RESEARCH ARTICLE

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Survival Analysis of Metastatic Young-Onset vs. Average-Onset Cholangiocarcinoma: A Population-Based Study

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Abstract

Background: The incidence of young-onset cholangiocarcinoma (YOCC) is rising, yet the survival outcomes and metastatic patterns of metastatic YOCC (mYOCC) compared to metastatic average-onset cholangiocarcinoma (mAOCC) remain unclear. This study evaluates differences in survival outcomes, metastatic patterns, and associated prognostic factors between mYOCC and mAOCC. **Methods:** A retrospective cohort study was conducted using the SEER database (2018–2021), including patients aged ≥18 years with metastatic cholangiocarcinoma (mCC). Patients were stratified into mYOCC (<50 years) and mAOCC (≥50 years). Clinical characteristics, metastatic sites, and treatment modalities were analyzed. Kaplan-Meier and Cox proportional hazards models were used to assess overall survival (OS) and cancer-specific survival (CSS). **Results:** Of 1,601 patients with mCC, 9.99% had mYOCC. mYOCC patients were younger (median age 44 vs. 66 years, p<0.001) and more frequently presented with bone (27.50% vs. 19.36%, p=0.015) and lung metastases (36.25% vs. 27.48%, p=0.021). They also had a higher prevalence of multiple-site metastases, including bone-liver-lung combinations (7.50% vs. 3.33%, p=0.008). Median survival was 12 months for mYOCC versus 9 months for mAOCC. mYOCC patients had a lower risk of mortality (aHR=0.74, 95% CI: 0.60–0.93, p=0.01). Treatment modalities, including chemotherapy and surgery, significantly improved survival, regardless of age at diagnosis. **Conclusion:** mYOCC demonstrates distinct metastatic patterns, including higher frequencies of bone and lung metastases, and is associated with better survival outcomes compared to mAOCC. These findings highlight the need for age-specific diagnostic and therapeutic approaches to improve outcomes for mYOCC patients. Further research is needed to understand the biological mechanisms underlying these differences and address disparities in survival outcomes.

Keywords: young-onset cholangiocarcinoma- metastatic cholangiocarcinoma- survival analysis- SEER database

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Introduction

The global incidence of young-onset gastrointestinal cancers, including young-onset cholangiocarcinoma (YOCC), is steadily increasing, with trends observed across various populations [1, 2]. In the United States, the annual incidence of cholangiocarcinoma (CC) has shown an upward trajectory, rising by approximately 0.16% to 4.36% from 2003 to 2012 [3]. This rise in incidence among younger individuals is particularly concerning, given that the precise factors driving this trend remain largely undefined [4].

Several established risk factors have been linked to both intrahepatic and extrahepatic cholangiocarcinoma, including primary sclerosing cholangitis, Caroli's disease, obesity, diabetes, non-alcoholic fatty liver disease, hepatitis B or C infection, and liver fluke infections [4, 5]. Despite the increasing awareness of these risk factors, their role in young-onset cholangiocarcinoma is not well understood, leaving a significant gap in the knowledge regarding its clinical features, progression, and treatment outcomes.

While young-onset cancers often demonstrate distinct biological behavior compared to their average-onset counterparts, the specific clinical characteristics and outcomes of metastatic YOCC remain underexplored [6]. Interestingly, previous studies have shown improved overall survival in younger patients with other gastrointestinal cancers, such as metastatic colorectal cancer [7]. Conversely, data on young-onset biliary tract cancers have been mixed, with some studies reporting no survival advantage compared to older patients receiving similar treatments [8], while others suggest a more favorable prognosis for YOCC [9].

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There remains a critical need to better understand how metastatic YOCC (mYOCC) compares to metastatic average-onset cholangiocarcinoma (mAOCC) in terms of overall survival, cancer-specific survival, and predictive factors influencing these outcomes. This study aims to compare metastatic YOCC and AOCC to understand differences in survival outcomes and the prognostic factors influencing them.

Materials and Methods

Study Design and Participants

We conducted a retrospective cohort analysis using de-identified data from the Surveillance, Epidemiology, and End Results (SEER) database. This study received an exemption from Institutional Review Board (IRB) oversight, as it utilized a nationally available database and did not require Ethics approval. The cohort comprised patients aged 18 years and older diagnosed with metastatic cholangiocarcinoma between 2018 and 2021. We excluded cases diagnosed prior to 2018 due to the unavailability of the "Derived Extent of Disease" variable before this year, which is essential for confirming stage IV status and specific metastatic sites. Inclusion criteria required patients to be coded with the ICD-O-3 topography code 8160/3 for cholangiocarcinoma, with histological confirmation of the diagnosis. We stratified the cohort into two groups: young-onset cholangiocarcinoma (YOCC), defined as patients diagnosed before the age of 50, and average-onset cholangiocarcinoma (AOCC), defined as patients diagnosed at or after 50 years of age. Additional inclusion criteria included having this cancer as the first and only malignancy, complete data on metastatic sites, and a known cause of death.

Variables

The study categorized race and ethnicity into five distinct groups: Non-Hispanic White (NHW), Hispanic (H), Non-Hispanic Black (NHB), Non-Hispanic Asian (NHA), and Non-Hispanic American Indian (NHAI). Additionally, we examined various sociodemographic factors, including biological sex, average annual household income, marital status, and residence in either rural or urban settings. In terms of clinical characteristics, we classified tumor locations into intrahepatic and extrahepatic cholangiocarcinoma. We also evaluated the presence of metastases in multiple sites, including the bone, brain, lung, liver, and distant lymph nodes. Furthermore, the study analyzed treatment modalities received by the patients, such as chemotherapy, surgery, and radiation therapy and lastly, surgery-chemotherapy sequence.

Statistical Analysis

The database was obtained using the SEERStat v8.4.2 interface and subsequently exported to STATA v18.0 for statistical analysis. Categorical variables were summarized as frequencies and percentages, while continuous variables were described using either mean and standard deviation or median and interquartile range (IQR), depending on the distribution. Comparisons between categorical variables were performed using the chi-squared test, while the U Mann-Whitney test was used for continuous variables after checking for normality. Survival analyses for both overall survival and cancer-specific survival were conducted using the Kaplan-Meier method, with differences between groups assessed by the log-rank test. To explore associations between exposure variables, all-cause mortality and cancer-specific survival, multivariate analysis was performed using Cox proportional hazards regression models, reporting adjusted hazard ratios (HR) as both with 95% confidence intervals (CI). Crude hazard ratios (HR) were not reported, as Table 4 presents the adjusted HR for both overall survival (OS) and cancer-specific survival (CSS). The multivariate model was refined through backward selection, including variables with a p-value of <0.05. Multicollinearity was evaluated using variance inflation factors (VIF), with a cutoff point of less than 5 indicating acceptable levels. Statistical significance was set at a p-value of <0.05.

Results

A total of 1,601 patients diagnosed with metastatic cholangiocarcinoma were included in this study. Among them, 9.99% were classified as having metastatic young-onset cholangiocarcinoma (mYOCC), while 90.01% were categorized as metastatic average-onset cholangiocarcinoma (mAOCC). In the mYOCC subgroup, most patients were male (51.25%), non-Hispanic White (55.62%), lived in urban areas (90%), and were married (61.88%). The tumors in this group were predominantly intrahepatic (91.88%), with a median survival of 12 months. Similarly, in the mAOCC group, most patients were male (51.63%), non-Hispanic White (61.76%), lived in urban areas (91.26%), and were married (62.60%). However, the median survival for this group was slightly lower, at 9 months. The median age at diagnosis was significantly younger in the mYOCC group at 44 years compared to 66 years in the mAOCC group ($p<0.001$). Further details about patient demographics, clinical characteristics, and patterns of metastasis are provided in Table 1.

In terms of metastatic patterns, patients with mYOCC exhibited a significantly higher frequency of bone metastases (27.50%) compared to those with mAOCC (19.36%, $p = 0.015$) and a greater prevalence of lung metastases (36.25% vs. 27.48%, $p = 0.021$). Additionally, mYOCC patients showed significantly higher rates of metastases involving multiple sites, including combinations like bone and liver (15% vs. 8.47%, $p = 0.006$), bone and lung (14.37% vs. 6.52%, $p < 0.001$), and liver and lung (20% vs. 13.60%, $p = 0.028$). Notably, specific patterns involving three metastatic sites, such as bone, liver, and lung (7.50% vs. 3.33%, $p = 0.008$), and liver, lung, and distant lymph nodes (DLN) (10% vs. 5.27%, $p = 0.015$), were also more frequent in the mYOCC group. These findings underscore the distinct metastatic patterns in mYOCC, with a higher occurrence of both single and multiple-site metastases, particularly in combinations involving bone, liver, and lung metastases, as detailed in Table 2. There were no statistically significant

Table 1. Demographic Data of Patients with YO-CC and AO-CC

Variable	Young-Onset CC (n=160)	Average-Onset CC (n=1,441)	p value
Age	44 (39-47)	66 (55-73)	<0.001
Sex			0.927
Male	82 (51.25%)	744 (51.63%)	
Female	78 (48.75%)	697 (48.37%)	
Race			0.12
Non-Hispanic White	89 (55.62%)	890 (61.76%)	
Hispanic	33 (20.62%)	216 (14.99%)	
Non-Hispanic Black	20 (12.50%)	129 (8.95%)	
Non-Hispanic Asian/PI	18 (11.25%)	198 (13.74%)	
Non-Hispanic American Indian	0 (0%)	8 (0.56%)	
Urban/Rural			0.596
Rural	16 (10%)	126 (8.74%)	
Urban	144 (90%)	1315 (91.26%)	
Income			0.067
<40,000	3 (1.88%)	10 (0.69%)	
40,000-79,999	59 (36.88%)	471 (31.69%)	
80,00-99,999	65 (40.62%)	542 (37.61%)	
≥100,000	33 (20.62%)	418 (29.01%)	
Marital Status			<0.001*
Single	53 (33.12%)	228 (15.82%)	
Married	99 (61.88%)	902 (62.60%)	
Divorced	6 (3.75%)	168 (11.66%)	
Widowed	2 (1.25%)	143 (9.92%)	
Bone Metastases			0.015*
Present	44 (27.50%)	279 (19.36%)	
Not present	116 (72.50%)	1162 (80.64%)	
Brain Metastases			
Present	1 (0.62%)	13 (0.90%)	0.721
Not present	159 (99.38%)	1428 (99.10%)	
Liver Metastases			0.448
Present	86 (53.75%)	729 (50.59%)	
Not present	74 (46.25%)	712 (49.41%)	
Lung Metastases			
Present	58 (36.25%)	396 (27.48%)	0.020*
Not present	102 (63.75%)	1045 (72.52%)	
Distant LN			0.183
Present	61 (38.12%)	474 (32.89%)	
Not present	99 (61.88%)	967 (67.11%)	
Chemotherapy			0.155
Received	152 (95%)	1323 (91.81%)	
Not received	8 (5%)	118 (8.19%)	
Surgery			0.671
Received	9 (5.62%)	70 (4.86%)	
Not received	151 (94.38%)	1371 (95.15%)	
Radiation			0.278
Received	32 (21.25%)	256 (17.77%)	
Not received	126 (78.75%)	34 (21.25%)	
Vital status			0.021*
Alive	61 (38.12%)	422 (29.29%)	
Dead	99 (61.88%)	1019 (70.71%)	
Location			<0.001
Intrahepatic	147 (91.88%)	1299 (90.15%)	
Extrahepatic	13 (8.12%)	142 (9.85%)	
Median survival months (IQR)	12 (18)	9 (13)	

*Chi square test performed with statistically significant results

differences between the groups in the prevalence of brain or distant lymph node metastases alone.

An analysis of factors associated with mYOCC is detailed in Table 3. Biological sex did not exhibit a significant association with mYOCC (aOR = 1.21, 95% CI: 0.86-1.71, p = 0.259). Marital status, however, showed a significant correlation; married individuals had a lower odds of being diagnosed with mYOCC (aOR = 0.51, 95% CI: 0.35-0.75, p < 0.001), similar to divorced (aOR = 0.15, 95% CI: 0.06-0.37, p < 0.001) and widowed individuals (aOR = 0.06, 95% CI: 0.015-0.28, p < 0.001). Residency in urban areas was not significantly associated with mYOCC (aOR = 0.77, 95% CI: 0.43-1.38, p = 0.394). Regarding metastatic sites, liver, lung, and brain metastases did not show significant associations. However, bone metastases were significantly associated with mYOCC (aOR = 1.56, 95% CI: 1.00-2.41, p = 0.047). Treatment modalities including chemotherapy, radiation, and surgery were not significantly associated with mYOCC, with respective aORs of 1.80 (95% CI: 0.83-3.92, p = 0.135), 1.10 (95% CI: 0.68-1.77, p = 0.695), and 1.38 (95% CI: 0.65-2.94, p = 0.397). Other factors such as the time from diagnosis to treatment initiation and presence of extrahepatic cholangiocarcinoma also did not show significant associations.

The analysis of mortality-related factors among patients with metastatic cholangiocarcinoma (mCC) is outlined in Table 4. Patients with metastatic young-onset cholangiocarcinoma (mYOCC) exhibited a decreased risk of mortality compared to those with metastatic average-onset cholangiocarcinoma (mAOCC), with an aHR of 0.74 (CI: 0.60-0.93, p=0.01). In contrast, Non-Hispanic Asians faced an increased mortality risk when compared to Non-Hispanic Whites (aHR of 1.25 CI: 1.05-1.50, p=0.012).

The presence of lung and bone metastases was associated with an increased risk of mortality (aHR 1.16 CI: 1.02-1.33, p=0.02 and aHR 1.39 CI: 1.18-1.64, p<0.001). Treatment modalities such as chemotherapy, radiation therapy, and surgery significantly reduced mortality risk (aHR 0.50 CI: 0.39-0.64, p<0.001), (aHR 0.62 CI: 0.51-0.74, p<0.001), and (aHR 0.47 CI: 0.30-0.73, p<0.001), respectively. Furthermore, systemic therapy administered both before and after surgery demonstrated the lowest mortality risk compared to other treatment sequences (aHR 0.37 CI: 0.16-0.86, p=0.022). The Kaplan-Meier curve analyzing overall survival between

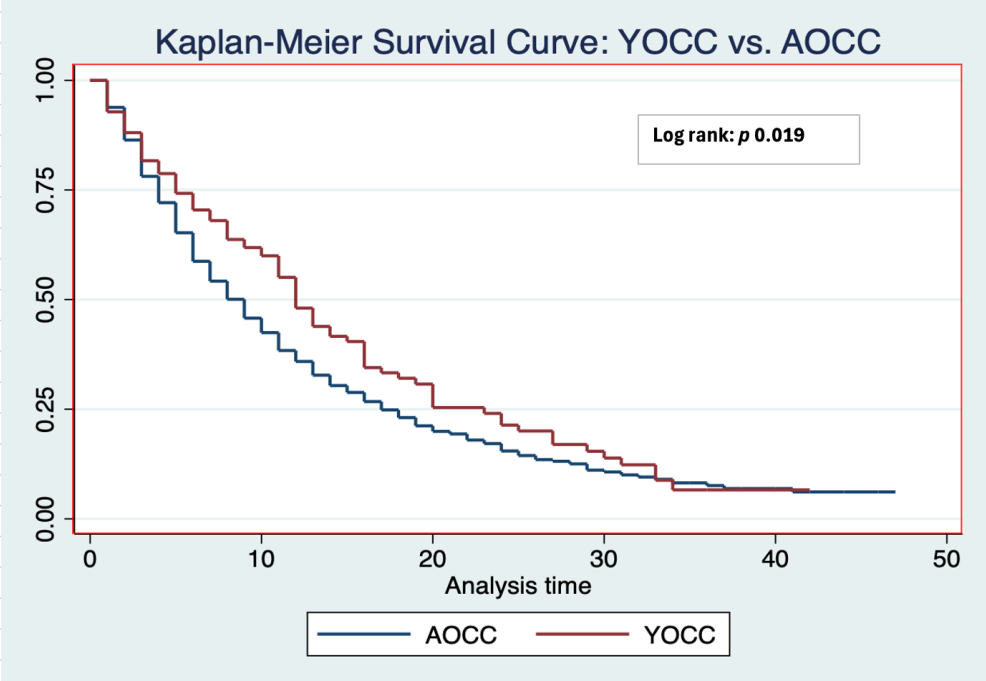

Figure 1: Kaplan-Meier Survival Curve Comparing Metastatic Young-Onset and Average-Onset Cholangiocarcinoma (mYOCC vs. mAOCC)

mYOCC and mAOCC is depicted in Figure 1. The log-rank test assessing differences in overall survival between the two groups yielded a statistically significant p-value of 0.019, indicating distinct survival outcomes for these subgroups.

Discussion

In our study, we found no significant differences in the prevalence of mYOCC by sex or race when compared to mAOCC. This contrasts with trends observed in other cancers, such as colorectal cancer, where incidence, survival, and mortality rates vary significantly by both race and sex [10, 11]. Interestingly, this lack of disparity in mYOCC aligns with findings from the CITY study by Pappas et al., which also reported no major demographic differences across these groups [12]. However, Kumar et al. highlighted a notable rise in cholangiocarcinoma incidence among Hispanic individuals, increasing from 1.5 to 2.8 cases per 100,000 annually between 2005 and 2017 [13]. These contrasting findings exhibit the need for further investigation into potential racial and ethnic disparities in cholangiocarcinoma, particularly to understand whether such differences are influenced by underlying genetic, environmental, or healthcare access factors.

Our study revealed that patients with mYOCC were more likely to present with bone and lung metastases compared to their mAOCC counterparts. This finding is consistent with observations by Reddy et al., who reported a higher prevalence of stage IV disease among younger cholangiocarcinoma patients [14]. Similar trends have been noted in other cancers, including young-onset gastric, colorectal, and breast cancers, where younger patients often exhibit more aggressive disease and distinct metastatic patterns [15-18]. These parallels suggest that young-onset cancers, including mYOCC, may exhibit unique biological behaviors that differentiate them from their average-onset counterparts, warranting further investigation into the underlying mechanisms driving these differences.

Regarding metastatic patterns, patients with mYOCC demonstrated a higher prevalence of bone and lung metastases compared to those with mAOCC. These sites, along with the peritoneum, are commonly reported locations for metastatic spread in CCA [19]. Previous studies have shown that metastatic spread patterns are influenced by multiple factors, including the primary tumor's location (intrahepatic vs. extrahepatic), histopathological characteristics, and the degree of cancer cell differentiation [19, 20]. Notably, our study found a significant association between bone metastases and mYOCC. This finding aligns with prior research linking bone metastases to a more aggressive cholangiocarcinoma phenotype and higher mortality rates [21]. Given the poor prognosis associated with bone metastases, these results emphasize the need for closer monitoring and tailored therapeutic strategies for patients presenting with this metastatic pattern.

Our study found that patients with metastatic mYOCC had a reduced risk of mortality compared to those with mAOCC, aligning with global trends showing better survival outcomes in younger patients. This survival advantage may reflect the generally better baseline health and higher treatment tolerance in younger individuals. Conversely, long-term survival tends to decline with age, particularly among patients diagnosed after the age of 55 [22, 23]. However, the presence of lung and bone metastases was significantly associated with increased mortality, consistent with previous findings linking these metastatic sites to poorer outcomes. Bone metastases have

Table 2. Frequencies of Metastatic Pattern

Metastatic Pattern	YOCC	AOCC	p-value †
One site			
Only bone	44 (27.50%)	279 (19.36%)	0.015
Only brain	1 (0.62%)	13 (0.90%)	0.721
Only liver	86 (53.75%)	729 (50.59%)	0.448
Only lung	58 (36.25%)	396 (27.48%)	0.021
Only DLN	61 (38.12%)	474 (32.89%)	0.183
Two sites			
Bone and brain	1 (0.62%)	3 (0.21%)	0.316
Bone and liver	24 (15%)	122 (8.47%)	0.006
Bone and lung	23 (14.37%)	94 (6.52%)	<0.001
Bone and DLN	19 (11.88%)	91 (6.32%)	0.008
Brain and liver	0 (0%)	6 (0.42%)	0.414
Brain and lung	0 (0%)	6 (0.42%)	0.414
Brain and DLN	1 (0.62%)	5 (0.35%)	0.585
Liver and lung	32 (20%)	196 (13.60%)	0.028
Liver and DLN	30 (18.75%)	203 (14.09%)	0.113
Lung and DLN	25 (15.62%)	141 (9.78%)	0.022
Three sites			
Bone and brain and liver	0 (0%)	1 (0.07%)	0.739
Bone and brain and lung	0 (0%)	3 (0.21%)	0.563
Bone and brain and DLN	1 (0.62%)	1 (0.07%)	0.059
Bone and liver and lung	12 (7.50%)	48 (3.33%)	0.008
Bone and liver and DLN	13 (8.12%)	48 (3.33%)	0.003
Bone and lung and DLN	11 (6.88%)	44 (3.05%)	0.012
Brain and liver and lung	0 (0%)	3 (0.21%)	0.563
Brain and liver and DLN	0 (0%)	5 (0.35%)	0.456
Brain and lung and DLN	0 (0%)	3 (0.21%)	0.563
Liver and lung and DLN	16 (10%)	76 (5.27%)	0.015
Four sites			
Bone and brain and liver and lung	0 (0%)	1 (0.07%)	0.739
Bone and brain and liver and DLN	0 (0%)	1 (0.07%)	0.739
Bone and brain and lung and DLN	0 (0%)	1 (0.07%)	0.739
Bone and liver and lung and DLN	7 (4.38%)	25 (1.73%)	0.024
Brain and liver and lung and DLN	0 (0%)	3 (0.21%)	0.563
Five sites			
Bone and brain and liver and lung and DLN	0 (0%)	1 (0.07%)	0.739

†, Chi-squared test

been associated with more aggressive disease and worse prognoses in cholangiocarcinoma [19, 20]. Our findings also highlight disparities in mortality risk by race. Non-Hispanic Asians demonstrated a higher mortality risk compared to Non-Hispanic Whites, reflecting previously reported trends of increased cholangiocarcinoma-related mortality in this population [23]. This disparity underscores the need for further research to explore potential contributing factors, such as differences in tumor biology, access to care, or treatment efficacy across racial and ethnic groups.

Several limitations should be considered in interpreting the findings of this study. Firstly, the retrospective design utilizing data from the SEER database inherently carries the risk of information bias and missing data. Despite efforts to utilize de-identified data, the study's reliance on existing medical records could introduce inaccuracies or omissions in clinical details or treatment modalities. Additionally, although efforts were made to stratify by age and include relevant clinical variables, residual confounding due to unmeasured or unaccounted factors remains a possibility. Furthermore, the exclusion of cases diagnosed before 2018 due to data limitations may have impacted the generalizability of findings to earlier cohorts. Lastly, the absence of detailed information on patient comorbidities, performance status, and specific treatment

Table 3. Factors Associated with Young-Onset Metastatic Cholangiocarcinoma

	OR (95% CI)	p value	aOR (95% CI)	p value
Sex				
Male	Ref.			
Female	1.01 (0.73-1.40)	0.927	1.21 (0.86-1.71)	0.259
Race				
Non-Hispanic White	Ref.			
Hispanic	1.52 (0.99-2.33)	0.051	1.39 (0.89-2.17)	0.142
Non-Hispanic Black	1.55 (0.92-2.60)	0.098	1.38 (0.80-2.39)	0.239
Non-Hispanic Asian	0.90 (0.53-1.54)	0.724	0.87 (0.51-1.51)	0.642
NHAI	-	-	-	-
Marital status				
Single	Ref.			
Married	0.47 (0.32-0.67)	<0.001	0.51 (0.35-0.75)	0.001
Divorced	0.15 (0.06-0.36)	<0.001	0.15 (0.06-0.37)	0.001
Widowed	0.06 (0.014-0.25)	<0.001	0.06 (0.015-0.26)	0.001
Rural/Urban				
Metropolitan	Ref.			
Urban	0.86 (0.49-1.49)	0.596	0.78 (0.44-1.39)	0.417
Location				
Intrahepatic CC	Ref.			
Extrahepatic CC	0.80 (0.44-1.46)	0.484	0.86 (0.47-1.60)	0.65
Liver metastases				
Not present	Ref.			
Present	1.13 (0.81-1.57)	0.448	1.14 (0.82-1.61)	0.418
Lung metastases				
Not present	Ref.			
Present	1.50 (1.06-2.11)	0.02	1.35 (0.94-1.93)	0.094
Brain metastases				
Not present	Ref.			
Present	0.69 (0.089-5.31)	0.722	0.49 (0.06-4.06)	0.511
Bone metastases				
Not present	Ref.			
Present	1.57 (1.09-2.28)	0.016	1.57 (1.06-2.31)	0.02
Distant lymph nodes				
Not present	Ref.			
Present	1.25 (0.89-1.76)	0.184	1.18 (0.84-1.68)	0.329

OR, odds ratio; 95% CI, 95% confidence intervals. Adjusted for sex, race, marital status, rural/urban, location, and metastatic sites

regimens limits the comprehensive understanding of treatment outcomes and survival differences observed among different demographic and clinical subgroups. These limitations underscore the need for cautious interpretation and further prospective studies to validate our findings in broader clinical settings. Furthermore, it is important to mention that Durvalumab was FDA-approved in 2022 for biliary tract cancer, therefore, not widely available in the time of our study.

In conclusion, our study highlights that metastatic young-onset cholangiocarcinoma (mYOCC) presents with distinct clinical and metastatic characteristics compared to its average-onset counterpart (mAOCC). The lack of significant differences in the incidence of mYOCC based on race and sex contrasts with other cancers and suggests a unique disease profile that warrants further investigation. The higher propensity for bone and lung metastases among mYOCC patients and the association of these metastases with increased mortality emphasize the need for age-specific diagnostic and treatment strategies.

Author Contribution Statement

Antoine Jeri-Yabar: Conceptualization, methodology, software, validation, formal analysis, writing, supervision. Liliana Vittini-Hernandez: Investigation, resources, data curation, writing. Brenda Salazar-Linares: Visualization, supervision, writing, conceptualization, methodology.

Table 4. Comparative Analysis of Factors Influencing Overall Survival and Cancer-Specific Survival in Metastatic Cholangiocarcinoma

Variable	aHR (95% CI) for OS	p value	aHR for CSS	p value
Age				
AOCC				
YOCC	0.74 (0.60-0.93)	0.01	0.78 (0.63-0.98)	0.034
Sex				
Male				
Female	0.89 (0.78-1.01)	0.072	0.91 (0.80-1.03)	0.157
Race				
Non-Hispanic White	Ref.			
Hispanic	1.00 (0.83-1.20)	0.99	1.03 (0.85-1.24)	0.741
Non-Hispanic Black	1.00 (0.81-1.23)	0.964	1.03 (0.83-1.28)	0.779
Non-Hispanic Asian	1.25 (1.05-1.50)	0.012	1.31 (0.83-1.28)	0.003
Non-Hispanic American Indian	1.71 (0.84-3.46)	0.133	1.93 (0.96-3.91)	0.065
Marital Status				
Single	Ref.			
Married	0.90 (0.76-1.07)	0.271	0.89 (0.74-1.06)	0.213
Divorced	1.09 (0.86-1.39)	0.429	1.06 (0.83-1.35)	0.616
Widowed	1.06 (0.81-1.38)	0.635	0.94 (0.71-1.25)	0.704
Rural/Urban				
Rural	Ref.			
Urban	1.02 (0.81-1.27)	0.844	1.09 (0.86-1.38)	0.472
Liver metastases	1.05 (0.92-1.19)	0.438	1.05 (0.93-1.20)	0.396
Lung Metastases	1.16 (1.02-1.33)	0.024	1.16 (1.01-1-33)	0.032
Brain Metastases	1.35 (0.73-2.50)	0.335	1.42 (0.76-2.61)	0.261
Bone Metastases	1.39 (1.18-1.64)	<0.001	1.39 (1.17-1.64)	<0.001
Distant LN	1.01 (0.89-1.16)	0.79	1-02 (0.89-1.17)	0.713
Chemotherapy received	0.50 (0.39-0.64)	<0.001	0.51 (0.40-0.66)	<0.001
Radiation Therapy received	0.62 (0.51-0.74)	<0.001	0.60 (0.49-0.72)	<0.001
Surgery received	0.47 (0.30-0.73)	0.001	0.51 (0.33-0.79)	0.003
Year of Diagnosis	0.92 (0.81-1.05)	0.254	0.91 (0.79-1.04)	0.173
Time from diagnosis to treatment	0.99 (0.99-0.99)	<0.001	0.99 (0.99-0.996)	<0.001
Site				
Intrahepatic				
Extrahepatic	0.89 (0.70-1.12)	0.35	0.76 (0.59-0.97)	0.032
Systemic Therapy-Surgery Sequence				
No systemic therapy or surgery				
Systemic therapy before surgery	0.45 (0.22-0.90)	0.025	0.38 (0.18-0.83)	0.015
Systemic therapy after surgery	0.64 (0.49-0.84)	0.001	0.83 (0.47-0.83)	0.001
Systemic therapy both before and after surgery	0.37 (0.16-0.86)	0.022	0.41 (0.18-0.95)	0.039
Surgery both before and after systemic therapy	3.04 (0.4-22.9)	0.279	2.39 (0.32-17.9)	0.394

*Income not included due to collinearity, VIF >10

Sebastian Prado-Nuñez: Conceptualization, methodology, software, validation, formal analysis, writing, resources

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Scientific Approval

This study has not been published elsewhere. It is not part of a student thesis.

Ethical Approval

This study did not need ethical approval due to being based off a public data-base.

Availability of Data

The data supporting this study are available in the SEER database.

Conflict of Interest

The authors declare that they have no conflicts of

interest.

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