RETH!NK LIVER CANCER

For better understanding, diagnosis and treatment of the primary liver cancer, cholangiocarcinoma

AMMF
THE CHOLANGIOCARCINOMA CHARITY

Lack of awareness is probably the single biggest obstacle you come across – not just as a patient, left with very little information after diagnosis, but also amongst GPs and hospital doctors in areas of the country where there are no centres with hepato-pancreato-biliary teams knowledgeable in cholangiocarcinoma, who often don't appreciate what they are up against and don't direct people on to an appropriate specialist.

My message to anyone who has been diagnosed is to be your own advocate. Be strong and don't take no for an answer. Keep pushing and pushing until you get a satisfactory answer – whether that's from your GP, your oncologist, your surgeon, for a second opinion or a third opinion, keep going.

Andrew Clay, diagnosed with cholangiocarcinoma, aged 53

AMMF
THE CHOLANGIOCARCINOMA CHARITY

RETHINK
LIVER CANCER

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Foreword

Helen Morement, AMMF Chief Executive

As the UK's only charity solely dedicated to supporting people diagnosed with cholangiocarcinoma – a primary liver cancer with one of the worst prognoses of any cancer – AMMF has seen first-hand how a lack of awareness of this disease (also called bile duct cancer and CCA) so frequently prevents patients from accessing the treatments and care they need and deserve.

Over two decades supporting these patients, representing their experiences and helping advocate for better outcomes, a key barrier to greater institutional support for people with CCA has been the lack of robust data to back up what we have been witnessing on the ground – that the incidence of CCA is rising, including among younger people; that there's significant variation in the way CCA is diagnosed and treated; and that early diagnosis and survival rates are not improving, in fact they are considerably worse than for other cancers.

There is an urgent need to discover the causes of CCA and develop more effective diagnostic tests and potentially curative treatments for this devastating disease. The first step towards making positive changes to health policy is to provide a robust evidence base to support the case for greater research, and rightly so. That's why AMMF commissioned and funded a first-of-its-kind data project from NHS England and Health Data Insight CIC (HDI) in collaboration with partners at Imperial College, London. Findings from our collaborative four-year project are detailed in this report, together with a series of evidence-based recommendations for better diagnosis, management and treatment of CCA.

Although up to now CCA has been firmly defined as a rare cancer, new evidence suggests that cases are rising significantly, with patient numbers almost doubling to rates that are similar to hepatocellular carcinoma (HCC) – the other, far more widely recognised primary liver cancer. Figures recently published by the NHS show the number of CCA cases recorded in 2020 in England (2,706) were almost the same as HCC (2,792)[1].

Historically, the term 'liver cancer' has been mostly used and understood by the public and in our health services to mean only HCC when there are, in fact, two quite different forms of primary liver cancer. CCA is also a primary liver cancer, but remains less well known, harder to diagnose and has significantly worse survival rates – all of which make a strong case for prioritising a greater focus and investment in this area.

That's why AMMF believes it's time to rethink liver cancer – in GP surgeries, community health and hospital services and within the planning of health policy and scientific research.

We hope that this report will help to support and inform those who have the influence to move the dial and improve the future for CCA patients and their families. Its publication marks the start of AMMF's Rethink Liver Cancer campaign, launched to raise public and professional awareness of CCA and to provide educational resources and support for clinicians and scientists, health policy decision makers and people diagnosed with CCA.

Visit **www.ammf.org.uk/rethink-liver-cancer** to find out more and how to get involved.

[1] https://www.cancerdata.nhs.uk/getdataout/liver

Shahid A Khan, Professor of Hepatology, Imperial College London and Imperial College NHS Trust

AMMF's Cholangiocarcinoma Data Project has confirmed what specialists like myself and Professor Mireille Toledano, who worked with me at Imperial College on the project, have known for some time: CCA incidence is much higher than previously thought by most medics and cases are rising; people with CCA are often diagnosed too late or not diagnosed at all.

Similarly, CCA patients may not always be getting the type of treatment they need or are not getting treatment at all. With a mortality rate that closely follows its incidence, CCA death rates are comparable if not actually higher than those for hepatocellular carcinoma (HCC), the more widely recognised primary liver cancer.

The findings have provided us with concrete evidence of the urgent need to do things differently. To improve the way CCA is diagnosed, managed and treated; and to address the lack of CCA awareness that exists throughout our health service and the wider public.

This project has also been about proving what we don't know as well as what we do. It has illustrated the gaps in data that exist due to the historical coding of CCA – for example, in ICD-10 (the World Health Organisation's International Classification of Diseases, version 10) and its previous iterations there is no code for perihilar CCA, which is the most commonly occurring type encountered clinically. These gaps have continued, even after the introduction of a new coding standard within ICD-11[2], which now distinguishes the three subtypes of CCA including perihilar, because the diagnosis of these subtypes can often be clinically difficult, and recording this uncertainty in a standardised way across all services, to support epidemiological studies, is a work in progress.

The only potentially curative treatment for CCA today is surgical resection or, in some very limited circumstances, liver transplantation.

Unfortunately, only a minority of CCA patients are eligible for resection or transplantation because by the time most patients are diagnosed, the cancer is too advanced for these treatments to be effective – hence the urgent need to raise CCA awareness and support action on earlier diagnosis – a call to action that sits squarely with the UK Government's aim of seeing 3 out of 4 of all cancers detected at an early stage by 2028[3]. Early signs can be vague and appear non-urgent, so will only trigger a rapid referral if GPs and other health professionals have raised awareness of this type of liver cancer and have access to knowledge that supports its earlier diagnosis and management.

If surgery is not an option, there are several other types of treatment which can help to control symptoms and delay progression of the cancer – and in some cases, may help to make surgery a possibility further down the line, after a reassessment.

That's why it's so important that every person diagnosed with CCA is given the opportunity for their case to be reviewed by a specialist Multi-Disciplinary Team (MDT) and that management of their cancer is undertaken at a centre of expertise – one of the key recommendations put forward in this paper.

Specialist MDTs and centres of expertise are essential for determining if patients are operable and for identifying the most appropriate – and up-to-date – treatment pathway, to take advantage of new treatments that are beginning to emerge in this field.

They are also key to addressing the inequalities and variation in practice highlighted in this report. Why are over 50% of CCA patients not given any cancer specific treatment at all? Is it because the disease is simply too advanced at presentation, or are there other reasons?

Understanding the answers to these questions will help create a more equal playing field for CCA patients. This report is an important first step in that direction.

[2] ICD-11, the 11th edition of the World Health Organisation's (WHO) International Classification of Diseases, was adopted by the 72nd World Health Assembly in 2019 and came into effect on 1st January 2022 – https://icd.who.int/en

[3] https://www.gov.uk/government/news/government-announces-plans-for-earlier-diagnosis-for-cancer-patients

About AMMF – The Cholangiocarcinoma Charity

AMMF is the UK's only cholangiocarcinoma charity, providing information and support to those who need it and campaigning to raise awareness of this little-known but devastating disease.

When it was set up in 2002 by Helen Morement as the Alan Morement Memorial Fund, the charity was the world's first dedicated solely to cholangiocarcinoma. It has since been joined by foundations in the USA and Thailand and groups in Tokyo and Milan. Today, the charity is officially **AMMF – The Cholangiocarcinoma Charity** and is a Charitable Incorporated Organisation (CIO) working across the UK and Europe and collaborating globally with medical and scientific experts and patient groups.

One of AMMF's major objectives is to support specialised research teams in their work to find the causes, methods of earlier diagnosis and effective treatments for CCA.

Since 2002, AMMF has awarded over £3m in grants to support CCA research at many of the UK's leading research institutions, and internationally.

> AMMF is a gateway to specialists, clinical trials and others in the same situation. All of a sudden, I had the confidence to challenge the opinion of local doctors who had little experience with this cancer and who appeared to have written me off... I'm now under one of the best medical teams in the UK, I have a treatment plan and the cancer is retreating.
>
> **Kevin Rodger, diagnosed with cholangiocarcinoma, aged 44**

Executive Summary

Why we need to Rethink Liver Cancer

The term 'liver cancer' is broadly used and accepted today to refer to the hepatocellular carcinoma (HCC) variant of liver cancer – but it is unhelpful messaging when it amplifies an existing and widespread lack of awareness that there are actually two different types of primary liver cancer, the other being cholangiocarcinoma (CCA).

To be able to associate CCA quickly and easily with the liver is a vital reference point from which AMMF, policymakers, professionals and the wider public can start to identify, advocate and prepare for the growing threat from this poorly known disease with one of the worst prognoses of any cancer.

Unlike HCC, where 9 out of 10 patients also have a history of cirrhosis and cancer screening is in place for this well-defined disease and cohort of patients, there isn't a 'standard' CCA patient. CCA is increasingly a disease of all ages where many patients do not have a history of liver disease and their cancer often presents without any clearly identifiable symptoms at all until its advanced stages. These characteristics all impact negatively on the wider perception that CCA today is an unknown or low-profile disease with a cause and symptoms that are not easy to explain or communicate. But new evidence points to an urgent need to better highlight and explain CCA, based on AMMF's data project that shows:

- CCA incidence counts and the number of deaths from 2001-2018 have more than doubled. In 2001, the incidence rate was 2.9 per 100,000 person-years, and in 2018 it was 4.6 per 100,000 person-years, an age-standardised incidence rate increase of more than 50%. If this trend continues then CCA will soon no longer be defined as a rare cancer (rare being defined as fewer than 6 per 100,000 person-years). This should be a significant cause for concern for all, given that the prognosis for CCA is currently so dismal. Compared to the England mean for all cancers (54%)[4], five-year survival rates for 'liver cancer' generally are already among the worst for cancers (13%)[5], but the five-year survival rate for CCA is even worse – 6-9% [6] for those diagnosed early enough to be eligible for potentially curative surgery, and as low as 2% for those receiving other forms of treatment.
- Numbers of people diagnosed with CCA at stage 1 and 2 (21%) fall well short of the 54% figure that currently applies across all cancers diagnosed at stage 1 and 2[7] and significantly below the national commitment to increase the percentage of cancers diagnosed early (stages 1 and 2) to 75% by 2028, as set out by The NHS Long Term Plan and re-emphasised in NHS England's 2023/24 priorities and operational planning guidance for cancer[8].
- Geographical disparities exist in incidence, mortality, routes to diagnosis and treatment given to CCA patients, including disparities that are positively linked to increased deprivation status.

A step change is needed in the way that CCA is currently perceived and understood, if delivery of national commitments on improvements for people with this cancer is to be achieved in terms of:

- elevating levels of awareness and understanding of CCA and the inequality and unwarranted variation in CCA health outcomes compared to other cancers;
- dramatically improving early diagnosis and maximising support for research into new and more effective diagnostic and treatment options that can enhance the disproportionately low chances of survival for people with CCA.

AMMF believes it is time to rethink liver cancer to raise awareness that 'liver cancer' includes CCA, which is not so much a rare cancer but a growing threat including among younger populations, with extremely poor health outcomes related to low early diagnosis rates, curative treatment interventions and survivability compared to many other cancers.

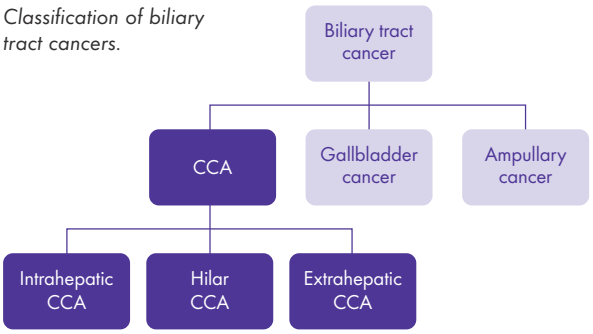
So that CCA is not missed, misdiagnosed or managed too late, AMMF is calling on clinicians, health planners and policy makers to rethink liver cancer, to help ensure that people with CCA receive the best possible chance of improving these health outcomes, in line with trends for people with other cancers, when the Government's 10-year Cancer Plan for England is implemented through its upcoming Major Conditions Strategy[9].

[4] https://researchbriefings.files.parliament.uk/documents/SN06887/SN06887.pdf
[5] https://www.nuffieldtrust.org.uk/resource/cancer-survival-rates
[6] Liao et al (2023), Disparities in care and outcomes for primary liver cancer in England during 2008–2018, https://doi.org/10.1016/j.eclinm.2023.101969
[7] https://www.cancerdata.nhs.uk/stage_at_diagnosis
[8] https://www.england.nhs.uk/wp-content/uploads/2022/12/PRN00021-23-24-priorities-and-operational-planning-guidance-v1.1.pdf
[9] https://www.gov.uk/government/consultations/major-conditions-strategy-call-for-evidence/major-conditions-strategy-call-for-evidence

About Cholangiocarcinoma

Cholangiocarcinoma (CCA), pronounced **'kol-an-gee-oh-car-sin-oh-ma'**, is also referred to as bile duct cancer. It is the second most common primary liver cancer in the world and is a biliary tract cancer (BTC). BTCs are those that occur within the biliary system, the network of ducts within the liver and the common bile duct outside the liver, and include cholangiocarcinoma, gallbladder cancer and ampullary cancer.

Classification of biliary tract cancers.

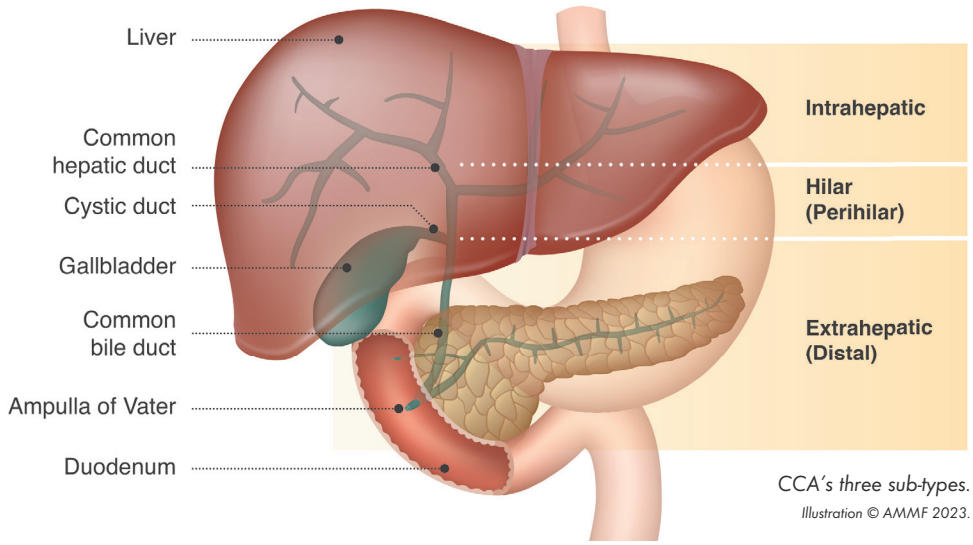


Cholangiocarcinoma has three sub-types and has historically been considered a rare cancer (defined by an age standardised rate of less than 6 per 100,000 person-years). CCA currently has a devastatingly poor prognosis for survival that is among the worst of all cancers.

A recent study, part of AMMF's CCA data project of the National Cancer Registration Dataset (NCRD)[10] of almost 51,000 BTCs diagnosed in England between 2001-2018, reported that CCA was by far the most commonly diagnosed BTC (63%) followed by gallbladder cancer (23%).

CCA's three sub-types[11,12] are categorised according to their anatomical site of origin:

- **Intrahepatic CCA –** This type originates in the bile ducts that are located inside the liver and accounts for **10–20%** of the total CCA cases.
- **Perihilar (or Hilar) CCA –** This type originates just outside the liver at the junction of two main ducts, the left and right hepatic ducts. This is the most common CCA subtype encountered clinically, accounting for **50–60%** of all cases.
- **Distal/Extrahepatic CCA –** This type originates in the common bile duct outside the liver anywhere from just below the cystic duct, which joins the common bile duct and the gallbladder, down to the small intestine. The common bile duct carries bile from the liver and the gallbladder down to the small intestine. This type accounts for **20–30%** of CCA cases.



CCA's three sub-types.

[10] Tataru et al. Cholangiocarcinoma Across England: a national study examining temporal changes in incidence and survival, and variation by region and deprivation. submitted 2023.
[11] Banales, J. M. et al. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. Nat Rev Gastroenterol Hepatol 17, 557–588 (2020).
[12] Khan, S. A., Tavolari, S. & Brandi, G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int 39 Suppl 1, 19–31 (2019).

Established risk factors[13] for CCA include primary sclerosing cholangitis (PSC), biliary-duct cysts, bile duct stones, exposure to certain toxins and, mainly in Southeast Asia, liver fluke infections. Possible risk factors may include inflammatory bowel disease, hepatitis, cirrhosis, diabetes, obesity, alcohol drinking and tobacco smoking.

In the UK, the age standardised incidence rate (ASR) for CCA more than doubled between 2001-2018. For a cancer with such a high rate of late diagnosis and associated very poor prognosis, improving CCA survival rates must be an urgent priority.

The stage at which a cancer is diagnosed describes the size of a tumour and how far it has spread from where it originated. Our data showed that, unfortunately, a large majority of current diagnoses are late stage (3 or 4), with only around 21% of staged cancers being early-stage (stage 1 or 2)[14,15], which is lower than other liver cancers and well below the proportion for all cancers generally (54%)[16]. This may be explained by a number of factors:

- In its early stages, there are few obvious CCA signs and symptoms and those that do occur (malaise, fatigue and weight loss, pale stools, dark urine and itching) are non-specific to CCA and can occur from other cancerous as well as non-cancerous causes in that area, such as gallstones and inflammation of the bile ducts.

- As well as non-specific symptoms, jaundice (yellowing of the skin and eyes), dark urine, pale stools and sometimes itching due to the cancer blocking the flow of bile are the commonest symptoms of advanced CCA. Jaundice is the most obvious and visible symptom associated with liver disease, both cancerous and benign.

- Continued lack of awareness and understanding of CCA will delay wider recognition in our health system of the need for optimised pathways. These pathways should include specialist MDTs linked to centres of expertise, which will improve earlier diagnosis and effective treatments for this primary liver cancer.

Cholangiocarcinoma is…

- A **primary** liver cancer
- **Rising** sharply in incidence
- Affecting significant numbers of **younger adults**
- A disease with one of the **worst prognoses** of any cancer
- Potentially curable **if caught early**
- **Difficult to spot** early
- Mostly **diagnosed late** via A&E
- **Often** missed, misdiagnosed and inappropriately managed

[13] Khan, S. A., Tavolari, S. & Brandi, G. Cholangiocarcinoma: Epidemiology and risk factors. Liver Int 39 Suppl 1, 19–31 (2019).
[14] Liao et al (2023), Disparities in care and outcomes for primary liver cancer in England during 2008–2018, https://doi.org/10.1016/j.eclinm.2023.101969
[15] Cohort study to assess geographical variation in Cholangiocarcinoma Treatment in England submitted to World J Gastrointest Oncol, with a publication date pending.
[16] https://digital.nhs.uk/data-and-information/publications/statistical/case-mix-adjusted-percentage-of-cancers-diagnosed-at-stages-1-and-2-in-england/2020/unadjusted-and-case-mix-adjusted-percentage-of-cancers-diagnosed-at-stages-1-and-2.

THE AMMF CHOLANGIOCARCINOMA DATA PROJECT

About The Project

This data project was commissioned by AMMF, and carried out by firstly, the National Disease Registration Service (part of NHS England), and latterly by Health Data Insight CIC (HDI) in partnership with the National Disease Registration Service. Professor Shahid Khan and Professor Mireille Toledano, both of Imperial College London, have given major input to this work.

Concerned that existing epidemiological data on CCA fails to reflect the charity's first-hand experience of rising numbers of patients and their changing demographic, AMMF funded this first-of-its-kind data 'deep-dive' to produce new and up-to-date insights that have not been available in England before.

It is the first review, to our knowledge, to explore regional variation and temporal trends across England, including a breakdown of CCA rates by socioeconomic or deprivation status, and changing patterns in the routes to diagnosis for CCA (this national study looked at each of the biliary tract cancers, which include cholangiocarcinoma, gallbladder cancer and ampullary cancer).

Key considerations

Patient, clinical and system-level factors contribute to the speed and effectiveness at which an individual's cancer is found ("route to diagnosis"). For example, individuals with cancer who first present to the healthcare system as an emergency, usually have severe symptoms or complications of their disease which are often associated with late diagnosis. By contrast, earlier diagnoses may be the result of a more 'managed' Two Week Wait (TWW) GP referral, where concerning symptoms are appropriately recognised as a potential indicator for cancer and flagged for urgent investigation in secondary care.

Identifying geographical (regional) variation across different Cancer Alliances is an important first step for understanding whether differences in route to diagnosis, access to treatment or patient outcomes can be explained by specific patient clinical characteristics, or whether there are differences in clinical practice that might have led to inequalities in the level of access to certain treatments.

Accurate and up-to-date evidence on routes to diagnosis, access to treatments and overall disease prevalence, incidence and survival is invaluable to policymakers and health professionals. Especially when it reveals previously unaccounted-for demand, which may be an unmet need due to an imbalance in allocation of resources and support based on incorrect data.

The overarching purpose of this project was twofold: to establish a more accurate evidence base of patient case numbers and to better understand and characterise elements of the current CCA patient pathway and its outcomes. These were achieved by considering incidence and survival rates and the context of variation in routes to diagnosis and rates of treatment, based on key patient and tumour characteristics (for example, tumour staging and a patient's area of residence).

Methodology

Data on 32,251 individuals diagnosed with cholangiocarcinoma between 2001-2018 was analysed from the National Cancer Registration Dataset (NCRD), a population-based cancer registry collated and maintained by NHS England's National Disease Registration Service (NDRS).

The wider data project consisted of three studies:

- **Study 1** analysed incidence, mortality and survival data for CCA diagnoses between 2001-2018.
- **Study 2** focused on routes to diagnosis of patients diagnosed 2006-2017.
- **Study 3** analysed treatments received for patients diagnosed 2014-2017.

The diagnosis years were selected for each study based on availability of key data items when performing the research.

NCRD data was linked to Hospital Episode Statistics[17] (HES) and the Systemic Anti-Cancer Therapy (SACT) dataset[18], both of which are high quality national datasets with full population coverage in England.

Geographic variation was determined by a patient's place of residence within one of England's network of 21 Cancer Alliances at time of diagnosis.

A variety of statistical analyses were applied to the data, to consider potentially confounding variables.

These highlight where variation exists that could indicate a systematic deviation in clinical practice.

The findings of this data project have resulted in the publication of three papers:

- **Regional variation in routes to diagnosis of cholangiocarcinoma in England from 2006 – 2017.** Published: June 28 2023. World Journal of Gastroenterology. doi: https://doi.org/10.3748/wjg.v29.i24.3825
- **Cholangiocarcinoma across England: Temporal changes in incidence, survival and routes to diagnosis by region and level of socioeconomic deprivation.** Published: December 14 2023. JHepReports. doi: https://doi.org/10.1016/j.jhepr.2023.100983
- **Cohort study to assess geographical variation in cholangiocarcinoma treatment in England.** Published: December 15 2023. World Journal of Gastrointestinal Oncology. doi: https://doi.org/10.4251/wjgo.v15.i12.2077

Map of NHS Cancer Alliances in England

1. Northern Cancer Alliance
2. Lancashire and South Cumbria Cancer Alliance
3. West Yorkshire and Harrogate Cancer Alliance
4. Humber, Coast and Vale Cancer Alliance
5. Cheshire and Merseyside Cancer Alliance
6. Greater Manchester Cancer Alliance
7. South Yorkshire and Bassetlaw Cancer Alliance
8. West Midlands Cancer Alliance
9. East Midlands Cancer Alliance
10. East of England – North Cancer Alliance
11. East of England – South Cancer Alliance
12. North Central London Cancer Alliance
13. North East London Cancer Alliance
14. RM Partners
15. South East London Cancer Alliance
16. Kent and Medway Cancer Alliance
17. Surrey and Sussex Cancer Alliance
18. Wessex Cancer Alliance
19. Thames Valley Cancer Alliance
20. Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance
21. Peninsula Cancer Alliance

[17] https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics
[18] https://digital.nhs.uk/ndrs/data/data-sets/sact

Key Findings

Patient Characteristics and Socioeconomic Variation

- Over 20% of patients were under 65 years old when diagnosed.
- Compared to HCC, where around 90% of people diagnosed also have underlying liver disease[19], only 7% of the study cohort diagnosed with intrahepatic cholangiocarcinoma were classified as having underlying liver disease, reinforcing the lack of any obvious predisposing clinical history, signs and symptoms that may be preventing earlier diagnosis and treatment of this condition.
- CCA age-standardised incidence rates are connected to deprivation status, with an incidence in 2016-2018 of 5.7 per 100,000 person-years in the most socioeconomically deprived group, compared to 4.1 per 100,000 person-years in the least deprived group.

Most deprived socioeconomic group had:

39% **higher incidence** of cholangiocarcinoma (2016-2018)

37% **higher mortality** from cholangiocarcinoma (2016-2018)

21% **more likely to be diagnosed** via emergency presentation (2006-2017)

33% **less likely to receive surgery** and **26%** less likely to receive systemic therapy (2014-2017)

- A higher proportion of patients in the highest quintile for deprivation were diagnosed via emergency presentation (54%) than those least deprived (45%) after adjusting for potential confounders.
- Patients with a higher deprivation status were associated with a lower probability of receiving surgery and systemic therapy.
- Age-standardised mortality rates (ASMRs) were almost 40% higher in the most socioeconomically deprived patient groups (5.9 per 100,000 person-years) compared to the least deprived (4.3 per 100,000 person-years).

Incidence

- Age-standardised incidence rates of CCA in the population in England have increased by over 50% from 2.9 in 2001-2003 to 4.6 per 100,000 person-years in 2016-2018 (HCC is 5.2[20]).
- CCA has a much higher incidence and rise in cases than other biliary tract cancers (gallbladder cancer and ampullary cancer) – a two-fold increase in the number diagnosed per year between 2001 (1,165) and 2018 (2,466).
- Intrahepatic cholangiocarcinoma (iCCA) has the highest age-standardised incidence rate of 3.4 per 100,000 person-years in 2016-2018 and the lowest overall survival rates, at 6% for 3-year survival. Extrahepatic CCA had an age-standardised incidence rate of 1.0 per 100,000 person-years in 2016-2018, and 14% overall 3-year survival rate.
- CCA age-standardised incidence rates are connected to deprivation status, with an incidence in 2016-2018 of 5.7 per 100,000 person-years in the most socioeconomically deprived group, compared to 4.1 per 100,000 person-years in the least deprived group.
- There is geographic variation in CCA age-standardised incidence across England, with northern Cancer Alliances showing the highest rates of incidence and London Cancer Alliances among the lowest rates of incidence.

[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9189467
[20] https://www.cancerdata.nhs.uk/getdataout/liver

Survival

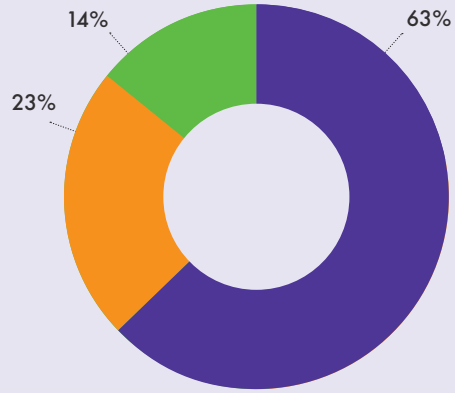
- A higher proportion of patients in the highest quintile for deprivation were diagnosed via emergency presentation (54%) than those least deprived (45%) after adjusting for potential confounders.
- The age-standardised mortality rate (ASMR) for CCA rose from 2.6 per 100,000 person-years in 2001-2003 to 4.9 per 100,000 person-years in 2016-2018, in parallel with incidence rates, which reinforces poor prognosis for long term survival.
- ASMRs were almost 40% higher in the most socioeconomically deprived patient groups (5.9 per 100,000 person-years) compared to the least deprived (4.3 per 100,000 person-years).
- 63% of biliary tract cancers diagnosed between 2001-2018 were CCA and 78% of biliary tract cancer deaths were from CCA, with the number of deaths for CCA doubling over the same period. There were 32,251 CCA diagnoses, and 31,411 deaths from CCA between 2001-2018 showing that mortality was more or less parallel to incidence.

Route to Diagnosis

- By far the most common route to diagnosis (RTD) for people with CCA is via an emergency presentation (50%), whilst only 13.8% were diagnosed via Two Week Wait (TWW) referrals. To put this in context, only 19% of patients across all cancers in England for 2017 were diagnosed via emergency presentation[21]. Clearly, interventions that reduce emergency route diagnoses are needed for people with CCA in order to meet the government's early diagnosis standard and demonstrate that the majority of cancers can be diagnosed via managed routes before the onset of acute symptoms that constitute an emergency.
- Statistically significant variation was found across Cancer Alliances, after accounting for potential confounders, in both patients diagnosed via TWW referral (from 9% to 19%) and via emergency presentation (from 37% to 57%). This warrants further investigation since areas with higher TWW and/or lower emergency presentation rates may have implemented interventions that improve diagnostic pathways and represent an opportunity to identify and share best practice between alliances.

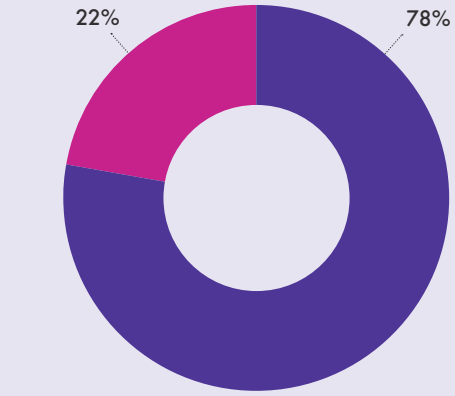
Most common and most lethal biliary tract cancers (2001-2018)

Number of diagnosed cases: **50,871**



- Cholangiocarcinoma – **32,251** cases
- Gallbladder – **11,742** cases
- Ampulla of Vater – **6,878** cases

Number of recorded deaths: **40,215**



- Cholangiocarcinoma – **31,411** cases
- Other (gallbladder and ampulla of Vater) – **8,804** cases

(Number of deaths recorded by the NHS in England 2001-2018)

[20] https://www.cancerdata.nhs.uk/getdataout/liver
[21] https://www.gov.uk/government/statistics/routes-to-diagnosis-2006-to-2017-results/routes-to-diagnosis-2006-to-2017-results

- Patients in the highest quintile for deprivation were more likely (54%) to be diagnosed via emergency presentation than those least deprived (45%) after adjusting for potential confounders.

- Comorbidity, increasing age and deprivation all result in higher probability of diagnosis via emergency presentation and lower probability of diagnosis via Two Week Wait referral.

Stage at Diagnosis

Stage at diagnosis is known to impact on available treatment options and prognosis for survival[22, 23, 24].

- Only 11% of patients had a stage 1 or 2 tumour diagnosis, which rose to 21% of patients that were staged (compared with the 54% of all staged cancers nationally).

- 43% of patients received a stage 3 or 4 tumour diagnosis, which was 79% of patients with staged cancers.

- 45% of patients had medical records with 'unknown stage' associated with their diagnosis, which means only 55% of CCA patients had records with complete staging, compared to 89% for colon cancers and 81% for pancreatic cancers[25].

Treatment Access

12% given potentially curative surgery

50.5% given no cancer treatment at all

(NHS patients in England 2014-2017)

Treatment

- Over half of patients studied (50.5%) were given no cancer specific treatment at all (potentially curative surgery, systemic therapy or a stent insertion), which mostly results in high short-term mortality.

- Patients had a lower probability of surgery and systemic therapy if they were more deprived and older. There was also significant geographic variation for both treatment types across Cancer Alliances, after accounting for potential confounders.

- The highest geographical treatment variation was found in the percentage of patients receiving stenting which ranged from 17% to 41% across Cancer Alliances after adjusting for potential confounders.

- Patients diagnosed with stage 2 disease had the highest unadjusted probability of surgery (59%), whilst patients with unknown staging had the lowest proportion of surgery (5%).

Disease Classification and Coding Limitations

The data project referenced 75% of cases diagnosed between 2001-2018 as intrahepatic CCA, 19% extrahepatic CCA, and 6% other CCA, with perihilar and distal CCA subtypes captured together as 'extrahepatic' CCA, due to the historical lack of coding of perihilar CCA in the World Health Organisation's (WHO) International Classification of Diseases 10th (ICD-10) and previous editions. This emphasises the need for better coding practices since perihilar CCA is the most commonly occurring sub-type encountered clinically and reported globally[26].

However, as ICD-11[27] now codes the three sub-types of CCA individually, it should be possible in future to ensure that perihilar CCA is more accurately recorded.

[22] Cohort study to assess geographical variation in Cholangiocarcinoma Treatment in England submitted to World J Gastrointest Oncol, with a publication date pending.
[23] Liao et al (2023), Disparities in care and outcomes for primary liver cancer in England during 2008–2018, https://doi.org/10.1016/j.eclinm.2023.101969
[24] https://digital.nhs.uk/data-and-information/publications/statistical/case-mix-adjusted-percentage-of-cancers-diagnosed-at-stages-1-and-2-in-england/2020/unadjusted-and-case-mix-adjusted-percentage-of-cancers-diagnosed-at-stages-1-and-2
[25] https://www.cancerdata.nhs.uk/stage_at_diagnosis (2017)
[26] https://www.nature.com/articles/s41575-020-0310-z
[27] ICD-11, the 11th edition of the World Health Organisation's (WHO) International Classification of Diseases, was adopted by the 72nd World Health Assembly in 2019 and came into effect on 1st January 2022 - https://icd.who.int/en

Conclusions

- These studies evidence an increasing incidence of CCA in England and an incidence rate that may be linked to levels of deprivation.
- Whilst TWW (Two Week Wait) diagnostic routes have increased over time, emergency presentation remains overwhelmingly the most common route to a diagnosis for CCA, particularly for people from the most deprived backgrounds and in all cases, an emergency route to diagnosis tends to result in a late state diagnosis which carries the worst prognosis.
- Emergency and late presentation leading to limited treatment options all result in very poor outcomes for people diagnosed with CCA. Efforts to rapidly increase earlier diagnosis for people with CCA is required, especially as numbers of people affected are increasing.
- The geographic and temporal variation in diagnosis routes suggest that sharing good practice across NHS organisations will be vital to improve positive current trends and reduce potential inequalities for people with CCA experiencing unwarranted variation in their treatment and health outcomes.
- Increasing mortality due to CCA, in parallel with incidence, shows that mortality rates have not improved for CCA over time, emphasising how important it is to achieve improvements in CCA diagnosis and management.
- Poorer CCA diagnosis, management and outcomes associated with socioeconomic deprivation warrant further investigation, as a priority, to meet the national ambition to reduce unwarranted variation and health inequalities.
- A high proportion of patients were not treated with surgery, systemic therapy or stent insertion. High short-term mortality and a lack of treatment may reflect where cases were too advanced at the point of diagnosis, for any active treatment to be considered beneficial.
- Large geographic variation in the probability of stent insertion suggests there may be gaps in clinical expertise or access for stenting. It could also be explained by differences in clinical case-mix as not every patient is eligible or in need of stent insertion.
- Local review of treatment pathways and more comprehensive guidelines for the management of CCA are likely to help reduce variation in routes to diagnosis and access to treatments received across regions.
- Better recording of CCA in healthcare records must be a priority, to monitor the disease profile of perihilar CCA – the most common type clinically encountered – more accurately and to bring CCA tumour staging recording (55%) into line with other staging completeness for all cancers (84%).

> Who you are and where you live should not affect your chances of living with and surviving a cholangiocarcinoma diagnosis. It's important that health service leaders work with patient advocates to further analyse and understand the regional variation and link with social deprivation uncovered by this research.
>
> **Judith Neptial, diagnosed with cholangiocarcinoma, aged 46, and now founder of 'From Me To You – The Art of Survival', an organisation working to support people living with cancer in the Black community in the UK**

RECOMMENDATIONS

For health policy and commissioners

Health outcomes for people with cholangiocarcinoma (CCA) currently lag far behind those for most other cancers. In addition, significant geographical and socioeconomic disparities in incidence, routes to diagnosis, access to treatment and mortality for people with CCA have been identified by new research outlined in this paper.

- **ACTION – Ensure that CCA receives the attention it needs in regional and national plans** for enabling earlier diagnosis, increasing access to treatments and reducing inequity for patients.
- **ACTION – Introduce more comprehensive guidelines on the management of CCA** to help reduce potential unwarranted variation in treatments received across regions.
- **ACTION – Prioritise support for CCA as part of ongoing plans to diagnose 75% of stageable cancers at stage 1 or 2 by 2028** and other cancer care commitments within the UK Government's Major Conditions Strategy.
- **ACTION – Review local treatment pathways to include opportunities for earlier diagnosis of CCA** by specialist Multi-Disciplinary Teams (MDTs) and screening as soon as techniques for this become available, with optimum access to specialised centres of expertise and the most timely possible care for CCA patients, based on the latest science and evidence-based practices.

For health professionals

'Liver cancer' is a term still used and understood by many to mean only one type of primary liver cancer – hepatocellular carcinoma (HCC) – when there are in fact two types of primary liver cancer. Cholangiocarcinoma (CCA) has a similar level of incidence to HCC but is harder to diagnose and has significantly worse survival rates, with emergency presentation overwhelmingly the most common route to a late diagnosis, rather than a more appropriately managed GP assessment and urgent referral to specialists. More needs to be done to address the lack of awareness of CCA that currently exists throughout our health service, and to improve accurate coding and staging on patient records to help future research support earlier diagnosis and increased treatment options.

ACTION – Stop and rethink 'liver cancer' as a term that only applies to HCC. Thinking CCA will help more of us spot and understand cholangiocarcinoma, more of the time – a type of liver cancer that can't currently be picked up by screening or necessarily be prevented by addressing lifestyle factors in the way that HCC can.

ACTION – Please consider urgent specialist assessment, even where symptoms are non-specific and could be caused by non-cancerous conditions, because a missed diagnosis could mean a patient loses the opportunity for surgery – currently the only potentially curative treatment for this disease. Earliest symptoms can be vague and insidious such as unexplained weight loss, general malaise and fatigue and only slightly abnormal liver function tests. Commonest symptoms of more advanced CCA are due to the blocking of the flow of bile – jaundice, dark urine, pale stools, a pain under the right ribs and sometimes itching.

ACTION – Find out how to facilitate access to a specialist second opinion for any CCA patient in need of reassurance regarding their diagnosis and to ensure their treatment pathway is optimal.

ACTION – Make sure your CCA patients have access to a hepatobiliary cancer nurse specialist who can provide expertise and support to the patient and their family.

ACTION – Know where to signpost CCA patients so that they can access timely support and information from a CCA-dedicated charity.

ACTION – Think about coding and stage completeness. All patients discussed at MDTs with CCA should be classified as best as possible into one of the three CCA sub-categories – intrahepatic, perihilar or distal. This should be clearly recorded alongside best efforts to obtain accurate and complete tumour staging in the MDT outcome.

More than half of the patients studied **(50.5%)** were given none of the treatments currently available for CCA.

For patients and carers

Too often patients hear that 'nothing that can be done', without being offered the option of a second opinion via referral to a specialist with knowledge and experience of CCA. Even when surgery is not an option, there are several other types of treatment which can help to control symptoms and delay progression of the cancer – and in some cases, that may help to make surgery a possibility further down the line.

ACTION – Be your own advocate – ask questions about your diagnosis and treatment and be aware of available options beyond your local hospital, if needed – including molecular profiling and relevant clinical trials.

ACTION – Don't be afraid to ask for a second opinion via a referral to a specialist with knowledge and experience of CCA.

I was told there was 'nothing they could do' and was given weeks to live. Giving up wasn't an option for me, I wanted to see my children grow up, be there for their key milestones in life – I had to stay strong for my family. I sought a second opinion at a different hospital and they agreed to operate to remove my tumour.

It was fantastic that they offered me this lifeline, but following my life-saving surgery we were again left without any form of treatment pathway. This only happened after my dad trawled the internet in search of anything he could find about this deadly cancer and found AMMF who put me in touch with specialists.

It shouldn't be up to patients and charities to facilitate a referral for a second opinion, when all patients should be worried about is getting through the treatment. All cholangiocarcinoma patients should be offered the opportunity to be seen by an appropriate specialist as part of a standardised diagnosis process.

Andrea Sheardown, diagnosed with cholangiocarcinoma, aged 44

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October 2023

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