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Temporal Trends in Mortality Location Among Patients With Intrahepatic Cholangiocarcinoma in the USA: A Retrospective Observational Analysis of National Center for Health Statistics Mortality Data

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ABSTRACT

Objectives: Intrahepatic cholangiocarcinoma (ICC) is a malignancy with rising incidence and mortality in the United States. This study aimed to investigate temporal trends in the place of death among patients with ICC and assess demographic disparities.

Methods: We used the CDC WONDER database (2003–2020) for a retrospective study of patients who died from intrahepatic cholangiocarcinoma identified through death certificates. Place of death was categorized as hospice, home, inpatient, nursing home, or other. Age-adjusted mortality rates were calculated per 100 000. Temporal trends were assessed using the Mann-Kendall trend test, and associations between demographic characteristics and place of death were examined using the χ^2 test.

Results: Of 101 631 ICC-related deaths (AAMR: 1.61; 95% CI 1.60–1.62), the AAMR rose from 1.19 (95% CI 1.15–1.23) in 2003 to 2.04 (95% CI 2.00–2.08) in 2020. Over the study period, home was the most frequent place of death (44.6%), followed by inpatient facilities (28.4%), hospice (11.1%), and nursing homes (9.5%). Deaths at home and in hospice increased significantly ($p < 0.01$), while inpatient and nursing home deaths declined ($p < 0.01$). Disparities were observed across race, sex, age groups, and urbanization. Younger patients more often died in inpatient facilities, and minority racial groups were less likely to die at home or utilize hospice.

Conclusions: ICC-related deaths in the USA nearly doubled over the study period, with a marked shift from inpatient and nursing home deaths to hospice and home. Demographic disparities in end-of-life care underscore the need for targeted interventions to improve equitable access to palliative services.

1 | Introduction

Intrahepatic cholangiocarcinoma (ICC) is the second most common type of primary hepatic malignancy, accounting for roughly 8% of total cases [1]. The incidence of ICC in the United States has seen an uptick over the last several decades and is projected to continue this trend [2–4]. ICC usually presents with nonacute symptoms or remains asymptomatic; hence, it commonly presents in advanced stages with unresectable disease [5]. Among patients who are initially deemed resectable on preoperative imaging, 30% are deemed unresectable on surgical exploration [6].

Over the past two decades, the age-adjusted mortality rate of ICC has risen to 1.5 per 100000 in the USA, and a similar upward trend in mortality was seen globally [7, 8]. The rising mortality trend is attributed to advanced disease stages at presentation, increased incidence in the elderly, and concomitant biliary tract disorders such as primary sclerosing cholangitis [9].

Surgery is the mainstay of treatment, and given the high probability of unresectable disease, many patients with ICC require palliative or hospice care. Integration of palliative care in terminal cancer is reported to improve quality of life, hospital costs, and survival [10]. Improved patient-related outcomes were observed in patients who died at hospice or home [11, 12]. Over the past two decades, deaths in hospice facilities and at home have steadily increased, with at-home death now being the most common place of death from all causes [13].

There is limited literature on the temporal trends of place of death in ICC patients. In this study, we aim to investigate the mortality trends in terms of place of death in the United States for patients with ICC and to gauge disparities in place of death between demographic and clinical subgroups. A growing body of literature in support of the integration of palliative medicine in oncology to improve patient outcomes emphasizes the need to identify gaps in end-of-life care.

2 | Materials and Methods

We followed the reporting of studies conducted using an observational routinely collected health data (RECORD) statement to report the findings in this study [14].

2.1 | Study Setting and Population

This is a retrospective study using death certificate data from the Centers for Disease Control and Prevention (CDC) Wide-ranging Online Data for Epidemiologic Research (WONDER) Database. All records from 1st January 2003 to 31st December 2020 were included. We identified all patients with intrahepatic cholangiocarcinoma using the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code C22.1, mentioned anywhere on the death certificate, either as the underlying or a contributing cause of death. No age restrictions were applied. Since the data used in this study is publicly available data, this study was exempt from an institutional review board (IRB).

2.2 | Study Design

We categorized the location of death into hospice, decedent's home, inpatient facility, nursing facility, and other (outpatient medical facility, emergency department, dead on arrival at the hospital, and unknown). We queried the CDC WONDER database for data on demographic characteristics: age, sex, race (White, Black, Native American/Alaska Native, and Asian/Pacific Islander), urbanization category, and year of death. The National Center for Health Statistics Urban–Rural Classification Scheme was used to classify rural (population < 50000) areas and urban (large metropolitan area [population ≥ 1 million], medium/small metropolitan area [population 50000–999999]) according to the 2013 US census classification [15]. Three age groups were considered: 1–34 years, 35–74 years, and ≥ 75 years.

2.3 | Statistical Analysis

We used the Mann-Kendall trend test to obtain Kendall's τ coefficient for identifying temporal trends in the proportion of total deaths by place of death by measuring the rank correlation of non-parametric ordinal variables. Kendall's τ coefficient tests if two variables (proportion of death in a location and year) may be regarded as statistically dependent. The χ^2 test was used to investigate associations between categorical variables and the location of death. We calculated crude mortality rates (CMRs) per 100000 with 95% confidence intervals (CIs) by dividing the number of deaths in a year by the corresponding US population of that year. Age-adjusted mortality rates (AAMRs) were obtained by standardizing the population to the US 2000 standard [16]. The analysis was conducted using RStudio. A p-value < 0.05 was considered statistically significant in all instances.

3 | Results

From 2003 to 2020, a total of 101631 deaths were recorded in patients with intrahepatic cholangiocarcinoma, giving an AAMR of 1.61 (95% CI: 1.60–1.62). The AAMR increased from 1.19 (95% CI: 1.15–1.23) in 2003 to 2.04 (95% CI: 2.00–2.08) in 2020.

The AAMR varied by census regions: Northeast, 1.77 (95% CI: 1.74–1.79); Midwest, 1.68 (95% CI: 1.66–1.70); West, 1.70 (95% CI: 1.67–1.72); and South, 1.43 (95% CI: 1.42–1.45). The highest AAMR was observed in Rhode Island (2.23, 95% CI: 2.04–2.43), while the lowest was observed in Mississippi (0.89, 95% CI: 0.81–0.97). During the study period, the decedent's home was the most common place of death (44.6%, $n = 45322$), followed by inpatient facilities (28.4%, $n = 28814$), hospice facilities (11.1%, $n = 11266$), and nursing homes and long-term care facilities (9.5%, $n = 9651$).

3.1 | Temporal Trends

The percentage of deaths in hospice facilities increased significantly from 2003 to 2020, from 0.7% in 2003 to 12.0% in 2020 ($\tau = 0.\ 0.817$, $p < 0.001$). The proportion of deaths at home also increased significantly from 43.6% in 2003 to 54.6% in 2020 ($\tau = 0.569$, $p = 0.001$). However, the proportion of deaths in inpatient hospitals decreased from 34.9% in 2003 to 22.1% in 2020 ($\tau = 0.922$, $p < 0.001$). Similarly, the proportion of deaths in nursing homes also decreased from 12.4% in 2003 to 5.6% in 2020 ($\tau = 0.869$, $p < 0.001$) (Figure 1).

3.2 | Age Groups

The proportion of hospice, inpatient, and nursing home deaths differed significantly by age ($p < 0.001$). Younger patients were more likely to die in inpatient facilities, while a significantly greater proportion of older patients died in nursing homes (Table 1). No significant difference was observed with the proportion of deaths at home across age groups ($p = 0.637$).

3.3 | Sex and Race

A similar proportion of males and females died at a hospice facility (11.0% vs. 11.2%, $p = 1.0$) and at home (44.5% vs. 44.7%, $p = 1.0$). However, males more frequently died in inpatient facilities (30.4% vs. 26.2%, $p < 0.001$), whereas females more

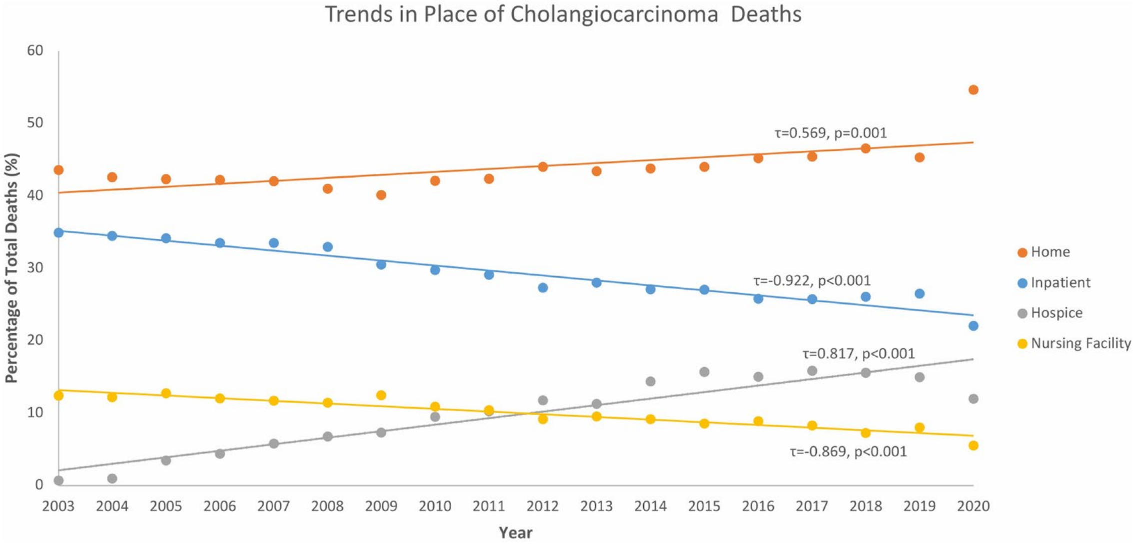

FIGURE 1 | Trends in place of death in intrahepatic cholangiocarcinoma patients in the United States.

TABLE 1 | Location of death in patients with intrahepatic cholangiocarcinoma in the USA from 2003 to 2020.

		Place of death (%)					
		Hospice	**Home**	**Inpatient**	**Nursing home/long-term care facility**	**Other**	***p***
Overall		11.1	44.6	28.4	9.5	6.5	
Age (years)	1–34	10.3	44.6	38.0	1.1	9.3	< 0.001
	35–74	11.4	41.3	31.4	6.0	6.3	
	> 75	10.6	44.2	23.5	15.1	6.7	
Sex	Male	11.0	44.5	30.4	8.1	6.0	< 0.001
	Female	11.2	44.7	26.2	10.9	7.0	
Race	White	11.3	46.0	26.5	9.7	6.4	< 0.001
	Black	11.6	32.8	39.9	7.9	7.8	
	Asian	6.7	43.4	35.3	8.8	5.8	
	American Indian	8.1	42.6	35.2	7.8	6.4	
Urbanization	Large metro	11.1	43.2	30.6	8.9	6.2	< 0.001
	Medium/small metro	13.1	45.9	24.8	9.2	6.9	
	Non-metro	7.0	47.0	27.5	12.0	6.6	

frequently died in nursing homes (10.9% vs. 8.1%, $p<0.001$). The proportion of hospice, home, inpatient, and nursing home deaths differed significantly by race ($p<0.001$ for all comparisons). Blacks showed the highest proportion of deaths at inpatient facilities (39.9%), and Whites showed the lowest (26.5%). Deaths in hospice were lower in Asians (6.7%) and American Indians (8.1%, $p<0.001$).

3.4 | Place of Death and Urbanization

The proportion of deaths in hospice was significantly different between patients in large metropolitan, medium/small metropolitan, and non-metropolitan areas (11.1% vs. 13.1% vs. 7.0%, $p<0.001$), as were inpatient deaths ($p<0.001$), deaths in nursing homes ($p<0.001$), and deaths at home ($p<0.001$).

4 | Discussion

The continuous increase in the incidence and mortality of the ICC provides the impetus for our study to review the trends in end-of-life care and place of death among ICC patients in the USA from 2003 to 2020. The AAMR increased from 1.19 in 2003 to 2.04 in 2020. There has been a significant increase in the proportion of deaths at home ($\tau=0.569$, $p=0.001$) and hospice ($\tau=0.817$, $p<0.001$), with a simultaneous decrease in the proportion of deaths in nursing facilities ($\tau=-0.869$, $p<0.001$) and inpatient settings ($\tau=-0.922$, $p<0.001$). During the study period, deaths at home have been the most common place of death (44.6%), followed by inpatient deaths (28.4%).

Our study has found various racial and gender disparities in terms of the place of death. As compared to white patients, home deaths were much lower in minority racial sub-groups (Table 1). The use of hospice was less frequent in Asian and American Indian populations compared to African American and White subgroups. The differences in at-home and hospice end-of-life care between racial groups have been proposed to stem from lower access to and preferences for palliative care, mistrust of the healthcare system, and differences in religious values, cultural norms, and patient education [17–20]. The literature consistently documents the knowledge gap among minority racial subgroups regarding palliative care as a source of such disparities [21]. A randomized control trial by Fischer et al. showed a significant improvement in advanced care planning in minority populations with culturally tailored bilingual educational material [22]. These racial disparities are particularly concerning, as socioeconomically disadvantaged and minority populations have a disproportionately high incidence of ICC [3].

In terms of gender, similar trends were seen in both groups across home and hospice. Male patients were found to be more likely to die in an in-patient setting compared to women. Various reports have found that the female gender is associated with a lower likelihood of undergoing aggressive treatment and late hospice enrollment [23, 24]. Despite the wide recognition of these gender-based differences across various disease processes, the reasons for these differences have not been fully elucidated. These differences have been explained in literature by a myriad of social, behavioral, and healthcare-related factors. Sharma et al. recognized the differences in physician recommendations and end-of-life care discussions as a contributing factor to this disparity [25].

Patients aged less than 35 had a higher number of deaths at inpatient facilities and fewer hospice and home deaths. Abdelaal et al. reported adolescents and young adults are more likely to receive high-intensity medical care at the end of life [26]. The discrepancies in the palliative care resources and referral trends are widely reported in pediatric patients [27, 28]. In terms of urbanization, inpatient deaths were more frequent in large metropolitans, hospice deaths in medium/small metropolitans, and home deaths in non-metropolitan areas. Gessert et al. found the rural caregiver views to be more accepting of death and lower acceptance of life-sustaining measures compared to urban caregivers, which explains the end-of-life care disparities we observed [29].

The exponential, almost two-fold increase in ICC-related mortality we observed is likely multifactorial. The increasing incidence of HCV virus, alcoholic liver disease, smoking, and obesity, widely reported risk factors for ICC, are the probable causes of increased incidence and mortality [30]. Data from the US show a general trend toward increased deaths at home in recent times, especially for cancer-related deaths [13]. 48.5% and 41.9% of at-home deaths occur in pancreatic and colon cancers, respectively, compared with the 44.6% of ICC deaths we observed.

The present study has several limitations. To identify decedents, we relied on the documented underlying causes of death on the death certificates. It is probable that some deaths were not properly captured or categorized due to errors or variations in how the cause of death was recorded. Furthermore, it is difficult to determine what proportion of patients dying at home had access to home hospice care due to the nature of the data in NCHS WONDER. The optimal time to initiate hospice care is promptly after a definitive diagnosis and early in the disease course [31]. For patients who ultimately died at hospice, it is not possible to determine from the data set at what point during their clinical course hospice and palliative care teams were involved. The absence of individual patient data also precludes a detailed multivariate analysis and identification of risk factors for patients dying in locations other than home or hospice.

Future studies are needed to elucidate the underlying reasons for the trends in end-of-life care seen in patients with ICC. Our data demonstrate the need for future work investigating the systemic and structural barriers to end-of-life care access, especially in racial minorities, with the aim to bridge gaps in understanding of factors leading to disparities in end-of-life care and place of death.

5 | Conclusions

There has been a significant increase in the proportion of patients with ICC dying at home or hospice in the US from 2003 to 2020. Disparities exist in the place of death in this patient population based on demographic and clinical factors, such as age, sex, race, and urbanization status.

Ethics Statement

Since the data used in this study is publicly available deidentified data, this study was exempt from an institutional review board (IRB) and therefore from an ethics approval.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data relevant to this study are publicly available from the CDC WONDER database (https://wonder.cdc.gov). The study protocol and statistical code can be made available upon request.

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