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The Cholangiocarcinoma in the Young (CITY) Study: Tumor Biology, Treatment Patterns, and Survival Outcomes in Adolescent Young Adults With Cholangiocarcinoma

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PURPOSE Increased awareness of the distinct tumor biology for adolescents and young adults (AYAs) with cancer has led to improvement in outcomes for this population. However, in cholangiocarcinoma (CCA), a paucity of data exist on the AYA population. To our knowledge, we present the largest study to date on AYA disease biology, treatment patterns, and survival outcomes in CCA.

METHODS A multi-institutional cohort of patients with CCA diagnosed with intrahepatic cholangiocarcinoma (ICC) or extrahepatic cholangiocarcinoma (ECC) was used for analysis. Retrospective chart review was conducted on patients who were 50 years old and younger (young; n = 124) and older than 50 years (older; n = 723).

RESULTS Among 1,039 patients screened, 847 patients met eligibility (72% ICC, 28% ECC). Young patients had a larger median tumor size at resection compared with older patients (4.2 *v* 3.6 cm; $P = .048$), more commonly had N1 disease (65% *v* 43%; $P = .040$), and were more likely to receive adjuvant therapy (odds ratio, 4.0; 95% CI, 1.64 to 9.74). Tumors of young patients were more likely to harbor an *FGFR2* fusion, *BRAF* mutation, or *ATM* mutation ($P < .05$ for each). Young patients were more likely to receive palliative systemic therapy (96% *v* 69%; $P < .001$), targeted therapy (23% *v* 8%; $P < .001$), and treatment on a clinical trial (31% *v* 19%; $P = .004$). Among patients who presented with advanced disease, young patients had a higher median overall survival compared with their older counterparts (17.7 *v* 13.5 months; 95% CI, 12.6 to 22.6 *v* 11.4 to 14.8; $P = .049$).

CONCLUSION Young patients with CCA had more advanced disease at resection, more commonly received both adjuvant and palliative therapies, and demonstrated improved survival compared with older patients. Given the low clinical trial enrollment and poor outcomes among some AYA cancer populations, data to the contrary in CCA are highly encouraging.

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INTRODUCTION

Cholangiocarcinoma (CCA) is an aggressive malignancy of the biliary duct epithelium with a rising incidence and mortality globally.[1,2] Although the median age at diagnosis of intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC) is 67 and 72 years, respectively,[1] young patients are increasingly affected by this disease. A recent study showed that people younger than 50 years had a higher rate of annual percentage growth in incidence of biliary tract cancers compared with those older than 50 years.[3] In addition, death rates because of intrahepatic biliary tract malignancies in the young adult population have been increasing since 1980.[4] Most young adult patients have no identifiable risk factor, and relatively little is known about their disease biology, treatment choices, and outcomes.

Adolescent and young adults (AYAs) with cancer have gained increasing attention as a distinct entity in oncology in recent years. The precise definition of this population has varied across studies, with the National Cancer Institute Progress Review Group on AYA in 2006 as patients aged 15 to 39 years old and other studies adopting upper limits of age at 45 or 50 years.[5-7] AYAs with cancer have experienced a relatively lower rate of improvement in survival outcomes compared with their older and younger counterparts.[8] Although AYAs tend to demonstrate better survival than older patients in most

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Cholangiocarcinoma (CCA) is an uncommon malignancy of the biliary tract with a poor prognosis, and a paucity of studies exist on the adolescent and young adult (AYA) patient population with this disease. To our knowledge, the current multi-institutional study of 847 patients represents the largest analysis of disease biology, treatment patterns, and survival outcomes in AYAs compared with older adults with CCA.

Knowledge Generated

Young adults (50 years and younger) with CCA more commonly had larger tumors and node-positive disease at resection. Their tumors more frequently harbored alterations such as *FGFR2* fusions, *BRAF* mutations, and *ATM* mutations. Young adults also more commonly received adjuvant and/or palliative systemic therapy, and they more commonly participated in a clinical trial. In our cohort, young patients who presented with advanced disease had a higher median survival than their older counterparts.

Relevance

Young patients with CCA appear to harbor distinct biology with multiple actionable alterations and receive a greater amount of treatment than older patients. Further prospective studies of AYA patients with CCA will be critical for tailoring treatment algorithms for these patients.

malignancies, notable exceptions include colorectal and breast cancers.[9,10] In colon cancer, where early onset disease is on the rise,[11,12] young patients present more frequently with advanced-stage disease and poor prognostic pathologic features compared with older patients. In line with this, multiple studies have shown poorer survival in young patients with colon cancer[13-15] although the data on prognosis are mixed with some recent studies showing similar or improved survival compared with older patients.[16-19] In breast cancer, studies have similarly shown an association between young age at diagnosis and poor prognostic features such as hormone receptor–negative disease, increased tumor grade, and lymphovascular involvement.[20-23] Given the above, increasing recognition has been given to the fact that young patients with cancer often have differences in tumor biology and treatment utilization compared with older patients with the same type of cancer.

In CCA, a rare malignancy, limited data exist regarding differences in disease biology and outcomes in the AYA population compared with other age groups. One study, in which age 45 years was used as a cutoff for AYA patients, showed no difference between AYAs and older patients in overall survival (OS) across all stages, but it did show a lower OS in AYAs with stage IV disease as compared with older patients.[7] The challenges of rare cancer research are reflected in the fact that this study involved 18 AYA patients from three hepatobiliary surgery centers in China and 32 AYA patients included from multiple public databases. Given the increasing overall incidence of CCA and the disproportionately increasing incidence of some biliary malignancies in younger patients, a detailed understanding of the biology and management patterns that differentiate young and older patients is paramount for improving clinical outcomes. Our multi-institutional Cholangiocarcinoma in the Young (CITY) Study examines the differences in clinical presentation, histologic and molecular pathology, patterns of treatment utilization, clinical trial enrollment rates, and survival outcomes in young versus older patients with CCA.

METHODS

Data Collection

Patients with CCA were identified from institutional tumor registries using the International Classification of Diseases (ICD) codes for CCA (ICD-9-155.1, 156.9, or 156.1; ICD-10 C22.1, 24.9, 24.8, 24.0) and from institutional biliary tract cancer databases. Eligibility criteria for the study included (1) age 18 years or greater, (2) histologic confirmation of CCA, and (3) diagnosis after June 1, 2009. A cutoff of June 1, 2009, was used to align with the date that gemcitabine and cisplatin became the standard-of-care treatment for advanced biliary tract cancer.[24] Participating institutions included Mass General Cancer Center, University of California San Francisco, MD Anderson Cancer Center, Mayo Clinic, Vanderbilt University, University of Virginia, Beth Israel Deaconess Medical Center, and St Vincent's Medical Center. This study was performed on a protocol approved by the Institutional Review Boards of each participating institution.

A set of prespecified definitions were used across institutions for uniform data collection as per Appendix Table A1. Data were extracted by medical trainees or trained research assistants, and attending medical oncologists adjudicated ambiguous cases.

Molecular Analysis

Results of tumor molecular profiling performed as a routine part of clinical care were obtained from retrospective chart review. Institutional platforms comprised MGH SNaPshot,[25] MSK IMPACT,[26] UCSF500 Cancer Gene Panel,[27] Columbia

University Combined Cancer Panel,[28] Mayo Clinic's CANCP, Dana Farber Cancer Institute's Oncopanel,[29] Jackson Laboratory's Cancer Treatment Profile,[30] and University of Wisconsin's Oncoplex.[29] Commercial panels used included FoundationOne.[31]

Statistics

Chi-square, Fisher's exact, and unpaired t-tests and Wilcoxon rank-sum tests were used to compare independent variables in young and older patients. Graph Pad Prism version 9 and MedCalc version 19.7 were used for statistical analysis (MedCalc Software Ltd, Ostend, Belgium; MedCalc[32]; 2020). STATA 17[33] was used in multivariate analyses. Multivariate analysis models for OS analyses included all variables that had a population representation of over 10% and resulted as significant on univariate analysis. *FGFR2* fusions and *BRAF* mutations were also added to the models, given their clinical significance in CCA. A *P* value of $<.05$ was considered significant. Progression-free survival (PFS), recurrence-free survival (RFS), and OS were calculated by Kaplan-Meier analysis, with log rank-sum tests being used to calculate *P* values between groups. Patients were censored at the time of last follow-up if they did not meet the specified end point.

RESULTS

Study Population

Among 1,039 patients evaluated for the study, 847 met eligibility criteria (Fig 1A). The most common reason for exclusion was diagnosis of gallbladder adenocarcinoma (n = 129), followed by the date of diagnosis of CCA being before June 1, 2009 (n = 60). Most patients had ICC (72%), and the remainder had ECC (28%). The median follow-up for the study was 14.7 months.

In defining the AYA population for this study, we assessed the percentage of patients in each age group in increments of 5 years. In a cohort of 847 patients, the 40 years and younger population, the 45 years and younger population, and the 50 years and younger population included 38 (4%), 78 (9%), and 124 (15%) patients, respectively. Therefore, we selected age 50 years as a cutoff to allow for sufficient statistical power in our analyses (Fig 1B).

Demographics, Risk Factors, and Disease Presentation

Patient demographics, anatomic subtype of CCA (ICC *v* ECC), and risk factors were compared in the young and older populations. No significant differences were detected in sex, race, or anatomic subtype, but differences were detected in the frequencies of some known risk factors (Table 1). Younger patients were more likely to have primary sclerosing cholangitis (13% *v* 2%; $P < .001$), as has been previously observed. Older patients were more likely to have diabetes (19% *v* 7%; $P = .012$) and a higher median BMI (27.3 *v* 25.9 kg/m^2; $P = .033$).

Disease presentation characteristics including extent of disease, patterns of metastases, tumor markers, and bilirubin were also examined by age group (Table 1). In both young and older patients, approximately 40% of patients presented with resectable disease, 20% with locally advanced disease, and 40% with primary metastatic disease. In evaluation of metastasis patterns among patients who presented with primary metastatic disease, older patients were more likely to have lung metastases (26% *v* 10%; $P = .047$).

Pathologic Differences From Surgical Resection and Tumor Molecular Profiling

Among patients who underwent surgical resection, tumor pathology was compared in young versus older patients (Appendix Table A3). In the overall population, 37% of patients underwent surgical resection, including 44% of young patients and 36% of older patients. In this population, young patients had a larger median tumor size on pathology (4.2 *v* 3.6 cm; $P = .048$). This observation held on multivariate analysis adjusted for anatomic subtype (ICC *v* ECC), with the median tumor size being 1.02 cm greater in young patients ($P = .007$). Young patients also more commonly had N1 disease compared with older patients (65% *v* 43% respectively; $P = .040$). Rates of margin positivity, lymphovascular invasion, and perineural invasion did not vary significantly by age. In patients who had a surgical resection or biopsy, there was no significant difference in tumor grade (Appendix Table A4).

Genomic profiling of tumors was also compared in the young and older populations. Molecular profiling data were available for 441 of 726 patients with advanced disease (61%), including 349 (64%) advanced patients with ICC and 92 (50%) patients with ECC (Fig 1A). The majority of patients underwent tumor profiling using MGH SNaPshot (n = 290) or Foundation One (n = 146) platforms. Among patients with advanced disease, young patients more often underwent genetic profiling when compared with older patients (74% *v* 58%; $P = .002$). Among older patients with advanced disease, profiling was more common in those with ICC compared with those with ECC (62% *v* 48%; $P = .003$); however, there was no significant difference in profiling frequency among young patients with ICC and ECC (76% *v* 64%; $P = .213$). Analysis of profiled tumors revealed that young individuals were more likely than older individuals to have an *FGFR2* fusion (28%, 14 of 50 *v* 15%, 34 of 234; $P = .021$) but not an *FGFR* mutation (5%, 4 of 77 *v* 4%, 13 of 363; $P = .505$). Young patients were also more likely to have a mutation in *ATM* (12%, 6 of 49 *v* 5%, 11 of 233; $P = .044$) or BRAF (8%, 6 of 76 *v* 3%, 11 of 363; $P = .046$) albeit numbers were relatively small. No other aberrations were found to differ significantly by age (Fig 2). When we applied a cutoff age of 40 years for the genomic analysis of our cohort, no differences in the landscape of genomic alterations were identified other than *FGFR1/2/3* amplifications, which were more frequently found in younger patients (11%, 2 of 18 *v* 1%, 2 of 282; $P = .001$). However, these data should be interpreted with caution given the

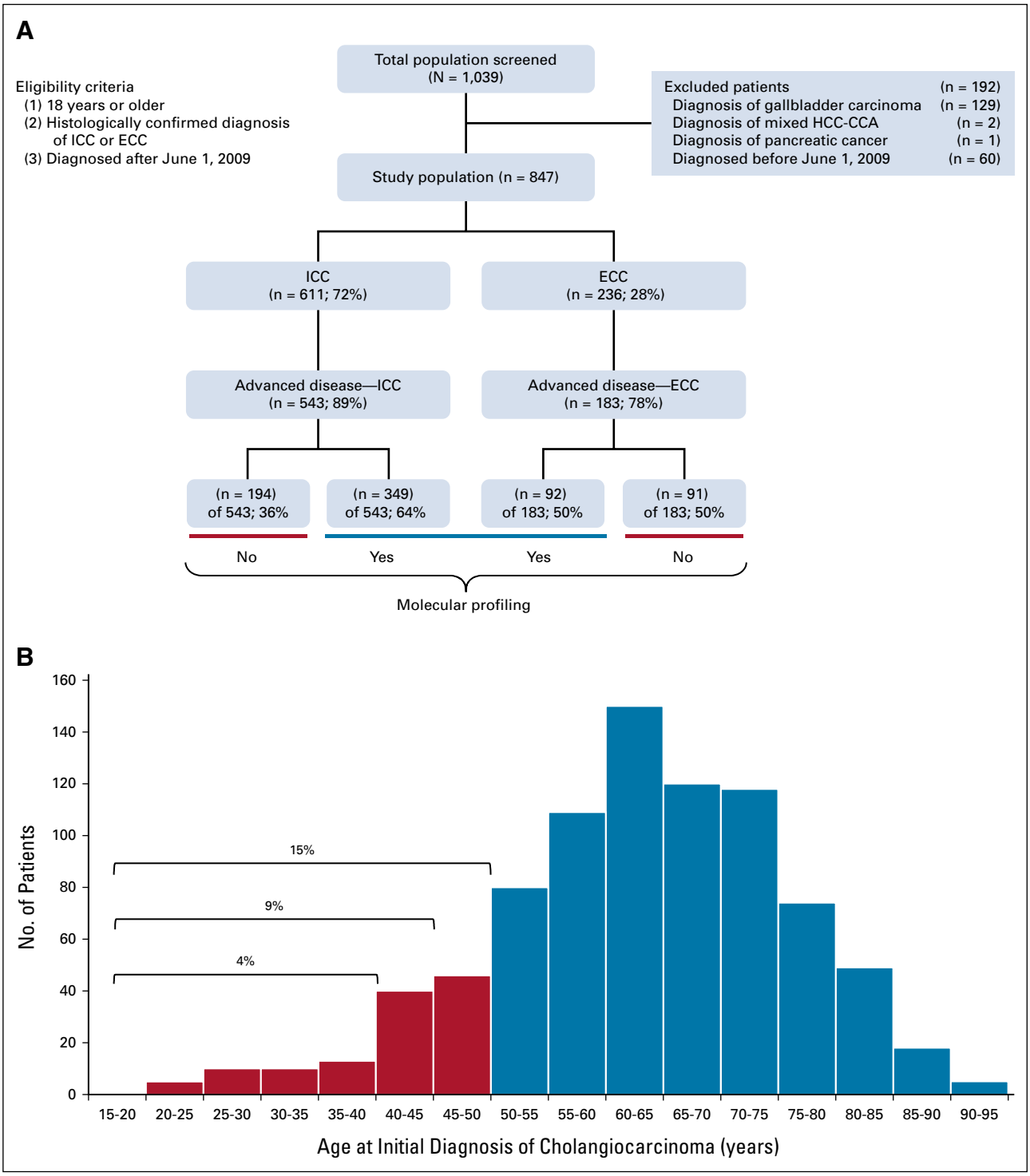

FIG 1. Baseline characteristics of the study population. (A) CONSORT diagram of the study depicting eligibility and exclusion criteria, the frequency of patients with ICC and ECC, and the frequency of molecular profiling among patients with advanced disease. (B) Histogram of patients stratified by age of initial diagnosis. The 847-patient cohort was subdivided into groups on the basis of age of initial CCA diagnosis, in increments of 5 years. Patients 50 years and younger represented 15% of the cohort. CCA, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

TABLE 1. Comparison of Clinical Characteristics Between Young and Older Patients With CCA (n = 847)

Characteristic	50 Years and Younger (n = 124)	Older Than 50 Years (n = 723)	*P*
Sex, No. (%)			
Male	58 (47)	378 (52)	.285
Female	66 (53)	345 (48)	
Race, No. (%)			
White	80/97 (82)	501/580 (86)	.308
Black	7/97 (7)	27/580 (5)	.285
Asian	6/97 (6)	44/580 (8)	.625
Others	4/97 (4)	8/580 (1)	.058
CCA anatomic subtype, No. (%)			
Intrahepatic	95/124 (77)	516/723 (71)	.278
Extrahepatic	29/124 (23)	207/723 (29)	
Risk factors, No. (%)			
Primary sclerosing cholangitis	15/115 (13)	17/700 (2)	**<.001**
Diabetes	5/72 (7)	96/519 (19)	**.012**
Cirrhosis	4/72 (6)	52/517 (10)	.286
Median BMI, kg/m^2	25.89	27.3	**.033**
BMI ≥30, kg/m^2	25/88 (28)	184/579 (32)	.622
HBV	4/71 (6)	14/321 (4)	.547
HCV	4/109 (4)	31/575 (5)	.636
Disease presentation, No. (%)			
Resected/resectable/transplanted	50/124 (40)	248/723 (34)	.195
Locally advanced	21/124 (17)	172/723 (24)	.093
Primary metastatic	53/124 (43)	303/723 (42)	.862
Patients with unresectable and/or metastatic disease at any time point, No. (%)			
Unresectable or metastatic disease	114/124 (92)	610/723 (84)	
Laboratory results at diagnosis			
Median bilirubin, mg/dL	0.7	0.8	.942
Median CEA, ng/mL	1.90	2.7	.051
Median CA 19-9, U/mL	77.0	96.9	.285
Sites of metastasis at presentation in patients with primary metastatic disease, No. (%)			
Liver	29/31 (94)	200/232 (86)	.253
Lymph node metastasis	13/31 (42)	113/232 (49)	.478
Lung	3/31 (10)	60/232 (26)	**.047**
Bone	6/31 (19)	29/232 (13)	.291
Peritoneum	7/31 (23)	34/232 (15)	.253
Others	1/31 (3)	13/232 (6)	.580

NOTE. Denominators refer to the number of patients with known status for that variable. *P* values considered statistically significant ($P < .05$) are highlighted in bold.

Abbreviations: CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; HBV, hepatitis B virus; HCV, hepatitis C virus.

small number of patients younger than 40 years in our cohort (Appendix Table A5).

Differences in Treatment Patterns

Treatment patterns were evaluated in the adjuvant and palliative setting for young and older patients (Table 2). Among those who underwent surgical resection, a trend was seen toward increased use of adjuvant therapy in the young compared with older population (69% *v* 51%; $P = .060$); when reanalyzed by multivariate analysis and adjusted for anatomic subtype of disease (ICC *v* ECC), this trend became significant with young patients more likely to receive adjuvant therapy (odds ratio, 4.0; 95% CI, 1.64 to 9.74). Notably, younger patients were more likely to receive

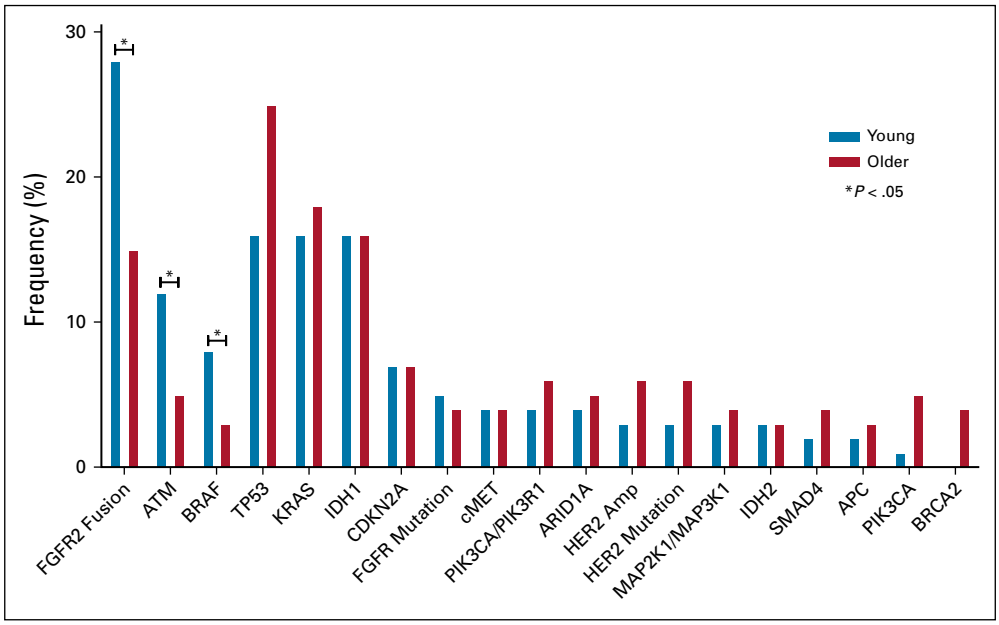

FIG 2. Genomic profiling of young (50 years and younger) versus older (older than 50 years old) patients with CCA. In an analysis of 459 patients who underwent genomic profiling for CCA, *FGFR2* fusions, *ATM* mutations, and *BRAF* mutations were more commonly seen in younger patients. Starred columns highlight genes with statistically significant differences in rates of alterations present between young and older patients (all $P < .05$). All gene labels indicate point mutations at the gene with the following exceptions, which include copy number alterations: *ATM*, *CDKN2A*, *cMET*, *PIK3CA/PIK3R1*, *ARID1A*, *PIK3CA*, and *SMAD4*. CCA, cholangiocarcinoma.

adjuvant chemotherapy (69% *v* 44%; $P = .026$). In addition, among patients who received adjuvant chemotherapy, rates of use of doublet or triplet regimens were not significantly different between young and older patients, at 55% and 42%, respectively ($P = .315$).

We next studied patterns of usage of liver-directed therapy and extrahepatic radiation in our cohort. Young patients were more likely to receive extrahepatic radiation, mainly for bone metastases, as compared with their older counterparts (21% *v* 10%, respectively; $P = .016$). No statistically significant difference was found between young and older patients for receipt of liver-directed therapies.

Patterns of receipt of palliative systemic therapy and enrollment in clinical trials were studied in patients with unresectable or metastatic disease, which included patients with locally advanced, primary metastatic, or recurrent metastatic disease (Table 2). We found that young patients were more likely to receive palliative systemic therapy compared with older patients (96% *v* 68%; $P < .001$). Among patients for whom the number of lines of therapy received was known, young patients received a median of two lines of systemic chemotherapy compared to one line in older patients ($P < .001$). Young patients were also more likely to receive targeted therapy (23% *v* 8%; $P < .001$) and enroll in a clinical trial (31% *v* 19%; $P = .004$). To assess if enrichment of *FGFR2* fusions in the younger populations accounted for the differences in targeted therapy receipt and clinical trial enrollment, we repeated the analysis excluding patients with *FGFR2* fusions. In this analysis, young patients still had a significantly higher frequency of receipt of targeted therapy (23% *v* 8%; $P < .001$), but the difference in rate of clinical trial enrollment became nonsignificant (23% *v* 16%; $P = .076$). The spectrum of targeted therapies used in young and older patients was similar, with *FGFR2* fusions, *IDH1* mutations, *BRAF* mutations, and *MET* amplifications being the most commonly targeted alterations (Fig 3). Most of these targeted therapies were administered via clinical trial. Encouragingly, we observed that the frequency of receipt of different targeted therapies was proportionate to the frequency with which the targetable alterations were found in our genomic data in the young and older cohorts (Figs 2 and 3).

Differences in Outcomes Between Young and Older Patients

Differences in OS were analyzed to examine whether young patients with CCA experienced different survival outcomes compared with older patients. Young patients who presented with unresectable or metastatic disease were found to have a higher median overall survival (mOS) from the date of diagnosis compared with their older counterparts (17.7 *v* 13.5 months; 95% CI, 12.6 to 22.6 *v* 11.4 to 14.8; $P = .049$; Fig 4). This difference held in a multivariate analysis model (Appendix Table A6). The mOS from initial diagnosis in the overall population, including those who presented with early-stage disease and underwent resection, was similar in younger versus older patients (23.5 *v* 19.2 months; 95% CI, 19.2 to 29.2 *v* 16.9 to 21,

TABLE 2. Treatment Patterns in Patients With Cholangiocarcinoma

Characteristic	50 Years and Younger	Older Than 50 Years	*P*
Study cohort who underwent surgery, No. (%)	55/124 (44)	257/723 (36)	.060
Adjuvant therapy, No. (%)			
Adjuvant therapy status known	32/55 (58)	185/257 (72)	NE
Treated with adjuvant therapy	22/32 (69)	94/185 (51)	**.060**[a]
Adjuvant chemotherapy	22/32 (69)	81/185 (44)	**.026**
Adjuvant chemoradiation	7/32 (22)	58/185 (31)	.280
Adjuvant singlet chemotherapy	10/22 (45)	46/80 (58)	.315
Adjuvant combination chemotherapy	12/22 (55)	34/80 (42)	.315
Study cohort with unresectable or metastatic disease	114/124 (92)	610/723 (84)	
Liver-directed therapy and extrahepatic radiation			
Known status of liver directed therapy	98/114	568/610	NE
Received liver-directed therapy, No. (%)	29/98 (30)	178/568 (31)	.813
Liver radiation, No. (%)	19/98 (19)	109/562 (19)	.995
Ablation, No. (%)	5/98 (5)	18/562 (3)	.342
Radioembolization	7/98 (7)	32/562 (6)	.572
Chemoembolization	4/98 (4)	19/562 (3)	.725
Bland embolization	2/98 (2)	3/562 (1)	.112
Irreversible electroporation	0/98 (0)	8/562 (1)	.235
Extrahepatic radiation	16/77 (21)	54/488 (10)	**.016**
Palliative systemic therapy			
Known status palliative systemic therapy, No. (%)	111/114 (97)	582/610 (95)	NE
Treated with palliative systemic therapy, No. (%)	107/111 (96)	394/582 (68)	**<.001**
Singlet first-line palliative therapy, No. (%)	16/106 (15.1)	50/391 (12.8)	.535
Doublet first-line palliative therapy, No. (%)	80/106 (75.5)	312/391 (79.8)	.333
Triplet first-line palliative therapy, No. (%)	10/106 (9.4)	29/391 (7.4)	.493
Median number of lines of systemic therapy, median (range)	2 (0-7)	1 (0-7)	**<.001**
One line of systemic therapy, No. (%)	17/61 (28)	133/372 (36)	.230
Two lines of systemic therapy No. (%)	18/61 (30)	73/372 (20)	.079
Three or more lines of systemic therapy, No. (%)	22/61 (36)	63/372 (17)	**.011**
Targeted therapy and clinical trials, No. (%)			
Received targeted therapy	25/108 (23)	47/582 (8)	**<.001**
Enrolled in a clinical trial	35/112 (31)	112/584 (19)	**.004**

NOTE. Denominators refer to the number of patients with known status for that variable. *P* values considered statistically significant ($P < .05$) are highlighted in bold.

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma; NE, not evaluated.

[a]Statistically significant on multivariate analysis adjusted for anatomic subtype (ICC *v* ECC), odds ratio, 4.0; 95% CI, 1.64 to 9.74.

respectively; $P = .166$). RFS in patients who underwent resection was also similar for young and older patients (9.3 *v* 10.1 months; 95% CI, 7.5 to 14.2 *v* 8.9 to 69.4; $P = .857$). Among patients who received at least one line of palliative systemic therapy for advanced disease, young patients had a similar mOS compared with older patients (19.8 *v* 14.9 months, respectively; 95% CI, 13.6 to 23.5 *v* 13.4 to 16.9; $P = .134$). Among patients treated on a clinical trial, younger patients had a higher mOS from the date of diagnosis of their advanced disease (young *v* older: 28.9 *v* 21.4 months; 95% CI, 23.5 to 51.4 *v* 15.6 to 28.2; $P = .022$). This result held when patients with *FGFR2* fusions were removed from the analysis (44.6 *v* 20.4 months; 95% CI, 21.4 to 58.8 *v* 14 to 28.2; $P = .019$); however, it did not hold in a multivariate analysis model (Appendix Table A7). No difference was seen in median PFS on frontline gemcitabine/cisplatin or second-line FOLFOX in young versus older patients.

DISCUSSION

To our knowledge, the CITY Study represents the largest multi-institutional analysis of AYAs with CCA and the first to compare

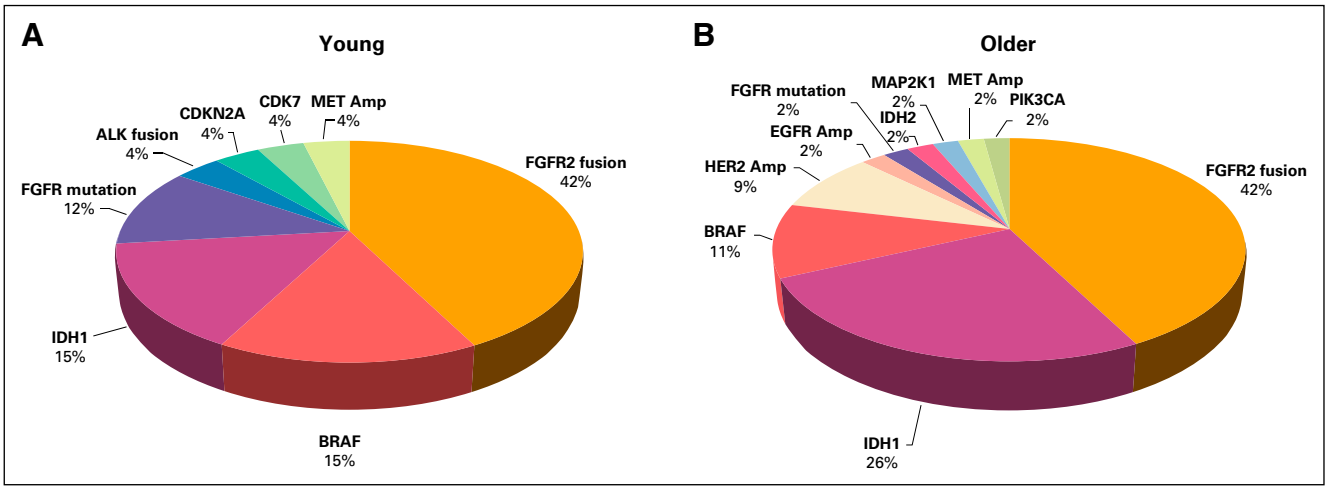

FIG 3. Spectrum of gene alterations targeted with targeted therapies in (A) young (50 years and younger) and (B) older (older than 50 years) patients in our cohort. Among patients who received targeted therapy, the majority in both age groups received targeted therapy directed at *FGFR2* fusions or *IDH1* mutations. Gene names without the type of alteration indicated refer to mutations of those genes. ALK, anaplastic lymphoma kinase; Amp, amplification; HER2, human epidermal growth factor receptor 2; MET, mesenchymal-epithelial transition factor.

clinical trial enrollment and treatment patterns in young and older patients with this disease. A key reason for paucity of data on AYAs with cancer is that cancer prevalence in this age group is low, and this population has only recently been recognized as a distinct entity warranting focused study.[34,35] Research in this population is additionally challenging given that the number of new cases of bile duct cancer in the United States is also fortunately low, with approximately 8,000 cases diagnosed annually, as compared with 284,000 for breast cancer and 150,000 for colorectal cancer.[36] Thus, multi-institutional collaboration is essential to drive understanding and progress in rare subpopulations of rare cancers, and indeed, the findings of this study are based on contributions from eight cancer centers with a commitment to improving outcomes for patients with CCA.

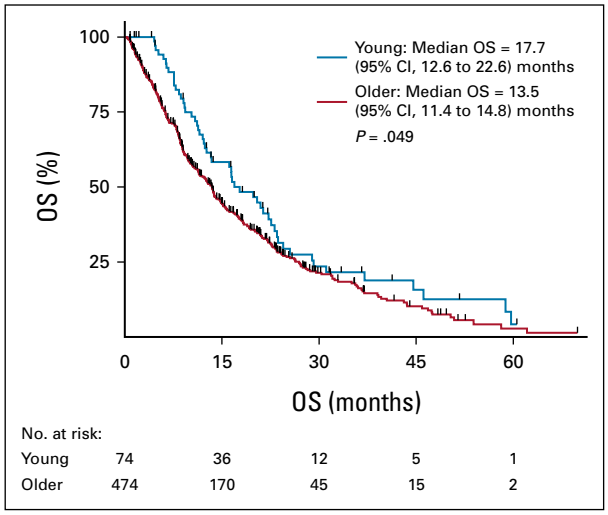

FIG 4. Differences in median overall survival between young (50 years and younger) and older (older than 50 years) patients who presented with advanced disease. Compared with older patients, young patients who presented with advanced disease had higher median OS. OS, overall survival.

A key finding of the study was that *FGFR2* fusions, *BRAF* mutations, and *ATM* mutations are enriched in young patients. Recognition of the clinical phenotype of patients with *FGFR2* fusions and *BRAF* mutations, most of which were *V600E*, is particularly relevant given the therapeutic implications of these alterations. The combination of trametinib and dabrafenib in patients with treatment-refractory *BRAF V600E*–mutant biliary malignancies showed an overall response rate of 47%.[37] Three selective ATP-competitive FGFR inhibitors, pemigatinib, infigratinib, and futibatinib, gained conditional regulatory approval in 2020, 2021, and 2022, respectively, on the basis of objective response rates of 23%-42% in patients with advanced, refractory *FGFR2* fusion or rearrangement-positive CCA. Multiple studies have demonstrated an enrichment of *FGFR2* fusions in younger patients,[38-40] and while all patients with CCA should undergo tumor molecular profiling given the high rate of actionable alterations in this disease, knowledge of this genotype-phenotype association can prompt patients and clinicians to pursue tumor profiling in young patients early and also maintain persistence if initial attempts at profiling fail because of insufficient tissue.

Across multiple cancer types, the AYA literature has consistently demonstrated that younger patients undergo surgery for more advanced-stage tumors and receive more lines of palliative therapy than older patients, and our findings stand consistent with this pattern of practice. The relatively improved outcomes of young patients after surgery have been attributed to higher rates of receipt of adjuvant therapy, fewer comorbidities leading to more radical surgical procedures, and increased lymph node excisions intraoperatively.[16,41] Similarly, in our study, young patients received adjuvant chemotherapy more often than

older patients, and notably, the median RFS after surgery in both age groups was similar despite young patients having higher rates of N1 disease. Studies in different cancers including colon cancer[42] and breast cancer[43,44] indicate that young patients receive more lines of therapy in the palliative setting for advanced disease, and again, our study in CCA stood consistent with this. The decision algorithms that lead to resection of later-stage disease, increased adjuvant and palliative therapy use across multiple AYA cancers, and the consequent clinical outcomes of these practices warrant further exploration to appropriately balance the risks and benefits of this practice.

Our study findings diverged from the AYA literature in the category of clinical trial enrollment. AYA patients with cancer have been shown to have a lower rate of accrual to clinical trials than pediatric and older patients.[8,35] However, we were encouraged to find that in patients with CCA, rates of clinical trial enrollment and receipt of targeted therapy did not significantly differ between young and older patients. Furthermore, young and older patients who enrolled on clinical trials had similar survival outcomes. The CITY Study encouragingly highlights that AYAs with CCA, unlike AYAs with some other cancers, are indeed accessing and benefiting from clinical trials, but it also raises awareness that a fair proportion of all patients still do not receive treatment on a trial.

Young patients with colorectal carcinoma and breast cancer present with more advanced disease stages and can often experience worse survival outcomes than older patients according to several studies.[45,46] By contrast, our study found that young patients with CCA who present with advanced stages of the disease live longer and may potentially harbor more favorable disease biology when compared with their peers with other malignancies.

A limitation of our study was that our patient population was derived mainly from people presenting to tertiary care cancer centers. This may potentially lead to selection bias as the population of patients referred to these institutions may be enriched for those who underwent tumor profiling and were found to have actionable tumor mutations conferring eligibility for clinical trial participation. Another limitation of our retrospective study is the issue of incomplete data for some variables; this was addressed by using a large data set to have sufficient power for analyses and only studying variables with sufficient datapoints to achieve statistical power.

In conclusion, the CITY Study highlights the power of multi-institutional collaboration in generating real-world data to gain insights into AYA populations with cancer. Epidemiology and outcomes among AYAs with cancer vary by cancer type,[47] and therefore, an in-depth study of AYA populations in each individual malignancy is needed. This study provides another example of a malignancy where AYAs receive more aggressive treatment, and understanding the risks and benefits of these choices is critical for optimizing both longevity and quality of life for this population. Further studies that stand to improve outcomes for AYAs include those focused on closing the equity gap as AYAs with poorer sociodemographic characteristics have been shown to have higher mortality rates.[48] Overall, although prioritization has historically been given to pediatric and adult populations with cancer, increasing recognition of AYAs as a unique entity allows for tailored interventions to support this previously under-recognized population of patients with cancer.

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APPENDIX

TABLE A1. Definitions of Key Terms Used Across Institutions

Term	Definition
Date of initial diagnosis	Date of histologic confirmation of the diagnosis of cholangiocarcinoma or the date of resection of the tumor in patients in whom no diagnostic biopsy was performed
Locally advanced disease	Unresectable tumor confined to one lobe of the liver without intralobar metastasis, irrespective of the status of regional lymph node involvement
Primary metastatic disease	Metastases within the liver or to distant sites including nonregional lymph nodes at the time of initial diagnosis
Recurrent metastatic disease	Recurrent disease after surgical resection or transplant that arose outside of the resection bed and distant from the margin
Site of metastatic disease	Lymph nodes measuring ≥1.5 cm in short axis (or nodes considered suspicious for metastasis radiographically or biopsy-proven nodes), intrahepatic or distant organ metastases
PFS	Duration from the first day of treatment administration to radiologic or clinical progression by chart review or death

Abbreviation: PFS, progression-free survival.

TABLE A2. Sites of Metastases at Most Recent Scan in Patients With Advanced Disease

Site of Metastasis	50 Years and Younger, No. (%)	Older Than 50 Years, No. (%)	*P*
Liver	63/70 (90)	368/456 (81)	.060
Lymph node(s)	41/70 (59)	235/455 (52)	.280
Lungs	23/70 (33)	160/453 (35)	.688
Bone	18/70 (26)	74/455 (16)	.053
Peritoneum	24/70 (34)	119/455 (26)	.155

TABLE A3. Tumor Pathology in Young and Older Patients Who Underwent Surgery (n = 312)

Characteristic	50 Years and Younger (n = 124)	Older Than 50 Years (n = 723)	*P*
Surgery			
Underwent surgery, No. (%)	55/124 (44)	257/723 (36)	.060
Median size of resected tumor, cm	4.2	3.6	**.048**[a]
Tumor size ≥5 cm, No. (%)	19/49 (39)	78/222 (35)	.630
Node status, No. (%)			
N0	8/23 (35)	80/142 (56)	.055
N1	15/23 (65)	60/142 (43)	**.040**
N2	0/23 (0)	2/142 (1)	.567
Margin status, No. (%)			
R0	37/43 (86)	199/237 (84)	.730
R1	4/43 (9)	33/237 (14)	.410
R2	2/43 (5)	5/237 (2)	.326
Lymphovascular invasion, No. (%)	23/30 (77)	107/175 (61)	.103

NOTE. Denominators refer to the number of patients with known status for that variable. *P* values considered statistically significant ($P < .05$) are highlighted in bold.

Abbreviations: ECC, extrahepatic cholangiocarcinoma; ICC, intrahepatic cholangiocarcinoma.

[a]Further statistically significant on multivariate analysis adjusted for anatomic subtype (ICC *v* ECC), $P = .007$.

TABLE A4. Tumor Differentiation Grade in Young and Older Patients Who Had a Biopsy or Surgery

Differentiation	50 Years and Younger (n = 98), No. (%)	Older Than 50 Years (n = 499), No. (%)	*P*
Well differentiated	7/98 (7)	47/499 (9)	.628
Moderately differentiated	53/98 (54)	250/499 (50)	
Poorly differentiated/ undifferentiated	38/98 (39)	210/499 (42)	

TABLE A5. Genomic Profiling of Patients 40 Years and Younger Versus Patients Older Than 40 Years With Cholangiocarcinoma

Gene Alteration	40 Years and Younger, No. (%)	Older Than 40 Years, No. (%)	*P*
IDH1	2/24 (8)	69/419 (16)	.291
FGFR2 fusions	5/22 (23)	45/322 (14)	.260
FGFR1/2/3 mutation	1/24 (4)	17/418 (4)	.981
FGFR1/2/3 amplification	2/18 (11)	2/282 (1)	**.001**
TP53 mutation	3/23 (13)	99/417 (24)	.237
HER2 mutation	1/21 (5)	23/403 (6)	.855
HER2 amplification	1/7 (14)	19/175 (11)	.776
BRAF mutation	2/23 (9)	15/418 (4)	.853
MET amplification	2/20 (10)	14/402 (3)	.136
BRCA1 mutation	1/16 (6)	5/195 (3)	.394
ATM mutation	3/16 (19)	14/195 (7)	.102
BAP1 mutation	1/14 (7)	9/138 (7)	.929
CDKN2A mutation	2/34 (6)	28/499 (6)	.947

NOTE. Alterations depicted are those for which there were at least 5% of patients who had the alteration within the 40 years and younger or older than 40 years group. *P* values considered statistically significant ($P < .05$) are highlighted in bold.

Abbreviations: HER2, human epidermal growth factor receptor 2; MET, mesenchymal-epithelial transition factor.

TABLE A6. Multivariate Analysis of Parameters Affecting OS in Patients With CCA Who Presented With Advanced Disease

	Kaplan-Meier	Cox Regression Univariate Analysis		Cox Regression Multivariate Analysis	
Characteristic	**Median OS (95% Median CI)**	**HR**	***P***	**HR**	***P***
Sex					
Female	14.6 (12.5 to 17.6)	1 (reference)	.026	1 (reference)	.607
Male	12.8 (11 to 15)	1.25		0.833	
CCA anatomic subtype					
ECC	12.5 (10.3 to 15.2)	1 (reference)	.047	1 (reference)	.692
ICC	13.8 (12.6 to 16.6)	0.78		0.812	
Age, years					
50 and younger	17.7 (12.6 to 22.6)	1 (reference)	.049	1 (reference)	.025
Older than 50	13.5 (11.4 to 14.8)	1.34		5.64	
Tbili					
≤3	14.6 (11.9 to 16.9)	1 (reference)	.015	1 (reference)	.882
>3	9 (8.3 to 12.4)	1.37		0.948	
CEA					
≤37	14.8 (12.6 to 17.3)	1 (reference)	.001	1 (reference)	.522
>37	8.7 (8 to 11.3)	1.52		1.23	
CA19-9					
≤35	14.1 (10.9 to 20.4)	1 (reference)	.049	1 (reference)	.942
>35	12.8 (10.4 to 15)	1.32		0.965	
CDKN2A mutation					
Yes	58.8 (7.6 to NA)	0.36	.008	0.342	.311
No	13.5 (11.6 to 15)	1 (reference)		1 (reference)	
FGFR2 fusion					
Yes	22.5 (12.8 to 35.8)	0.75	.243	0.184	.026
No	14.9 (12.5 to 17.7)	1 (reference)		1 (reference)	
IDH1 mutation					
Yes	22.6 (15 to 39)	0.56	.002	0.425	.066
No	13.6 (11.5 to 16.1)	1 (reference)		1 (reference)	
TP53 alteration					
Yes	9.4 (7.6 to 14.9)	1.53	.008	2.16	.019
No	16.1 (13.6 to 19.8)	1 (reference)		1 (reference)	
BRAF mutation					
Yes	18 (6.7 to NA)	0.69	.374	0.939	.953
No	14.6 (12.6 to 16.2)	1 (reference)		1 (reference)	
Receipt of palliative systemic therapy					
Yes	15.6 (13.6 to 18)	0.63	<.001	0.408	.016
No	8.5 (6.6 to 11.4)	1 (reference)		1 (reference)	

NOTE. Variables included in the multivariate analysis were (1) those that were significant on univariate analysis and had at least 10% of values with known status, (2) *BRAF* mutations, and (3) *FGFR2* fusions.

Abbreviations: CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; ECC, extrahepatic cholangiocarcinoma; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; NA, not available; OS, overall survival.

TABLE A7. Multivariate Analysis of Parameters Affecting OS in Patients With CCA Who Enrolled on a Clinical Trial

	Kaplan-Meier	Cox Regression Univariate Analysis		Cox Regression Multivariate Analysis	
Characteristic	**Median OS (95% Median CI)**	**HR**	***P***	**HR**	***P***
Sex					
Female	28.2 (19.5 to 35.8)	1 (reference)	.024	1 (reference)	.014
Male	21.4 (15.6 to 24.5)	1.63		2.57	
CCA anatomic subtype					
ECC	11 (8.1 to 18.4)	1 (reference)	.001	1 (reference)	<.001
ICC	26.7 (22.2 to 31.9)	0.37		0.12	
Age, years					
50 and younger	28.9 (23.5 to 51.4)	1 (reference)	.022	1 (reference)	.902
Older than 50	21.4 (15.6 to 28.2)	1.80		1.05	
HCV					
Yes	5.8 (5.8 to NA)	18.8	.000	30.5	.007
No	24.5 (20.9 to 28.9)	1 (reference)		1 (reference)	
FGFR2 fusion					
Yes	24.5 (19.4 to 35.8)	0.98	.954	1.36	.439
No	31.9 (18.3 to 44.6)	1 (reference)		1 (reference)	
CDKN2A mutation					
Yes	59.7 (36.6 to NA)	0.18	.004	0.26	.084
No	24.3 (18.4 to 28.9)	1 (reference)		1 (reference)	
cMET alteration					
Yes	8 (3.7 to NA)	2.55	.046	3.66	.053
No	24.5 (20.9 to 35.8)	1 (reference)		1 (reference)	
BRAF mutation					
Yes	36.6 (14 to NA)	0.53	.212	0.44	.453
No	23.5 (18.3 to 29.2)	1 (reference)		1 (reference)	

NOTE. Variables included in the multivariate analysis were (1) those that were significant on univariate analysis and had at least 10% of values with known status, (2) *BRAF* mutations, and (3) *FGFR2* fusions.

Abbreviations: CCA, cholangiocarcinoma; ECC, extrahepatic cholangiocarcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICC, intrahepatic cholangiocarcinoma; NA, not available; OS, overall survival.