

Analysis of hospital incidence and direct medical costs of intrahepatic cholangiocarcinoma in Spain (2000-2018)

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Abstract

Introduction: Intrahepatic cholangiocarcinomas (iCCA) are aggressive tumours, often diagnosed in advanced stages and with limited curative treatment options. Their incidence has raised in the past years, increasing their associated economic burden. This study aimed to measure hospital incidence and mortality of iCCA and to evaluate direct medical costs.

Methods: Records of admissions due to iCCA between 1 Jan 2000 and 31 Dec 2018 were obtained from a Spanish National discharge database. Hospital incidence and mortality were measured within the hospitalised population and medical costs were assessed for specialised healthcare.

Results: Admission files corresponded to 23,315 patients, with a median age of 73 years (IQR=17) and 55.9% of males. Cholangiocarcinoma presented a hospital incidence of 6.9 per 10,000 persons in 2018, increasing significantly over the study period. In-hospital mortality was 31.5% the year 2018 and remained stable over the study period. The mean annual direct medical cost of secondary care was €9417 per patient the year 2017, and increased significantly between 2000 and 2008, stabilising after 2009.

Conclusion: The incidence of iCCA in Spain increased over the past years. The medical costs of iCCA per patient stabilised after 2008 but total costs are expected to increase if incidence continues to raise.

Keywords: cholangiocarcinoma; intrahepatic bile ducts; incidence; mortality; direct medical costs.

Introduction

Cholangiocarcinomas (CCAs) are a group of malignant tumours characterised by clinical aggressiveness and limited treatment options; according to their anatomical location, CCAs can be classified as intrahepatic (iCCAs), perihilar (pCCAs) and distal cholangiocarcinomas (dCCAs) [1]. Similarly to the other types of CCA, the carcinoma of intrahepatic bile ducts (iCCA) is diagnosed in advanced stages, often unresectable or metastatic, and it has been historically misdiagnosed: symptoms are often unspecific (right upper quadrant pain, weight loss, etc.), and many patients are asymptomatic. For these reasons, an accurate diagnosis and tumour staging are central to iCCA management, to determine resectability and prognosis. Several guidelines provide guidance for iCCA staging; the 8th edition of the AJCC Cancer Staging Manual provides an updated classification for cholangiocarcinoma, using the TNM Classification of Malignant Tumours, into six stages (IA, IB, II, IIIA, IIIB and IV) [2,3].

The incidence of CCA displays a significant geographical variation; in most countries it is considered a rare cancer, with an incidence of less than 6 cases per 100,000 people [4]. In Spain, estimates situate the incidence of cholangiocarcinoma around the 0.5 cases per 100,000 people [4]. The incidence of intrahepatic CCA is presumably lower, considering that this tumour type represents around 10% of all cholangiocarcinomas [5].

Currently, surgical resection of the tumour is considered the only potential curative approach in CCA, however, loco-regional recurrence or distant metastasis are frequent, with patients requiring adjuvant treatments [6,7]. The reported 5-year survival rate after resection is 22-44% for iCCA, which justifies the need for further research in the field [1]. In addition, despite its low incidence, the number of iCCA diagnosed cases and mortality have risen in the past few decades [8,9]; mortality rates from iCCA increased between 2002 and 2012 in many countries worldwide [9].

Epidemiologic data is scarce for this cancer type in Spain, where its incidence is expected to increase similarly to other European countries, partly due to the improved diagnostic methods [10]. In this direction, the analysis of real-world data permits to evaluate epidemiology and disease management, providing a basis for budget allocation decision in public healthcare [11,12].

This study aimed to revise the epidemiology and costs of cholangiocarcinoma at the hospital level in Spain and to analyse any trends in hospital incidence and mortality between 2000 and 2018 via the revision of hospital records.

Methods

Study setting

Admission records of patients admitted in hospitals and specialised care centres in Spain between 1 Jan 2000 and 31 Dec 2018 were analysed in a retrospective multicentre study. Specialised care records were extracted from a Spanish National discharge database, which covers 90% of hospitals in Spain and is representative of all Spanish regions. Data was codified at the hospital level by means of the International Statistical Classification of Diseases and Related Health Problems, 9th version (ICD-9) prior to 2016 and 10th version (ICD-10) after the year 2016 [13,14]. The database is validated internally and subjected to periodic audits; in this process, errors and unreliable data are eliminated.

Data extraction

Hospital admission records (inpatient and outpatient) in which an intrahepatic bile duct carcinoma was registered as the admission motive were identified from the database using the ICD-9 and ICD-10 codes: 155.1 and C22.1. Any parameters identifying healthcare centres or medical history were re-coded within the healthcare centres to maintain records anonymised, in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. This research did not involve human participants and there was

no access to identifying information; in this context the Spanish legislation does not require patient consent and ethics committee approval [15]. The Spanish Ministry of Health ensures compliance with current data protection legislation [16].

Study variables

The variables obtained and included in the analysis were: patients' sex and age, date of admission, type of admission, date of discharge, type of discharge (including death), readmission rate (defined as a subsequent readmission for the same cause within 30-days after discharge), admission motive, secondary diagnoses registered during the admission, medical procedures and admission costs. Admission costs were not available for the year 2018 at the time of the study.

Data analysis

The analysis of patient characteristics was based on the first admission registered per patient during the study period. All admission files were used to analyse admission type, length, readmission rate, medical procedures and admission costs. The analysis considered two age groups: patients' under 72 years of age and those aged 72 years and older. A sub analysis was performed considering patients that registered metastatic tumours. Hospital incidence was measured as the number of patients admitted with a cholangiocarcinoma within the hospital discharge database, in-hospital mortality was calculated as the annual number of deaths registered within the patients with a cholangiocarcinoma. Direct medical costs were calculated based on the admission costs registered in the database; these are assigned according to the standardised average expenses of admissions and medical procedures determined by the Spanish Ministry of Health (include all expenses related to the admission: examination, medication, surgery, diet, costs associated to personnel, medical equipment and resources). Mean admission costs were calculated by age and per admission type, considering urgent/scheduled

admissions, length of stay, readmission status and medical procedure/therapeutic approach. The costs incurred outside of the healthcare centre, such as those of prescribed medication, were not available.

Frequencies and percentages are presented for dichotomous variables and mean and standard deviation or median and range or interquartile range (IQR) were calculated for quantitative variables as appropriate. Normality was tested with the Kolmogorov-Smirnov test. Two-tailed T-student or one-way analysis of variance were used as appropriate and two-sample Z tests were used to test for differences in sample proportions, with a $p < 0.05$ considered statistically significant.

Statistical analyses were performed using Microsoft Excel© Professional Plus 2010 (Microsoft Corporation, Redmond, WA, USA) and StataSE 12 for Windows (StataCorp LP, 2011. Stata Statistical Software: Release 12. College Station, TX, USA).

Results

Patient characteristics

The 31,760 admission files analysed in the study corresponded to 23,315 patients. Median age was 73 years (IQR=17), and 55.9% of the patients were males. The percentage of male patients was increased when considering patients under 72 years of age (Table 1). Overall, 28.1% of the admissions were associated with the presence of metastatic tumours. Patients presented essential hypertension, diabetes and hyperlipidaemia in 50.5%, 29.9% and 24.6% of admissions. The obstruction of bile ducts and other disorders of the biliary tract were registered in 29.4% of all admissions.

Hospital incidence and mortality

The hospital incidence of cholangiocarcinoma was 6.9 per 10,000 persons in 2018, and increased significantly over the study period (2000 vs. 2018; $p < 0.001$). Additionally, hospital incidence the year 2018 was significantly higher in men than in women, with

incidences of 8.4 vs. 5.6 per 10,000 persons ($p < 0.001$) (Figure 1a). Hospital incidence was too significantly higher in patients aged 72 years and older versus that in patients under 72 years of age, with incidences of 10.5 and 4.7 per 10,000 persons in 2018 ($p < 0.001$) (Figure 1b).

In-hospital mortality was stable over the study period, being 31.5% the year 2018. Overall, no differences appeared in the mortality rate between men and women (Figure 1c). In-hospital mortality was significantly higher in patients aged 72 years and older versus those under 72 years of age, being 31.4% and 30.1% the year 2018, respectively (Figure 1d). In-hospital mortality in patients diagnosed with metastatic tumours reached the 39.2% in 2018.

Use of medical resources and costs

The majority of admissions (67.1%) were urgent or non-scheduled, this percentage increased to the 74.0% in patients aged 72 years and older (Table 2). Patients with metastatic tumours were admitted through urgent admissions in 73.1% of the cases. No changes were found in the length of hospital stay (LOHS) within patient groups, yet, LOHS decreased significantly over the study period (2000 vs. 2018; $p < 0.001$). No significant differences appeared in LOHS between men and women or by age (Figure 2a,b). Most admissions were registered in digestive, internal medicine, surgery and oncology services.

Diagnostic procedures were predominant in hospital admissions, mostly represented by computerised axial tomography of thorax and abdomen (45.7%), diagnostic ultrasounds (42.2%) and magnetic resonance imaging (15.3%) (Table 3). Tumour resection techniques were registered in only 15.0% of all admissions, and the administration of chemotherapy in 10.7%. Procedures of incision of the biliary ducts, principally the endoscopic insertion of a stent, biliary endoscopy via existing T-tube or other tract and

endoscopic sphincterotomy and papillotomy, were registered in 47.2% of all admissions. Interestingly, patients aged 72 years and older registered a lower frequency of admissions for the administration of chemotherapy (9.5% vs. 16.4% in patients < 72 years); a similar trend was observed in the frequency of admissions in which tumour resection was registered (8.9% vs. 29.7% in patients < 72 years).

Regarding medical costs, the mean annual direct medical cost of secondary care of cholangiocarcinoma was €6233 per admission, €8491 per patient (€9417 the year 2017) (Table 4). Costs increased in stays longer than 14 days vs. those under 14 days. The mean cost of admissions in which tumour resection was registered reached the €13,843.

Direct medical costs increased significantly between 2000 and 2008 ($p < 0.001$). Direct medical costs per patient were higher in men versus females ($p = 0.047$) (Figure 2c), and in patient under 72 years of age versus those age 72 and older ($p < 0.001$) (Figure 2d). Patients with metastatic tumours represented a mean cost per admission of €6061, €8444 per patient.

Discussion

Intrahepatic cholangiocarcinoma is an aggressive rare cancer, often diagnosed at advanced stages and with poor prognosis. Patients identified in this study had a median age of 73 years, and displayed comorbid conditions common in the population over 55 years of age. Essential hypertension, hyperlipidaemia and diabetes were found in 19.8%, 17.9% and 7.8% of the Spanish population, respectively, according to the Spanish Ministry of Health, while these percentages were 29.82%, 30.77% and 11.77% in the population between 55 and 64 years of age the same year [17]. Chronic liver disease and primary sclerosing cholangitis can be a risk factors for the development of iCCA [18,19], and were registered herein in 11.0% and 10.6% of admissions, respectively. In addition,

symptoms affecting the bile ducts were common in these patients, consequence of the abnormal cell growth within the biliary tract.

In this study, the hospital incidence of iCCA displayed an increasing trend between 2000 and 2018 in both men and women. This trend, found in most western countries has been previously associated with the improvement of diagnostic techniques that reduced the rate of misdiagnosis and misclassification [8,20,21]. The year 2018, hospital incidence of iCCA was 8.4 per 10,000 men and 5.6 per 10,000 women, a relatively high incidence that cannot be compared to those found in the general population.

In terms of mortality, no major differences were observed during the study period. The improved and earlier diagnosis of these tumours should reduce mortality, however, this is not visible in this database. A bias towards more severe cases, treated in bigger hospitals, cannot be discarded. An early diagnosis is central to increase survival, which is about the 40% at 5-years after resection [22]. The importance of diagnosis techniques is reflected in this register, following standard diagnosis practices that include computerised axial tomography, diagnostic ultrasounds and magnetic resonance imaging [23,24]. Unfortunately, the registration of medical procedures within the database appeared incomplete, and tumour resection and chemotherapy were presumably under registered, hampering the analysis of disease management. Nonetheless, a lower frequency of admissions for the administration of chemotherapy or tumour resection were registered in patients aged 72 years and older, which could be derived from the application of different disease management protocols in older patients.

The medical costs of iCCA have not been fully evaluated and economic data regarding this cancer type is scarce; the only data available aimed to compare the cost-effectivity of various treatments [25-27]. This study evaluated the direct medical costs incurred in hospital settings. The mean annual direct medical cost of secondary care of iCCA was

€8491 per patient, €9417 the year 2017. The most frequent curative approach registered in younger patients is seemingly associated to higher direct medical costs in this patient group. Medical costs per patient increased significantly between 2000 and 2008 and stabilised after 2009. The upwards revision of unit costs registered by the Spanish Ministry of Health must be taken into account when interpreting this data; the mean unit cost associated to hepatobiliary cancer was €3935 in 2002 and €6043 in 2017 [28]. In addition, an increase in incidence may reflect as a raise in total costs. To increase data relevance and reliability further studies are recommended to evaluate medical costs at the European level; nonetheless, this study may guide further assessment.

It is plausible that a number of limitations may have influenced the results obtained. The patients included in the database may not reflect the total patient population, a bias towards severe cases, treated in bigger hospitals, is plausible. This applies to disease management and comorbidity. In addition, data obtained from the database only allows the calculation of hospital incidence and in-hospital mortality. Further analyses will be required to evaluate any general trends in survival. Finally, the incomplete registry of medical procedures hampered the evaluation of disease management.

Conclusions

This study provides relevant data for the assessment of the current situation of iCCA in Spain and its costs. The incidence of iCCA in the country continues to raise, as in most western regions. Patients' old age should be taken into account in prospect disease management protocols given the generalised presence of chronic comorbidity in this patient group. The medical costs of specialised care of iCCA per patient appeared stable but total costs are expected to increase with its growing incidence.

Declarations

Ethics approval and consent to participate

Ethics committee approval and consent were not required for this study.

Data Availability Statement

The data that support the findings of this study is available from the Spanish Ministry of Health via the Unit of Health Care Information and Statistics (Spanish Institute of Health Information) for researchers who meet the criteria for access to confidential data at <https://www.mscbs.gob.es/estadEstudios/sanidadDatos/home.htm>

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Declaration of financial and other interest

The authors declare that they have no competing interests.

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Tables

Table 1 Characteristics of patients included in the study by age (2000-2018).

	All patients (N=23,315)	Patients aged < 72 years(N=10,399)	Patients aged ≥ 72 years (N=12,916)
Admission files, N	31,760	15,064	16,696
Median age, years (interquartile range)	73 (17)	63 (12)	79 (9)
Males, %	55.9	63.4	49.9
In-hospital mortality, %	31.5	28.1	34.2
Essential hypertension, % of admissions	50.5	42.3	59.0
Diabetes, % of admissions	29.9	27.4	33.0
Presence of metastatic tumours, % of admissions	28.1	33.0	23.6
Hyperlipidaemia, % of admissions	24.6	25.7	24.4
Obstruction of bile duct, % of admissions	16.4	15.5	17.8
Specified disorders of biliary tract[¶], % of admissions	13.0	11.1	15.1
Anaemia, % of admissions	12.0	12.0	12.4
Cholelithiasis, % of admissions	11.9	9.0	14.7
Bacterial infection, % of admissions	11.2	12.6	10.5
Chronic liver disease and cirrhosis, % of admissions	11.0	16.9	6.7
Chronic obstructive pulmonary disease, % of admissions	10.6	8.3	12.9
Primary sclerosing cholangitis, % of admissions	10.6	9.6	11.8
Hyperplasia of prostate, % of admissions	9.9	6.1	13.3
Ascites, % of admissions	8.8	12.0	6.6

[¶] Bile duct adhesions, bile duct atrophy, bile duct stasis, bile duct hypertrophy, bile duct cyst, bile duct ulcer.

Table 2 Admission details per age groups (2000-2018).

	Admissions all patients (N=31,760)	Admissions patients aged < 72 years(N=15,064)	Admissions patients aged ≥ 72 years (N=16,696)
Urgent admissions, %	67.1	59.4	74.0
Length of hospital stay, days, mean, median (range)	14.2, 10 (0-331)	14.2, 10 (0-195)	14.2, 11 (0-331)
Readmission, %	16.3	18.6	14.2
Admissions into digestive services, %	24.6	19.5	27.2
Admissions into internal medicine services, %	18.9	13.3	22.6
Admissions into digestive and general surgery services, %	11.9	12.4	10.3
Admissions into oncology services, %	11.4	14.5	7.2

Table 3 Most frequent medical procedures registered in patients with cholangiocarcinoma by age.

	Admissions all patients (N=31,760)	Admissions patients aged < 72 years(N=15,064)	Admissions patients aged ≥ 72 years (N=16,696)
Computerised axial tomography of thorax, abdomen	45.7	59.4	47.2
Diagnostic ultrasound	42.2	52.7	45.1
Diagnostic procedures on biliary tract	28.8	30.1	34.7
Magnetic resonance imaging	15.3	20.3	15.5
Biliary tract x-ray	13.4	17.4	13.8
Routine chest x-ray	13.5	15.4	15.3
Liver biopsy	11.3	20.7	7.7
Microscopic examination of blood	7.7	9.9	8.0
Partial or total hepatectomy	7.8	16.2	4.1
Cholecystectomy	5.1	9.6	3.3
Local excision or destruction of lesion or tissue of biliary ducts	2.1	3.9	1.5
Injection or infusion of chemotherapy	10.7	16.4	9.5
Incision of biliary tract	44.6	48.0	52.6
Injection of antibiotic	7.5	9.9	7.7
Transfusion of packed cells	6.7	9.6	6.3

Table 4 Mean admission cost (€) by age per admission type, length of stay, readmission status and medical procedures.

	Admissions all patients (N=31,760)	Admissions patients aged < 72 years(N=15,064)	Admissions patients aged ≥ 72 years (N=16,696)
Total	€6233	€6670	€5839
Urgent admission	€5805	€6143	€5559
Scheduled admission	€7984	€7453	€6652
Length of stay ≤ 14 days	€5233	€5446	€5034
Length of stay > 14 days	€7984	€8924	€7186
Readmission – No	€6667	€7215	€6218
Readmission - Yes	€7085	€7454	€6651
Diagnostic procedures	€6851	€7388	€6408
Tumour resection	€13,843	€13,606	€14,342
Chemotherapy	€6558	€6666	€6444

Figures

Figure 1 Hospital incidence of cholangiocarcinoma by sex (a) and age (b), and in-hospital mortality by sex (c) and age (d) (2000-2018).

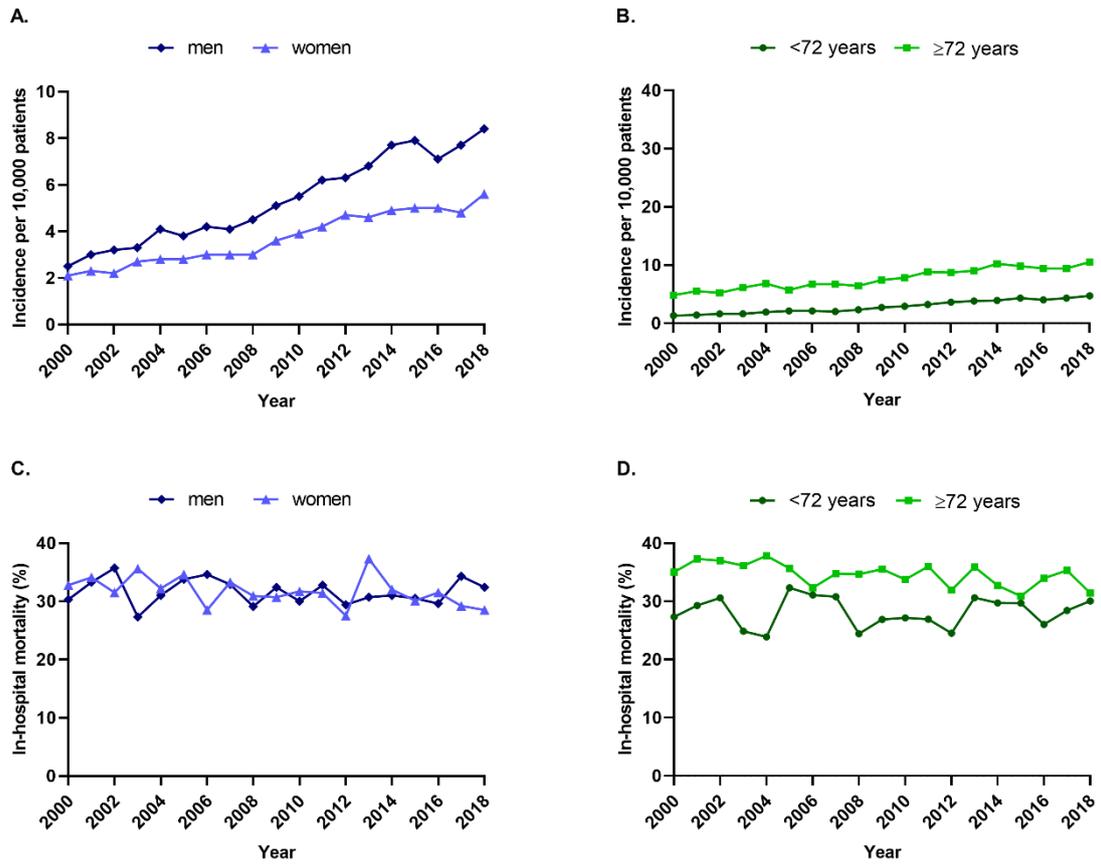


Figure 2 Mean length of hospital stay (LOHS) by sex (a) and age (b) (2000-2018), and mean direct medical cost per patient by sex (c) and age (d) (2000-2017).

