Malignant biliary strictures in patients with a normal bilirubin and/or normal liver enzymes

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Abstract

Background: To date, no studies have sought to determine the frequency of malignancy in patients presenting with a putative biliary stricture and normal liver function tests (LFTs). The primary aim of this retrospective cohort study was to determine the likelihood of malignancy in patients presenting with a biliary stricture and normal LFTs, a normal bilirubin level either alone or in combination with normal levels of liver enzymes [alkaline phosphatase (ALP) and alanine transaminase (ALT)]. A secondary aim was to determine any clinical/biochemical/sonographic features that may be associated with malignancy.

Methods: Patients presenting over a 10-year period were included. Fifteen variables were analysed to determine their association with malignant disease.

Results: Eight hundred and thirty patients with putative biliary strictures were included. Primary hepatopancreaticobiliary (HPB) cancers presented with a normal bilirubin and normal liver enzymes (ALP and ALT) in 6% of cases. Patients with a putative biliary stricture and a normal bilirubin level whose final diagnoses were pancreatic cancer, ampullary cancer, distal cholangiocarcinoma and hilar cholangiocarcinoma represented 21%, 13%, 7% and 9% of individuals diagnosed with these pathologies, respectively. Hypoalbuminaemia and isolated intrahepatic duct dilatation on ultrasound were significantly associated with malignancy in patients with normal bilirubin and completely normal LFTs.

Conclusions: This study has shown that patients with a putative biliary stricture and completely normal LFTs are unlikely to have a primary HPB malignancy. Those presenting with a normal bilirubin level, but deranged liver enzymes (ALP and/or ALT), are more likely to have malignant disease, and this should necessitate a higher degree of clinical suspicion.

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Introduction

Differentiating between benign and malignant biliary strictures can be challenging despite the utilization of advanced imaging modalities and endoscopic techniques. Pre-operative histological confirmation of malignancy is not usually possible prior to surgical exploration and resection. Biopsies, brushings and fine-needle aspiration (FNA) samples obtained during endoscopic retrograde cholangiopancreatography (ERCP) may yield a definitive tissue diagnosis; however, the combined sensitivity of these techniques is in the region of 60%.1,2 The reported sensitivity of endoscopic ultrasound (EUS) and FNA for the diagnosis of a malignant stricture varies widely from 43% to 86%.3–5 The combination of ERCP and EUS may improve the rate of pre-operative histological confirmation of malignancy; however, for a significant proportion of patients the decision to operate is based on a review of clinical, biochemical and radiological features.

Appearances on cross-sectional imaging and levels of tumour markers, particularly CA19-9 (carbohydrate antigen 19-9), are routinely used in the assessment of suspicious biliary strictures. Also, elevated liver function tests (LFTs) at presentation, including bilirubin, alkaline phosphatase (ALP) and alanine transaminase (ALT), can be suggestive of malignancy. 6

This study was presented at the 18th AUGIS Annual Scientific Meeting, 18-19 September 2014, Brighton, UK.
transaminase (ALT) have been associated with an increased likelihood of malignancy.\textsuperscript{6–10} Bilirubin levels, in particular, have been consistently identified as a strong predictor of malignant disease, indeed the higher the bilirubin level at presentation the greater the likelihood of malignancy.\textsuperscript{11} To date, no studies have sought to determine the likelihood of malignancy in patients presenting with normal LFTs. The aim of this study was to investigate the probability of malignant disease in patients presenting with a putative biliary stricture and normal LFTs (either a normal bilirubin level alone or normal bilirubin and normal liver enzymes). A secondary aim was to determine any clinical, biochemical or sonographic features in patients with normal LFTs that may be discernable at presentation and associated with an increased likelihood of malignancy.

**Patients and methods**

Patients with putative biliary strictures who were discussed at the Leicester Hepatopancreaticobiliary (HPB) Multidisciplinary Team (MDT) meeting during the last 10 years were included in the study. Data relating to demographics, symptoms and blood test results at presentation, radiological/intervention findings and final diagnoses were extracted from our prospective database. Patients’ case notes were also reviewed for further information. Patients with only a normal bilirubin at presentation and those with three normal parameters (ALP, ALT and bilirubin) were analysed in groups according to whether they had benign or malignant disease. Final diagnoses were based on histology (using either resected specimens, tissue obtained at surgical exploration, brushings from ERCP or biopsy material acquired radiologically/laparoscopically), interval imaging (at least two cross-sectional scans performed ≥6 months apart, all reviewed at the HPB MDT meeting and showing no disease progression in the case of benign disease) and findings during interventions such as ERCP and surgery.

**Statistical methods**

Fifteen variables were used to compare groups; patients presenting with a normal bilirubin and benign/malignant disease and patients presenting with three normal LFTs and benign/malignant disease. The 15 variables utilized were demographic factors (age, gender), symptoms at presentation (pain, weight loss and anorexia), blood results at presentation (haemoglobin, white cell count, neutrophil to lymphocyte ratio, platelet count, CA 19.9 and albumin) and ultrasound (USS) findings common bile duct (CBD) size, isolated CBD dilatation, isolated intrahepatic duct (IHD) dilatation and dilatation of both the CBD and IHD; CBD dilatation was defined as >7 mm in diameter, IHD dilatation was defined as either ≥2 mm diameter or >40% of the diameter of an adjacent portal vein branch. Depending on the nature of the variable, its association with benign/malignant disease, was determined using the unpaired t-test (with normality confirmed using the Shapiro-Wilk test) and chi-squared/Fisher’s tests. Statistical significance was defined as $P < 0.05$. Those variables that were significantly associated with either benign or malignant disease were analysed in further detail. Sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were calculated, along with the area under the curve (AUC) from receiver-operating characteristic (ROC) analysis. For calculation of sensitivity, specificity, PPV and NPV continuous data were dichotomized on the basis of the normal range for the variable. Statistical analyses were performed using Statistical Package for the Social Sciences 20.0© (SPSS, Chicago, IL, USA).

**Results**

A total of 830 patients with putative biliary strictures were discussed at the specialist HPB MDT meeting. Of these discussed biliary strictures, 492 were benign, 269 were malignant and the remainder were uncertain in nature (owing to patients either declining or being too frail for further investigation). (Fig. 1) Of the 269 patients with malignant disease, the diagnosis was based on histology in 127 (47%); this was obtained endoscopically, percutaneously and at laparoscopy and laparotomy in 11, 25, 47 and 44 patients, respectively. A diagnosis of malignancy in the remaining 142 patients was based on cross-sectioning imaging showing clear evidence of metastatic disease. Histological confirmation was not sought in this group as they were managed palliatively.

**Likelihood of malignancy in patients with normal bilirubin**

A normal bilirubin level at presentation was observed in 267 patients with a benign stricture (54%) and 59 patients with a malignant stricture (22%). Patients with a putative biliary stricture and a normal bilirubin level whose final diagnoses were pancreatic cancer, ampullary cancer, distal cholangiocarcinoma and hilar cholangiocarcinoma represented 21%, 13%, 7% and 9% of individuals diagnosed with these pathologies, respectively. Table 1 summarizes demographic data and the final diagnoses for this group of patients.

**Likelihood of malignancy in patients with normal bilirubin and normal liver enzymes (ALP and/or ALT)**

Bilirubin, ALP and ALT levels were all within normal limits in 126 patients with benign disease (26%) and 16 patients with malignant disease (6%). Table 2 summarizes demographic data and final diagnoses for this group.

**Predictors of malignancy in patients with normal bilirubin**

Clinical factors significantly associated with malignant disease in the presence of a normal bilirubin level were weight loss ($P = 0.002$), anorexia ($P = 0.006$), hypoalbuminaemia
and isolated dilatation of the intrahepatic ducts on USS ($p < 0.001$). Although these variables exhibited high specificity ($>85\%$) and NPV ($>82\%$) sensitivity and PPV were low ($<31\%$ and $<47\%$, respectively). Consequently, ROC analysis revealed poor AUC values for these variables ($\leq 0.6$) (Table 3).

**Table 1** Characteristics of patients with biliary strictures and a normal bilirubin

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Malignant ($n = 59$)</th>
<th>Benign ($n = 267$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, n (%)</td>
<td>18 (31)</td>
<td>102 (38)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>71 (25–95)</td>
<td>68 (18–94)</td>
</tr>
<tr>
<td>Stricture aetiology, n (%)</td>
<td>Cholangiocarcinoma, 28 (47)</td>
<td>Stones/Sludge, 82 (31)</td>
</tr>
<tr>
<td></td>
<td>Pancreatic cancer, 5 (8)</td>
<td>Benign stricture, 34 (13)</td>
</tr>
<tr>
<td></td>
<td>Other, 26 (44)$^a$</td>
<td>Physiological, 33 (12)</td>
</tr>
<tr>
<td></td>
<td>Chronic pancreatitis, 26 (10)</td>
<td>Post cholecystectomy, 16 (6)</td>
</tr>
<tr>
<td></td>
<td>Other, 85 (32)$^a$</td>
<td></td>
</tr>
</tbody>
</table>

$^a$Other causes which individually represent $<5\%$ of the total.

($p = 0.033$) and isolated dilatation of the intrahepatic ducts on USS ($p < 0.001$). Although these variables exhibited high specificity ($>85\%$) and NPV ($>82\%$) sensitivity and PPV were low ($<31\%$ and $<47\%$, respectively). Consequently, ROC analysis revealed poor AUC values for these variables ($\leq 0.6$) (Table 3).

**Predictors of benign disease in patients with normal bilirubin**

Clinical factors significantly associated with benign disease in the presence of a normal bilirubin were isolated dilatation of the CBD ($p < 0.001$), dilatation of both the intrahepatic ducts and CBD ($p = 0.023$) and the degree of CBD dilatation ($p = 0.001$). The PPV for these variables were notably high ($>86\%$); however, an inverse correlation between sensitivity and specificity was present. AUC values compared favourably with those obtained for variables associated with malignancy and a normal bilirubin, but the absolute numbers were poor ($\leq 0.69$) (Table 4).
Predictors of malignancy in patients with a normal bilirubin and normal liver enzymes (ALP and/or ALT)

A leukocytosis, thrombocytosis, hypoalbuminaemia and isolated dilatation of the IHD on USS were all significantly associated with malignant disease in the presence of completely normal LFTs. Further analysis revealed comparable results with those obtained for variables significantly associated with malignant disease in patients with normal bilirubin. High specificities (>88%) and NPV (>89%) were evident, with low sensitivities (<44%), PPV (≤40%) and AUC (≤0.66) (Table 3).

Discussion

This large series of patients who were investigated for putative biliary strictures demonstrates that primary malignant HPB pathology is extremely uncommon in the presence of completely normal LFTs. Patients with completely normal LFTs who received final diagnoses of pancreatic cancer, ampullary cancer, distal and hilar cholangiocarcinomas represented 6% of individuals with these pathologies. Patients with a normal bilirubin, but deranged liver enzymes (ALP and/or ALT), who were investigated for a possible biliary stricture were far more likely to have a primary HPB malignancy. For example, 21% of patients who were investigated for putative stricture and diagnosed with pancreatic cancer had a normal bilirubin at initial presentation, with elevated ALP and/or ALT levels. It may be that patients presenting with a normal bilirubin are at an earlier stage in the natural course of these malignancies. This is supported by the fact that a greater proportion of patients with hilar cholangiocarcinomas had resectable disease when they presented with a normal rather than a high bilirubin (14% versus 4%) although the numbers involved were small and, therefore, not statistically significant. No differences were observed in the rates of resection between individuals presenting with a putative stricture and a normal or raised bilirubin level in whom the final diagnoses were pancreatic cancer, ampullary cancer or distal cholangiocarcinoma. However, these conditions represented a smaller proportion of the series of malignant biliary strictures compared with hilar cholangiocarcinomas.

Previous studies which have sought to determine clinical factors associated with malignancy in patients with a biliary stricture have consistently identified a high bilirubin level, along with derangements in other LFTs, as the best predictors of malignant disease. In addition, high levels of CA19-9, age, weight loss, anorexia and IHD dilation on USS have been associated with malignancy (Table 5). To date, these studies have involved relatively small numbers of patients and have not addressed patients presenting with a normal bilirubin or LFTs. This study has shown that a number of factors are significantly associated with malignant disease in the presence of a normal bilirubin and normal LFTs (Table 3). Although highly specific (>85%), the sensitivity

Table 3 Analysis of factors significantly associated with malignant disease in patients with a normal bilirubin and patients with three normal LFTs

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bilirubin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight loss</td>
<td>30.5</td>
<td>85.9</td>
<td>31.6</td>
<td>85.3</td>
<td>0.58</td>
<td>0.50–0.67</td>
</tr>
<tr>
<td>Anorexia</td>
<td>10.2</td>
<td>97.5</td>
<td>46.2</td>
<td>83.5</td>
<td>0.54</td>
<td>0.45–0.62</td>
</tr>
<tr>
<td>Low albumin (&lt;35 g/l)</td>
<td>11.3</td>
<td>94.4</td>
<td>31.6</td>
<td>82.2</td>
<td>0.53</td>
<td>0.44–0.62</td>
</tr>
<tr>
<td>Isolated dilatation IHD</td>
<td>28.6</td>
<td>91.5</td>
<td>46.2</td>
<td>83.4</td>
<td>0.60</td>
<td>0.52–0.68</td>
</tr>
<tr>
<td>Three normal LFTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High white cell count (&lt;11 × 10⁹/l)</td>
<td>43.8</td>
<td>88.3</td>
<td>35.0</td>
<td>91.6</td>
<td>0.66</td>
<td>0.50–0.82</td>
</tr>
<tr>
<td>High platelet count (&lt;400 × 10⁹/l)</td>
<td>25.0</td>
<td>90.1</td>
<td>26.7</td>
<td>89.3</td>
<td>0.58</td>
<td>0.41–0.74</td>
</tr>
<tr>
<td>Low albumin (&lt;35 g/l)</td>
<td>12.5</td>
<td>97.6</td>
<td>40.0</td>
<td>89.8</td>
<td>0.55</td>
<td>0.39–0.71</td>
</tr>
<tr>
<td>Isolated IHD dilatation</td>
<td>33.3</td>
<td>93.3</td>
<td>37.5</td>
<td>92.1</td>
<td>0.62</td>
<td>0.46–0.78</td>
</tr>
</tbody>
</table>

LFTs, liver function tests; IHD, intrahepatic duct; PPV, positive predictive values; NPV, negative predictive values; AUC, area under the curve.

Table 4 Analysis of factors significantly associated with benign disease in patients with a normal bilirubin

<table>
<thead>
<tr>
<th>Factor</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>AUC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated dilatation CBD</td>
<td>33.9</td>
<td>92.9</td>
<td>94.9</td>
<td>26.4</td>
<td>0.65</td>
<td>0.58–0.72</td>
</tr>
<tr>
<td>Dilatation CBD and IHD</td>
<td>41.2</td>
<td>74.4</td>
<td>86.1</td>
<td>24.8</td>
<td>0.60</td>
<td>0.52–0.68</td>
</tr>
<tr>
<td>Degree of CBD dilatation</td>
<td>79.3</td>
<td>58.8</td>
<td>91.8</td>
<td>32.8</td>
<td>0.69</td>
<td>0.59–0.79</td>
</tr>
</tbody>
</table>

IHD, intrahepatic duct; PPV, positive predictive values; NPV, negative predictive values; AUC, area under the curve, CI, confidence interval.
of these variables is low (<44%) yielding low AUC values (≤0.66). Hypoalbuminaemia and isolated IHD dilatation on USS were significantly associated with malignancy in both the presence of a normal bilirubin and normal LFTs. Hypoalbuminaemia secondary to nutritional deficiency and cachexia typify terminal HPB cancers. In the earlier stages, it has been postulated that reductions in serum albumin concentrations arise from Systemic Inflammatory Response Syndrome (SIRS) initiated by the presence of malignant cells. Hypoalbuminaemia as a consequence of SIRS may result from reduced synthesis, enhanced degradation and altered distribution.\textsuperscript{12–14} Isolated IHD dilatation, along with hyperbilirubinaemia, has been significantly associated with malignancy in previous studies.\textsuperscript{6,7} This series shows that IHD dilatation remains a predictor of malignancy even in the absence of jaundice. Isolated IHD dilatation implies obstruction at the hilum or beyond which would arise less commonly from benign aetiologies. In addition, the degree of obstruction arising from benign conditions is likely to be less pronounced. For example, up to one-third of bile duct calculi are found in non-dilated ducts.\textsuperscript{15}

Despite previous studies having shown significant associations between elevated levels of CA19-9 and the presence of malignant biliary strictures,\textsuperscript{8} this series failed to demonstrate such an association. A range of benign HPB conditions have been associated with abnormal elevations of CA19-9, such as Mirizzi syndrome and autoimmune pancreatitis. Also, previous data have shown a correlation between hyperbilirubinaemia and elevated levels of CA19-9\textsuperscript{16} which may explain why this series, focusing on patients with normal LFTs, failed to establish an association between CA19-9 level and the presence of malignancy. The CA19-9 level is associated with disease progression\textsuperscript{17} and a low CA19-9 level, with a normal bilirubin suggests early stage disease.

A number of findings on USS were significantly associated with the presence of benign disease; isolated CBD dilatation, dilatation of the CBD and IHD and the degree of CBD dilatation. An inverse correlation between sensitivity and specificity for these variables resulted in ROC analysis yielding poor AUC values (≤0.69). Isolated dilatation of the CBD exhibited a notably high specificity for benign disease (92.9%). In accordance with this finding, four recent studies have demonstrated a very low yield of malignant pathology from performing EUS in individuals with CBD dilatation and normal LFTs.\textsuperscript{18–21} Bruno \textit{et al.}\textsuperscript{19} report one case of malignancy, pancreatic cancer, detected by EUS.

Although a number of factors in this study were associated with the presence of benign/malignant biliary strictures, the sensitivity of these variables was low yielding low AUC values. Additional variables that could be considered as potential discriminators between benign and malignant disease in future studies include other factors present in the history, for example symptom duration. It would also be interesting to consider the potential correlations between specific LFTs and the presence of malignancy, ALP and ALT but also aspartate aminotransferase (AST) and Gamma-Glutamyl Transpeptidase. Although outside the scope of this study, which focused on variables available at presentation, further discriminators between benign and malignant disease may include specific appearances on cross-sectional imaging.

**Conclusion**

This study has shown that patients with a putative stricture and completely normal LFTs are unlikely to have primary HPB malignant pathology. Those presenting with a normal bilirubin but deranged ALP and/or ALT are more likely to have malignant disease necessitating a higher degree of clinical suspicion. This is particularly important as patients with normal bilirubin may have earlier stage disease that could be amenable to resection. Hypoalbuminaemia and isolated IHD dilatation on USS are significantly associated with the presence of malignancy in patients with normal bilirubin and normal LFTs, exhibiting a high degree of specificity. Isolated dilatation of the CBD is significantly associated with benign disease in patients with normal bilirubin and is a highly specific finding.

**Conflicts of interest**

None to declare.

**Funding sources**

None.

**References**


