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***Retrospective Cohort Study***

**Cohort study to assess geographical variation in cholangiocarcinoma treatment in England**

Jose S *et al*. Variation in CCA treatment in England

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**Abstract**

BACKGROUND

Outcomes for cholangiocarcinoma (CCA) are extremely poor owing to the complexities in diagnosing and managing a rare disease with heterogenous sub-types. Beyond curative surgery, which is only an option for a minority of patients diagnosed at an early stage, few systemic therapy options are currently recommended to relieve symptoms and prolong life. Stent insertion to manage disease complications requires highly specialised expertise. Evidence is lacking as to how CCA patients are managed in a real-world setting and whether there is any variation in treatments received by CCA patients.

AIM

To assess geographic variation in treatments received amongst CCA patients in England.

METHODS

Data used in this cohort study were drawn from the National Cancer Registration Dataset (NCRD), Hospital Episode Statistics and the Systemic Anti-Cancer Therapy Dataset. A cohort of 8853 CCA patients diagnosed between 2014-2017 in the National Health Service in England was identified from the NCRD. Potentially curative surgery for all patients and systemic therapy and stent insertion for 7751 individuals who did not receive surgery were identified as three end-points of interest. Linear probability models assessed variation in each of the three treatment modalities according to Cancer Alliance of residence at diagnosis, and for socio-demographic and clinical characteristics at diagnosis.

RESULTS

Of 8853 CCA patients, 1102 (12.4%) received potentially curative surgery. The mean [95% confidence interval (CI)] percentage-point difference from the population average ranged from -3.96 (-6.34 to -1.59)% to 3.77 (0.54 to 6.99)% across Cancer Alliances in England after adjustment for patient sociodemographic and clinical characteristics, showing statistically significant variation. Amongst 7751 who did not receive surgery, 1542 (19.9%) received systemic therapy, with mean [95%CI] percentage-point difference from the population average between -3.84 (-8.04 to 0.35)% to 9.28 (1.76 to 16.80)% across Cancer Alliances after adjustment, again showing the presence of statistically significant variation for some regions. Stent insertion was received by 2156 (27.8%), with mean [95%CI] percentage-point difference from the population average between -10.54 (-12.88 to -8.20)% to 13.64 (9.22 to 18.06)% across Cancer Alliances after adjustment, showing wide and statistically significant variation from the population average. Half of 8853 patients (*n* = 4468) received no treatment with either surgery, systemic therapy or stent insertion.

CONCLUSION

Substantial regional variation in treatments received by CCA patients was observed in England. Such variation could be due to differences in case-mix, clinical practice or access to specialist expertise.

**Key Words:** Cholangiocarcinoma; Biliary tract cancer; Liver cancer; Treatment; Surgery; Systemic therapy; Chemotherapy; Stent; England

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**Core Tip:** Outcomes for cholangiocarcinoma (CCA) are extremely poor, with late presentation meaning curative surgery is not an option for many. Systemic therapies to prolong life are limited and stent insertion for disease management is complex. In a national cohort, treatments received (surgery, systemic therapy, stent insertion) by CCA patients across geographic areas were investigated. Half of patients did not receive any of the treatments considered. The proportion that received treatments significantly varied across England. These data provide novel evidence of low and varied treatment rates for CCA patients, warranting further investigation by healthcare providers to try to improve outcomes and reduce inequality.

**INTRODUCTION**

Cholangiocarcinoma (CCA) is a malignancy arising from epithelial cells along the biliary tree within or external to the liver[1,2]. CCA are sub-classified into three main sub-types according to their anatomical site of origin: Intrahepatic CCA (iCCA), within the liver parenchyma, proximal to the second order bile ducts, perihilar, and distal CCA, often collectively referred to as extrahepatic CCA (eCCA)[3–5]. iCCA comprise the second most common form of primary liver cancer worldwide, after hepatocellular carcinoma[6]. The CCA sub-types exhibit some differences in their respective clinical presentations, risk factors, routes to diagnosis and clinical management, as well as exhibiting distinct epidemiological, clinical, molecular and genetic characteristics[3,7]. Of note, multiple epidemiological studies have reported rising incidence and mortality rates for CCA over the past few decades[8-10].

All CCA carries a high mortality as it typically presents at an advanced stage, usually too late for surgical resection or transplantation, the only potentially curative treatment options. Most cases are sporadic *i.e.,* they do not occur on the background of known risk factors and no screening strategy has been proven effective at reducing mortality[3]. Most CCA patients require systemic chemotherapy, with the current standard of care first line treatment being combination gemcitabine and cisplatin, or capecitabine in an adjuvant setting[3,4]. The other main treatment required by most patients is stenting to relieve biliary obstruction. In patients with high levels of jaundice, endoscopic or percutaneous stent placement is commonly used to reduce hyperbilirubinaemia prior to surgery in patients with resectable disease, or before systemic therapy, or for palliation[3,4]. Although the overall prognosis of CCA is poor, with only a minority of patients surviving more than 3 years after diagnosis, these treatments have been shown to improve overall survival[3,6].

The management of CCA is complex, requiring a highly specialised multi-disciplinary approach and should be carried out at centres of expertise to achieve the best clinical outcomes[3]. Data on CCA patients’ access to cancer-specific treatment is lacking. One recent United Kingdom study assessed variation in the surgical management of iCCA patients only, in selected hepatobiliary centres, finding variation in surgery volumes and in the proportions of patients treated with adjuvant chemotherapy[11]. A recent observational study from the European Reference Network for the Study of CCA investigated the clinical course of 2234 CCA patients from 26 referral Healthcare Centres from 11 European countries over a 10-year period (from 2010)[12]. The study found that CCA was frequently diagnosed at an advanced stage with almost 60% of patients presenting with locally advanced or metastatic disease. Furthermore, around 20% did not receive any specific cancer therapy, but best supportive care only. Although this was an important and large multicentre study, data was collected from self-selected expert centres and the findings may not be representative of the whole population of individual participating countries.

Variation in access to cancer-specific treatment for CCA across England has not previously been reported. The aim of this study was to investigate if there is geographical variation across England of access to surgery, systemic therapy and stenting. Results are reported at the Cancer Alliance level, representing distinct geographic areas within which key health and social care stakeholders collaborate to plan and coordinate local cancer pathways.

**MATERIALS AND METHODS**

CCA patients were selected from the National Cancer Registration Dataset[13]. The following ICD-10 diagnosis codes were used to define CCA: C221, C240, C248, C249 of any morphology or C220, C222, C223, C224, C227, C229 with ICD-O2 histology code 8160. Patients were considered if resident in England at the time of diagnosis and were diagnosed between 2014 and 2017. This was the most recent diagnostic period at the time of the analysis with sufficient follow-up available to assess treatment initiation. Patients were followed to the earliest of death or 15 mo following recorded date of diagnosis. The first registered tumour per individual in this time period was used for the analysis and patient and tumour characteristics associated with this diagnosis are reported. Further inclusion criteria were recorded male or female gender, and age at diagnosis between 0 and 200 years. Individuals diagnosed with cancer on their death certificate only were excluded as such patients would not have been offered treatment.

Linked patient records from the Hospital Episode Statistics (HES) Admitted Patient Care (APC) dataset, Systemic Anti-Cancer Therapy dataset and National Radiotherapy Dataset[14-16] were used to determine the treatment received by each patient. Potentially curative surgery was defined based on a list of OPCS-4 procedure codes (Supplementary Table 1) dated between one month prior and 12 mo following the date of CCA diagnosis, irrespective of any other treatments received, as per the National Disease Registration Services’ standard operating procedure[17]. Amongst individuals with no evidence of surgery as defined above, the presence of systemic therapy and/or stent insertion was assessed. Systemic therapy was defined as the delivery of any systemic anti-cancer therapy regimen initiated between the one month prior and 15 mo following diagnosis. A second list of OPCS-4 codes was used to define stent insertion (Supplementary Table 1), and these were similarly searched for in the interval two months prior to and up to 15 mo following diagnosis.

Geographic variation in treatment was analysed at the Cancer Alliance level according to boundaries defined in 2020. The Cancer Alliance for each tumour was assigned according to the main residence of the patient on the date of diagnosis. Other patient characteristics of interest, identified a priori as possible confounding variables of the relationship between geography and receipt of treatment were: Person-stated gender (male/female); age at diagnosis (0-44/45-54/55-64/65-74/75-84/85+ years); area income deprivation component of the index of multiple deprivation, 2019 (quintiles); year of diagnosis; tumour sub-type (iCCA/eCCA/other); tumour morphology (adenocarcinoma/other); Charlson comorbidity index (score 0/1/2/3+)[18]; underlying liver disease (yes/no) and route to diagnosis (urgent two-week wait general practitioner referral (TWW)/emergency presentation/other/unknown)[19]. To identify underlying liver disease, HES APC episodes from 5 years prior to 1 year after diagnosis were searched for diagnostic codes indicative of chronic hepatitis C or B, primary biliary cholangitis, autoimmune hepatitis, haemochromatosis, alcoholic liver disease, or non-alcoholic liver disease (NAFLD). NAFLD was defined as fatty (change of) liver, not elsewhere classified, or by the presence of cirrhosis combined with obesity or diabetes without the presence of any other underlying liver disease[20].

Linear probability models were performed for each of the following three binary outcomes: Potentially curative surgery regardless of other treatments received (yes/no); systemic therapy where no surgery was received (yes/no); stent insertion where no surgery was received (yes/no). For each outcome, bivariate models were conducted to assess the association with each covariate of interest without adjustment for other patient and tumour factors (referred to as ‘unadjusted’). An adjusted model was then fit for each outcome that included all covariates, defined a priori as being of interest, concurrently. No interactions between covariates were assessed. Covariates were Cancer Alliance, age at diagnosis, gender, area income deprivation quintile, Charlson comorbidity score, prior liver disease, tumour sub-type, tumour morphology, route to diagnosis.

Weighted effect coding was applied such that estimates generated by each linear probability model are interpretable as percentage-point deviations from the sample mean[21]. Results from the linear probability models are presented as funnel plots with significance thresholds denoting two and three SD from the sample mean, being approximately equivalent to 95.0% and 99.7% confidence intervals, respectively. A statistical significance threshold of 5% was used.

A sensitivity analysis was undertaken that additionally adjusted for stage at diagnosis in a subgroup of the cohort who had a known stage at diagnosis. This was due to the high level of missing data for this variable (45.5%). The adjusted models for each outcome were repeated in this subgroup to determine how reducing the cohort to patients with known stage impacted model estimates, before stage was additionally adjusted for in this group.

**RESULTS**

There were 8872 people diagnosed with CCA between 2014 and 2017. No exclusions were made due to age or gender data quality checks. After excluding 19 (0.2%) individuals diagnosed on death certificate only, a final cohort of 8853 individuals was available for analysis. Of these, 20.9% were under 65 years old and 50.9% were women (Table 1). The majority were diagnosed with an iCCA (77.6%). Comorbidities as measured by the Charlson comorbidity index were present in 29.7% of individuals and 9.1% were classified as having underlying liver disease.The largest proportion of diagnoses were situated in the West Midlands Cancer Alliance (11.4%), with the smallest in North Central London Cancer Alliance (1.6%).

Of the 8853 patients, 12.4% (*n* = 1102) received potentially curative surgery. In the 7751 patients with no evidence of surgery, 19.9% (*n* = 1542) received systemic therapy, 27.8% (*n* = 2156) received a stent insertion, and 42.4% (*n* = 3283) received either modality alone or in combination. Of note, half (50.5%) of the initial cohort received none of the three treatments considered (Table 1).

***Geographic variation in potentially curative surgery***

Variation in the unadjusted percentage of patients who received potentially curative surgery was observed across the Cancer Alliances, ranging from 8.8% to 16.2% (*P* < 0.001). In a linear probability model that included only Cancer Alliance, the percentage treated with surgery was more than two SD higher than the sample mean in one Cancer Alliance (*P* < 0.05), but more than two SD lower than average for two Cancer Alliances [Table 2A (unadjusted) and Figure 1A]. This finding remained present after adjustment for all patient and tumour characteristics being considered [Table 2A (adjusted) and Figure 1B].

***Geographic variation in systemic therapy***

Amongst those not treated with surgery, variation in the crude percentage of patients treated with systemic therapy was observed. Across Cancer Alliances the percentage in receipt of systemic therapy ranged from 12.4% to 29.4%. In a linear probability model that included Cancer Alliance as the only independent variable, the percentage treated with systemic therapy was more than two SD above the sample mean for two Cancer Alliances, and below the mean for two Cancer Alliances [Table 2B (unadjusted) and Figure 2A, *P* < 0.001)]. Adjustment for patient and tumour characteristics attenuated this difference for two Cancer Alliances such that only one was observed to have a significantly lower percentage of patients receiving systemic therapy than the sample mean [Table 2B (adjusted) and Figure 2B].

***Geographic variation in stent insertion***

There was wide variation in the percentage of individuals who received a stent insertion amongst those not treated with potentially curative surgery. The unadjusted percentage across all Cancer Alliances ranged from 29.7% to 55.0% and was significantly higher than the sample mean for six Cancer Alliances, and significantly lower than the sample mean for five Cancer Alliances [Table 2C (unadjusted) and Figure 3A]. Adjustment for patient demographics, comorbidities and tumour characteristics did not alter this finding [Table 2C (adjusted) and Figure 3B].

***Treatment associations with patient and tumour characteristics***

The lowest percentage treated with potentially curative surgery was observed in the 85+ age group (Table 2A unadjusted). Age remained associated with the likelihood of surgery in a model that included all other cofactors of interest, with the highest proportion amongst those aged 0-44 [adjusted percentage point difference (pp): 20.69, 95% confidence interval (CI): 13.91 to 27.47]. Likewise, in those who did not receive surgery, older age at diagnosis was associated with a lower likelihood of systemic therapy in both unadjusted and adjusted analyses (adjusted pp: -17.16, 95%CI: -18.08 to -16.23 for age 85+ years). However, the relationship between age and likelihood of stent insertion was not similarly linear (Table 2C adjusted).

Although there was a difference between male and female gender in the crude percentage that received surgery (Table 2A unadjusted), this was attenuated after adjustment (adjusted pp: -0.49, 95%CI: -1.13 to 0.16 for women). Amongst those who did not receive surgery, women were less likely than men to receive a stent insertion (adjusted pp: -1.18, 95%CI: -2.13 to -0.24), but more likely to receive systemic therapy (adjusted pp: 1.21, 95%CI: 0.43 to 2.00).

High area income deprivation was associated with a lower probability of both surgery (adjusted pp: -2.77, 95%CI: -4.10 to -1.43 for most deprived areas) and systemic therapy in the absence of surgery (adjusted pp: -2.91, 95%CI: -4.59 to -1.22) but was not strongly associated with the probability of stent insertion in those who did not receive surgery (adjusted pp; -0.34, 95%CI: -2.33 to 1.65).

Compared to the population average, iCCA patients had a lower probability of treatment with surgery (adjusted pp: -2.65, 95%CI: -3.09 to -2.22), systemic therapy amongst those without surgery (adjusted pp: -0.47, 95%CI: -0.92 to -0.02) and stent insertion amongst those without surgery (adjusted pp: -3.89, 95%CI: -4.47 to -3.31) in adjusted models.

Those diagnosed *via* an emergency route had a lower-than-average probability of surgery (adjusted pp: -3.75, 95%CI: -4.42 to -3.08) and systemic therapy in those without surgery (adjusted pp: -5.31, 95%CI: -6.11 to -4.51), but a higher probability of stent insertion without surgery (adjusted pp: =2.10, 95%CI: 1.14 to 3.07) than the population average. Whilst a TWW referral route was not strongly associated with the probability of surgery (adjusted pp: -0.58, 95%CI: -2.08 to 0.91), a TWW referral route was associated with a higher probability of systemic therapy (adjusted pp: 8.57, 95%CI: 6.55 to 10.59) and stent insertion (adjusted pp: 2.29, 95%CI: 0.06 to 4.51) among patients that did not receive surgery.

Patients with the highest categorised burden of comorbidities (3+) had a lower-than-average probability of surgery (adjusted pp: -3.19, 95%CI: -4.79 to -1.60), systemic therapy (adjusted pp: -7.06, 95%CI: -8.93 to -5.20) and stent insertion (adjusted pp: -5.53, 95%CI: -8.33 to -2.74). Conversely, of patients with evidence of liver disease specifically, there was no association with systemic therapy (adjusted pp: -0.43, 95%CI: -3.55 to 2.69), a higher-than-average probability of treatment with surgery (adjusted pp: 3.47, 95%CI: 0.96 to 5.97) and lower than average probability of stent insertion without surgery (adjusted pp: -4.19, 95%CI: -7.29 to -1.08).

***Sensitivity analysis***

Of the 8853 CCA patients in the study cohort, 4832 (54.5%) had a known stage at diagnosis and were included in the sensitivity analysis for potentially curative surgery. Of these, 3925 (81.2%) did not receive curative surgery and were analysed for the probability of treatment with systemic therapy or stent insertion.

The proportion of people staged varied by Cancer Alliance, from 36.7% to 74.7% (*P* < 0.001). Those with unknown stage at diagnosis were more likely to be older, diagnosed in an earlier year, have a high comorbidity score and an ‘other’ tumour sub-type or morphology (all *P* < 0.001, results not shown). Repeating the adjusted model of the main analysis in these subgroups identified different Cancer Alliances as having treatment probabilities that varied significantly (>2 SD) from the population average (Supplementary Table 2). This suggests that the subgroup of individuals with known stage at diagnosis was not generalisable to the whole cohort of individuals with CCA.

Adding adjustment for stage at diagnosis did not appear to explain much of the variation in the probability of surgery observed between Cancer Alliances. (Supplementary Table 2, model A). One Cancer Alliance no longer had a probability of potentially curative surgery that was >2 SD higher than average, but two additional Cancer Alliances were identified as having higher probabilities of surgery. Amongst patients who were not treated with surgery but had a known stage at diagnosis, adjustment for stage identified one additional Cancer Alliance that had a lower-than-average probability of systemic therapy, again indicating that adjustment for stage did not explain variation observed in the main analysis (Supplementary Table 2, model B). One less Cancer Alliance was observed to have a lower-than-average probability of stent insertion after adjusting for stage at diagnosis, leaving three Cancer Alliances with a significantly lower probability of stent insertion than average (Supplementary Table 2, model C).

**DISCUSSION**

After adjustment for patient and tumour factors, there was significant variation amongst English Cancer Alliances in CCA patients receiving cancer-specific treatments, including potentially curative surgery, systemic therapy without curative surgery or stent insertion without curative surgery. To our knowledge, this is the first study to look at potential variation in CCA treatment at a national level. There was evidence of significant variation amongst Cancer Alliances in the percentage receiving surgery, or systemic therapy in the absence of surgery. Most variation however was observed in the percentage receiving stent insertion in the absence of surgery, suggesting there may be gaps in expertise, access and/or clinical expertise for this treatment modality. In so far as we were able to adjust for differences in patient populations between Cancer Alliances, this adjustment did not reduce the level of variation observed. However, not every CCA patient will be clinically eligible or in need of stent insertion and our inability to account for clinical status with the available data means the observed variation might still be explainable by differences in clinical case-mix and not necessarily evidence of varied or poor practice.

Whilst we have analysed treatment modalities separately, there is a possibility that the propensity toward each treatment within an area is linked, due to local expertise, protocols or capacity. An area with lower rates of surgery may have correspondingly higher rates of systemic therapy, for example. This did not often appear to be borne out in the data, with no such correspondence between Cancer Alliances that significantly varied from average in the proportion who received systemic therapy compared to either stent insertion or surgery. Two Cancer Alliances that showed lower than average proportions receiving surgery showed higher than average proportions receiving stent insertion in the absence of surgery.

In terms of patient factors that we were able to adjust for, higher income deprivation was associated with a lower likelihood of receiving surgery or systemic therapy, independently of geography. There is already evidence that socioeconomic factors play a powerful role in determining the health of individuals[22,23]. As regards cancer, the importance of socioeconomic factors has been demonstrated in association with screening, incidence, stage at diagnosis, and survival, especially in private health care settings[24,25]. However, relatively little has been reported on how socioeconomic factors affect access to cancer system therapies, especially in publicly funded health systems such as the United Kingdom National Health Service (NHS), where cancer care at the point of service is free of charge[26,27]. A study conducted in Canada’s Public payer Universal healthcare system examined the association between material deprivation and receipt of cancer care among patients with advanced gastrointestinal cancer. It found that patients from the most deprived communities were significantly less likely to see an oncology specialist after a diagnosis and significantly less likely to receive radiation and/or chemotherapy compared to those living in the least materially deprived communities[28]. To our knowledge, this is the first study to report a similar theme in patients with CCA.

Increasing co-morbidities and emergency presentation were both associated with a lower probability of surgery, in keeping with the fact that higher surgical risk may preclude treatment for the former group and likely advanced CCA stage at presentation may preclude treatment for the latter.

That half of CCA patients in England received none of the main treatments for CCA is of interest. To our knowledge, regarding CCA, no previous study of national data has studied or reported this before. The Surveillance, Epidemiology and End Results (SEER) cancer registry, representing around 28% of the population of the United States, recently showed that approximately 50% of eCCA patients and 40% of iCCA patients did not receive surgery or adjuvant therapy over a comparable calendar period[29]. This indicates a higher proportion of CCA patients receive surgical treatment in the United States than our data showed for England. However, differences in the treatment end-points defined, differences between the healthcare systems and CCA populations of the United States and England, and the select coverage of the SEER study make these findings difficult to directly compare and interpret. In the European Reference Network for the Study of CCA study, 20% of patients did not receive any specific cancer therapy, but best supportive care only[12]. Data for their study was collected from self-selected expert centres in those hospitals who chose to send in their data. These centres are large expert referral centres and the study data is not therefore reflective of “real world” overall public healthcare. Our study involved the entire NHS (all public, government-funded hospitals), so all patients from all NHS hospitals were included. The high rates of short-term mortality observed in this group may well explain the observed lack of treatment, as their case may have been too advanced for any active treatment to be considered beneficial. Further studies are warranted to explore if this high proportion of patients had adequate clinical reasons to not receive any of the main treatments for CCA. Nonetheless, this highlights the importance of increasing the therapeutic options available to those diagnosed with CCA to prolong survival, either through earlier diagnosis to preserve current treatment options or through increased research into more effective systemic therapy options.

With the available data we were unable to account for certain relevant features of clinical status, such as degree of liver disease and performance status at the time of diagnosis, which could be key prognostic factors for treatment options. Performance status data were missing for 75.1% of the cohort at diagnosis, whereas degree of liver disease is not possible to abstract from the data sources available. Our intention to account for differences in the stage at diagnosis was hindered due to missing data for 45.5% of the cohort. Although a sensitivity analysis in those with reported stage was performed, the subgroup of individuals with known stage could have been highly selected and therefore their findings may not be generalisable to the entire CCA population. This highlights the importance of documenting and collecting information on stage of CCA at diagnosis in the future. It is unclear why completeness is relatively poor for this tumour site compared to other cancers. That said, in the group where CCA stage was known, the stage at diagnosis did not appear to explain much, if any, of the variation observed.

Based on a national cohort of CCA patients, these data are highly representative of CCA patients and treatment in England, where treatment is free at point of access *via* the NHS. However, these findings will be less generalisable to other countries that have different healthcare systems and guidelines as to the management of CCA.

**CONCLUSION**

Certainly, some Cancer Alliances appear to have lower than average rates of treatment for CCA patients. The reasons for this require further investigation that would be aided by more detail on patient clinical status and clinical case-mix than was available *via* this national registration database. It is important to understand whether observed differences are due to differences in clinical practice, case mix or geographical differences in access to expert facilities, in order to successfully implement evidence-based solutions to reduce variation and inequality in treatments received.

**ARTICLE HIGHLIGHTS**

***Research background***

Cholangiocarcinoma (CCA) is a cancer with poor survival outcomes that is increasing in incidence worldwide. In clinical practice there can be barriers to providing treatments that can improve outcomes for those with CCA. Potentially curative surgery is not an option for those diagnosed with advanced disease, which represents the majority of patients. Stent insertion to manage disease complications is a complex procedure requiring access to specialist expertise that is not routinely available in all areas. There are currently relatively few recommended systemic treatment options available that can prolong survival.

***Research motivation***

Due to the complexity of treating CCA, we hypothesise that there could be variation in the treatments received by CCA patients. Such variation could contribute to the poor outcomes experienced by CCA patients. There is very little data to evidence variation in the care and management of CCA in England, so research into this area is needed. Identifying variation that could point to inequality is the first step toward improving patient outcomes, leading to further research into understanding why this variation exists and ultimately improvement strategies to reduce these variations in care.

***Research objectives***

We aimed to investigate whether there was evidence of geographic variation in the proportion of CCA patients that received each of three main cancer-specific treatments: potentially curative surgery; systemic therapy amongst those that did not receive surgery; stent insertion amongst those that did not receive surgery.

***Research methods***

We conducted a retrospective cohort study including patients diagnosed with CCA from 2014-2017 in England. We used linear probability models to investigate geographic variation in the proportions of that received either potentially curative surgery, systemic therapy (in the absence of surgery) or stent insertion (in the absence of surgery) across Cancer Alliance areas in England, adjusting for potential confounders.

***Research results***

Half of CCA patients in England received none of the cancer treatments we investigated in this study. Only 12.4% received potentially curative surgery. Across all Cancer Alliance areas, the mean percentage-point difference from the population average [95% confidence interval (CI)] ranged from -3.96 (-6.34 to -1.59)% to 3.77 (0.54 o 6.99)% after adjustment for patient sociodemographic and clinical characteristics, showing statistically significant variation.

Amongst those who did not receive surgery, 19.9% received systemic therapy, with mean percentage-point difference from the population average [95%CI] ranging from -3.84 (-8.04 to 0.35)% to 9.28 (1.76 to 16.80)% across Cancer Alliances after adjustment. Stent insertion was received by 27.8%. Across Cancer Alliances, after adjustment for confounders, the mean percentage-point difference from population average [95%CI] ranged between -10.54 (-12.88 to -8.20)% and 13.64 (9.22 to 18.06)%, showing wide and statistically significant variation from the population average.

It is unknown whether the observed variation is evidence of inequality in access to treatment and differing clinical practice or can be explained by factors we were unable to account for in our analysis, such as patient choice and differences in the clinical case-mix of patients in these areas.

***Research conclusions***

We found statistically significant geographic variation in the proportions of CCA patients receiving surgery, systemic therapy and stent insertion across Cancer Alliance areas in England.

***Research perspectives***

Local detailed review of treatment pathways should be undertaken to understand in more detail why rates of treatment were low and whether the observed variation indicates disparities in access to care or differences in clinical practice. Greater understanding of why variation in care is present can support the development of future strategies to reduce unwarranted variation and improve outcomes.

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**REFERENCES**

1 **Khan SA**, Thomas HC, Davidson BR, Taylor-Robinson SD. Cholangiocarcinoma. *Lancet* 2005; **366**: 1303-1314 [PMID: 16214602 DOI: 10.1016/S0140-6736(05)67530-7]

2 **Brindley PJ**, Bachini M, Ilyas SI, Khan SA, Loukas A, Sirica AE, Teh BT, Wongkham S, Gores GJ. Cholangiocarcinoma. *Nat Rev Dis Primers* 2021; **7**: 65 [PMID: 34504109 DOI: 10.1038/s41572-021-00300-2]

3 **Rushbrook S**. BSG Guidelines for the diagnosis and treatment of cholangiocarcinoma. Gut 2023; In press

4 **Khan SA**, Davidson BR, Goldin RD, Heaton N, Karani J, Pereira SP, Rosenberg WM, Tait P, Taylor-Robinson SD, Thillainayagam AV, Thomas HC, Wasan H; British Society of Gastroenterology. Guidelines for the diagnosis and treatment of cholangiocarcinoma: an update. *Gut* 2012; **61**: 1657-1669 [PMID: 22895392 DOI: 10.1136/gutjnl-2011-301748]

5 **Nakeeb A**, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. *Ann Surg* 1996; **224**: 463-73; discussion 473-5 [PMID: 8857851 DOI: 10.1097/00000658-199610000-00005]

6 **Banales JM**, Marin JJG, Lamarca A, Rodrigues PM, Khan SA, Roberts LR, Cardinale V, Carpino G, Andersen JB, Braconi C, Calvisi DF, Perugorria MJ, Fabris L, Boulter L, Macias RIR, Gaudio E, Alvaro D, Gradilone SA, Strazzabosco M, Marzioni M, Coulouarn C, Fouassier L, Raggi C, Invernizzi P, Mertens JC, Moncsek A, Rizvi S, Heimbach J, Koerkamp BG, Bruix J, Forner A, Bridgewater J, Valle JW, Gores GJ. Cholangiocarcinoma 2020: the next horizon in mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 557-588 [PMID: 32606456 DOI: 10.1038/s41575-020-0310-z]

7 **Khan SA**, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int* 2019; **39 Suppl 1**: 19-31 [PMID: 30851228 DOI: 10.1111/liv.14095]

8 **Taylor-Robinson SD**, Toledano MB, Arora S, Keegan TJ, Hargreaves S, Beck A, Khan SA, Elliott P, Thomas HC. Increase in mortality rates from intrahepatic cholangiocarcinoma in England and Wales 1968-1998. *Gut* 2001; **48**: 816-820 [PMID: 11358902 DOI: 10.1136/gut.48.6.816]

9 **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**: 806-813 [PMID: 12445422 DOI: 10.1016/S0168-8278(02)00297-0]

10 **Vithayathil M**, Khan SA. Current epidemiology of cholangiocarcinoma in Western countries. *J Hepatol* 2022; **77**: 1690-1698 [PMID: 35977611 DOI: 10.1016/j.jhep.2022.07.022]

11 **McClements J**, Valle JW, Blackburn L, Brooks A, Prachalias A, Dasari BVM, Jones C, Harrison E, Malik H, Prasad KR, Sodergren M, Silva M, Kumar N, Shah N, Bhardwaj N, Nunes Q, Bhogal RH, Pandanaboyana S, Aroori S, Hamady Z, Gomez D; UK HPB Research Collaborative Group. Variation in treatment of intrahepatic cholangiocarcinoma: a nationwide multicentre study. *Br J Surg* 2023 [PMID: 37611144 DOI: 10.1093/bjs/znad259]

12 **Izquierdo-Sanchez L**, Lamarca A, La Casta A, Buettner S, Utpatel K, Klümpen HJ, Adeva J, Vogel A, Lleo A, Fabris L, Ponz-Sarvise M, Brustia R, Cardinale V, Braconi C, Vidili G, Jamieson NB, Macias RI, Jonas JP, Marzioni M, Hołówko W, Folseraas T, Kupčinskas J, Sparchez Z, Krawczyk M, Krupa Ł, Scripcariu V, Grazi GL, Landa-Magdalena A, Ijzermans JN, Evert K, Erdmann JI, López-López F, Saborowski A, Scheiter A, Santos-Laso A, Carpino G, Andersen JB, Marin JJ, Alvaro D, Bujanda L, Forner A, Valle JW, Koerkamp BG, Banales JM. Cholangiocarcinoma landscape in Europe: Diagnostic, prognostic and therapeutic insights from the ENSCCA Registry. *J Hepatol* 2022; **76**: 1109-1121 [PMID: 35167909 DOI: 10.1016/j.jhep.2021.12.010]

13 **Henson KE**, Elliss-Brookes L, Coupland VH, Payne E, Vernon S, Rous B, Rashbass J. Data Resource Profile: National Cancer Registration Dataset in England. *Int J Epidemiol* 2020; **49**: 16-16h [PMID: 31120104 DOI: 10.1093/ije/dyz076]

14 **Bright CJ**, Lawton S, Benson S, Bomb M, Dodwell D, Henson KE, McPhail S, Miller L, Rashbass J, Turnbull A, Smittenaar R. Data Resource Profile: The Systemic Anti-Cancer Therapy (SACT) dataset. *Int J Epidemiol* 2020; **49**: 15-15l [PMID: 31340008 DOI: 10.1093/ije/dyz137]

15 **Sandhu S**, Sharpe M, Findlay Ú, Roe C, Broggio J, Spencer K, Thackray K. Cohort profile: radiotherapy dataset (RTDS) in England. *BMJ Open* 2023; **13**: e070699 [PMID: 37339842 DOI: 10.1136/bmjopen-2022-070699]

16 **Herbert A**, Wijlaars L, Zylbersztejn A, Cromwell D, Hardelid P. Data Resource Profile: Hospital Episode Statistics Admitted Patient Care (HES APC). *Int J Epidemiol* 2017; **46**: 1093-1093i [PMID: 28338941 DOI: 10.1093/ije/dyx015]

17 **National Disease Registration Service.** CAS-SOP #4.8 Linking treatment tables: chemotherapy, tumour resections and radiotherapy. [cited 22 June 2023]. Available from: https://digital.nhs.uk/ndrs/our-work/ncras-work-programme/treatment-data/cas-sop-4.8

18 **Crooks CJ**, West J, Card TR. A comparison of the recording of comorbidity in primary and secondary care by using the Charlson Index to predict short-term and long-term survival in a routine linked data cohort. *BMJ Open* 2015; **5**: e007974 [PMID: 26048212 DOI: 10.1136/bmjopen-2015-007974]

19 **Elliss-Brookes L**, McPhail S, Ives A, Greenslade M, Shelton J, Hiom S, Richards M. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. *Br J Cancer* 2012; **107**: 1220-1226 [PMID: 22996611 DOI: 10.1038/bjc.2012.408]

20 **Driver RJ**, Balachandrakumar V, Burton A, Shearer J, Downing A, Cross T, Morris E, Rowe IA. Validation of an algorithm using inpatient electronic health records to determine the presence and severity of cirrhosis in patients with hepatocellular carcinoma in England: an observational study. *BMJ Open* 2019; **9**: e028571 [PMID: 31292182 DOI: 10.1136/bmjopen-2018-028571]

21 **Te Grotenhuis M**, Pelzer B, Eisinga R, Nieuwenhuis R, Schmidt-Catran A, Konig R. When size matters: advantages of weighted effect coding in observational studies. *Int J Public Health* 2017; **62**: 163-167 [PMID: 27796415 DOI: 10.1007/s00038-016-0901-1]

22 **Braveman P**, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. *Public Health Rep* 2014; **129 Suppl 2**: 19-31 [PMID: 24385661 DOI: 10.1177/00333549141291S206]

23 **Galea S**, Tracy M, Hoggatt KJ, Dimaggio C, Karpati A. Estimated deaths attributable to social factors in the United States. *Am J Public Health* 2011; **101**: 1456-1465 [PMID: 21680937 DOI: 10.2105/AJPH.2010.300086]

24 **Pruitt SL**, Shim MJ, Mullen PD, Vernon SW, Amick BC 3rd. Association of area socioeconomic status and breast, cervical, and colorectal cancer screening: a systematic review. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2579-2599 [PMID: 19815634 DOI: 10.1158/1055-9965.EPI-09-0135]

25 **Manser CN**, Bauerfeind P. Impact of socioeconomic status on incidence, mortality, and survival of colorectal cancer patients: a systematic review. *Gastrointest Endosc* 2014; **80**: 42-60.e9 [PMID: 24950641 DOI: 10.1016/j.gie.2014.03.011]

26 **Maddison AR**, Asada Y, Urquhart R. Inequity in access to cancer care: a review of the Canadian literature. *Cancer Causes Control* 2011; **22**: 359-366 [PMID: 21221758 DOI: 10.1007/s10552-010-9722-3]

27 **Sinding C**, Warren R, Fitzpatrick-Lewis D, Sussman J. Research in cancer care disparities in countries with universal healthcare: mapping the field and its conceptual contours. *Support Care Cancer* 2014; **22**: 3101-3120 [PMID: 25120008 DOI: 10.1007/s00520-014-2348-3]

28 **Davis LE**, Coburn NG, Hallet J, Earle CC, Liu Y, Myrehaug S, Mahar AL. Material deprivation and access to cancer care in a universal health care system. *Cancer* 2020; **126**: 4545-4552 [PMID: 32745271 DOI: 10.1002/cncr.33107]

29 **Jiang Y**, Jiang L, Li F, Li Q, Yuan S, Huang S, Fu Y, Yan X, Chen J, Li H, Li S, Liu J. The epidemiological trends of biliary tract cancers in the United States of America. *BMC Gastroenterol* 2022; **22**: 546 [PMID: 36581813 DOI: 10.1186/s12876-022-02637-8]

**Footnotes**

**Institutional review board statement:** The study was reviewed and approved for publication by our Institutional Reviewer.

**Informed consent statement:** NHS England and has a special legal instruction to collect patient data without needing informed consent. This instruction is granted under section 254 of the Health and Social Care Act 2012.

**Conflict-of-interest statement:** Dr Jose reports grants from AMMF-The Cholangiocarcinoma Charity, during the conduct of the study.

**Data sharing statement:** The data that support the findings of this study are available from NHS England. Restrictions apply to the access and use of the data used to undertake this study. A data dictionary is available at https://digital.nhs.uk/ndrs/data/access-to-data.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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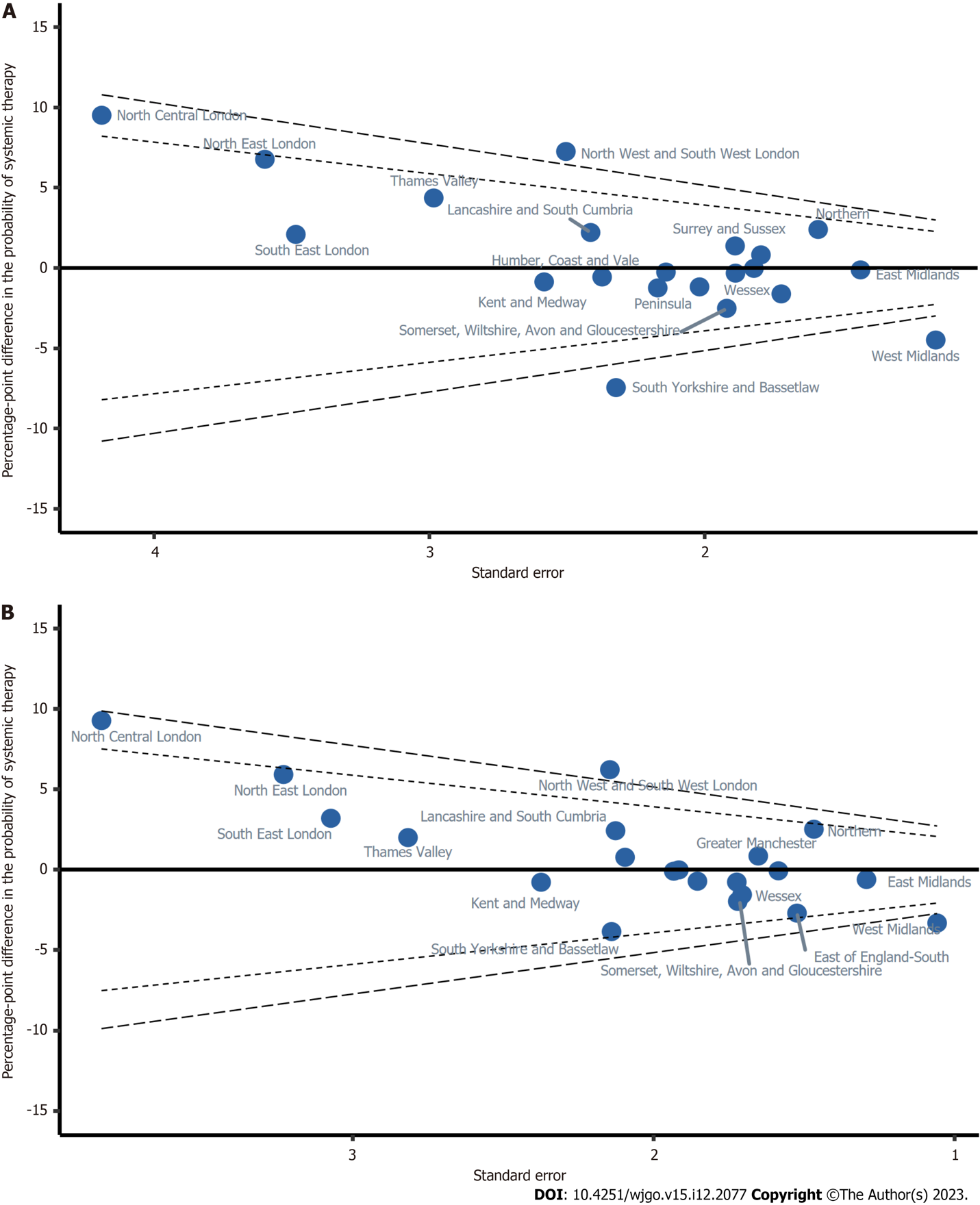
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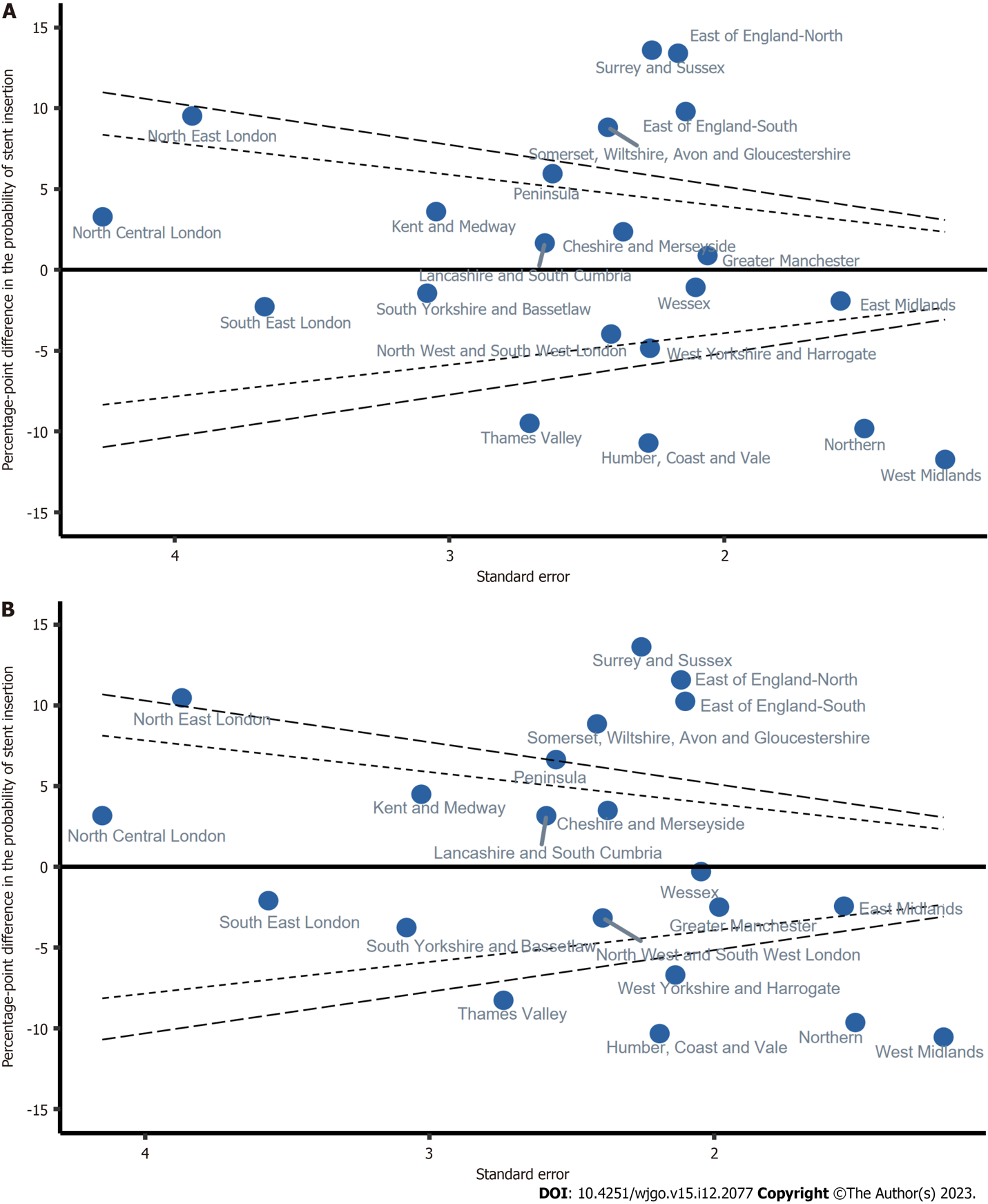
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**Figure 1 Percentage of cholangiocarcinoma patients treated with potentially curative surgery in each Cancer Alliance in England, 2014-2017.** A: Unadjusted; B: Adjusted. Adjustment for: age, gender, income deprivation quintile, Charlson comorbidity index, underlying liver disease at diagnosis, diagnosis year, tumour morphology, tumour sub-type, and routes to diagnosis. Inner dashed line = two standard deviations difference from average. Outer dashed line = three standard deviations difference from average.



**Figure 2 Percentage of cholangiocarcinoma patients treated with systemic therapy amongst those who did not receive surgery in each Cancer Alliance in England, 2014-2017.** A: Unadjusted; B: Adjusted. Adjustment for: age, gender, income deprivation quintile, Charlson comorbidity index, underlying liver disease at diagnosis, diagnosis year, tumour morphology, tumour sub-type, and routes to diagnosis. Inner dashed line = two standard deviations difference from average. Outer dashed line = three standard deviations difference from average.



**Figure 3 Percentage of cholangiocarcinoma patients treated with stent insertion amongst those who did not receive surgery in each Cancer Alliance in England, 2014-2017.** A: Unadjusted; B: Adjusted. Adjustment for: age, gender, income deprivation quintile, Charlson comorbidity index, underlying liver disease at diagnosis, diagnosis year, tumour morphology, tumour sub-type, and routes to diagnosis. Inner dashed line = two standard deviations difference from average. Outer dashed line = three standard deviations difference from average.

**Table 1 Description of cholangiocarcinoma patients diagnosed between 2014 and 2017 in England, and subgroup who did not receive surgery up to 12 mo after diagnosis**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Total** | **Did not receive surgery** |
| Total patients (*n*, %) | 8853 (100.0) | 7751 (100.0) |
| Age at diagnosis (yr) |  |  |
| 0-44 | 180 (2.0) | 117 (1.5) |
| 45-54 | 442 (5.0) | 320 (4.1) |
| 55-64 | 1231 (13.9) | 962 (12.4) |
| 65-74 | 2407 (27.2) | 1963 (25.3) |
| 75-84 | 2814 (31.8) | 2615 (33.7) |
| > 84 | 1779 (20.1) | 1774 (22.9) |
| Gender |  |  |
| Male | 4343 (49.1) | 3721 (48.0) |
| Female | 4510 (50.9) | 4030 (52.0) |
| Year of diagnosis |  |  |
| 2014 | 2055 (23.2) | 1802 (23.2) |
| 2015 | 2213 (25.0) | 1951 (25.2) |
| 2016 | 2259 (25.5) | 1983 (25.6) |
| 2017 | 2326 (26.3) | 2015 (26.0) |
| Route to diagnosis |  |  |
| Emergency presentation | 4276 (48.3) | 3975 (51.3) |
| TWW referral | 1490 (16.8) | 1306 (16.8) |
| Other GP referral | 1844 (20.8) | 1500 (19.4) |
| Other | 979 (11.1) | 729 (9.4) |
| Unknown | 264 (3.0) | 241 (3.1) |
| Stage at diagnosis |  |  |
| 1 | 310 (3.5) | 203 (2.6) |
| 2 | 686 (7.7) | 283 (3.7) |
| 3 | 330 (3.7) | 26 (2.9) |
| 4 | 3506 (39.6) | 3213 (41.5) |
| Missing | 4021 (45.4) | 3826 (49.4) |
| Tumour sub-type |  |  |
| CCA Other | 391 (4.4) | 378 (4.9) |
| eCCA | 1595 (18.0) | 1200 (15.5) |
| iCCA | 6867 (77.6) | 6173 (79.6) |
| Tumour morphology |  |  |
| Adenomas and adenocarcinomas | 8570 (96.8) | 7484 (96.6) |
| Other | 283 (3.2) | 267 (3.4) |
| English Index of Multiple Deprivation, income component |  |  |
| Quintile 1 (least deprived) | 1715 (19.4) | 1466 (18.9) |
| Quintile 2 | 1863 (21.0) | 1609 (20.8) |
| Quintile 3 | 1797 (20.3) | 1589 (20.5) |
| Quintile 4 | 1806 (20.4) | 1590 (20.5) |
| Quintile 5 (most deprived) | 1672 (18.9) | 1497 (19.3) |
| Charlson comorbidity index |  |  |
| 0 | 6220 (70.3) | 5340 (68.9) |
| 1 | 1140 (12.9) | 1025 (13.2) |
| 2 | 678 (7.7) | 623 (8.0) |
| 3+ | 815 (9.2) | 763 (9.8) |
| Underlying liver disease |  |  |
| No | 8044 (90.9) | 7101 (91.6) |
| Yes | 809 (9.1) | 650 (8.4) |
| Cancer Alliance at diagnosis |  |  |
| Cheshire and Merseyside | 427 (4.8) | 358 (4.6) |
| East Midlands | 795 (9.0) | 703 (9.1) |
| East of England-North | 524 (5.9) | 478 (6.2) |
| East of England-South | 558 (6.3) | 476 (6.1) |
| Greater Manchester | 521 (5.9) | 453 (5.8) |
| Humber, Coast and Vale | 310 (3.5) | 269 (3.5) |
| Kent and Medway | 251 (2.8) | 226 (2.9) |
| Lancashire and South Cumbria | 330 (3.7) | 285 (3.7) |
| North Central London | 141 (1.6) | 119 (1.5) |
| North East London | 173 (2.0) | 150 (1.9) |
| North West and South West London | 358 (4.0) | 302 (3.9) |
| Northern | 715 (8.1) | 628 (8.1) |
| Peninsula | 362 (4.1) | 311 (4.0) |
| Somerset, Wiltshire, Avon and Gloucestershire | 417 (4.7) | 374 (4.8) |
| South East London | 163 (1.8) | 141 (1.8) |
| South Yorkshire and Bassetlaw | 229 (2.6) | 201 (2.6) |
| Surrey and Sussex | 488 (5.5) | 442 (5.7) |
| Thames Valley | 234 (2.6) | 202 (2.6) |
| Wessex | 475 (5.4) | 419 (5.4) |
| West Midlands | 1013 (11.4) | 883 (11.4) |
| West Yorkshire and Harrogate | 369 (4.2) | 331 (4.3) |
| Treatment received |  |  |
| Surgery only | 507 (5.7) | 0 (0.0) |
| Surgery + systemic therapy | 367 (4.1) | 0 (0.0) |
| Surgery + stent insertion | 118 (1.3) | 0 (0.0) |
| Surgery + systemic therapy + stent insertion | 110 (1.2) | 0 (0.0) |
| Systemic therapy only | 1127 (12.7) | 1127 (14.5) |
| Stent insertion only | 1741 (19.7) | 1741 (22.5) |
| Systemic therapy + stent insertion | 415 (4.7) | 415 (5.4) |
| None of surgery, systemic therapy or stent insertion | 4468 (50.5) | 4468 (57.6) |

iCCA: Intrahepatic cholangiocarcinoma; eCCA: Extrahepatic cholangiocarcinoma; GP: General practitioner; TWW: Two week wait.

**Table 2 Estimated percentage of cholangiocarcinoma patients in England 2014-2017 that received**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **A: Potentially curative surgery** | | | | **B: Systemic therapy in those who did not receive surgery** | | | | **C: Stent insertion in those who did not receive surgery** | | | |
| **Unadjusted** | | **Adjusted** | | **Unadjusted** | | **Adjusted** | | **Unadjusted** | | **Adjusted** | |
| **Estimate (95%CI)** | | **Estimate 95%CI** | | **Estimate (95%CI)** | | **Estimate 95%CI** | | **Estimate (95%CI)** | | **Estimate 95%CI** | |
| Population average (intercept) | 12.45 | (11.76, 13.14) | 12.45 | (11.81, 13.09) | 19.89 | (19.01, 20.78) | 19.89 | (19.1, 20.69) | 27.82 | (26.85, 28.78) | 27.82 | (26.85, 28.78) |
| Cheshire and Merseyside | 3.71 | (0.32, 7.10) | 3.77 | (0.54, 6.99) | -1.18 | (-5.13, 2.78) | -0.09 | (-3.88, 3.70) | 2.35 | (-2.29, 6.99) | 3.50 | (-1.15, 8.16) |
| East Midlands | -0.88 | (-3.00, 1.25) | -1.11 | (-3.10, 0.87) | -0.12 | (-2.93, 2.69) | -0.60 | (-3.14, 1.93) | -1.93 | (-5.02, 1.16) | -2.43 | (-5.45, 0.60) |
| East of England - North | -3.67 | (-6.05, -1.29) | -3.96 | (-6.34, -1.59) | 0.82 | (-2.70, 4.34) | -0.06 | (-3.17, 3.04) | 13.40 | (9.15, 17.65) | 11.59 | (7.44, 15.74) |
| East of England - South | 2.25 | (-0.59, 5.08) | 1.33 | (-1.36, 4.01) | -1.62 | (-4.99, 1.76) | -2.70 | (-5.68, 0.29) | 9.79 | (5.59, 13.98) | 10.26 | (6.14, 14.38) |
| Greater Manchester | 0.60 | (-2.20, 3.41) | -1.32 | (-3.93, 1.29) | -0.03 | (-3.59, 3.54) | 0.86 | (-2.38, 4.09) | 0.88 | (-3.16, 4.92) | -2.48 | (-6.37, 1.40) |
| Humber, Coast and Vale | 0.78 | (-2.93, 4.49) | 2.14 | (-1.29, 5.58) | -0.56 | (-5.21, 4.09) | 0.78 | (-3.33, 4.88) | -10.72 | (-15.18, -6.25) | -10.32 | (-14.62, -6.03) |
| Kent and Medway | -2.49 | (-6.16, 1.19) | -2.14 | (-5.75, 1.47) | -0.87 | (-5.93, 4.19) | -0.77 | (-5.43, 3.88) | 3.60 | (-2.38, 9.58) | 4.51 | (-1.43, 10.44) |
| Lancashire and South Cumbria | 1.19 | (-2.45, 4.82) | 1.63 | (-1.72, 4.98) | 2.21 | (-2.52, 6.94) | 2.43 | (-1.74, 6.60) | 1.66 | (-3.54, 6.86) | 3.18 | (-1.90, 8.25) |
| North Central London | 3.16 | (-2.84, 9.15) | 2.36 | (-3.22, 7.94) | 9.52 | (1.30, 17.73) | 9.28 | (1.76, 16.80) | 3.28 | (-5.08, 11.63) | 3.18 | (-4.95, 11.32) |
| North East London | 0.85 | (-4.19, 5.89) | -0.05 | (-4.79, 4.69) | 6.77 | (-0.28, 13.82) | 5.93 | (-0.41, 12.26) | 9.52 | (1.80, 17.23) | 10.48 | (2.89, 18.06) |
| North West and South West London | 3.19 | (-0.48, 6.87) | 2.68 | (-0.79, 6.15) | 7.26 | (2.35, 12.17) | 6.23 | (2.02, 10.43) | -3.97 | (-8.70, 0.75) | -3.16 | (-7.84, 1.53) |
| Northern | -0.28 | (-2.58, 2.02) | -0.10 | (-2.20, 2.00) | 2.40 | (-0.71, 5.51) | 2.52 | (-0.35, 5.40) | -9.82 | (-12.74, -6.90) | -9.63 | (-12.58, -6.69) |
| Peninsula | 1.64 | (-1.87, 5.15) | 1.72 | (-1.43, 4.87) | -1.24 | (-5.50, 3.01) | -0.01 | (-3.76, 3.75) | 5.95 | (0.80, 11.09) | 6.65 | (1.64, 11.66) |
| Somerset, Wiltshire, Avon and Gloucestershire | -2.14 | (-5.00, 0.73) | -1.37 | (-4.02, 1.29) | -2.51 | (-6.28, 1.25) | -1.97 | (-5.34, 1.41) | 8.82 | (4.07, 13.57) | 8.87 | (4.14, 13.59) |
| South East London | 1.05 | (-4.19, 6.28) | 2.51 | (-2.6, 7.62) | 2.09 | (-4.74, 8.92) | 3.20 | (-2.82, 9.23) | -2.28 | (-9.48, 4.91) | -2.08 | (-9.08, 4.91) |
| South Yorkshire and Bassetlaw | -0.22 | (-4.43, 3.98) | 1.66 | (-2.28, 5.59) | -7.46 | (-12.01, -2.91) | -3.84 | (-8.04, 0.35) | -1.45 | (-7.49, 4.59) | -3.75 | (-9.79, 2.29) |
| Surrey and Sussex | -3.02 | (-5.56, -0.48) | -3.79 | (-6.27, -1.30) | 1.37 | (-2.33, 5.07) | -0.76 | (-4.14, 2.61) | 13.59 | (9.15, 18.02) | 13.64 | (9.22, 18.06) |
| Thames Valley | A1.23 | (-3.13, 5.58) | 0.07 | (-3.96, 4.10) | 4.36 | (-1.49, 10.21) | 2.00 | (-3.52, 7.52) | -9.50 | (-14.81, -4.19) | -8.26 | (-13.63, -2.89) |
| Wessex | -0.66 | (-3.49, 2.17) | -0.36 | (-2.99, 2.27) | -0.32 | (-4.02, 3.38) | -1.55 | (-4.89, 1.80) | -1.09 | (-5.21, 3.04) | -0.29 | (-4.30, 3.72) |
| West Midlands | 0.39 | (-1.55, 2.32) | 1.48 | (-0.33, 3.29) | -4.49 | (-6.77, -2.22) | -3.31 | (-5.39, -1.24) | -11.73 | (-14.08, -9.39) | -10.54 | (-12.88, -8.20) |
| West Yorkshire and Harrogate | -2.15 | (-5.20, 0.90) | -2.47 | (-5.40, 0.46) | -0.26 | (-4.45, 3.94) | -0.71 | (-4.35, 2.92) | -4.86 | (-9.31, -0.40) | -6.69 | (-10.88, -2.50) |
| Age 0-44 | 22.14 | (15.21, 29.08) | 20.69 | (13.91, 27.47) | 37.29 | (28.28, 46.31) | 36.41 | (27.47, 45.35) | -1.37 | (-9.44, 6.70) | -1.59 | (-9.41, 6.24) |
| Age 45-54 | 15.07 | (11.03, 19.11) | 13.24 | (9.38, 17.11) | 30.34 | (24.98, 35.70) | 28.96 | (23.77, 34.15) | -4.91 | (-9.47, -0.34) | -5.80 | (-10.26, -1.34) |
| Age 55-64 | 9.38 | (7.31, 11.46) | 7.59 | (5.58, 9.61) | 23.18 | (20.34, 26.03) | 21.61 | (18.82, 24.40) | -0.07 | (-2.73, 2.59) | -0.39 | (-3.00, 2.21) |
| Age 65-74 | 6.11 | (4.86, 7.36) | 4.84 | (3.64, 6.04) | 10.60 | (8.94, 12.26) | 9.59 | (7.97, 11.21) | 1.47 | (-0.27, 3.21) | 1.75 | (0.06, 3.44) |
| Age 75-84 | -5.41 | (-6.29, -4.53) | -4.83 | (-5.69, -3.96) | -8.88 | (-9.95, -7.81) | -8.68 | (-9.73, -7.63) | 1.49 | (0.07, 2.90) | 1.53 | (0.16, 2.90) |
| Age 85+ | -12.21 | (-12.9, -11.52) | -9.55 | (-10.28, -8.83) | -19.18 | (-20.05, -18.30) | -17.16 | (-18.08, -16.23) | -2.81 | (-4.6, -1.01) | -2.83 | (-4.64, -1.02) |
| Female | -1.81 | (-2.49, -1.13) | -0.49 | (-1.13, 0.16) | -0.30 | (-1.16, 0.56) | 1.21 | (0.43, 2.00) | -1.09 | (-2.05, -0.12) | -1.18 | (-2.13, -0.24) |
| Male | 1.88 | (1.17, 2.58) | 0.51 | (-0.16, 1.18) | 0.33 | (-0.60, 1.26) | -1.32 | (-2.16, -0.47) | 1.18 | (0.13, 2.22) | 1.28 | (0.25, 2.31) |
| Income deprivation quintile 1 (least deprived) | 2.12 | (0.63, 3.61) | 2.04 | (0.64, 3.43) | 3.15 | (1.22, 5.08) | 3.17 | (1.41, 4.92) | 0.98 | (-1.11, 3.08) | 0.47 | (-1.59, 2.52) |
| Income deprivation quintile 2 | 1.23 | (-0.15, 2.61) | 1.17 | (-0.11, 2.45) | 1.44 | (-0.34, 3.22) | 1.88 | (0.29, 3.47) | 1.07 | (-0.91, 3.04) | 0.30 | (-1.60, 2.20) |
| Income deprivation quintile 3 | -0.90 | (-2.24, 0.43) | -0.21 | (-1.47, 1.05) | -0.21 | (-1.96, 1.54) | 0.24 | (-1.32, 1.79) | 1.14 | (-0.85, 3.13) | 0.66 | (-1.26, 2.59) |
| Income deprivation quintile 4 | -0.50 | (-1.84, 0.85) | -0.38 | (-1.63, 0.88) | -2.53 | (-4.23, -0.84) | -2.32 | (-3.85, -0.79) | -0.98 | (-2.93, 0.98) | -1.08 | (-2.98, 0.82) |
| Income deprivation quintile 5 (most deprived) | -2.03 | (-3.38, -0.68) | -2.77 | (-4.10, -1.43) | -1.70 | (-3.48, 0.07) | -2.91 | (-4.59, -1.22) | -2.28 | (-4.28, -0.27) | -0.34 | (-2.33, 1.65) |
| Diagnosis year 2014 | -0.16 | (-1.41, 1.08) | 0.49 | (-0.67, 1.65) | -1.46 | (-3.05, 0.12) | 0.08 | (-1.35, 1.50) | -1.85 | (-3.64, -0.06) | -1.81 | (-3.53, -0.09) |
| Diagnosis year 2015 | -0.64 | (-1.81, 0.54) | -0.48 | (-1.57, 0.61) | -0.77 | (-2.29, 0.75) | -0.56 | (-1.93, 0.81) | -0.55 | (-2.27, 1.16) | -0.29 | (-1.95, 1.36) |
| Diagnosis year 2016 | -0.24 | (-1.42, 0.93) | -0.30 | (-1.41, 0.80) | 0.69 | (-0.85, 2.22) | 0.08 | (-1.29, 1.46) | 0.82 | (-0.90, 2.53) | 1.04 | (-0.62, 2.69) |
| Diagnosis year 2017 | 1.00 | (-0.19, 2.20) | 0.32 | (-0.79, 1.43) | 1.41 | (-0.14, 2.95) | 0.39 | (-0.99, 1.77) | 1.42 | (-0.31, 3.14) | 0.88 | (-0.77, 2.53) |
| Adenomas and adenocarcinomas | 0.23 | (0.14, 0.32) | 0.24 | (0.14, 0.35) | 0.49 | (0.38, 0.59) | 0.23 | (0.10, 0.36) | -0.04 | (-0.23, 0.15) | 0.40 | (0.18, 0.61) |
| Other morphology | -6.82 | (-9.54, -4.10) | -7.35 | (-10.55, -4.16) | -13.58 | (-16.57, -10.59) | -6.38 | (-10.05, -2.72) | 1.08 | (-4.31, 6.48) | -11.15 | (-17.12, -5.18) |
| eCCA sub-type | 12.40 | (10.56, 14.23) | 12.34 | (10.58, 14.10) | 1.64 | (-0.50, 3.78) | 2.89 | (0.92, 4.87) | 19.07 | (16.51, 21.62) | 19.28 | (16.7, 21.86) |
| iCCA sub-type | -2.35 | (-2.78, -1.93) | -2.65 | (-3.09, -2.22) | 0.10 | (-0.35, 0.55) | -0.47 | (-0.92, -0.02) | -3.66 | (-4.20, -3.13) | -3.89 | (-4.47, -3.31) |
| Other sub-type | -9.17 | (-11.00, -7.33) | -3.70 | (-6.01, -1.38) | -6.74 | (-10.12, -3.36) | -1.52 | (-4.98, 1.94) | -0.62 | (-5.01, 3.78) | 2.37 | (-2.50, 7.24) |
| Emergency presentation diagnosis route | -5.45 | (-6.14, -4.76) | -3.75 | (-4.42, -3.08) | -7.95 | (-8.80, -7.09) | -5.31 | (-6.11, -4.51) | 1.52 | (0.55, 2.49) | 2.10 | (1.14, 3.07) |
| GP referral diagnosis route | 6.16 | (4.65, 7.68) | 4.61 | (3.17, 6.05) | 6.10 | (4.15, 8.04) | 4.18 | (2.39, 5.97) | -4.60 | (-6.54, -2.65) | -5.28 | (-7.16, -3.40) |
| IP and OP diagnosis route | 13.04 | (10.54, 15.55) | 9.44 | (7.09, 11.79) | 12.54 | (9.35, 15.73) | 7.65 | (4.69, 10.61) | -2.76 | (-5.77, 0.25) | -2.75 | (-5.69, 0.18) |
| TWW referral diagnosis route | -0.14 | (-1.66, 1.37) | -0.58 | (-2.08, 0.91) | 10.96 | (8.75, 13.18) | 8.57 | (6.55, 10.59) | 2.92 | (0.65, 5.19) | 2.29 | (0.06, 4.51) |
| Unknown diagnosis route | -2.99 | (-7.06, 1.07) | -3.21 | (-6.51, 0.08) | -5.61 | (-10.73, -0.49) | -8.05 | (-11.96, -4.15) | -5.21 | (-11.31, 0.89) | -5.94 | (-11.07, -0.81) |
| Charlson score - 0 | 1.69 | (1.28, 2.10) | 0.69 | (0.30, 1.09) | 3.19 | (2.65, 3.73) | 1.02 | (0.51, 1.53) | 1.52 | (0.86, 2.18) | 1.38 | (0.73, 2.04) |
| Charlson score - 1 | -2.31 | (-3.98, -0.64) | -0.28 | (-1.85, 1.29) | -3.40 | (-5.56, -1.25) | 0.42 | (-1.52, 2.37) | -1.73 | (-4.26, 0.80) | -2.00 | (-4.45, 0.45) |
| Charlson score - 2 | -4.32 | (-6.35, -2.29) | -2.06 | (-3.96, -0.17) | -6.06 | (-8.71, -3.40) | -0.81 | (-3.25, 1.63) | -1.97 | (-5.30, 1.35) | -1.77 | (-4.94, 1.40) |
| Charlson score - 3+ | -6.07 | (-7.74, -4.39) | -3.19 | (-4.79, -1.60) | -12.84 | (-14.71, -10.97) | -7.06 | (-8.93, -5.20) | -6.73 | (-9.52, -3.93) | -5.53 | (-8.33, -2.74) |
| Liver disease-no | -0.73 | (-0.99, -0.47) | -0.35 | (-0.60, -0.10) | -0.51 | (-0.80, -0.21) | 0.04 | (-0.25, 0.32) | 0.46 | (0.17, 0.75) | 0.38 | (0.10, 0.67) |
| Liver disease-yes | 7.23 | (4.65, 9.82) | 3.47 | (0.96, 5.97) | 5.53 | (2.33, 8.73) | -0.43 | (-3.55, 2.69) | -4.99 | (-8.11, -1.86) | -4.19 | (-7.29, -1.08) |

Apart from the intercept, estimates represent the percentage-point difference from the weighted cohort average probability of each route. CI: Confidence interval; iCCA: Intrahepatic cholangiocarcinoma; eCCA: Extrahepatic cholangiocarcinoma; GP: General Practitioner; IP: Inpatient; OP: Outpatient; TWW: Two week wait.



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