Jaundice in primary care: a cohort study of adults aged >45 years using electronic medical records

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Background. Jaundice is a rare but important symptom of malignant and benign conditions. When patients present in primary care, understanding the relative likelihood of different disease processes can help GPs to investigate and refer patients appropriately.

Objective. To identify and quantify the various causes of jaundice in adults presenting in primary care.

Design. Historical cohort study using electronic primary care records.

Setting. UK General Practice Research Database.

Methods. Participants (186 814 men and women) aged >45 years with clinical events recorded in primary care records between 1 January 2005 and 31 December 2007. Data were searched for episodes of jaundice and explanatory diagnoses identified within the subsequent 12 months. If no diagnosis was found, the patient’s preceding medical record was searched for relevant chronic diseases.

Results. From the full cohort, 277 patients had at least one record of jaundice between 1 January 2005 and 31 December 2006. Ninety-two (33%) were found to have bile duct stones; 74 (27%) had an explanatory cancer [pancreatic cancer 34 (12%), cholangiocarcinoma 13 (5%) and other diagnosed primary malignancy 27 (10%)]. Liver disease attributed to excess alcohol explained 26 (9%) and other diagnoses were identified in 24 (9%). Sixty-one (22%) had no diagnosis related to jaundice recorded.

Conclusion. Although the most common cause of jaundice is bile duct stones, cancers are present in over a quarter of patients with jaundice in this study, demonstrating the importance of urgent investigation into the underlying cause.

Keywords. Primary health care, jaundice, diagnosis.

Introduction

Jaundice, or icterus, describes the yellow appearance of the skin and eyes resulting from elevated plasma bilirubin, a degradation product of haemoglobin. The symptom (or sign) of jaundice can arise from several diseases, including benign and malignant ones.\textsuperscript{1} It arises either from increased production or reduced excretion of bilirubin. The bilirubin may be conjugated or unconjugated, depending on the disease process. Pre-hepatic jaundice may result from overproduction of bilirubin (as in haemolysis) or reduced conjugation (as seen in Gilbert’s syndrome). Parenchymal liver disease leads to elevated levels of conjugated or unconjugated bilirubin. Hepatic causes of raised bilirubin include cirrhosis, viral, autoimmune or drug-induced hepatitis or extensive replacement of the liver by metastases. Extra-hepatic cholestasis may be due to obstruction of the bile duct by stones, or primary malignancy (pancreatic or cholangiocarcinoma), and is typically associated with elevated conjugated bilirubin.

Clinically, jaundice becomes apparent when bilirubin levels are $\sim$40 $\mu$mol/l, which is two to three times the normal value, depending on the laboratory’s selected reference range.\textsuperscript{1} The incidence of clinically apparent jaundice in primary care has not been described, although experience suggests it is relatively rare. One study has reported the effectiveness of a rapid access jaundice clinic in diagnosis and treatment time.\textsuperscript{2} Of 107 patients referred, biliary malignancy was present in 30 cases, common bile duct stones in 26 and alcohol-related liver disease in 9
patients. Viral or drug-induced hepatitis and autoimmune liver disease were present in 15, with Gilbert’s syndrome in 2 and congestive cardiac failure in 1. Three other UK studies have addressed the subject, though all identified participants from routine laboratory tests. In a Welsh study, 121 participants with a bilirubin of ≥120 μmol/l were investigated; probable causes of the jaundice were identified from hospital records, supplemented by communication with GPs where necessary. Only 4% of the cohort was wholly managed within primary care. The most frequent causes were malignancy 35%, sepsis/shock 22% (most of whom developed jaundice in hospital), common bile duct stones 13% and cirrhosis 8%. An incorrect or no diagnosis was found in 19% of patients. In an English study, the entry criterion was abnormal liver function (not necessarily jaundice) and similar methods were used to identify relevant investigations. One hundred and fifty-seven (18%) of the patients were not under hospital review and had incomplete investigation. These patients were offered repeat testing, and only diagnoses in this subgroup were reported. Of the 157 retested patients, 97 (62%) were diagnosed with conditions requiring hospital intervention or follow-up, including alcoholic liver disease, inherited chronic liver disease and hepatitis (both viral and autoimmune). A Scottish study retrospectively investigated patient’s outcomes following liver function testing in primary care, finding only 1.15% with serious liver disease. However, patients who had a bilirubin of >35 μmol/l (i.e. those who would be clinically jaundiced) were specifically excluded from the study. Other studies have originated in secondary care, with acute and chronic parenchymal disease, malignant obstructive jaundice and gallstones being the major causes. When GPs were asked their view of the likely causes of jaundice, gallstones, malignant biliary obstruction and viral hepatitis were identified most frequently, followed by cirrhosis and liver metastases.

While jaundiced patients may present directly to hospital, they frequently present in primary care and GPs will manage and refer these patients. At present, ‘obstructive’ jaundice in particular is included within the NICE Referral Guidelines for Suspected Cancer. It would help GPs to formulate a plan for investigation if the various underlying causes of jaundice in primary care settings were identified, and their relative importance established. This study aimed to do that, using primary care data.

Methods

Identification of the study population
The study was embedded within a large programme of cancer research, the DISCOVERY Programme (http://www.discovery-programme.org). The relevant part of that research programme uses the General Practice Research Database (GPRD). This database records anonymized primary care data for 4.8 million patients across the UK, including details of every consultation, referral, prescription and major outcome. For the programme, all patients aged ≥40 years on 1 January 2000 with 1 of 13 specific cancers (listed in Table 1) diagnosed between 2000 and 2009 were identified. If >5000 patients with a specific cancer were found, 5000 were selected using computerized random numbers. For each cancer case, up to five controls were randomly selected, matched to gender, year of birth and registered at the same GP practice. Controls were excluded if they had a record of the same cancer as their case at any time. However, they could have been diagnosed with any other cancers. The study reported here used only the ‘control’ population, as a reasonable sample of the ‘healthy’ population, albeit one whose age distribution matched the age distribution of cancer in the UK. To avoid any possible confusion, these controls are now called ‘participants’.

Participants were included if they had any clinical event recorded in their records between 2005 and 2007. They were excluded if they had at any time refused upload of data onto the national electronic database.

Identification of jaundice and possible causes
The dataset of eligible participants was searched to identify patients with jaundice from 1 January 2005 to 31 December 2006. The patients with jaundice were identified by searching for clinical events that contained codes relating to jaundice (see Appendix 1 for results). The GPRD has its own coding system, which maps on to Read codes. Each GPRD code has a description, which is the item visible to the GP when entering a record. A list of jaundice codes was extracted from the 100 035 available codes within the whole GPRD system and agreed by consensus between AT and WH. Patient records were searched for codes that related to causes of jaundice. Diagnoses were accepted as relevant if they were recorded within 12 months of the jaundice entry. For any patient with no relevant diagnostic code, their preceding medical record was searched to identify chronic or malignant illness that could provide an explanation.

Mortality was calculated by searching for codes pertaining to death over a 12-month period instead of using the de-registration date contained within the GPRD data, which can arise either from the death of a patient or from their departure from the practice.

Results

After application of the eligibility criteria, 186 814 participants were available for study. Their origin is shown in Table 1, and demographics in Table 2.
Two hundred and seventy-seven patients (0.15% of participants or annual incidence of 0.74 per 1000 patients >45 years) were found to have one or more codes relating to jaundice over the 2 years, with 412 jaundice codes recorded in total. Most codes used related to jaundice over the 2 years, with participants or annual incidence of 0.74 per 1000 patients >45 years of age. Malignancy (pancreatic, cholangiocarcinoma and metastases) accounted for over a quarter of patients. Alcohol-related cirrhosis or hepatitis was the third largest category. We could not identify a cause in nearly a quarter, based on reviewing each patient’s primary care medical record for relevant, coded diagnoses.

Strengths and limitations
This study has several limitations. It is wholly dependent upon accurate data recording by GPs. Several studies have examined symptoms in the GPRD, often using case–control methods. Most previous studies compared symptom reporting in cases and controls, making systematic under-recording of diagnoses less important. We cannot know how many patients with jaundice did not have the symptom recorded, possibly because the GP preferred to record a specific diagnosis. Generally, GPs prefer to document diagnoses instead of symptoms—though in the example of jaundice, it would have been rare that the underlying diagnosis could have been apparent at the initial consultation, allowing them to do so. A further limitation is that our dataset was matched by age and sex to patients with cancer. This means that they are not a random selection of all adults >45 years but have higher representation of the age group who suffer cancer. Thus, cancers are probably over-represented in our

Table 1 Origin of participants (split by cancer site in DISCOVERY Programme)

<table>
<thead>
<tr>
<th>Cancer site of matched case</th>
<th>Number of potential participants before application of eligibility criteria</th>
<th>Number of eligible participants (% that consulted in 2005-07)</th>
<th>Participants by gender [male, female (percentage)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>24 098</td>
<td>20 102 (83.4)</td>
<td>14 435 (71.8), 5667 (28.2)</td>
</tr>
<tr>
<td>Breast</td>
<td>23 028</td>
<td>20 356 (88.4)</td>
<td>255 (1.3), 20 101 (98.7)</td>
</tr>
<tr>
<td>Cervix*</td>
<td>5409</td>
<td>4653 (86.0)</td>
<td>9 (0.2), 4644 (99.8)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>8455</td>
<td>7045 (83.3)</td>
<td>5092 (72.3), 1953 (27.7)</td>
</tr>
<tr>
<td>Kidney</td>
<td>15 716</td>
<td>13 624 (86.7)</td>
<td>8274 (60.7), 5350 (39.3)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>22 946</td>
<td>19 378 (84.5)</td>
<td>11 048 (57.0), 8330 (43.0)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>23 703</td>
<td>20 185 (85.2)</td>
<td>10 588 (52.5), 9597 (47.5)</td>
</tr>
<tr>
<td>Myeloma</td>
<td>13 503</td>
<td>11 263 (83.4)</td>
<td>5936 (52.7), 5327 (47.3)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>24 248</td>
<td>19 592 (80.8)</td>
<td>12 756 (65.1), 6836 (34.9)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>17 919</td>
<td>15 172 (84.7)</td>
<td>7103 (46.8), 8069 (53.2)</td>
</tr>
<tr>
<td>Stomach</td>
<td>24 116</td>
<td>19 192 (79.6)</td>
<td>12 364 (64.4), 6828 (35.6)</td>
</tr>
<tr>
<td>Testis*</td>
<td>1489</td>
<td>1258 (84.5)</td>
<td>1248 (99.2), 10 (0.8)</td>
</tr>
<tr>
<td>Uterus*</td>
<td>16 786</td>
<td>14 994 (89.3)</td>
<td>514 (3.4), 14 480 (96.6)</td>
</tr>
</tbody>
</table>

*The erroneous genders can be (partially) explained. Two cases of testicular cancer (thus 10 controls) were actually tunica vaginalis tumour (which can be in the ovary). The uterine anomalies arose from all leiomyosarcomas being ascribed to uterus by the GPRD (which is not necessarily the case). No explanation can be found for the cervical anomalies. This is of little importance to our study as the controls (our participants) were assigned the correct gender.

Discussion

Summary of main findings
The study showed that bile duct stones are the most common cause of jaundice in patients presenting in primary care >45 years of age. Malignancy (pancreatic, cholangiocarcinoma and metastases) accounted for over a quarter of patients. Alcohol-related cirrhosis or hepatitis was the third largest category. We
A breakdown of the diagnoses is presented in Figure 1. Sus; for instance, a patient with gallstones and a later
Eight patients had more than one explanatory code:
jaundice, initially from diseases listed in our literature
(22%) of females died within 1 year of the onset of
jaundice.

Our study highlights the large proportion of patients
with jaundice. This warrants investigation
through urgent blood tests and imaging of patients

Implications for clinical practice
Our results should help GPs with jaundiced patients. Our study highlights the large proportion of patients in
whom the cause of jaundice is not identified. In
some patients, the diagnosis and management are
clear. There are several studies linking jaundice with
sepsis, which would commonly occur in the context of
a critically ill patient: the only patients with acute in-
fec tion in our cohort were those with ascending cholangitis. These patients would generally be recognized
as acutely unwell and would usually be ill enough to
require urgent hospital care. Such patients have been
described in secondary care studies of jaundice. The
same goes for those with decompensated liver disease
or those unwell with advanced malignancy. The re-
mainder, however, would normally be well enough to
have elective investigation, potentially following the
suggested referral pathway suggested in a previous
study.2

The high percentage of patients with an underlying
malignancy presenting with jaundice suggests that
GPs should instigate urgent investigation into the
cause, by means of immediate blood tests (which may
identify hepatic causes such as viral hepatitis or au-
immune liver disease), and urgent referral for transab-
dominal ultrasonography, to identify not only cancer
but also many of the other diagnoses in our study. We
would also recommend concurrent urgent referral to
specialist centres when the clinical picture suggests
a malignant cause, for example unexplained weight
loss, severe fatigue or symptoms suggestive of a pri-
mary malignancy at an extra-hepatobiliary site. This
would involve extending current NICE guidance7 to
include all new jaundice, whether obstructive or not.

Conclusions
Although the most common cause of jaundice in
adults aged >45 years in primary care is non-malignant
bile duct stones, cancers are present in over a quarter
of patients with jaundice. This warrants investigation
through urgent blood tests and imaging of patients
presenting with jaundice, as this will not only identify malignancy but also many other causes of jaundice. Concurrent urgent referral to specialist services is also recommended for adults aged >45 years who present with jaundice in primary care, given the significant proportion likely to have underlying malignancy.

Appendix 1. Jaundice symptom codes

<table>
<thead>
<tr>
<th>Medcode</th>
<th>Readcode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25418</td>
<td>1675</td>
<td>Yellow/jaundiced colour</td>
</tr>
<tr>
<td>45632</td>
<td>AA00.11</td>
<td>Spirochaetal jaundice</td>
</tr>
<tr>
<td>5996</td>
<td>2274.11</td>
<td>O/E—jaundiced</td>
</tr>
<tr>
<td>38877</td>
<td>R024z00</td>
<td>[D]Jaundice (not of newborn) NOS</td>
</tr>
<tr>
<td>6419</td>
<td>65V3.00</td>
<td>Notification of infectious jaundice</td>
</tr>
<tr>
<td>3121</td>
<td>J66y600</td>
<td>Obstructive jaundice NOS</td>
</tr>
<tr>
<td>39682</td>
<td>D100.11</td>
<td>Acholuric familial jaundice</td>
</tr>
<tr>
<td>6000</td>
<td>1675.11</td>
<td>Jaundice—symptom</td>
</tr>
<tr>
<td>355</td>
<td>R024.00</td>
<td>[D]Jaundice (not of newborn)</td>
</tr>
<tr>
<td>29488</td>
<td>2274</td>
<td>O/E—jaundiced colour</td>
</tr>
<tr>
<td>2612</td>
<td>R024111</td>
<td>[D]Jaundice</td>
</tr>
<tr>
<td>18574</td>
<td>R024100</td>
<td>[D]Icterus NOS</td>
</tr>
<tr>
<td>57309</td>
<td>AA00.00</td>
<td>Leptospirosis icterohaemorrhagica</td>
</tr>
<tr>
<td>18019</td>
<td>1675.12</td>
<td>Yellow—symptom</td>
</tr>
</tbody>
</table>

The GPRD stores its clinical entries as medcodes, which map onto Read codes, and are visible to the GP entering data as the description given in the third column.

Declaration

Funding: AT is an Academic F2 Doctor working at University Hospitals Bristol and the University of Bristol.

Ethics approval: Independent Scientific Advisory Committee for MHRA database research; reference 09_110.

Conflict of interest: none.

References