pISSN: 2508-5778 • eISSN: 2508-5859
Ann Hepatobiliary Pancreat Surg 2024;28:144-154
https://doi.org/10.14701/ahbps.23-136

AHBPS
Annals of Hepato-Biliary-Pancreatic Surgery

Original Article

Associations between income and survival in cholangiocarcinoma: A comprehensive subtype-based analysis

Calvin X. Geng[1], Anuragh R. Gudur[1], Jagannath Kadiyala[1], Daniel S. Strand[2], Vanessa M. Shami[2], Andrew Y. Wang[2], Alexander Podboy[2], Tri M. Le[3], Matthew Reilley[3], Victor Zaydfudim[4], Ross C. D. Buerlein[2]

[1]Department of Medicine, University of Virginia, Charlottesville, VA, USA,
[2]Division of Gastroenterology and Hepatology, Department of Medicine, University of Virginia, Charlottesville, VA, USA,
[3]Division of Hematology and Oncology, Department of Medicine, University of Virginia, Charlottesville, VA, USA,
[4]Division of Surgical Oncology, Department of Surgery, University of Virginia, Charlottesville, VA, USA

Backgrounds/Aims: Socioeconomic determinants of health are incompletely characterized in cholangiocarcinoma (CCA). We assessed how socioeconomic status influences initial treatment decisions and survival outcomes in patients with CCA, additionally performing multiple sub-analyses based on anatomic location of the primary tumor.

Methods: Observational study using the 2018 submission of the Surveillance, Epidemiology, and End Results (SEER)-18 Database. In total, 5,476 patients from 2004–2015 with a CCA were separated based on median household income (MHI) into low income (< 25th percentile of MHI) and high income (> 25th percentile of MHI) groups. Seventy-three percent of patients had complete follow up data, and were included in survival analyses. Survival and treatment outcomes were calculated using R-studio.

Results: When all cases of CCA were included, the high-income group was more likely than the low-income to receive surgery, chemotherapy, and local tumor destruction modalities. Initial treatment modality based on income differed significantly between tumor locations. Patients of lower income had higher overall and cancer-specific mortality at 2 and 5 years. Non-cancer mortality was similar between the groups. Survival differences identified in the overall cohort were maintained in the intrahepatic CCA subgroup. No differences between income groups were noted in cancer-specific or overall mortality for perihilar tumors, with variable differences in the distal cohort.

Conclusions: Lower income was associated with higher rates of cancer-specific mortality and lower rates of surgical resection in CCA. There were significant differences in treatment selection and outcomes between intrahepatic, perihilar, and distal tumors. Population-based strategies aimed at identifying possible etiologies for these disparities are paramount to improving patient outcomes.

Key Words: Social determinants of health; Cholangiocarcinoma

INTRODUCTION

Cholangiocarcinoma (CCA) is the most common biliary tract malignancy and the second most common primary hepatic malignancy, with a steadily increasing incidence and mortality rate over the past forty years [1,2].

The classification of CCA has changed dramatically over the past decade. The current schema of CCA is subdivided into three separate classes based on location relative to the liver, with intrahepatic CCA (iCCA), perihilar CCA (pCCA), and distal CCA (dCCA) groups all noting different clinical risk factors, epidemiologic patterns, and distinct genetic profiles

Received: October 31, 2023, **Revised:** January 9, 2024,
Accepted: January 14, 2024, **Published online:** February 15, 2024

Corresponding author: Calvin X. Geng, MD
Department of Medicine, University of Virginia, 1215 Lee Street, Charlottesville 22903, VA, USA
Tel: +1-512-633-0810, Fax: +1-434-297-9469, E-mail: muh7zj@virginia.edu
ORCID: https://orcid.org/0000-0001-7583-9191

[3]. While treatment is primarily centered on tumor staging and anatomy, with emphasis on surgery as the only potentially curative treatment [4], most patients present with inoperable, advanced-stage disease, explaining a poor overall median survival of only 24 months [3]. While targeted systemic therapies are improving outcomes for some patients with non-surgical disease, the majority of these patients have limited treatment options [5]. However, advances in both interventional endoscopy and radiology have greatly expanded the possible therapeutic avenues for treating nonresectable CCA. Access to these therapies needs to be standardized, and not center-specific. At present, there are significant treatment variations based on institutional resources and provider expertise [6]. Socioeconomic status (SES) disparities in cancer-related care have been reported to influence access to advanced treatment interventions for gastrointestinal malignancies, including CCA [7-9]. However, these previous analyses have not included the more recently adopted anatomic classification schema for CCA.

Our aim was to investigate the impact of SES on outcomes and access to treatments for anatomically differentiated iCCA, pCCA, and dCCA.

MATERIALS AND METHODS

Patients diagnosed with primary CCA from 2004–2015 via the November 2018 submission of the Surveillance, Epidemiology, and End Results (SEER) Program provided by the National Cancer Institute (NCI) were included, after application to, and approval by, the University of Virginia Institutional Review Board (IRB protocol no. 17949). Given the retrospective study design using SEER, informed consent was waived. The SEER Program is a contract-supported program of the NCI, which collects population-based cancer statistics from U.S. cancer registries (http://www.seer.cancer.gov). The SEER–18 report, released in November 2018, includes 18 cancer registries that cover approximately 30% of the U.S. population.

International Classification of Diseases for Oncology 3rd Edition (ICD-O-3 code 8160) and SEER clinical schema (CS) codes were used to identify cases of CCA. The TNM 7/CS v0204+ Schema codes were provided in SEER, and were used to distinguish intrahepatic, perihilar, and distal subtypes. Gallbladder tumors were a separate tumor category provided in SEER, and were not included. Static county attributes (SCAs) are validated measures designed to assess the socio-economic characteristics of patients in the SEER database [10], and reflect the average socioeconomic attributes of the county of the patient's home address. They are calculated every 5 years, and made available in SEER. In the 2018 submission of SEER, SCAs are linked to survival data at the individual patient level, allowing for inclusion of these socioeconomic factors in survival analysis. County level data for median household income (MHI), % of persons currently smoking in the county, % of persons making < 150% of the poverty line in the county, % of persons with a bachelor's degree level of education in the county, unemployment rate in the county, and % of persons ever having an endoscopy performed were extracted. MHI was defined as the 2010–2014 SCA estimate for the MHI of the patient's county of residence. Low- and high-income groups were defined based on a patient's MHI being less (low income), or greater (high income), than the 25th percentile of the average MHI for the entire study cohort. Other demographic data, including age at diagnosis, sex, race, tumor size, tumor grade (well, moderately, poorly, anaplastic, unknown), radiation therapy (yes, no/unknown), chemotherapy (yes, no), and year of diagnosis, were also collected.

The intervention modality was determined using SEER treatment codes. Surgery was defined as "Hepatectomy (includes transplant)," "lobectomy," "wedge or segmental resection," and "surgery, not otherwise specified." Local tumor destruction was defined as "photodynamic therapy (PDT)," "transarterial chemoembolization (TACE)," and "radiofrequency ablation (RFA)."

Overall survival, cancer-specific mortality, and non-cancer related mortality at 2 and 5 years were calculated. Overall survival was defined as the proportion of patients alive at 24 and 60 months among all patients (alive or dead). Cancer-specific mortality was defined as the proportion of patients who died from their malignancy. Non-cancer-related mortality was defined as the proportion of patients who died from some cause other than their malignancy.

Statistical analysis

Figure creation and statistical analyses were performed using R studio (R version 3.6.1). Comparisons between groups were conducted via Student's t-test and Mann–Whitney U Test for parametric and non-parametric variables, respectively. For parametric continuous variables, all statistical tests were two-sided, and p-values ≤ 0.05 were considered statistically significant. Stratified survival distributions were assessed using the Kaplan–Meier method, and clinical significance between survival curves was determined via the log-rank (Mantel–Cox) test. Cox proportional hazards method was performed to determine hazard ratios (HRs) for variables associated with cancer-specific mortality. Using an alpha level < 0.1, a non-automated forward selection method was used to determine the independent variables included in the multivariate analysis; variables with known clinical associations with the outcome were also included. Appropriateness of fit was determined using model concordance values. The SCAs, including smoking, education rates, and unemployment, were provided as percentages in SEER. Multivariate HRs were labeled "adjusted," while univariate regression HRs were labeled "crude."

RESULTS

Demographic analysis

A total of 5,476 cases of primary CCA for the period 2004–2015 were included in the demographic analysis (Table 1). Patients were classified into 2 income groups based on their county of residence's MHI percentile. There were 1,372 patients in the lower income group (at or below the 25th percentile of MHI, $23,820–$52,360), and 4,104 patients in the higher income group (greater than the 25th percentile of MHI, $52,361–$101,930).

There was no difference in age at the time of diagnosis be-

Table 1. Demographics, tumor characteristics, and treatment by income group

	Overall	Low income	High income	*p*-value
Number	5,476	1,372	4,104	
Age at diagnosis (yr)	69.88 ± 12.07	70.15 ± 12.07	69.79 ± 12.07	0.341
Male sex	2,864 (52.3)	691 (50.4)	2,173 (52.9)	0.104
Year of diagnosis				0.001
2004–2007	1,482 (27.1)	411 (30.0)	1,071 (26.1)	
2008–2011	1,776 (32.4)	462 (33.7)	1,314 (32.0)	
2012–2015	2,218 (40.5)	499 (36.4)	1,719 (41.9)	
Race				< 0.001
American Indian/Alaska Native	79 (1.4)	62 (4.5)	17 (0.4)	
Asian or Pacific Islander	900 (16.4)	70 (5.1)	830 (20.2)	
Black	374 (6.8)	147 (10.7)	227 (5.5)	
Unknown	12 (0.2)	0 (0)	12 (0.3)	
White	4,111 (75.1)	1,093 (79.7)	3,018 (73.5)	
Tumor location				0.108
Distal	641 (11.7)	172 (12.5)	469 (11.4)	
Intrahepatic	2,867 (52.4)	685 (49.9)	2,182 (53.2)	
Perihilar	1,968 (35.9)	515 (37.5)	1,453 (35.4)	
Tumor grade[a]				0.137
Well differentiated (Grade 1)	220 (11.7)	45 (11.3)	175 (11.8)	
Moderately differentiated (Grade 2)	846 (45.0)	193 (48.5)	653 (44.1)	
Poorly differentiated (Grade 3)	774 (41.2)	148 (37.2)	626 (42.3)	
Undifferentiated/anaplastic (Grade 4)	39 (2.1)	12 (3.0)	27 (1.8)	
Tumor stage[b]				0.219
Stage 1	1,061 (24.7)	265 (26.8)	796 (24.1)	
Stage 2	781 (18.2)	163 (16.5)	618 (18.7)	
Stage 3	772 (18.0)	179 (18.1)	593 (17.9)	
Stage 4	1,682 (39.2)	382 (38.6)	1,300 (39.3)	
Tumor size (mm)	52.94 ± 50.47	53.15 ± 65.86	52.88 ± 45.02	0.91
Treatment				< 0.001
Surgery	1,085 (19.8)	244 (17.8)	841 (20.5)	
No surgery	4,168 (76.1)	1,055 (76.9)	3,113 (75.9)	
Local tumor destruction	67 (1.2)	9 (0.7)	58 (1.4)	
Treatment unknown	156 (2.8)	64 (4.7)	92 (2.2)	
No radiation or unknown radiation therapy	4,637 (84.7)	1,156 (84.3)	3,481 (84.8)	0.647
Received chemotherapy	2,136 (39.0)	468 (34.1)	1,668 (40.6)	< 0.001
% Bachelor's degree	34.44 ± 11.02	22.22 ± 5.99	38.53 ± 9.14	< 0.001
% Unemployed	8.10 ± 2.80	10.02 ± 4.29	7.45 ± 1.64	< 0.001
Median household income (ten thousands)	6,491.17 ± 1,591.54	4,368.47 ± 535.43	7,200.29 ± 1,129.19	< 0.001
% Current smoking	18.22 ± 5.05	23.05 ±2.72	16.61 ± 4.60	< 0.001

Values are presented as number only, mean ± standard deviation, or number (%).
[a]Only patients with complete tumor grade information were included (n = 1,879).
[b]Only patients with complete tumor stage information were included (n = 4,296).

Table 2. Demographics, tumor characteristics, and treatment by income group

	Intrahepatic tumor				Perihilar tumor				Distal tumor			
	Overall	Low income	High income	*p*-value	Overall	Low income	High income	*p*-value	Overall	Low income	High income	*p*-value
Number	2,867	685	2,182		1,968	515	1,453		641	172	469	
Age (yr)	68.33 ± 12.14	68.87 ± 12.10	68.17 ± 12.16	0.186	71.47 ± 11.90	71.33 ± 12.12	71.52 ± 11.82	0.749	71.90 ± 11.33	71.70 ± 11.28	71.97 ± 11.36	0.794
Male sex	1,466 (51.1)	335 (48.9)	1,131 (51.8)	0.196	1,047 (53.2)	264 (51.3)	783 (53.9)	0.33	351 (54.8)	92 (53.5)	259 (55.2)	0.763
Year of diagnosis				0.005				0.006				0.206
2004–2007	664 (23.2)	183 (26.7)	481 (22.0)		812 (41.3)	228 (44.3)	584 (40.2)		6 (0.9)	0 (0)	6 (1.3)	
2008–2011	931 (32.5)	232 (33.9)	699 (32.0)		638 (32.4)	179 (34.8)	459 (31.6)		207 (32.3)	51 (29.7)	156 (33.3)	
2012–2015	1,272 (44.4)	270 (39.4)	1,002 (45.9)		518 (26.3)	108 (21.0)	410 (28.2)		428 (66.8)	121 (70.3)	307 (65.5)	
Race				< 0.001				< 0.001				< 0.001
American Indian/Alaska Native	40 (1.4)	33 (4.8)	7 (0.3)		22 (1.1)	17 (3.3)	5 (0.3)		17 (2.7)	12 (7.0)	5 (1.1)	
Asian or Pacific Islander	482 (16.8)	37 (5.4)	445 (20.4)		321 (16.3)	23 (4.5)	298 (20.5)		97 (15.1)	10 (5.8)	87 (18.6)	
Black	191 (6.7)	65 (9.5)	126 (5.8)		150 (7.6)	67 (13.0)	83 (5.7)		33 (5.1)	15 (8.7)	18 (3.8)	
Unknown	7 (0.2)	0 (0)	7 (0.3)		2 (0.1)	0 (0)	2 (0.1)		3 (0.5)	0 (0)	3 (0.6)	
White	2,147 (74.9)	550 (80.3)	1,597 (73.2)		1,473 (74.8)	408 (79.2)	1,065 (73.3)		491 (76.6)	135 (78.5)	356 (75.9)	
Tumor grade[a]				0.253				0.062				0.163
Well differentiated (Grade 1)	98 (9.8)	12 (6.2)	86 (10.7)		89 (14.5)	21 (14.9)	68 (14.3)		33 (12.3)	12 (19.0)	21 (10.2)	
Moderately differentiated (Grade 2)	455 (45.7)	92 (47.4)	363 (45.3)		272 (44.2)	71 (50.4)	201 (42.4)		119 (44.4)	30 (47.6)	89 (43.4)	
Poorly differentiated (Grade 3)	424 (42.6)	85 (43.8)	339 (42.3)		239 (38.9)	43 (30.5)	196 (41.4)		111 (41.4)	20 (31.7)	91 (44.4)	
Undifferentiated/anaplastic (Grade 4)	19 (1.9)	5 (2.6)	14 (1.7)		15 (2.4)	6 (4.3)	9 (1.9)		5 (1.9)	1 (1.6)	4 (2.0)	
Tumor stage[b]				0.602				0.373				0.446
Stage 1	511 (23.1)	117 (24.6)	394 (22.7)		397 (25.8)	103 (27.4)	294 (25.3)		153 (28.1)	45 (32.6)	108 (26.5)	
Stage 2	181 (8.2)	33 (6.9)	148 (8.5)		431 (28.0)	92 (24.5)	339 (29.1)		169 (31.0)	38 (27.5)	131 (32.2)	
Stage 3	540 (24.4)	118 (24.8)	422 (24.3)		160 (10.4)	41 (10.9)	119 (10.2)		72 (13.2)	20 (14.5)	52 (12.8)	
Stage 4	980 (44.3)	207 (43.6)	773 (44.5)		551 (35.8)	140 (37.2)	411 (35.3)		151 (27.7)	35 (25.4)	116 (28.5)	
Tumor size (mm)	67.35 ± 49.60	69.14 ± 69.61	66.89 ± 42.95	0.465	33.48 ± 39.31	38.85 ± 66.28	31.64 ± 23.82	0.028	29.59 ± 53.02	25.52 ± 17.03	30.99 ± 60.61	0.4
Treatment				< 0.001				0.209				0.202
Surgery	442 (15.4)	87 (12.7)	355 (16.3)		423 (21.5)	100 (19.4)	323 (22.2)		220 (34.3)	57 (33.1)	163 (34.8)	
No surgery	2,244 (78.3)	541 (79.0)	1,703 (78.0)		1,505 (76.5)	400 (77.7)	1,105 (76.0)		419 (65.4)	114 (66.3)	305 (65.0)	
Local tumor destruction	60 (2.1)	7 (1.0)	53 (2.4)		7 (0.4)	2 (0.4)	5 (0.3)		0 (0)	0 (0)	0 (0)	
Treatment unknown	121 (4.2)	50 (7.3)	71 (3.3)		33 (1.7)	13 (2.5)	20 (1.4)		2 (0.3)	1 (0.6)	1 (0.2)	
No radiation or unknown radiation therapy	2,508 (87.5)	598 (87.3)	1,910 (87.5)	0.923	1,619 (82.3)	421 (81.7)	1,198 (82.5)	0.771	510 (79.6)	137 (79.7)	373 (79.5)	> 0.999
Received chemotherapy	1,203 (42.0)	251 (36.6)	952 (43.6)	0.001	678 (34.5)	160 (31.1)	518 (35.7)	0.068	255 (39.8)	57 (33.1)	198 (42.2)	0.047
% Bachelor's degree	34.62 ± 10.93	22.31 ± 6.40	38.48 ± 9.04	< 0.001	34.56 ± 11.35	22.08 ± 5.70	38.99 ± 9.38	< 0.001	33.30 ± 10.30	22.27 (5.08)	37.35 (8.64)	< 0.001
% Unemployed	7.90 ± 2.71	9.57 ± 4.29	7.37 ± 1.66	< 0.001	8.24 ± 2.87	10.31 ± 4.32	7.51 ± 1.59	< 0.001	8.53 ± 2.89	10.96 (3.98)	7.64 (1.65)	< 0.001
Median household income (ten thousands)	6,540.60 ± 1,566.63	4,393.97 ± 555.74	7,213.51 ± 1,108.68	< 0.001	6,475.92 ± 1,622.87	4,359.74 ± 503.71	7,225.98 ± 1,151.82	< 0.001	6,316.97 ± 1,594.17	4,293.19 ± 540.46	7,059.17 ± 1,145.15	< 0.001
% Current smoking	18.09 ± 4.99	23.10 ± 2.81	16.51 ± 4.47	< 0.001	18.18 ± 5.15	23.08 ± 2.61	16.44 ± 4.69	< 0.001	18.96 ± 4.93	22.77 (2.70)	17.56 (4.82)	< 0.001

Values are presented as number only, mean ± standard deviation, or number (%).
[a]Only patients with complete tumor grade information were included (n = 996).
[b]Only patients with complete tumor stage information were included (n = 2,212).

Table 3. Survival based on income for all tumors

	Overall	Low income	High income	*p*-value
Number	3,996	998	2,998	
Overall mortality	3,559 (89.1)	919 (92.1)	2,640 (88.1)	0.001
2-year mortality	3,201 (80.1)	846 (84.8)	2,355 (78.6)	< 0.001
5-year mortality	3,501 (87.6)	908 (91.0)	2,593 (86.5)	< 0.001
Overall cancer-specific mortality	3,275 (82.0)	844 (84.6)	2,431 (81.1)	0.015
2-year cancer-specific mortality	2,971 (74.3)	783 (78.5)	2,188 (73.0)	0.001
5-year cancer-specific mortality	3,239 (81.1)	839 (84.1)	2,400 (80.1)	0.006
Overall non-cancer mortality	284 (7.1)	75 (7.5)	209 (7.0)	0.612
2-year non-cancer mortality	230 (5.8)	63 (6.3)	167 (5.6)	0.427
5-year non-cancer mortality	262 (6.6)	69 (6.9)	193 (6.4)	0.651

Values are presented as number only or number (%).

tween income groups (mean 69.9 years for both). Overall, 52.3% of the patients were male. The higher income bracket had a significantly higher percentage of Asian/Pacific Islander patients (20.2% vs. 5.1%), and a smaller percentage of Black patients (5.5% vs. 10.7%), compared to the lower income bracket ($p < 0.001$). The diagnosis of CCA increased over time, with 40.5% of the total cases diagnosed for the period 2012–2015, in contrast to 27.1% of the total cases diagnosed for the period 2004–2007. The majority of tumors were intrahepatic (52.4%), followed by perihilar (35.9%), and distal (11.7%). The most common clinical stage at diagnosis was stage 4, with 39.2% of tumors diagnosed at this stage. Importantly, there were no differences between income groups with respect to tumor location, clinical stage, histologic grade, and tumor size at diagnosis.

When all cases of CCA were included together, the high-income group was more likely to receive chemotherapy ($p < 0.001$) and local tumor destruction modalities, including PDT, TACE, and RFA ($p < 0.001$), as compared to the lower income bracket (Table 1). The high-income group was also more likely to receive surgery, compared to the low-income group (20.5% vs. 17.8%, $p < 0.001$). Subanalysis based on CCA location demonstrated the high-income group underwent chemotherapy (43.6% vs. 36.6%, $p = 0.001$), surgery (16.3% vs. 12.7%, $p < 0.001$), and local tumor destruction (2.4% vs. 1.0%, $p < 0.001$) more in the iCCA subgroup (Table 2). Absolute rates of local tumor destruction modalities in the management of iCCA were low (< 2.4% of all cases managed with these interventions). These findings were not noted in pCCA or dCCA (Table 2). High-income patients with dCCA patients (34.3%) underwent surgery more frequently than patients with iCCA (15.4%) or pCCA (21.5%), $p < 0.001$ (Supplementary Table 1).

Survival analysis

A total of 3,996 patients (73.0%) had complete follow-up data of 155 months, and were included in the survival analysis. Table 3 displays the survival outcomes based on income group for all tumors. Patients in the lower income group had higher overall mortality at 2 years (84.8% vs. 78.6%, $p < 0.001$), 5 years (91.0% vs. 86.5%, $p < 0.001$), and at the end of the follow-up period (92.1% vs. 88.1%, $p = 0.001$), compared to the high-income group. Similarly, the lower income group had higher cancer-specific mortality at 2 years (78.5% vs. 73.0%, $p = 0.001$), 5 years (84.1% vs. 80.1%, $p = 0.006$), and at the end of the follow-up period (84.6% vs. 81.1%, $p = 0.015$), compared to the high-income group. Non-cancer mortality was similar between the groups. Fig. 1 shows the Kaplan–Meier survival distribution for overall mortality based on income group (log-rank test $p < 0.001$).

Multivariable regression using the Cox proportional hazard model was performed for overall mortality (Table 4), and showed excellent concordance of 0.76. Variables independently associated with overall mortality on univariate analysis included age, year of diagnosis, tumor size, clinical stage, tumor grade (as determined by histology), receipt of surgery, receipt

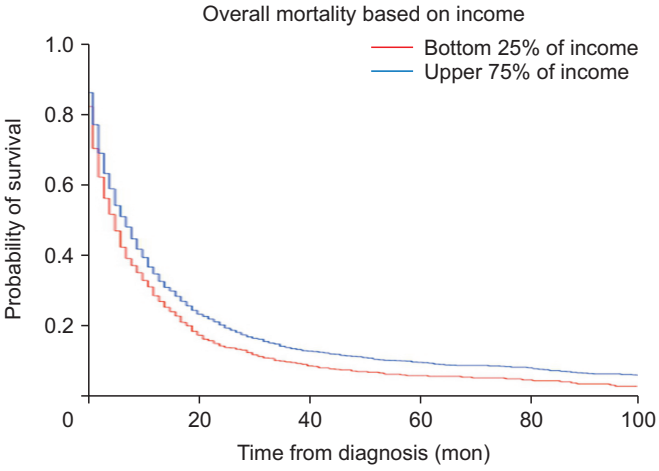

Fig. 1. Kaplan–Meier model of overall mortality based on income for all tumors. *p*-value (log-rank) = $3e^{-7}$.

Table 4. Cox proportional-hazards model for overall mortality

Variable	Univariate analysis		Multivariate analysis	
	Crude hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Sex				
Female	Reference			
Male	0.97 (0.92–1.05)	0.52		
Race				
White	Reference		Reference	
Black or African American	1.13 (0.99–1.29)	0.06	1.25 (0.94–1.66)	0.12
Asian/American Indian/other	0.98 (0.89–1.06)	0.51	1.16 (0.96–1.40)	0.12
Age at diagnosis (every 1 year increase)	1.023 (1.02–1.03)	< 0.001	1.02 (1.01–1.03)	< 0.001
Year of diagnosis				
2004–2007	Reference		Reference	
2008–2011	0.97 (0.90–1.06)	0.55	0.94 (0.77–1.14)	0.37
2012–2015	0.91 (0.84–0.99)	< 0.05	0.88 (0.72–1.07)	0.13
Tumor size (every 1 mm increase)	1.003 (1.002–1.003)	< 0.001	1.003 (1.0008–1.005)	0.008
Tumor location				
Intrahepatic	Reference		Reference	
Perihilar	0.99 (0.93–1.07)	0.98	1.15 (0.95–1.40)	0.94
Distal	0.84 (0.75–0.93)	< 0.002	1.01 (0.79–1.29)	0.09
Clinical stage				
Stage 1	Reference		Reference	
Stage 2	1.05 (0.93–1.18)	0.43	1.31 (1.30–2.03)	< 0.001
Stage 3	1.31 (1.16–1.47)	< 0.001	2.67 (2.11–3.38)	< 0.001
Stage 4	2.60 (2.35–2.87)	< 0.001	5.81 (4.55–7.42)	< 0.001
Grade				
Well differentiated (Grade 1)	Reference		Reference	
Moderately differentiated (Grade 2)	1.13 (0.93–1.38)	0.21	0.98 (0.77–1.26)	0.92
Poorly differentiated (Grade 3)	1.70 (1.39–2.07)	< 0.01	1.41 (1.10–1.81)	0.007
Undifferentiated/anaplastic (Grade 4)	2.18 (1.42–3.32)	< 0.01	1.21 (0.66–2.20)	0.54
Surgery				
No surgery	Reference		Reference	
Received surgery	0.29 (0.26–0.31)	< 0.001	0.36 (0.30–0.43)	< 0.001
Chemotherapy				
No/unknown	Reference		Reference	
Yes	0.60 (0.56–0.64)	< 0.001	0.53 (0.45–0.64)	< 0.001
Radiation				
No/unknown	Reference		Reference	
Yes	0.62 (0.56–0.67)	< 0.001	1.06 (0.92–1.35)	0.29
MHI percentile				
Bottom 25th	Reference		Reference	
Upper 75th	0.82 (0.76–0.89)	< 0.001	0.74 (0.62–0.89)	< 0.002

CI, confidence interval; MHI, median household income.

of chemotherapy and radiation, and income group. Receiving surgery had a HR of 0.36 (95% confidence interval [CI], 0.30–0.43; $p < 0.001$) for overall mortality, compared to not receiving surgery, in the multivariable model. High income had a HR of 0.74 (95% CI, 0.62–0.89; $p < 0.002$) for overall mortality, compared to low income in multivariable (adjusted) regression.

Subgroup survival analyses based on tumor location are provided in Table 5 (iCCA, pCCA, and dCCA). Survival differences identified in the overall cohort were maintained in the iCCA subgroup, specifically with the high-income group having reduced overall mortality and reduced cancer-specific mortality, compared to the lower income group, without differences in non-cancer mortality. While higher income patients with dCCA noted improved overall mortality at 2 years ($p = 0.009$),

Table 5. Survival based on income for intrahepatic, perihilar, and distal tumors

	Intrahepatic				Perihilar				Distal			
	Overall	Low income	High income	*p*-value	Overall	Low income	High income	*p*-value	Overall	Low income	High income	*p*-value
Number	2,082	486	1,596		1,424	371	1,053		490	141	349	
Overall mortality	1,844 (88.6)	448 (92.2)	1,396 (87.5)	0.005	1,311 (92.1)	348 (93.8)	963 (91.5)	0.185	404 (82.4)	123 (87.2)	281 (80.5)	0.101
2-year mortality	1,674 (80.4)	421 (86.6)	1,253 (78.5)	< 0.001	1,162 (81.6)	308 (83.0)	854 (81.1)	0.458	365 (74.5)	117 (83.0)	248 (71.1)	0.009
5-year mortality	1,823 (87.6)	446 (91.8)	1,377 (86.3)	0.002	1,276 (89.6)	339 (91.4)	937 (89.0)	0.231	402 (82.0)	123 (87.2)	279 (79.9)	0.076
Overall cancer-specific mortality	1,737 (83.4)	427 (87.9)	1,310 (82.1)	0.003	1,190 (83.6)	315 (84.9)	875 (83.1)	0.467	348 (71.0)	102 (72.3)	246 (70.5)	0.765
2-year cancer-specific mortality	1,580 (75.9)	400 (82.3)	1,180 (73.9)	< 0.001	1,077 (75.6)	286 (77.1)	791 (75.1)	0.49	314 (64.1)	97 (68.8)	217 (62.2)	0.201
5-year cancer-specific mortality	1,717 (82.5)	425 (87.4)	1,292 (81.0)	0.001	1,176 (82.6)	312 (84.1)	864 (82.1)	0.416	346 (70.6)	102 (72.3)	244 (69.9)	0.671
Overall non-cancer mortality	107 (5.1)	21 (4.3)	86 (5.4)	0.415	121 (8.5)	33 (8.9)	88 (8.4)	0.833	56 (11.4)	21 (14.9)	35 (10.0)	0.169
2-year non-cancer mortality	94 (4.5)	21 (4.3)	73 (4.6)	0.912	85 (6.0)	22 (5.9)	63 (6.0)	> 0.999	51 (10.4)	20 (14.2)	31 (8.9)	0.115
5-year non-cancer mortality	106 (5.1)	21 (4.3)	85 (5.3)	0.445	100 (7.0)	27 (7.3)	73 (6.9)	0.916	56 (11.4)	21 (14.9)	35 (10.0)	0.169

Values are presented as number only or number (%).

no differences in cancer-specific mortality at 2 and 5 years were noted. No differences between income groups were noted in cancer-specific or overall mortality for pCCA.

Table 6 reports the subgroup survival analyses based on clinical stage and income level. In the overall cohort, higher income patients with stage I–III disease had reduced overall mortality and reduced cancer-specific mortality, but no difference in non-cancer related mortality, compared to lower income patients. There was no survival difference based on income in patients with stage IV disease. When only including patients with iCCA, survival differences based on income were again maintained in patients with stage I–III disease, but not for stage IV disease. Mortality (both cancer-specific and non-cancer specific) did not differ significantly in the pCCA and dCCA subgroups for stages I–III or stage IV disease.

DISCUSSION

Demographic and clinical risk factors for CCA are well-documented, and continue to be updated in the literature. In contrast, the effects of socioeconomic factors, including income, on survival have not been comprehensively investigated. In this population-level study, we report multiple disparities in outcomes and treatments based on income and the anatomic location of the primary tumor. Lower household income patients experienced higher overall and cancer-specific mortality, but no differences in non-cancer mortality. When assessing by tumor location, higher income patients with iCCA were also noted to have higher rates of surgery, higher rates of endobiliary ablation, and higher total rates of chemotherapy, compared to similar tumor stage patients of low income.

The reasons underlying the association between lower income and poorer survival in CCA are multifactorial. It has been previously reported for other cancers that access to screening, stage of disease at diagnosis, and even treatment options are influenced by demographic factors, such as race and ethnicity, which ultimately contribute to differences in survival [8,11-13]. For cases of iCCA in particular, education level, insurance status, and marital status have been noted as independent predictors of overall survival [9]. However, prior studies have failed to control for the effects of tumor histology, tumor size, or treatment modality on survival. Here, using a multivariable regression including these influential factors, we demonstrate that lower income level is independently associated with significantly increased cancer-specific mortality in iCCA.

These survival benefits may be partially explained as patients of higher income were more likely than those of lower income to receive chemotherapy or local therapies, such as RFA and PDT, as part of their initial treatment. RFA and PDT for CCA are not widely available, and are often only performed in large tertiary referral centers. The differences in rates identified in higher income patients may indicate that these patients either

Table 6. Treatment and survival outcomes based on income group for selected subgroups

	Overall	Low income	High income	*p*-value
Clinical stage I-III only (all subtypes)				
Number	1,937	459	1,478	
2-year overall mortality	1,332 (68.8)	350 (76.3)	982 (66.4)	< 0.001
5-year overall mortality	1,549 (80.0)	395 (86.1)	1,154 (78.1)	< 0.001
2-year cancer specific mortality	1,224 (63.2)	323 (70.4)	901 (61.0)	< 0.001
5-year cancer specific mortality	1,419 (73.3)	364 (79.3)	1,055 (71.4)	0.001
2-year non-cancer mortality	108 (5.6)	27 (5.9)	81 (5.5)	0.833
5-year non-cancer mortality	130 (6.7)	31 (6.8)	99 (6.7)	> 0.999
Clinical stage IV only (all subtypes)				
Number	1,309	295	1,014	
2-year overall mortality	1,213 (92.7)	278 (94.2)	935 (92.2)	0.294
5-year overall mortality	1,263 (96.5)	288 (97.6)	975 (96.2)	0.303
2-year cancer specific mortality	1,153 (88.1)	261 (88.5)	892 (88.0)	0.893
5-year cancer specific mortality	1,201 (91.7)	271 (91.9)	930 (91.7)	> 0.999
2-year non-cancer mortality	60 (4.6)	17 (5.8)	43 (4.2)	0.346
5-year non-cancer mortality	62 (4.7)	17 (5.8)	45 (4.4)	0.431
Intrahepatic clinical stage I-III only				
Number	905	198	707	
2-year overall mortality	598 (66.1)	151 (76.3)	447 (63.2)	0.001
5-year overall mortality	699 (77.2)	168 (84.8)	531 (75.1)	0.005
2-year cancer specific mortality	552 (61.0)	144 (72.7)	408 (57.7)	< 0.001
5-year cancer specific mortality	645 (71.3)	161 (81.3)	484 (68.5)	0.001
2-year non-cancer mortality	46 (5.1)	7 (3.5)	39 (5.5)	0.348
5-year non-cancer mortality	54 (6.0)	7 (3.5)	47 (6.6)	0.143
Intrahepatic clinical stage IV only				
Number	770	163	607	
2-year overall mortality	709 (92.1)	153 (93.9)	556 (91.6)	0.431
5-year overall mortality	743 (96.5)	160 (98.2)	583 (96.0)	0.288
2-year cancer specific mortality	682 (88.6)	145 (89.0)	537 (88.5)	0.972
5-year cancer specific mortality	715 (92.9)	152 (93.3)	563 (92.8)	0.961
2-year non-cancer mortality	27 (3.5)	8 (4.9)	19 (3.1)	0.392
5-year non-cancer mortality	28 (3.6)	8 (4.9)	20 (3.3)	0.459
Perihilar clinical stage I-III only				
Number	733	180	553	
2-year overall mortality	540 (73.7)	139 (77.2)	401 (72.5)	0.251
5-year overall mortality	627 (85.5)	161 (89.4)	466 (84.3)	0.111
2-year cancer specific mortality	504 (68.8)	128 (71.1)	376 (68.0)	0.489
5-year cancer specific mortality	581 (79.3)	147 (81.7)	434 (78.5)	0.418
2-year non-cancer mortality	36 (4.9)	11 (6.1)	25 (4.5)	0.51
5-year non-cancer mortality	46 (6.3)	14 (7.8)	32 (5.8)	0.435
Perihilar clinical stage IV only				
Number	421	103	318	
2-year overall mortality	397 (94.3)	96 (93.2)	301 (94.7)	0.759
5-year overall mortality	408 (96.9)	99 (96.1)	309 (97.2)	0.834
2-year cancer specific mortality	378 (89.8)	91 (88.3)	287 (90.3)	0.714
5-year cancer specific mortality	389 (92.4)	94 (91.3)	295 (92.8)	0.774
2-year non-cancer mortality	19 (4.5)	5 (4.9)	14 (4.4)	> 0.999
5-year non-cancer mortality	19 (4.5)	5 (4.9)	14 (4.4)	> 0.999

Table 6. Continued

	Overall	Low income	High income	*p*-value
Distal clinical stage I-III only				
Number	299	81	218	
2-year overall mortality	194 (64.9)	60 (74.1)	134 (61.5)	0.058
5-year overall mortality	223 (74.6)	66 (81.5)	157 (72.0)	0.128
2-year cancer specific mortality	168 (56.2)	51 (63.0)	117 (53.7)	0.191
5-year cancer specific mortality	193 (64.5)	56 (69.1)	137 (62.8)	0.382
2-year non-cancer mortality	26 (8.7)	9 (11.1)	17 (7.8)	0.501
5-year non-cancer mortality	30 (10.0)	10 (12.3)	20 (9.2)	0.552
Distal clinical stage IV only				
Number	118	29	89	
2-year overall mortality	107 (90.7)	29 (100)	78 (87.6)	0.105
5-year overall mortality	112 (94.9)	29 (100)	83 (93.3)	0.343
2-year cancer specific mortality	93 (78.8)	25 (86.2)	68 (76.4)	0.39
5-year cancer specific mortality	97 (82.2)	25 (86.2)	72 (80.9)	0.712
2-year non-cancer mortality	14 (11.9)	4 (13.8)	10 (11.2)	0.969
5-year non-cancer mortality	15 (12.7)	4 (13.8)	11 (12.4)	> 0.999

Values are presented as number (%).

have access to, or knowledge of and the ability to travel to, these specialized centers. More affluent patients may also have more consistent transportation or the ability to travel longer distances to seek care, which have previously been reported as barriers to care in colorectal cancer in a Veteran's population [14]. Lee et al. [15] reported that Black patients and patients enrolled in Medicaid or without insurance were less likely to receive surgery as initial therapy for CCA, despite having tumors of similar stage. Given that there were no differences in income and survival in patients with stage 4 disease, special emphasis should be placed on improving access to care in patients with stage 1–3 disease.

The reasons for why iCCA was associated with such significant variations in treatment, and why these differences were not noted in pCCA and dCCA, are unknown. Intuitively, it is reasonable to assert that lower income and its associated socioeconomic correlates should negatively affect all CCA patients, not just iCCA. It is possible that interventions for pCCA or dCCA are more widely available, whereas iCCA is more influenced by access to more novel therapies.

The survival differences based on income seen in iCCA, but not in pCCA or dCCA, could be explained in part by disease misclassification, which is a known challenge in CCA that has previously been reported [16-18], such as the inability to identify or the inadvertent classification of mixed or combined hepatocellular carcinoma and intrahepatic carcinoma into intrahepatic ductal tumors alone. However, these tumors are rare, and more recent American Joint Committee on Cancer (AJCC) pathology reports code specifically for this overlap. Moreover, the most frequently cited coding error is misattribution of pCCA, the most common type of CCA, as iCCA [19]. However, if a large population of pCCA was misclassified to iCCA, survival differences identified between iCCA and pCCA would not be expected, which supports the validity of our results. The effects of metastatic disease to the liver misclassified as iCCA should be marginal, as SEER provides separate diagnostic codes for non-hepatic primary tumors that have metastasized to the liver.

Several limitations to our work must be acknowledged. As with all retrospective database research, the results reported here are subject to possible selection bias and misclassification or misattribution bias. However, the NCI's SEER database represents the most authoritative and largest cancer registry in North America, with excellent validation in real world cohorts. Patient comorbidities are not variables included in SEER–18, so the impact of this was unable to be assessed. It is possible that the lower income group had more comorbidities, which could contribute to worse survival. However, severe comorbidities that influence cancer-specific mortality would be expected to influence non-cancer specific mortality concurrently, which was not seen in our analysis. It is possible that there is a survival bias, in that patients with higher comorbidities more commonly died from their cancer, and additional investigations into the influence of comorbidities on outcomes is warranted. It is also important to note that even though there are statistically significant differences in survival, the absolute mortality rates are still very high (approximating 90%), regardless of income level. The impact of newer immune checkpoint inhibitor therapies on survival was also unable to be assessed with this population study. Specifics of chemotherapy (palliative vs. adjuvant, number of cycles, regimen selection) were not available. Similarly, different modalities of endobiliary therapy were not

able to be differentiated, such as the use of transcatheter arterial chemoinfusion vs. drug-eluding bead transcatheter arterial chemoembolization vs. intra-arterial brachytherapy using yttrium–90. Although we report here on mortality, morbidity is affected by income as well, and future studies investigating quality of life based on socioeconomic determinants of health are warranted. Finally, the SEER–18 data does not provide data on rurality, which is likely related to both income level and access to treatment, and is an important avenue for future research. Whether income is associated with resectability at presentation, or if lower income patients are more often offered palliative intent therapies, are important questions for future studies.

In conclusion, we demonstrate in patients with CCA (especially iCCA) that when compared to similar patients in the higher income group, lower income level is associated with reduced overall and cancer-specific survival, as well as reduced rates of receiving chemotherapy and endobiliary ablation. Population-based strategies focused on improving access to screening and subsequent treatment, while also identifying other possible causes of these disparities, are pivotal to improving patient outcomes. Ultimately, income represents one, among many, social factors that exist in conjunction with tumor specific factors that affect a patient's treatment and survival outcomes. Our results add to the growing literature on risk factors and outcomes in this rare, but lethal, malignancy.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.14701/ahbps.23-136.

FUNDING

None.

CONFLICT OF INTEREST

Dr. Shami is a consultant for Olympus Medical and Cook Medical. No co-authors have conflicts of interest that pertain to this work.

ORCID

Calvin X. Geng, https://orcid.org/0000-0001-7583-9191
Anuragh R. Gudur, https://orcid.org/0000-0002-1348-9816
Jagannath Kadiyala, https://orcid.org/0009-0001-7583-6107
Daniel S. Strand, https://orcid.org/0000-0001-5573-6291
Vanessa M. Shami, https://orcid.org/0000-0001-7528-5141
Andrew Y. Wang, https://orcid.org/0000-0002-6519-7882
Alexander Podboy, https://orcid.org/0000-0001-9353-4965
Tri M. Le, https://orcid.org/0009-0001-8498-6414
Matthew Reilley, https://orcid.org/0000-0002-4725-0459
Victor Zaydfudim, https://orcid.org/0000-0003-4572-7038
Ross C. D. Buerlein, https://orcid.org/0000-0002-1033-9783

AUTHOR CONTRIBUTIONS

Conceptualization: CXG, AP, RCDB. Data curation: CXG, AP. Methodology: CXG, AP, RCDB. Writing - original draft: CXG, AP, RCDB. Writing - review & editing: ARG, JK, DSS, VMS, AYW, TML, MR, VZ.

REFERENCES

1. Gad MM, Saad AM, Faisaluddin M, Gaman MA, Ruhban IA, Jazieh KA, et al. Epidemiology of cholangiocarcinoma; United States incidence and mortality trends. Clin Res Hepatol Gastroenterol 2020;44:885-893.
2. Patel N, Benipal B. Incidence of cholangiocarcinoma in the USA from 2001 to 2015: a US cancer statistics analysis of 50 states. Cureus 2019;11:e3962.
3. Rizvi S, Gores GJ. Pathogenesis, diagnosis, and management of cholangiocarcinoma. Gastroenterology 2013;145:1215-1229.
4. Cillo U, Fondevila C, Donadon M, Gringeri E, Mocchegiani F, Schlitt HJ, et al. Surgery for cholangiocarcinoma. Liver Int 2019;39 Suppl 1:143-155.
5. Brindley PJ, Bachini M, Ilyas SI, Khan SA, Loukas A, Sirica AE, et al. Cholangiocarcinoma. Nat Rev Dis Primers 2021;7:65.
6. Uppal DS, Wang AY. Advances in endoscopic retrograde cholangiopancreatography for the treatment of cholangiocarcinoma. World J Gastrointest Endosc 2015;7:675-687.
7. Singh GK, Jemal A. Socioeconomic and racial/ethnic disparities in cancer mortality, incidence, and survival in the United States, 1950-2014: over six decades of changing patterns and widening inequalities. J Environ Public Health 2017;2017:2819372.
8. Geng CX, Gudur AR, Radlinski M, Buerlein RCD, Strand DS, Sauer BG, et al. Socioeconomic disparities affect outcomes in early-stage esophageal adenocarcinoma: a SEER analysis. Clin Gastroenterol Hepatol 2023;21:2797-2806.e6.
9. Zhu MX, Li Y. The correlations between socioeconomic status and intrahepatic cholangiocarcinoma in the United States: a population-based study. Transl Cancer Res 2020;9:4931-4942.
10. National Cancer Institute. Static county attributes [Internet]. NIH 2022 [cited 2022 Jul 11]. Available from: https://seer.cancer.gov/seerstat/variables/countyattribs/static.html-:~:text=The%20static%20county%20attributes%20are,populations%20from%20survey%20sample%20data.
11. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. Ann Oncol 2006;17:5-19.
12. Wrigley H, Roderick P, George S, Smith J, Mullee M, Goddard J. Inequalities in survival from colorectal cancer: a comparison of the impact of deprivation, treatment, and host factors on observed and cause specific survival. J Epidemiol Community Health 2003;57:301-309.
13. Thomson CS, Hole DJ, Twelves CJ, Brewster DH, Black RJ; Scottish

Cancer Therapy Network. Prognostic factors in women with breast cancer: distribution by socioeconomic status and effect on differences in survival. J Epidemiol Community Health 2001;55:308-315.
14. Zullig LL, Jackson GL, Provenzale D, Griffin JM, Phelan S, van Ryn M. Transportation: a vehicle or roadblock to cancer care for VA patients with colorectal cancer? Clin Colorectal Cancer 2012;11:60-65.
15. Lee RM, Liu Y, Gamboa AC, Zaidi MY, Kooby DA, Shah MM, et al. Race, ethnicity, and socioeconomic factors in cholangiocarcinoma: what is driving disparities in receipt of treatment? J Surg Oncol 2019; 120:611-623.
16. Welzel TM, McGlynn KA, Hsing AW, O'Brien TR, Pfeiffer RM. Impact of classification of hilar cholangiocarcinomas (Klatskin tumors) on the incidence of intra- and extrahepatic cholangiocarcinoma in the United States. J Natl Cancer Inst 2006;98:873-875.
17. Walter D, Ferstl P, Waidmann O, Trojan J, Hartmann S, Schnitzbauer AA, et al. Cholangiocarcinoma in Germany: epidemiologic trends and impact of misclassification. Liver Int 2019;39:316-323.
18. Khan SA, Emadossadaty S, Ladep NG, homas HC, Elliott P, Taylor-Robinson SD, et al. Rising trends in cholangiocarcinoma: is the ICD classification system misleading us? J Hepatol 2012;56:848-854.
19. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: epidemiology and risk factors. Liver Int 2019;39 Suppl 1:19-31.