 (52)	12 (48)	0.71
First line systemic treatment, n (%)			
Cisplatin – Gemcitabine	20 (45.5)	24 (55.5)	0.58

Table 4 Multivariate cox regression between variables and OS

	Multivariate analysis	
	HR 95% CI	*p*
Gender, *female*	0.59 (0.38–0.92)	**0.02**
Lymph node dissection, *present*	1.12 (0.35–3.53)	0.83
Lymph node metastasis, *present*	1.63 (0.83–3.23)	0.15
Increased Ca19.9 level, *present*	1.56 (0.90–2.70)	0.11
Increased CEA level, *present*	1.24 (0.75–2.06)	0.39
Stage at initial diagnosis, *stage IV*	3.34 (2.01–5.55)	**<0.001**
Grade, *grade 3*	1.56 (0.73–3.31)	0.24
Primary surgery, *present*	1.73 (0.66–4.53)	0.26

The results of the multivariate analysis demonstrated that female gender (HR 0.59, 95% CI 0.38–0.92, $p=0.02$) and stage at initial diagnosis, stage IV (HR 3.34, 95% CI 2.01–5.55, $p<0.001$), were significantly associated with longer OS (Table 4).

Discussion

Despite the availability of new treatment options, survival rates remain poor in patients diagnosed with BTC. In this study, the survival differences observed between male and female patients with biliary tract tumors are striking. Female patients demonstrated better OS compared to male patients, despite having similar disease stages and receiving comparable treatment protocols. Hormonal factors, immune system differences, and BRCA gene mutations may contribute to these distinct outcomes. This gender-related survival disparity raises critical questions about the influence of gender on BTC prognosis. Our study draws attention to this gap in

the literature and provides a basis for better understanding the impact of gender differences on treatment response and prognostic outcomes

Several studies have suggested that female gender is associated with a more favorable prognosis in BTC. For instance, a systematic review analyzing 587 cholangiocellular cancer patients from different centers found that survival was longer in women than in men (Ledenko et al. 2022). A meta-analysis summarizing seventeen prospective study publications and three retrospective study publications involving nearly 1,000 participants, response rates to gemcitabine and cisplatin-based chemotherapy were 10% higher in women than in men (Park et al. 2015). In a study of 313 matched pairs of patients with intrahepatic cholangiocarcinoma, male gender was an independent risk factor for overall survival and tumor recurrence (Zou et al. 2024). More recently, data from the United States have shown that mortality from CCA is lower among females, with a risk ratio of 0.78 (95% CI 0.77–0.79) (Yao et al. 2016). Our study also reveals the difference of better survival in female gender in patients with BTC and makes a valuable contribution to the literature.

Furthermore, our analysis revealed that 73% of patients were diagnosed in the metastatic stage, which is associated with reduced treatment efficacy. The results of our study indicate that the gender factor, which represents a significant gap in treatment research, should be taken into consideration in this patient group, which is predominantly diagnosed at an advanced stage and has a poor prognosis. The effect of sex hormones may be one of the factors responsible for the significant difference in long-term prognosis between male and female BTC patients. Previous studies have investigated the association between sex hormones and the risk of ICC in women. A recent study on menopausal hormone therapy and the risk of biliary tract cancers revealed that estrogen-only formulations were associated with a lower risk of cholangiocarcinoma (Stieger et al. 2000). Although these results are on the risk of developing CCA, they suggest that estrogen may also have a protective effect during the treatment process. Addressing the gender factor adequately may clarify the reasons for survival differences and guide personalized treatment options to improve survival outcomes in this high-risk group.

Sex-specific differences in cancer mortality are most pronounced for malignant melanoma, lung, larynx, oesophagus and bladder cancers (Cook et al. 2009, 2011). Apart from cancer causes and hormonal regulation, differences in the immune system are believed to contribute to this male biased mortality rate. Studies indicate that women exhibit a stronger immune response than men, which may contribute to a reduced cancer mortality rate (Cook, Dawsey, Freedman, Inskip, Wichner, Quraishi, Devesa and McGlynn 2009; Cook et al. 2011; Klein and Flanagan 2016; Pennell et al. 2012). These immune system differences may impact tumor progression and treatment response in BTC patients, potentially hindering treatment efficacy in males.

Another possible explanation for the higher survival rates in women with BTC may be gender differences in CYP3A4 enzyme activity, which plays a critical role in drug metabolism. The CYP3A4 enzyme is involved in the processing of various drugs and steroid hormones, and generally has higher activity in women compared to men (Su et al. 2017; Yang et al. 2012). This may positively influence women's treatment response and therefore survival rates, particularly by affecting the rate at which drugs used in some cancer treatments are metabolized. The higher activity of the CYP3A4 enzyme may lead to faster clearance of drugs in women, reducing the risk of side effects and making treatments easier to tolerate (Klein and Zanger 2013). This difference may also be reflected in the processing of hormones, as CYP3A4 may accelerate the breakdown of steroid hormones, influencing hormone-induced tumor development. These factors may potentially provide the biological basis for women responding better to bile cancer treatments than men. Addressing the gender factor more thoroughly could shed light on the mechanisms behind these survival differences and enable the development of personalized treatment options that enhance outcomes for both sexes.

It should be noted that this study is subject to several limitations. First, the relatively small number of patients included in this retrospective analysis limits the statistical power and generalizability of our findings. Second, the heterogeneity of the patient cohort, encompassing both early-stage and advanced-stage patients, may introduce variability that could affect the interpretation of gender-related survival differences. Third, the limited sample size restricted our ability to perform subgroup analyses, which could have provided more nuanced insights into the observed disparities. Fourth, the lack of data on differences in treatment care standards between patients prevents a comprehensive evaluation of how variations in clinical management might influence survival outcomes. Additionally, hormone levels and detailed pathological subtypes were not included in the analysis due to limitations in the data collected, which may restrict the scope of our interpretation. These limitations highlight the need for caution when interpreting our results and underscore the importance of further research to validate and expand upon the conclusions drawn from this study.

Conclusion

Our study findings suggest that female patients with BTC have better overall survival rates compared to male patients. The reasons behind this observed gender-related survival disparity remain unclear. Despite the well-documented biological and physiological differences between men and women, as well as extensive literature on the impact of gender on drug pharmacokinetics, pharmacodynamics, and efficacy, therapeutic approaches are rarely designed or tested with gender-specific considerations in mind. Furthermore, comprehensive biomolecular analyses are needed to investigate the roles of hormonal influences, genetic factors, and immune differences in the pathogenesis of BTC. In this patient group with gender-related survival differences, the lack of prospective studies examining the impact of gender on survival in larger, homogeneous patient populations is particularly striking. Addressing these gaps in the literature will be crucial for reaching more definitive conclusions, and future studies should aim to explore the potential for gender-specific therapies in BTC.

Author contributions Conceptualization, N.S and M.S; Data curation, N.S, E.Y., E.K. and P.E.; Formal analysis, N.S and S.I; Investigation, N.S. and E. Y.; Methodology, N.S and M.S; Project administration, N.S and M.S; Resources, Y.A, A.K.G. and R.A.; Software, N.S. and M.S; Supervision, M.S; Validation, N.S, A.Ç, N.M. and O.K; Visualization, İ.V.B. and O.K; Writing – original draft, N.S, O.K. and M.S; Writing – review & editing, N.S. O.K. and M.S. All authors have read and agreed to the published version of the manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

Cook MB, Dawsey SM, Freedman ND et al (2009) Sex disparities in cancer incidence by period and age. Cancer Epidemiol Biomarkers Prev 18:1174–1182. https://doi.org/10.1158/1055-9965.EPI-08-1118

Cook MB, McGlynn KA, Devesa SS, Freedman ND, Anderson WF (2011) Sex disparities in cancer mortality and survival. Cancer Epidemiol Biomarkers Prev 20:1629–1637. https://doi.org/10.1158/1055-9965.EPI-11-0246

Desbois M, Udyavar AR, Ryner L et al (2020) Integrated digital pathology and transcriptome analysis identifies molecular mediators of T-cell exclusion in ovarian cancer. Nat Commun 11:5583. https://doi.org/10.1038/s41467-020-19408-2

Guven DC, Erul E, Kaygusuz Y, Akagunduz B, Kilickap S, De Luca R, Rizzo A (2023) Immune checkpoint inhibitor-related hearing loss: a systematic review and analysis of individual patient data. Support Care Cancer 31:624. https://doi.org/10.1007/s00520-023-08083-w

He XD, Liu W, Tao LY, Cai L, Zhou L, Qu Q (2010) Gender-specific prognostic markers of patients with gallbladder cancer after surgical resection. Am Surg 76:1269–1274

Klein SL, Flanagan KL (2016) Sex differences in immune responses. Nat Rev Immunol 16:626–638. https://doi.org/10.1038/nri.2016.90

Klein K, Zanger UM (2013) Pharmacogenomics of cytochrome P450 3A4: recent progress toward the Missing Heritability Problem. Front Genet 4:12. https://doi.org/10.3389/fgene.2013.00012

Kur P, Kolasa-Wolosiuk A, Misiakiewicz-Has K, Wiszniewska B (2020) Sex hormone-dependent physiology and diseases of Liver. Int J Environ Res Public Health 17. https://doi.org/10.3390/ijerph17082620

Ledenko M, Antwi SO, Arima S et al (2022) Sex-related disparities in outcomes of cholangiocarcinoma patients in treatment trials. Front Oncol 12:963753. https://doi.org/10.3389/fonc.2022.963753

Park JO, Oh DY, Hsu C et al (2015) Gemcitabine Plus Cisplatin for Advanced biliary tract Cancer: a systematic review. Cancer Res Treat 47:343–361. https://doi.org/10.4143/crt.2014.308

Pennell LM, Galligan CL, Fish EN (2012) Sex affects immunity. J Autoimmun 38:J282–291. https://doi.org/10.1016/j.jaut.2011.11.013

Ricci AD, Rizzo A, Brandi G (2020) The DNA damage repair (DDR) pathway in biliary tract cancer (BTC): a new Pandora's box? ESMO Open 5:e001042. https://doi.org/10.1136/esmoopen-2020-001042

Rizzo A, Santoni M, Mollica V et al (2021) Peripheral neuropathy and headache in cancer patients treated with immunotherapy and immuno-oncology combinations: the MOUSEION-02 study. Expert Opin Drug Metab Toxicol 17:1455–1466. https://doi.org/10.1080/17425255.2021.2029405

Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, Volk ML (2015) The epidemiology of cirrhosis in the United States: a Population-based study. J Clin Gastroenterol 49:690–696. https://doi.org/10.1097/MCG.0000000000000208

Stieger B, Fattinger K, Madon J, Kullak-Ublick GA, Meier PJ (2000) Drug- and estrogen-induced cholestasis through inhibition of the hepatocellular bile salt export pump (bsep) of rat liver. Gastroenterology 118:422–430. https://doi.org/10.1016/s0016-5085(00)70224-1

Su S, Liao J, Liu J et al (2017) Blocking the recruitment of naive CD4(+) T cells reverses immunosuppression in breast cancer. Cell Res 27:461–482. https://doi.org/10.1038/cr.2017.34

Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX (2021) Biliary tract cancer. Lancet 397:428–444. https://doi.org/10.1016/S0140-6736(21)00153-7

Yang L, Li Y, Hong H et al (2012) Sex differences in the expression of drug-metabolizing and transporter genes in Human Liver. J Drug Metab Toxicol 3:1000119. https://doi.org/10.4172/2157-7609.1000119

Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA (2016) Increasing mortality in the United States from Cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. BMC Gastroenterol 16:117. https://doi.org/10.1186/s12876-016-0527-z

Zhang L, Miao R, Zhang X et al (2015) Exploring the diagnosis markers for gallbladder cancer based on clinical data. Front Med 9:350–355. https://doi.org/10.1007/s11684-015-0402-2

Zou Y, Xu X, Wu T et al (2024) Sex disparity in clinical characteristics and long-term prognosis after liver resection for patients with intrahepatic cholangiocarcinoma: a propensity score matching analysis. Heliyon 10:e29910. https://doi.org/10.1016/j.heliyon.2024.e29910