Ann Surg Oncol (2019) 26:1993–2000
https://doi.org/10.1245/s10434-019-07175-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – HEALTH SERVICES RESEARCH AND GLOBAL ONCOLOGY

Intrahepatic Cholangiocarcinoma: Socioeconomic Discrepancies, Contemporary Treatment Approaches and Survival Trends from the National Cancer Database

Johannes Uhlig, MD MPH[1,2], Cortlandt M. Sellers, BS[1], Charles Cha, MD[3,4], Sajid A. Khan, MD[3,4], Jill Lacy, MD[4,5], Stacey M. Stein, MD[4,5], and Hyun S. Kim, MD[1,4,5]

[1]Division of Interventional Radiology, Department of Radiology and Biomedical Imaging, Yale School of Medicine, New Haven, CT; [2]Department of Diagnostic and Interventional Radiology, University Medical Center Goettingen, Goettingen, Germany; [3]Division of Surgical Oncology, Department of Surgery, Yale School of Medicine, New Haven, CT; [4]Yale Cancer Center, Yale School of Medicine, New Haven, CT; [5]Division of Medical Oncology, Department of Medicine, Yale School of Medicine, New Haven, CT

ABSTRACT

Objective. The aim of this study was to evaluate socioeconomic discrepancies in current treatment approaches and survival trends among patients with intrahepatic cholangiocarcinoma (ICC).

Methods. The 2004–2015 National Cancer Database was retrospectively analyzed for histopathologically proven ICC. Treatment predictors were evaluated using multinomial logistic regression and overall survival via multivariable Cox models.

Results. Overall, 12,837 ICC patients were included. Multiple factors influenced treatment allocation, including age, education, comorbidities, cancer stage, grade, treatment center, and US state region (multivariable $p < 0.05$). The highest surgery rates were observed in the Middle Atlantic (28.7%) and lowest rates were observed in the Mountain States (18.4%). Decreased ICC treatment likelihood was observed for male African Americans with Medicaid insurance and those with low income (multivariable $p < 0.05$). Socioeconomic treatment discrepancies translated into decreased overall survival for patients of male sex (vs. female; hazard ratio [HR] 1.21, 95% confidence interval [CI] 1.16–1.26, $p < 0.001$), with low income (< $37,999 vs. ≥ $63,000 annually; HR 1.07, 95% CI 1.01–1.14, $p = 0.032$), and with Medicaid insurance (vs. private insurance; HR 1.13, 95% CI 1.04–1.23, $p = 0.006$). Both surgical and non-surgical ICC management showed increased survival compared with no treatment, with the longest survival for surgery (5-year overall survival for surgery, 33.5%; interventional oncology, 11.8%; radiation oncology/chemotherapy, 4.4%; no treatment, 3.3%). Among non-surgically treated patients, interventional oncology yielded the longest survival versus radiation oncology/chemotherapy (HR 0.73, 95% CI 0.65–0.82, $p < 0.001$).

Conclusions. ICC treatment allocation and outcome demonstrated a marked variation depending on socioeconomic status, demography, cancer factors, and US geography. Healthcare providers should address these discrepancies by providing surgery and interventional oncology as first-line treatment to all eligible patients, with special attention to the vulnerable populations identified in this study.

The incidence of bile duct cancer (cholangiocarcinoma) in the US is increasing and currently accounts for 3% of gastrointestinal cancers.[1–3] Depending on its origin, cholangiocarcinoma can be further categorized into extrahepatic and intrahepatic cholangiocarcinoma (ICC), with the latter accounting for approximately 8% of all cholangiocarcinomas.[4] Although outpaced in incidence by hepatocellular carcinoma, ICC is currently the leading

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07175-4) contains supplementary material, which is available to authorized users.

First Received: 10 September 2018;
Published Online: 28 January 2019

H. S. Kim, MD
e-mail: kevin.kim@yale.edu

cause of liver cancer-related mortality in the US, with 2.4 deaths/100,000 citizens.[5, 6] Several ICC risk factors have been identified that are mainly associated with chronic inflammation of the biliary tract, including primary sclerosing cholangitis (PSC), parasitic infections, and hepatolithiasis, as well as viral hepatitis and cirrhosis.[7] Further risk factors include chemical exposure, for example to Thorotrast, or congenital biliary tree abnormalities, such as Caroli disease.[7]

Surgical resection is considered the only curative treatment option for ICC, with 5-year overall survival reported at 22–36%.[8, 9] In surgically ineligible patients, ablative techniques, local radiotherapy, and systemic chemotherapy might be indicated, although randomized trials specifically on ICC are missing.[7, 10]

Despite the increasing ICC incidence and cancer-related mortality, there are currently no large-scale studies evaluating treatment approaches and associated outcomes. Therefore, the aim of our study was to analyze the utilization and effectiveness of current ICC therapies, and to assess whether socioeconomic factors influenced ICC treatment decisions and patient survival.

MATERIALS AND METHODS

This retrospective study received approval from the Institutional Review Board and was Health Insurance Portability and Accountability Act compliant.

Study Cohort

The early 2018 participant user file of the National Cancer Database (NCDB), sponsored jointly by the American College of Surgeons and the American Cancer Society, was retrospectively analyzed, including patients diagnosed with ICC between 2004 and 2015. The follow-up period ended 1 January 2016, after which patients were right-censored. Established in 1989, the NCDB comprises 34 million patient records from hospital cancer registries in the US. Annually, the NCDB captures approximately 70% of newly diagnosed cancer cases in the US.

For our study, patients with a histopathologically proven diagnosis of ICC were included. Exclusion criteria were age < 18 years, unknown survival status and follow-up time, as well as unknown or missing insurance status.

Socioeconomic variables and tumor factors were evaluated as potential predictors of ICC treatment approaches. The primary outcome of interest was overall survival, defined as the time from ICC diagnosis to death or censoring.

Variables

The NCDB provides information on patient comorbidities using the Charlson–Deyo score, stratified as scores of 0, 1, 2, and ≥ 3. The surgical treatment subgroup included patients who received surgical resection of the primary tumor with or without the addition of chemotherapy or radiotherapy, whereas the non-surgical management subgroup included patients who were treated via interventional oncology (including radioembolization and percutaneous local tissue destruction with or without additional chemotherapy), radiation oncology (including external beam radiation and brachytherapy to the liver), and chemotherapy. In our study, patients with unknown treatment were conservatively classified as not receiving the respective treatment.

Statistical Analyses

Continuous variables were provided as mean with standard deviation (SD), and categorical variables were provided as absolute number with percentage. Across strata, continuous variables were compared using the Wilcoxon rank-sum test and categorical variables were compared using the Chi square test.

Multinomial logistic regression was performed to evaluate the socioeconomic and cancer variables as predictors of ICC treatment, with simultaneous assessment of surgical and non-surgical approaches. Overall survival was evaluated using Cox proportional hazards regression models. All regression models were implemented both as univariate and multivariate models. The proportional hazards assumption was tested via visual assessment of Schoenfeld residuals. A priori, an interaction test between year of ICC diagnosis and treatment approach was planned to account for advancements in ICC treatment. For plotting of regional differences in overall survival rates across the US, stratified Cox models that adjusted for potential confounders were used.

All statistical analyses were performed using R version 3.4.3 (R Core Development Team, Vienna, Austria) and RStudio version 1.1.414 (RStudio Inc., Boston, MA, USA). An alpha-level of < 0.05 was considered statistically significant, and reported p values are two-sided.

RESULTS

Patient Population

A total of 18,343 patients with an ICC diagnosis between 2004 and 2015 were identified from the NCDB database, of which 12,837 patients fulfilled the inclusion criteria. Electronic supplementary Fig. 1 details the

inclusion and exclusion of patients from the NCDB, while electronic supplementary Table 1 provides information on baseline characteristics, cancer factors, treatment approaches and outcomes among the included patients.

ICC patients were diagnosed at a mean age of 50 years, with equal incidence among male and female patients. Approximately 58% of patients were diagnosed with stage III or IV disease.

Historical and Geographical Trends in Intrahepatic Cholangiocarcinoma (ICC) Treatment Allocation

During the study period, the number of ICC patients receiving non-surgical management continuously increased—from 37% in 2004 to 51% in 2014 (Fig. 1). Over the same period, the number of untreated ICC patients decreased from 41 to 26%, while the proportion of surgically resected patients stayed constant.

Using a multivariable multinomial logistic regression model, several independent predictors of ICC treatment allocation were identified, including sociodemographic variables and cancer factors (electronic supplementary Table 2). ICC treatment also showed variability by treating facility type and location, with higher treatment likelihood for patients presenting at academic or research centers in East, North, and Central States ($p < 0.05$). Figure 2 shows geographic variation in surgical treatment rates across the US. Furthermore, ICC treatment allocation varied by socioeconomic status, as detailed below.

Socioeconomic Status: Impact on Treatment Allocation

As shown in electronic supplementary Tables 2 and 3, patients with high socioeconomic status were more likely to receive treatment in academic or research facilities ($p < 0.001$). High-income patients were more likely to receive non-surgical management over no treatment ($p < 0.05$), whereas income was not a predictor of surgical treatment ($p > 0.05$). Comparably, patients with higher education were more likely to receive surgery or non-surgical management ($p < 0.05$). Adjuvant and neoadjuvant chemotherapy was more frequently administered in surgical patients with high income (> $48,000 vs. < 48,000: 44.6 vs. 40%, $p = 0.013$) and with high education (proportion of non-graduating residents < 13 vs. ≥ 13%: 45.1 vs. 39%, $p < 0.001$).

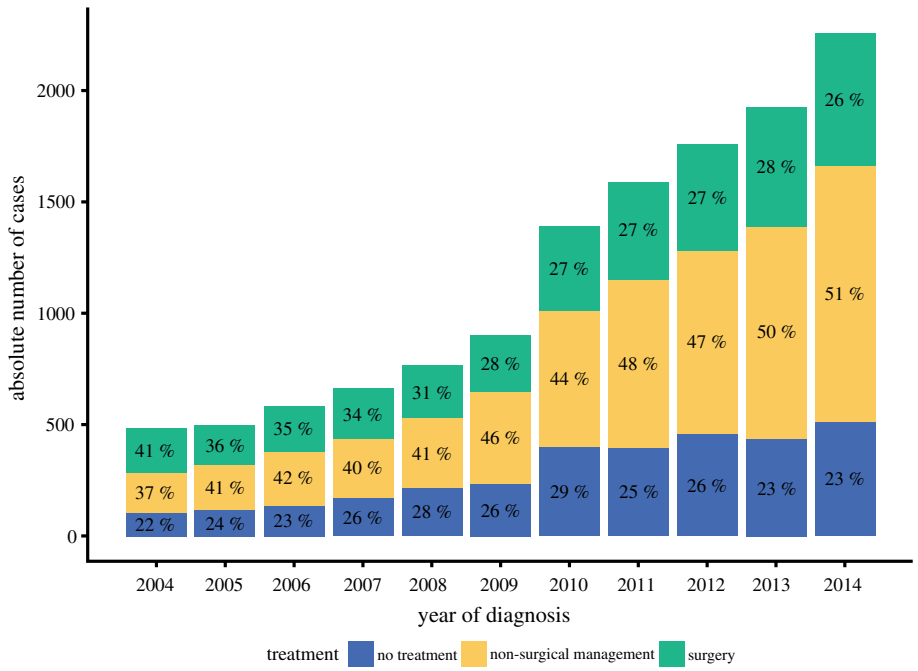

FIG. 1 Changes in ICC treatment allocation from 2004 to 2015. Surgery ($n = 3182$) included additional chemotherapy ($n = 962$, 30.2%), local radiotherapy and chemotherapy ($n = 388$, 12.2%), and SIRT/local radiotherapy ($n = 57$, 1.5%). Surgery was performed as a wedge/segmental resection ($n = 1444$, 45.4%), lobectomy ($n = 1386$, 43.5%), and hepatectomy with liver transplant ($n = 275$, 8.6%). For 77 patients (2.4%), surgical technique was not specified. The non-surgical subgroup ($n = 5962$) included interventional oncology ($n = 241$, 4.1%), interventional oncology and chemotherapy ($n = 160$, 2.7%), radiation oncology ($n = 246$, 4.1%), radiation oncology and chemotherapy ($n = 530$, 8.9%), and systemic chemotherapy alone ($n = 4749$, 80.1%). *ICC* intrahepatic cholangiocarcinoma, *SIRT* selective internal radiation therapy

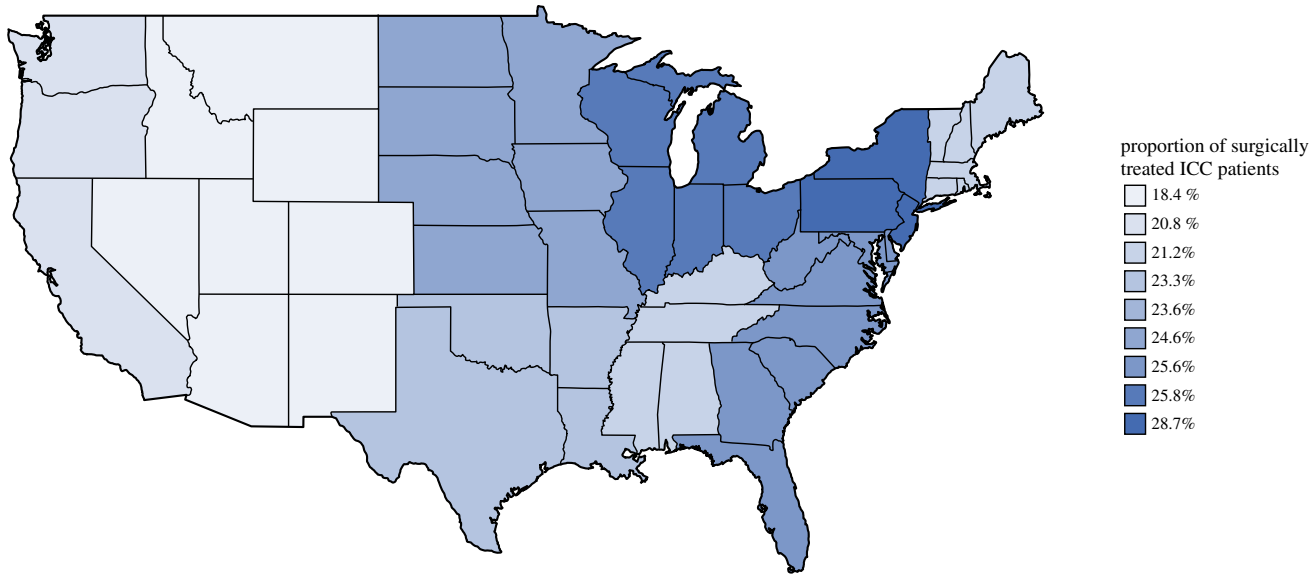

FIG. 2 Proportion of ICC patients receiving surgery depending on region in the US. *ICC* intrahepatic cholangiocarcinoma

Survival Disparities by Socioeconomic Status and ICC Treatment

Median follow-up time was 48.6 months (interquartile range 29.5–72.4 months). Multivariable Cox regression models were implemented to evaluate socioeconomic patient variables and treatment approaches as predictors of overall survival. Visual assessment of Schoenfeld residuals did not reveal violations of the proportional hazards assumption.

As detailed in Table 1, independent predictors of overall survival were patient age, comorbidities, income, insurance, ICC stage, treatment approach, treatment center type, treatment location, and year of diagnosis.

Higher income was associated with increased survival ($48,000–$62,999 vs. < $37,999: hazard ratio [HR] 0.92, 95% confidence interval [CI] 0.87–0.98, $p = 0.013$; > $63,000 vs. < $37,999: HR 0.93, 95% CI 0.88–0.99, $p = 0.032$), as depicted in Fig. 3. All treatment approaches were associated with a survival benefit versus no treatment (Fig. 4); this benefit was largest for surgery (HR 0.19, 95% CI 0.18–0.21, multivariable $p < 0.001$). Among the non-surgical treatment options, interventional oncology showed superior overall survival compared with radiation oncology/chemotherapy (HR 0.73, 95% CI 0.65–0.82, multivariable $p < 0.001$).

DISCUSSION

In the US, ICC incidence and cancer-related mortality have shown relevant increases.[2] Currently, ICC is the leading cause of liver cancer-related deaths in the US; [5,6] however, there are no large-scale studies evaluating ICC treatment approaches, survival trends, and potential socioeconomic discrepancies.

Using the US-based NCDB, we demonstrated an increase of non-surgical ICC management from 2004 to 2015, accounting for 51% of cases in 2014. This expanding utilization most likely results from non-surgical treatment of formerly untreated patients as their proportion decreased from 41 to 26% during the same period. This increase probably also reflects emerging evidence on the effectiveness of non-surgical strategies regarding patient survival and local tumor control.[7]

Our study also reveals significant geographical variation in ICC treatment allocation across the US; surgical resection rates ranged between 18.4% in Mountain States and 28.7% in Middle Atlantic States. These findings might well originate from diverging availability and experience of ICC treatment across the US.[11] Furthermore, regional variations in underlying liver disease might contribute to our findings. For example, South East Central States have a lower rate of alcohol consumption but higher incidence of non-alcohol-related liver cirrhosis than other regions, potentially due to higher rates of obesity and non-alcoholic fatty liver disease.[12–15]

Socioeconomic status and demographic factors emerged as major predictors of ICC treatment allocation and overall survival in our study, independent from tumor stage and grade probably related to unresectability of locally advanced or metastatic ICC.[16] A strong association was noted between socioeconomic status and race, insurance status, treatment facility type, and cancer stage. Nonetheless, on multivariable analyses, socioeconomic status proved independent from these correlated factors, thus

TABLE 1 Multivariable Cox proportional hazards regression model for overall survival

Predictor	HR	Lower 95% CI	Upper 95% CI	*p* Value
Age, years	1.011	1.009	1.013	< 0.001
Race				
Caucasian	Reference			
African American	1	0.927	1.08	0.99
Other race	0.87	0.803	0.942	< 0.001
Sex				
Female	Reference			
Male	1.21	1.164	1.259	< 0.001
Comorbidities (Charlson score)				
0	Reference			
1	1.137	1.084	1.194	< 0.001
2	1.25	1.152	1.357	< 0.001
≥ 3	1.514	1.382	1.658	< 0.001
Annual income, US$				
< $37,999	Reference			
$38,000–$47,999	0.986	0.925	1.052	0.672
$48,000–$62,999	0.922	0.865	0.983	0.013
$63,000+	0.934	0.877	0.994	0.032
Insurance				
Medicaid	Reference			
Private insurance	0.888	0.816	0.966	0.006
Medicare	0.91	0.832	0.995	0.039
Other government	0.844	0.695	1.025	0.087
Cancer stage				
I	Reference			
II	1.548	1.429	1.677	< 0.001
III	1.753	1.616	1.901	< 0.001
IV	2.349	2.194	2.515	< 0.001
Unknown	1.581	1.457	1.715	< 0.001
Cancer grade				
I	Reference			
II	1.326	1.193	1.475	< 0.001
III	1.69	1.52	1.88	< 0.001
IV	1.958	1.521	2.522	< 0.001
Unknown	1.38	1.247	1.527	< 0.001
Treatment				
No treatment	Reference			
Surgery	0.195	0.182	0.208	< 0.001
Interventional oncology	0.31	0.276	0.35	< 0.001
Radiation oncology/chemotherapy	0.425	0.405	0.446	< 0.001
Facility type				
Academic/research program	Reference			
(Comprehensive) community cancer program	1.146	1.097	1.197	< 0.001
Other cancer programs	1.1	1.025	1.181	0.008
Facility location				
East South Central	Reference			
East North Central	0.882	0.803	0.969	0.009
Middle Atlantic	0.738	0.671	0.812	< 0.001

TABLE 1 continued

Predictor	HR	Lower 95% CI	Upper 95% CI	*p* Value
Mountain	0.839	0.737	0.956	0.008
New England	0.888	0.791	0.996	0.043
Pacific	0.868	0.785	0.959	0.005
South Atlantic	0.869	0.793	0.952	0.003
West North Central	0.772	0.696	0.857	< 0.001
West South Central	0.735	0.659	0.82	< 0.001
Year of diagnosis (since 2004)	0.973	0.966	0.981	< 0.001

HR hazard ratio, *CI* confidence interval

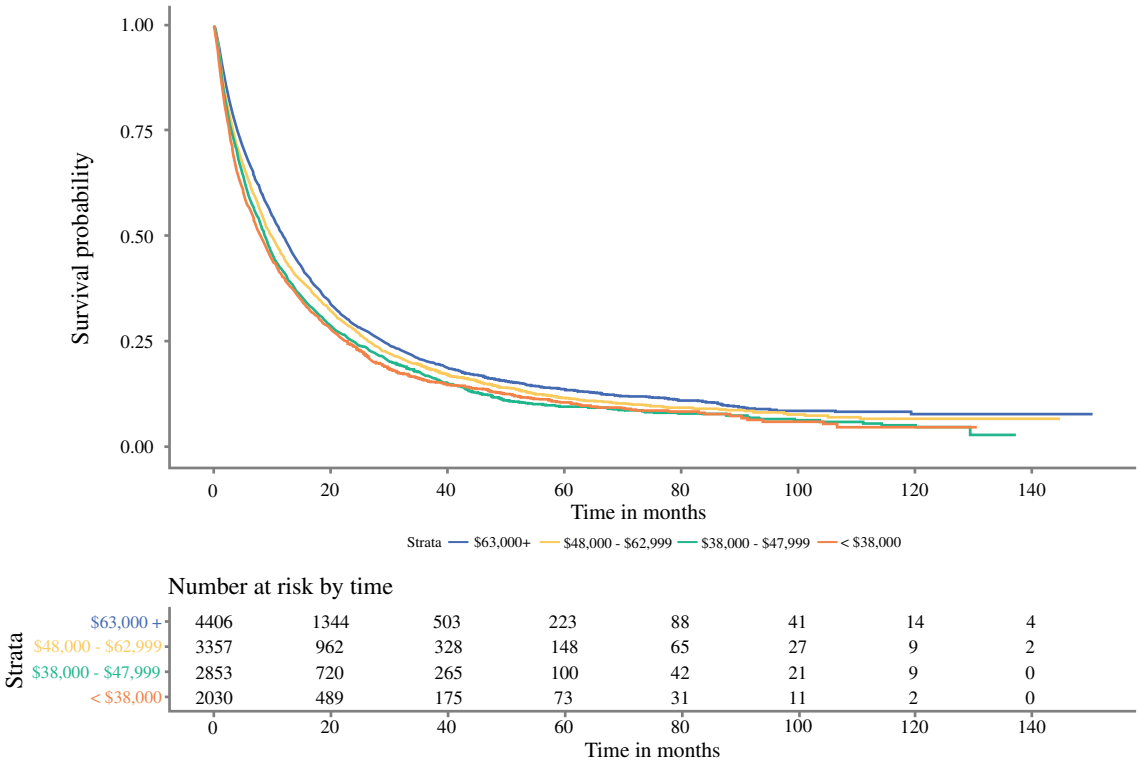

FIG. 3 Overall survival of ICC patients depending on income, with significant effect after multivariable adjustment ($48,000–$62,999 vs. < $37,999, HR 0.92, 95% CI 0.87–0.98, $p = 0.013$; > $63,000 vs. < $37,999, HR 0.93, 95% CI 0.88–0.99, $p = 0.032$). *ICC* intrahepatic cholangiocarcinoma, *HR* hazard ratio, *CI* confidence interval

underlining its influence on ICC treatment allocation and prognosis. In our study, low socioeconomic status was an independent predictor of lower ICC treatment rates, and was associated with a decreased likelihood for adjuvant and neoadjuvant chemotherapy in surgical patients. These discrepancies may be explained by the extent of underlying hepatic disease, as well as healthcare access; low socioeconomic status has been linked to a higher degree of liver cirrhosis in several studies, in part due to continued substance abuse.[17–20] A higher degree of liver cirrhosis not only limits treatment options but has also been described as an independent survival predictor in liver cancer.[21] Furthermore, low socioeconomic status might delay healthcare contact and reduce treatment compliance, for example due to problems with transportation or fear of missed wages.[20,22,23] The enrollment of low-income patients in high-deductible health plans (HDHPs) might further limit their healthcare access. Several studies have shown that low-income patients with high cost-sharing HDHPs are less engaged with the management of their healthcare plans and have reduced screening participation and more adverse health consequences.[24–26] Restricted healthcare access for

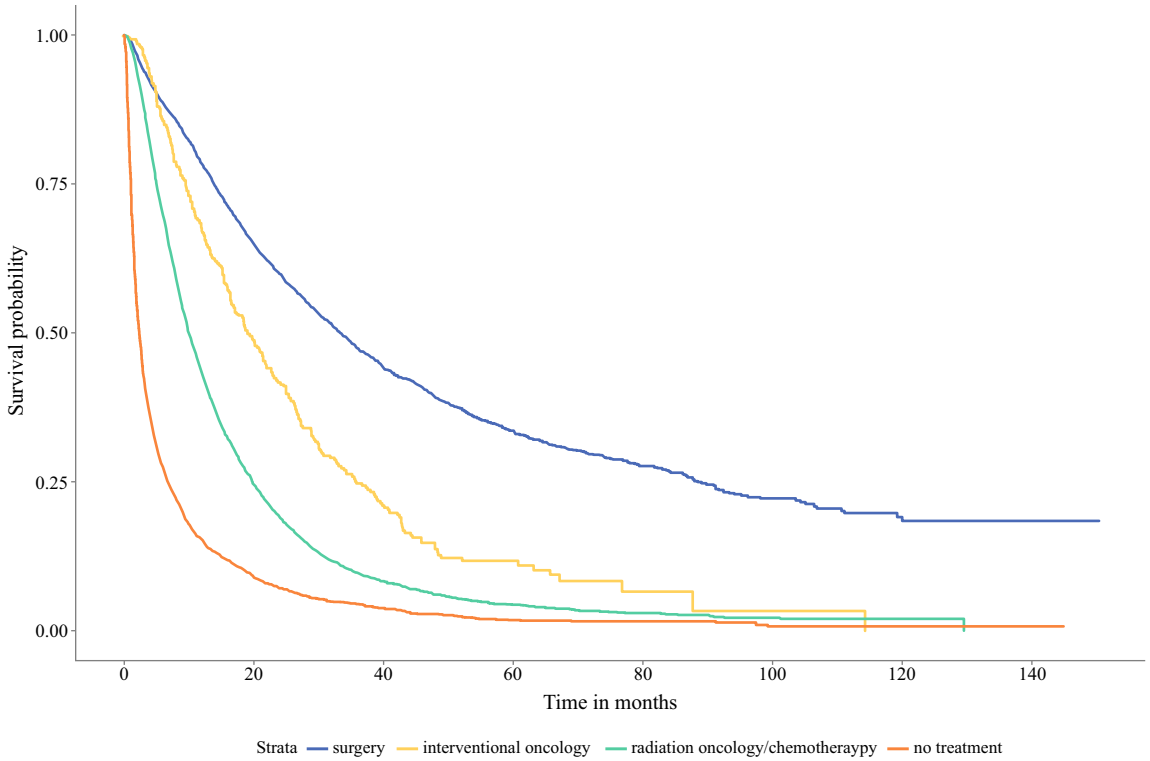

FIG. 4 Overall survival of ICC patients depending on treatment approach with best outcomes observed for surgical treatment, followed by interventional oncology (multivariable $p < 0.001$ vs. radiation oncology/chemotherapy and no treatment). *ICC* intrahepatic cholangiocarcinoma

patients with low socioeconomic status may also delay diagnosis, and thus explains the higher proportion of late-stage ICC observed in our study.

ICC treatment demonstrated relevant survival discrepancies, with a highest 5-year overall survival rate of up to 33.5% observed for surgical resection. These survival rates underline that surgery is the only curative treatment option of ICC, supported by the current literature.[9] Careful selection of surgical candidates with high performance status and localized disease probably underlies this finding.[9], [27] Survival in non-surgically managed patients was inferior to surgery but showed improved outcomes over no treatment. Although the optimal treatment algorithm for unresectable ICC is unclear, our data demonstrate improved survival for patients treated with interventional oncology compared with radiation oncology and chemotherapy.[28] Interventional oncology with local tumor ablation has been previously reported as an effective treatment option for recurrent ICC and may even be comparable to surgical resection in selected patients.[29,30]

To reduce the observed discrepancies in ICC treatment and outcomes, several clinical strategies are possible. Surgical resection should be considered as first-line treatment for all surgically resectable ICC patients based on its superior outcome. In surgically ineligible patients, interventional oncology should be considered. Healthcare providers must direct special attention to vulnerable populations, including African Americans with high comorbidities and those with low socioeconomic status and Medicaid insurance, where underutilization of surgery and neoadjuvant treatments is currently observed. The benefit of ICC treatment in academic settings can potentially be scaled to other centers by implementation of local multidisciplinary tumor boards optimizing treatment schemes on an individual patient basis.

Our study is not devoid of limitations. Although covering approximately 70% of annually diagnosed cancer cases in the US, there are concerns that the NCDB database is not representative of the US population, which may limit the generalizability of our results. Given the NCDBs' registry design, there was an absence of data on patients' substance abuse, exact comorbidities, liver function and extent of liver disease, cancer relapse, and repeated treatments. It remains unclear whether residual confounding by the aforementioned variables is sufficient to completely explain away the observed effects of socioeconomic discrepancies and treatment approaches. While the NCDB reports the primary payer at diagnosis and treatment, insurance status changes are not reported and might have affected follow-up care.

CONCLUSIONS

Our large-scale study on ICC patients in the US demonstrates marked variation in treatment allocation and outcome depending on socioeconomic status, demographic variables, cancer factors, and US geography. Male sex, low income, and Medicaid insurance were independent predictors of absent ICC treatment and were associated with decreased overall survival. Healthcare providers should address these discrepancies, for example by providing surgery and interventional oncology as first-line ICC treatments in surgically eligible or ineligible patients, respectively. Special attention should be direct to vulnerable populations with underutilization of surgery and neoadjuvant treatment, including those with low socioeconomic status.

AUTHOR CONTRIBUTIONS Conceptualization: JU, HSK. Methodology: JU. Validation: JU, HSK. Formal analysis: JU. Investigation: JU, CMS, HSK. Resources: CC, JL, SMS, HSK. Data curation: JU, CMS, HSK. Writing of the original draft: JU, CMS, CC, SAK, JL, SMS, HSK. Visualization: JU. Supervision: HSK. Project administration: CC, SAK, JL, SMS, HSK.

DISCLOSURE Johannes Uhlig, Cortlandt M. Sellers, Charles Cha, Sajid A. Khan, Jill Lacy, Stacey M. Stein, and Hyun S. Kim have no conflicts of interest to declare.

REFERENCES

1. Patel T. Increasing incidence and mortality of primary intrahepatic cholangiocarcinoma in the United States. *Hepatology.* 2001;33(6):1353–57.
2. Shaib Y, El-Serag HB. The epidemiology of cholangiocarcinoma. *Semin Liver Dis.* 2004;24(2):115–25.
3. Vauthey JN, Blumgart LH. Recent advances in the management of cholangiocarcinomas. *Semin Liver Dis.* 1994;14(2):109–14.
4. DeOliveira ML, Cunningham SC, Cameron JL, et al. Cholangiocarcinoma: thirty-one-year experience with 564 patients at a single institution. *Ann Surg*. 2007;245(5):755–62.
5. Khan SA, Taylor-Robinson SD, Toledano MB, Beck A, Elliott P, Thomas HC. Changing international trends in mortality rates for liver, biliary and pancreatic tumours. *J Hepatol.* 2002;37(6):806–13.
6. Yao KJ, Jabbour S, Parekh N, Lin Y, Moss RA. Increasing mortality in the United States from cholangiocarcinoma: an analysis of the National Center for Health Statistics Database. *BMC Gastroenterol.* 2016;16:117.
7. Esnaola NF, Meyer JE, Karachristos A, Maranki JL, Camp ER, Denlinger CS. Evaluation and management of intrahepatic and extrahepatic cholangiocarcinoma. *Cancer.* 2016;122(9):1349–69.
8. Khan SA, Davidson BR, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut.* 2002;51 Suppl 6:Vi1–9.
9. Jarnagin WR, Shoup M. Surgical management of cholangiocarcinoma. *Semin Liver Dis.* 2004;24(2):189–99.
10. Valle J, Wasan H, Palmer DH, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362(14):1273–81.
11. Konstantinidis IT, Arkadopoulos N, Ferrone CR. Surgical management of intrahepatic cholangiocarcinoma in the modern era: advances and challenges. *Chin Clin Oncol.* 2016;5(1):9.
12. Dwyer-Lindgren L, Flaxman AD, Ng M, Hansen GM, Murray CJ, Mokdad AH. Drinking patterns in US counties from 2002 to 2012. *Am J Public Health.* 2015;105(6):1120–7.
13. Yoon Y-H, Chen CM. *Surveillance report #105: Liver cirrhosis mortality in the United States: national, state, and regional trends, 2000–2013.* Arlington, VA. Department of Health and Human Services, Public Health Service, National Institutes of Health; 2016.
14. Overweight and 0besity. 2018. https://www.cdc.gov/obesity/index.html.
15. Younossi ZM, Stepanova M, Afendy M, et al. Changes in the prevalence of the most common causes of chronic liver diseases in the United States from 1988 to 2008. *Clin Gastroenterol Hepatol.* 2011;9(6):524–30.e521; quiz e560.
16. Sarmiento JM, Nagorney DM. Hepatic resection in the treatment of perihilar cholangiocarcinoma. *Surg Oncol Clin N Am.* 2002;11(4):893–908, viii–ix.
17. Lewis CE, Smith E, Kercher C, Spitznagel E. Predictors of mortality in alcoholic men: a 20-year follow-up study. *Alcohol Clin Exp Res.* 1995;19(4):984–91.
18. Leyland AH, Dundas R, McLoone P, Boddy FA. Cause-specific inequalities in mortality in Scotland: two decades of change. A population-based study. *BMC Public Health.* 2007;7:172.
19. Najman JM, Williams GM, Room R. Increasing socioeconomic inequalities in male cirrhosis of the liver mortality: Australia 1981–2002. *Drug Alcohol Rev.* 2007;26(3):273–8.
20. Jepsen P, Vilstrup H, Andersen PK, Sorensen HT. Socioeconomic status and survival of cirrhosis patients: a Danish nationwide cohort study. *BMC Gastroenterol.* 2009;9:35.
21. Pinter M, Trauner M, Peck-Radosavljevic M, Sieghart W. Cancer and liver cirrhosis: implications on prognosis and management. *ESMO Open.* 2016;1(2):e000042.
22. Arpey NC, Gaglioti AH, Rosenbaum ME. How socioeconomic status affects patient perceptions of health care: a qualitative study. *J Prim Care Commun Health.* 2017;8(3):169–75.
23. Kullgren JT, Galbraith AA, Hinrichsen VL, et al. Health care use and decision-making among lower-income families in high-deductible health plans. *Arch Intern Med.* 2010;170(21):1918–25.
24. Hibbard JH, Cunningham PJ. How engaged are consumers in their health and health care, and why does it matter? *Res Brief.* 2008;8:1–9.
25. Trivedi AN, Rakowski W, Ayanian JZ. Effect of cost sharing on screening mammography in Medicare health plans. *N Engl J Med.* 2008;358(4):375–83.
26. Trivedi AN, Moloo H, Mor V. Increased ambulatory care copayments and hospitalizations among the elderly. *N Engl J Med.* 2010;362(4):320–8.
27. Nakeeb A, Tran KQ, Black MJ, et al. Improved survival in resected biliary malignancies. *Surgery.* 2002;132(4):555–63; discission 563–554.
28. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol.* 2014;60(6):1268–89.
29. Shindoh J. Ablative therapies for intrahepatic cholangiocarcinoma. *Hepatobil Surg Nutr.* 2017;6(1):2–6.
30. Zhang SJ, Hu P, Wang N, et al. Thermal ablation versus repeated hepatic resection for recurrent intrahepatic cholangiocarcinoma. *Ann Surg Oncol.* 2013;20(11):3596–602.