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Original research

Widespread gaps in the quality of care for primary biliary cholangitis in UK

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ABSTRACT

Objective Primary biliary cholangitis (PBC) is a progressive, autoimmune, cholestatic liver disease affecting approximately 15 000 individuals in the UK. Updated guidelines for the management of PBC were published by The European Association for the Study of the Liver (EASL) in 2017. We report on the first national, pilot audit that assesses the quality of care and adherence to guidelines.

Design Data were collected from 11 National Health Service hospitals in England, Wales and Scotland between 2017 and 2020. Data on patient demographics, ursodeoxycholic acid (UDCA) dosing and key guideline recommendations were captured from medical records. Results from each hospital were evaluated for target achievement and underwent χ^2 analysis for variation in performance between trusts.

Results 790 patients' medical records were reviewed. The data demonstrated that the majority of hospitals did not meet all of the recommended EASL standards. Standards with the lowest likelihood of being met were identified as optimal UDCA dosing, assessment of bone density and assessment of clinical symptoms (pruritus and fatigue). Significant variations in meeting these three standards were observed across UK, in addition to assessment of biochemical response to UDCA (all $p < 0.0001$) and assessment of transplant eligibility in high-risk patients ($p = 0.0297$).

Conclusion Our findings identify a broad-based deficiency in 'real-world' PBC care, suggesting the need for an intervention to improve guideline adherence, ultimately improving patient outcomes. We developed the PBC Review tool and recommend its incorporation into clinical practice. As the first audit of its kind, it will be used to inform a future wide-scale reaudit.

Significance of this study

What is already known on this topic

► Guidelines on management and diagnosis of primary biliary cholangitis (PBC) were published in 2017 and 2018. They emphasised on long-term, individualised treatment with consideration for the symptom burden of the disease.

What this study adds

► In the first audit of its kind, we have demonstrated significant shortcomings, across the 11 UK-based hospitals involved, in meeting recommended targets published in European Association for the Study of the Liver guidelines for PBC. This indicates the need for widespread analysis of PBC care in UK and improvement of services.

How might it impact on clinical practice in the foreseeable future

► This study will inform future quality improvement projects in PBC and promote awareness of existing management guidelines, ultimately improving the quality of PBC services and patient outcomes.

INTRODUCTION

Primary biliary cholangitis (PBC) is an autoimmune, cholestatic liver disease characterised by destruction of intra-hepatic cholangiocytes and progressive fibrosis.¹⁻³ The chronic disease course culminates in end-stage biliary cirrhosis and its associated complications such as portal hypertension.¹⁻³ The UK prevalence of PBC is estimated to be 15 000.²

Clinical features and the impact of PBC on the quality of life (QoL) are highly variable.^{4 5} Common features include



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pruritus, fatigue, memory problems and decreased bone mineral density.⁶ The aims of life-long treatment are to minimise the symptom burden, slow down disease progression and manage complications.¹⁴ Individuals with inadequate biochemical response to first-line therapy, ursodeoxycholic acid (UDCA), following 1 year of treatment, are regarded as high risk of progressive disease.^{12,7}

Updated guidelines for PBC management were published in 2017 by European Association for the Study of the Liver (EASL) and in 2018 by the British Society of Gastroenterology (BSG) in collaboration with UK-PBC—both recommend the utilisation of audit tools.^{1,2} At the time of writing, no formal analysis has been undertaken on the management of PBC nationally.

This pilot audit aims to gain insight into the performance within the UK National Health Service (NHS). We aim to identify whether key targets are being met on an individual and national level.

MATERIALS AND METHODS

This study is a multicentre, retrospective pilot audit of PBC management across UK.

Site recruitment

Site recruitment was undertaken through electronic emailing and collaborative efforts between clinicians. All hospitals in the UK managing patients with PBC were eligible. The recruitment process commenced in May 2017 until March 2020. Appointed audit leads used a clinical audit tool for data collection—a

Microsoft Excel spreadsheet with predefined standards based on EASL guidelines.¹ The accompanying audit proforma is provided in online supplemental materials.

A total of 11 NHS hospitals from England, Wales and Scotland contributed data towards this audit. Their trusts are listed below:

- ▶ Royal Free London NHS Foundation Trust.
- ▶ Imperial College Healthcare NHS Trust London.
- ▶ London North West University Healthcare NHS Trust.
- ▶ York Teaching Hospital NHS Foundation Trust.
- ▶ University Hospitals of Derby and Burton NHS Foundation Trust.
- ▶ Aneurin Bevan University Health Board.
- ▶ Betsi Cadwaladr University Health Board.
- ▶ Swansea Bay University Health Board
- ▶ Hywel Dda University Health Board.
- ▶ Cardiff & Vale University Health Board.
- ▶ NHS Grampian.

The involved hospitals have been anonymised for publication purposes and will be referred by their corresponding number in table 1 where they are summarised.

Audit standards

Audit standards were developed according to the 2017 EASL guidelines for PBC management. BSG/UK-PBC guidelines were published following the development of the audit standards and did not directly contribute.² Standards were chosen according to guideline recommendations and feasibility of data collection from electronic records.

Table 1 Summary of the NHS hospitals involved in this audit

NHS hospital	Data collection period	Number of patients	Number of patients with concurrent AIH (% of total patients)	% of female patients (number)	Mean age (SD)
Hospital 1*	June–July 2018	122	43 (35.3)	-	-
Hospital 2*	October–November 2018	75	17 (22.7)	-	66.9 (10.43)
Hospital 3*	2017–2018	10	1 (10.00)	100.0 (10)	57.2 (13.52)
Hospital 4	February–March 2020†	19	2 (10.5)	94.7 (18)	62.5 (17.95)
Hospital 5*	December 2017–January 2018	166	6 (4.00)	95.0 (151/159)‡	58.3 (11.44)
Hospital 6*	August–December 2019	69	10 (14.00)	95.7 (66)	68.7 (12.82)
Hospital 7*	2017–2018	123	-	-	-
Hospital 8	2017–2018	18	3 (16.7)	77.8 (14)	69.4 (14.83)
Hospital 9*	2017–2018	82	15 (18.3)	-	-
Hospital 10	September–October 2017	18	2 (11.1)	-	-
Hospital 11*	2017–2018	88	12 (13.6)	-	60.9 (13.89)
Total dataset		790	111 (14.1)		62.1 (13.16)

Incomplete or absent datasets are indicated with a hyphen (-).

Data on number of patients, concurrent autoimmune hepatitis (AIH) diagnosis, percentage of women and mean age for the cohorts from each hospital is shown where available.

*Indicates hospitals with dedicated hepatology clinics. Hospitals with general gastroenterology clinics are unmarked.

†The patient list was obtained in December 2017, however, data collection was delayed due to staffing disruption. Data collection in 2020 was undertaken using the same list of patients obtained in 2017 to ensure consistency with other datasets.

‡Data on sex were absent for seven patients who were therefore omitted from the percentage calculation.

AIH, autoimmune hepatitis; NHS, National Health Service.

Specific audit standards with their respective EASL recommended targets shown in brackets, which include¹:

- ▶ Prescription of the recommended UDCA dose (13–15 mg/kg/day) (90%).
- ▶ Assessment of biochemical response to UDCA following 1 year of treatment (80%).
- ▶ Recorded symptom assessment of pruritus and/or fatigue (90%).
- ▶ Assessment of bone density via a dual-energy X-ray absorptiometry (DEXA) scan within 5 years since diagnosis (80%) and appropriate medical intervention for patients with abnormal results such as supplementation with vitamin D (no recommended target).
- ▶ Assessment of patients with severe disease for liver transplant eligibility (90%).

Patient recruitment, exclusion criteria and data collection

All patients over the age of 18, diagnosed with PBC and managed at each site, with available medical records were included. Patient lists were generated via coding departments; hospital biochemistry labs (patients positively testing for antimitochondrial antibodies (AMA) or PBC-specific antinuclear antibodies (ANA)); local databases and/or histopathology results. Patients who were under investigation for suspected PBC, had missing records or had been transferred to a different site at the time of data collection were excluded.

Collected data included age, sex, weight, UDCA dosage, UDCA discontinuation, record of assessment of UDCA response at 1 year from initial UDCA prescription, record of assessment of pruritus, fatigue and bone density within 5 years of diagnosis, intervention for abnormal bone density findings and record of assessment of transplant eligibility for high-risk patients.

Symptom assessment was evaluated via information in clinic letters. Assessment involved subjective evaluation in the majority of cases, however, a few clinicians used objective assessments such as the PBC-40 questionnaire.⁴

Data analysis and statistics

Data were combined into a single master-audit database. Hospitals were omitted from comparisons if data sets were missing or inputted incorrectly. Data were grouped according to country (England, Scotland, Wales) and the level of hepatology service provided, general gastroenterology clinic (GGC) or dedicated hepatology clinic (DHC). Averages were calculated using mean and SD. χ^2 analysis was undertaken to enable assessment of variation in compliance to EASL guidelines between hospitals. For the comparison of GGC versus DHC, Fisher's exact test was undertaken in preference to χ^2 due to increased accuracy. Statistical analysis was performed using GraphPad Prism V.8. As the study design did not include analysis of factors contributing to discrepancies in performance—such as

the local clinical service structure, patients' comorbidities, compliance and ethnic background—no regression models were applied.

Governance and support

Approval was obtained from each site as per local policy. No patient-identifying information was collected and patient management was not affected. This project was supported by the PBC Foundation. Dr Falk Pharma UK supported local audits with materials such as the audit proforma. No funding was received. Neither Dr Falk Pharma nor PBC Foundation was involved in data analysis or report writing.

RESULTS

Population

Data from 790 patients at 11 hospitals were obtained from May 2017 to March 2020. The number of patients involved in data collection at each site ranged from 10 patients (hospital 3) to 166 patients (hospital 5). The mean age at the time of data collection was 62.1 years (SD, 13.16). Across the five hospitals that provided data on sex distribution, the percentage of female patients was 94.2% (259 of 275 patients). [table 1](#) details each hospital involved in the audit. Supplementary data are presented in online supplemental materials.

UDCA dosing and assessment of response at 1 year

Across all 11 hospitals, 670 of 790 (84.8%) patients had records of UDCA prescription, with 65 of 670 (9.7%) patients discontinuing treatment ([figure 1A](#)). Documentation of reasoning behind discontinuation was limited and inconsistent. The most frequent reasons were intolerance—notably nausea, vomiting and diarrhoea—or that the patient had received a liver transplant.

Of the patients remaining on UDCA treatment, 292 of 605 (48.3%) patients had been prescribed the recommended UDCA dose of 13–15 mg/kg/day, 288 of 605 (47.6%) patients were prescribed an alternative dose and 25 of 605 (4.1%) patients were prescribed an unspecified dose. None of the 11 hospitals met the EASL target of 90% for prescription of the recommended UDCA dose. Significant variation was observed between hospitals, ranging from 15.8% (hospital 8) to 88.8% (hospital 5) ($p < 0.0001$) ([figure 1A](#)).

Data on assessment of UDCA response were available from 10 hospitals, comprising of 524 patients remaining on UDCA treatment (86.6% of 605 patients remaining on UDCA in all 11 hospitals). Assessment of UDCA response at 1 year was recorded in 414 of 524 (79.0%) patients. Five of the 10 assessed hospitals met the EASL target of 80%. A significant variation was observed between hospitals, ranging from 53.3% (hospital 9) to 100% (hospital 3) ($p < 0.0001$) ([figure 1B](#)).

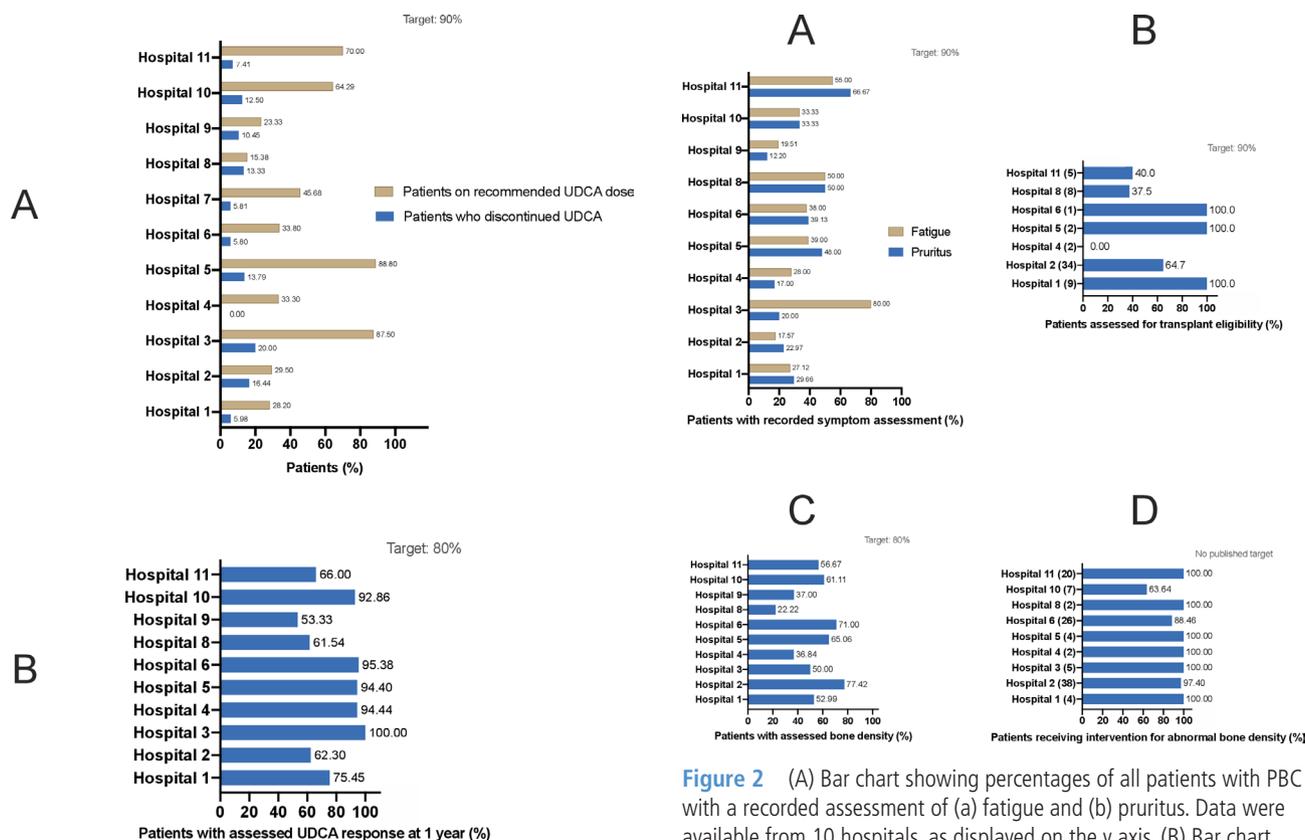


Figure 1 (A) Bar chart showing (a) percentages of the total number of patients with PBC initially prescribed UDCA who discontinued treatment and (b) percentages of the patients with ongoing UDCA treatment who were prescribed the recommended dose of 13–15 mg/kg daily. Data were available from all 11 hospitals, as displayed on the y axis. (B) Bar chart showing the percentages of patients with PBC with ongoing UDCA treatment that underwent a biochemical assessment of UDCA response following 1 year of treatment. Data were available from 10 hospitals, as displayed on the y axis. PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

Symptom assessment

Data on symptom assessment were available from 592 of 667 (88.8%) patients across 10 hospitals. Pruritus assessment was recorded in 209 of 592 (35.3%) patients and fatigue assessment in 197 of 592 (33.3%) patients. None of the hospitals met the EASL target of 90%. Significant variation was observed between hospitals for recorded assessments of both pruritus and fatigue (ranges: pruritus—12.2%–66.7%, fatigue—17.6%–80.0%) ($p < 0.0001$) (figure 2A).

Transplant consideration

Data on transplant consideration were available from seven hospitals. Sixty-one of 557 (11%) patients were recorded as high risk. Thirty-nine of 61 (63.9%) high-risk patients underwent assessment for liver transplant eligibility. Four of the seven assessed hospitals met the EASL target of 90%. Significant variation was observed between hospitals, ranging from 0% (hospital 4) to 100% (multiple hospitals) ($p = 0.0297$) (figure 2B).

Figure 2 (A) Bar chart showing percentages of all patients with PBC with a recorded assessment of (a) fatigue and (b) pruritus. Data were available from 10 hospitals, as displayed on the y axis. (B) Bar chart showing the percentages of high-risk patients undergoing assessment for liver transplant eligibility. Data were available from seven hospitals, as displayed on the y axis. The number of patients classified as high-risk is shown in brackets for individual hospitals. (C) Bar chart showing the percentages of all patients with PBC undergoing assessment of bone density within 5 years of PBC diagnosis. Data were available from 10 hospitals, as displayed on the y axis. (D) Bar chart showing the percentages of patients with PBC with abnormal bone density findings that received an appropriate intervention. Data were available from nine hospitals, as displayed on the y axis. Number of patients with abnormal bone density readings is shown in brackets for individual hospitals. PBC, primary biliary cholangitis.

Bone density assessment

Bone density assessment within 5 years of PBC diagnosis was recorded in 358 of 621 (57.6%) patients across 10 hospitals. None of the hospitals met the EASL target of 80%. Significant variation was observed between hospitals, ranging from 22.2% (hospital 8) to 77.4% (hospital 2) ($p < 0.0001$) (figure 2C). The proportions of patients with abnormal bone density that were provided an appropriate intervention ranged from 88.5% (hospital 6) to 100% (multiple hospitals). There was no significant variation observed among hospitals ($p = 0.6148$) (figure 2D).

Comparison between England, Wales and Scotland

Significant variation in performance was observed between England (five hospitals, 339 patients), Wales (five hospitals, 329 patients) and Scotland (one hospital, 122 patients) in all recorded standards except pruritus assessment (figure 3A). Adherence to the

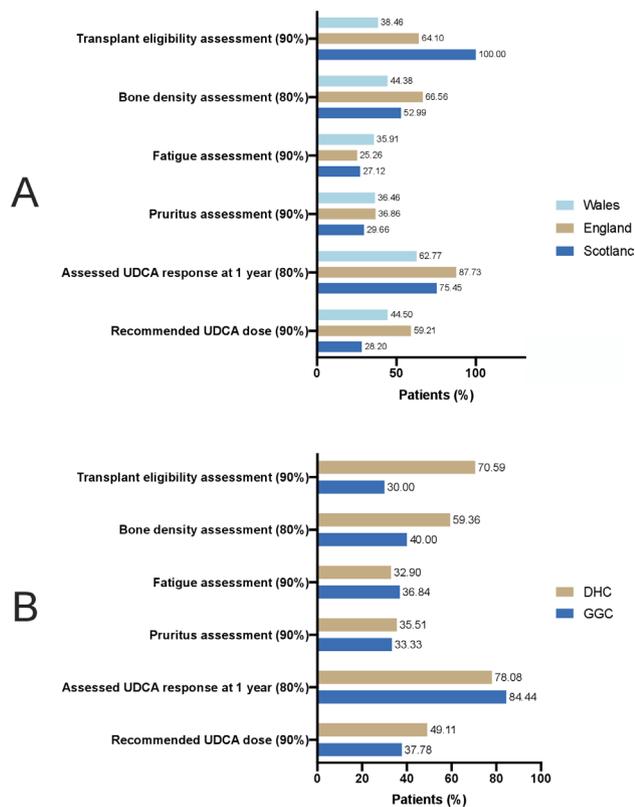


Figure 3 (A) Bar chart showing the performance of England (five hospitals), Wales (four to five hospitals) and Scotland (one hospital) for all assessed targets, as displayed on the y axis. One Welsh hospital provided data for recommended UDCA dosing only and for no other standards. Data on assessment of transplant eligibility were available from four English and two Welsh hospitals. (B) Bar chart showing the performance of GGC (two to three hospitals) and DHC (eight hospitals) for all assessed targets, as displayed on the y axis. One DHC hospital provided data for recommended UDCA dosing only and for no other standards. Data on assessment of transplant eligibility were available from two GGC hospitals and five DHC hospitals. DHC, dedicated hepatology clinics; GGC, general gastroenterology clinics; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

guidelines in England was greater for recommended UDCA dosing (59.2% vs 44.5% Wales, 28.2% Scotland), assessment of UDCA response (87.7% vs 62.8% Wales, 75.5% Scotland) and assessment of bone density within 5 years (66.6% vs 44.4% Wales, 53.0% Scotland). Raw data and statistical analysis are shown in online supplemental materials.

Comparison between DHC and GGC

Depending on the hospital, patients with PBC were either seen in DHC or GGC. For two of the six assessed standards—assessments of bone density and transplant eligibility—significantly greater performance was observed in DHC (eight hospitals, 735 patients) compared with GGC (three hospitals, 55 patients) (figure 3B). The 80% target for assessment of UDCA response at 1 year was met by GGC only (84.4%). Raw data and statistical analysis are shown in online supplemental materials.

DISCUSSION

In the first nationwide pilot audit of PBC management, our primary aim was to gain an indication of the quality of PBC care to inform a potential widespread audit. We obtained a large sample size, treated across 11 large hospitals. This is representative of the population of patients with PBC managed within the NHS and enables examination of care quality and nationwide variability. Real-world data were captured, ensuring that our findings are reflective of clinical practice.

None of the hospitals met all the recommended EASL targets, and targets were often substantially missed. The poor adherence to recommended UDCA dosing is a cause for concern. Surprisingly, 50% of hospitals met the target for assessment of UDCA response, which may reflect an emphasis on risk stratification in PBC education.⁸ Poor survival has been reported in individuals responding poorly to UDCA.^{9 10} The early identification of high-risk individuals and provision of second-line treatments could significantly improve disease outcomes.^{11 12} Undertreatment of UDCA via sub-optimal dosing has been suggested as a predictive factor in the development of cirrhosis, HCC and liver failure.^{13–16}

No hospital met the target for symptom screening or bone density assessment. Regular assessment of symptom burden has been highlighted as a key aspect of lifelong PBC management.¹⁷ One study observed that approximately 51% of patients develop PBC symptoms within 5 years after diagnosis.¹⁸ Furthermore, up to 44% of patients with PBC are affected by osteoporosis, with the majority having osteopenia.² This pilot audit was based on EASL guidelines alone, which recommend the use of DEXA scan in all patients with PBC. BSG/UK-PBC guidelines recommend risk assessment—using the FRAX or QFracture score—and a subsequent DEXA scan when scores indicate treatment.² This disparity may explain the poor performance for this target across hospitals.

This audit has identified statistically significant variation in performance across individual hospitals, between countries and between GGC and DHC. Caution should be undertaken when interpreting the GGC versus DHC comparison due to the differences in population sizes between the assessed groups (55 vs 735 patients, respectively). This may be due to the increased availability of PBC-related databases within DHC. For this reason, not every hospital was able to participate and hospitals with DHC were more willing to contribute to the study. Geographic variation in UDCA use has been reported.¹⁹ Additionally, a global cohort study—which included the UK—previously reported a large number of patients who were underdosed with UDCA.¹⁶

An intervention is necessary to improve clinical practice. Simple techniques, such as the implementation of a short review form or checklist to use at follow-up,

may provide a promising strategy.^{20 21} Until recently, the only PBC-specific health-related QoL assessment was the PBC-40 questionnaire.^{4 22} Guidelines recommend symptom assessment but do not specify tools to score symptoms objectively. The PBC-10 questionnaire has recently been developed and validated for this purpose.²³

We have developed a PBC Review tool—based on guideline recommendations and the PBC-10—for use in hospitals. This is provided in online supplemental materials. A copy of this tool, with our findings, will be provided to the contributing hospitals. We aim to establish a national PBC registry for data collection to facilitate future quality improvement projects.

There are some limitations to our pilot audit. Audits were initially intended to be carried out for local purposes. Compilation of data into a national aggregate and subsequent analysis was undertaken by different authors. As a result, there is potential variation in the quality and consistency of data collection between sites. We did not report on the use of second-line treatments, such as obeticholic acid, as they were not widely prescribed at the time of audit development. Hospitals that reported second-line prescription are shown in online supplemental materials. At the time of writing, EASL and BSG-UK-PBC guidelines have been established for at least 2 years; however, most hospitals collected data in 2017 and 2018. Improvement in PBC management may have occurred since, thus, results may not accurately reflect current practice.

This pilot audit was not designed to assess the causes of deficiencies in PBC care. Consideration should be made for the likely influence of potential conflict between patient choice and recommended guidelines on target failures. Data from a limited number of involved hospitals included notes such as ‘poor tolerance of recommended UDCA dosage’, ‘reluctance to increase UDCA dose’ after years on a lower-than-recommended dose and ‘failure to attend appointments’. Data have not been obtained for individual consultants, such as specialism into hepatology or luminal gastroenterology, which may influence knowledge of existing guidelines and quality of care. Formal analysis of these factors should be considered in a future audit to investigate the extent of their influence on guideline non-adherence. Analysis should also include explicit documentation of reasons for failure in guideline adherence and include data on second-line therapies, referral to tertiary care and biochemistry.

We have revealed clear gaps in quality of national PBC care, with notable failures in UDCA dosing and symptom assessment. Our findings justify the recommendation of incorporating a PBC review tool into clinical practice. We recommend that managing clinicians review clinical guidelines and ensure departmental practice are up to date. Optimal patient management is crucial to minimising disease progression

and maximising QoL. A refined, wide-scale national reaudit will be developed in the near future.

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REFERENCES

- European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;67:145–72.
- Hirschfield GM, Dyson JK, Alexander GJM, *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;67:1568–94.
- Onofrio FQ, Hirschfield GM, Gulamhusein AF. A practical review of primary biliary cholangitis for the gastroenterologist. *Gastroenterol Hepatol* 2019;15:145–54.
- Jacoby A, Rannard A, Buck D, *et al.* Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut* 2005;54:1622–9.
- Mells GF, Pells G, Newton JL, *et al.* Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. *Hepatology* 2013;58:273–83.
- Galoosian A, Hanlon C, Zhang J, *et al.* Clinical updates in primary biliary cholangitis: trends, epidemiology, diagnostics, and new therapeutic approaches. *J Clin Transl Hepatol* 2020;8:49–60.
- Lindor KD, Bowlus CL, Boyer J, *et al.* Primary biliary cholangitis: 2018 practice guidance from the American association for the study of liver diseases. *Hepatology* 2019;69:394–419.
- Corrigan M, Hirschfield G, Greenfield S, *et al.* Barriers to implementation of stratified care in primary biliary cholangitis: a scoping exercise. *BMJ Open Gastroenterol* 2019;6:e000226.
- Parés A, Caballería L, Rodés J. Excellent long-term survival in patients with primary biliary cirrhosis and biochemical response to ursodeoxycholic acid. *Gastroenterology* 2006;130:715–20.
- Corpechot C, Abenavoli L, Rabahi N, *et al.* Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. *Hepatology* 2008;48:871–7.
- Bowlus CL, Pockros PJ, Kremer AE, *et al.* Long-Term obeticholic acid therapy improves histological endpoints in patients with primary biliary cholangitis. *Clin Gastroenterol Hepatol* 2020;18:1170–8.
- Trauner M, Nevens F, Shiffman ML, *et al.* Long-term efficacy and safety of obeticholic acid for patients with primary biliary cholangitis: 3-year results of an international open-label extension study. *Lancet Gastroenterol Hepatol* 2019;4:445–53.
- Prince M, Chetwynd A, Newman W, *et al.* Survival and symptom progression in a geographically based cohort of patients with primary biliary cirrhosis: follow-up for up to 28 years. *Gastroenterology* 2002;123:1044–51.
- Corpechot C, Chazouillères O, Poupon R. Early primary biliary cirrhosis: biochemical response to treatment and prediction of long-term outcome. *J Hepatol* 2011;55:1361–7.
- Corpechot C, Carrat F, Bahr A, *et al.* The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. *Gastroenterology* 2005;128:297–303.
- Harms MH, van Buuren HR, Corpechot C, *et al.* Ursodeoxycholic acid therapy and liver transplant-free survival in patients with primary biliary cholangitis. *J Hepatol* 2019;71:357–65.
- Tripathi D, Stanley AJ, Hayes PC, *et al.* U.K. guidelines on the management of variceal haemorrhage in cirrhotic patients. *Gut* 2015;64:1680–704.
- Prince MI, Chetwynd A, Craig WL, *et al.* Asymptomatic primary biliary cirrhosis: clinical features, prognosis, and symptom progression in a large population based cohort. *Gut* 2004;53:865–70.
- Lu M, Li J, Haller IV, *et al.* Factors associated with prevalence and treatment of primary biliary cholangitis in United States health systems. *Clin Gastroenterol Hepatol* 2018;16:1333–41.
- Ebben RHA, Siqeca F, Madsen UR, *et al.* Effectiveness of implementation strategies for the improvement of guideline and protocol adherence in emergency care: a systematic review. *BMJ Open* 2018;8:e017572.
- Treadwell JR, Lucas S, Tsou AY. Surgical checklists: a systematic review of impacts and implementation. *BMJ Qual Saf* 2014;23:299–318.
- Newton JL, Hudson M, Tachtatzis P, *et al.* Population prevalence and symptom associations of autonomic dysfunction in primary biliary cirrhosis. *Hepatology* 2007;45:1496–505.
- Alrubaiy L, Mells G, Flack S, *et al.* PBC-10: a short quality of life measure for clinical screening in primary biliary cholangitis. *Aliment Pharmacol Ther* 2019;50:1223–31.

SUPPLEMENTARY MATERIAL

Manuscript Title: Widespread Gaps in the Quality of Care for Primary Biliary Cholangitis in the United Kingdom

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3. Imperial College Healthcare NHS Trust, London, UK
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5. York Teaching Hospital NHS Foundation Trust, York, UK
6. Aberdeen Royal Infirmary, Aberdeen, UK
7. Cardiff and Vale University Health Board, Cardiff, UK
8. University Hospital of Derby and Burton NHS Foundation Trust, Derby, UK
9. Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle, UK
10. Newcastle University, Newcastle, UK

Authorship Footnotes:

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- Mathuri Sivakumar's¹ current institution is University of Birmingham College of Medical and Dental Sciences, Birmingham, UK

KEYWORDS: Standards; Liver Cirrhosis, Biliary; Liver Diseases; Hepatitis, Autoimmune; Guideline; Ursodeoxycholic Acid.

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PBC AUDIT PROFORMA

The 2-page supporting proforma provided to hospitals for data collection.

PBC Audit

Patient #	Age
M/F	Weight kg
Date patient last weighed	Year of Diagnosis
/ /	

	Y	N
1. Clinical diagnosis:		
Accurate diagnosis with ≥ 2 of diagnostic criteria (ANA/AMA > 1 in 40, cholestatic LFTs, consistent histology)?		
2. Treatment:		
a. Is there ongoing treatment with Ursodeoxycholic Acid 13-15mg/kg/day? <i>[If YES go to question 'f', if NO go to question 'b']</i>		
b. Is there treatment with Ursodeoxycholic Acid at an alternative dose? <i>[If YES go to question 'f' if NO go to question 'c']</i>		
c. Is the patient on UDCA at an unspecified dose? <i>[If YES go to question 'f', if NO go to question 'd']</i>		
d. Has the patient had treatment with UDCA and discontinued? <i>[If YES please give the reason if known, if NO go to question 'e']</i>		
e. The patient has no recorded treatment with UDCA? <i>[If YES go to question 'f']</i>		
f. Is there a record of assessing response at 1 year? (ALP < 1.67 ULN)	Full	Part
	None	No record
3. In the past 12 months, record of presence/absence of:		
a. Pruritus?		
b. Fatigue?		

PBC Audit

	Y	N
4. Bone density:		
a. Assessment within the last 5 years <input type="text"/>		
b. If abnormal (T ≤ -score 2.5), record of appropriate action plan in notes? <input type="text"/>		
5. Is patient high risk? Defined as bilirubin > 50 µmol/L OR dropping albumin <input type="text"/> OR patient is decompensating (variceal bleed, ascites or encephalopathy?)		
6. If high risk, has patient been considered for transplant in the past 3 months? <input type="text"/>		
7. If cirrhotic, record of screening for:		
a. HCC within the last year? (or offered and patient declined) <input type="text"/>		
b. Varices within the last year? (or offered and patient declined) <input type="text"/>		
c. If No: Is there record of varices screening in the last 2 years? <input type="text"/>		
8. If co-existing Autoimmune Hepatitis, record of diagnostic biopsy? <input type="text"/>		

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Supplementary Table 1. Summary of the performance in England, Wales and Scotland.

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Recorded symptom assessment of pruritus	90	108/293 (36.9)	66/181 (36.5)	35/118 (29.7)	0.3566
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Prescription of the recommended UCDA dose of 13-15mg/kg daily	90	17/45 (37.8)	275/560 (49.1)	0.1640
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Methods

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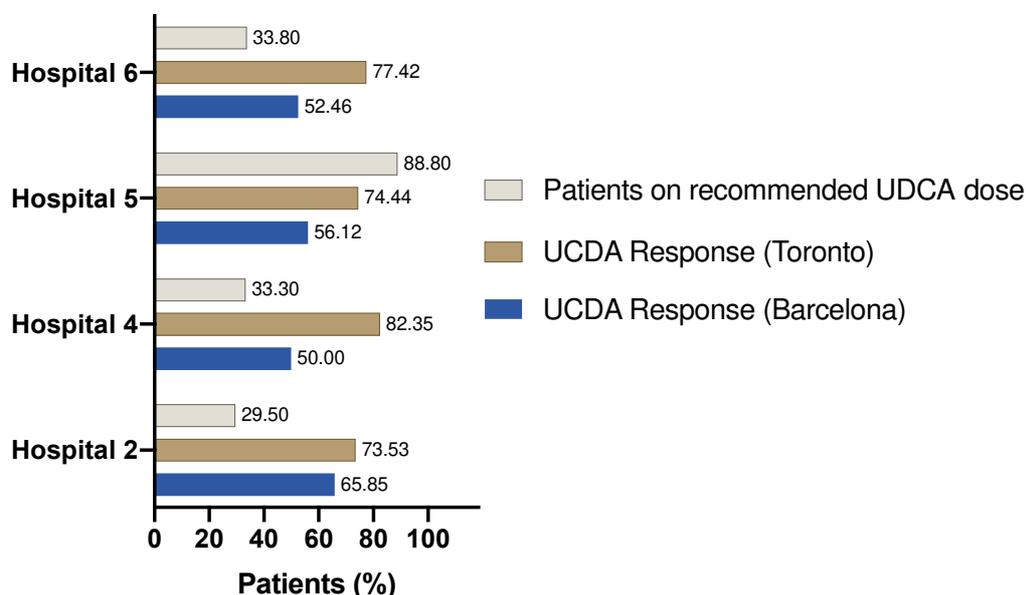
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UDCA Treatment Response

The percentages of patients classified as demonstrating UDCA response according to the Barcelona criteria were 65.9% (Hospital 2), 50.0% (Hospital 4), 56.1% (Hospital 5) and 52.5% (Hospital 6). No significant correlation was observed between the percentage of patients prescribed the correct UDCA dose and the percentage of patients demonstrating UDCA response ($p=0.4678$) (**Supplementary Figure 1**).

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(**Supplementary Figure 1**).



Supplementary Figure 1. Bar chart showing the percentages of PBC patients classified with UDCA treatment response according to Barcelona criteria and Toronto criteria. Percentages of patients on the recommended UDCA dose are shown for comparison. Four hospitals provided the necessary data on ALP profile for this analysis, as displayed on the y-axis.

Interpretation of UDCA Treatment Response

Although we expected to observe a significant relationship between the percentage of patients prescribed the appropriate UDCA dose and the percentage of patients exhibiting treatment response, as suggested by guidelines and existing literature[1,5,6] – we did not observe a statistically significant relationship. Our analysis of the UDCA treatment response was mostly based on ALP due to the limited collection of biochemical test results and our inability to use other criteria, such as Paris-I or Rotterdam.[1] Interestingly, the observed biochemical response, according to the Toronto criteria, was slightly higher than that measured using the Barcelona criteria. Prospective research is needed to validate the different biochemical response criteria in PBC patients.

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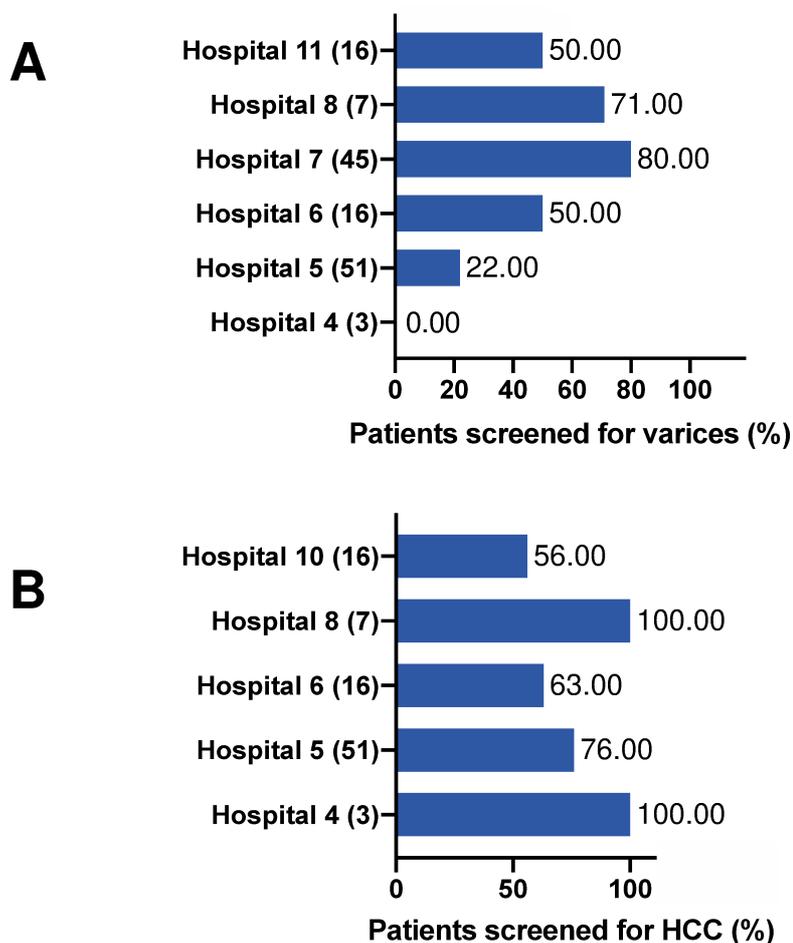
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Trust (number of PBC patients)	% of patients with positive antibody titre (number)			% of patients currently prescribed obeticholic acid (number)	% of patients who underwent liver elastography (number)	% of patients with steatosis (number)	Mean MELD of cirrhotic patients (SD)	Mean UKELD of cirrhotic patients (SD)
	AMA	PBC- specific ANA	ASMA					
Hospital 2 (75)	-	-	-	13.33% (10)	46.67% (35)	-	-	-
Hospital 4 (19)	100% (19)	42.11% (8)	5.26% (1)	0% (0)	73.68% (14)	31.58% (6)	7 (1)	48.33 (3.215)
Hospital 5 (166)	90% (149)	36.14% (60)	4.22% (7)	2.41% (4)	86.75% (144)	7.23% (12)	7.31 (1.545)	45.67 (3.617)
Hospital 6 (69)	78% (54)	30.43% (21)	-	1.45% (1)	-	-	-	-

Screening for Cirrhotic Complications

Data on cirrhotic patients was available from six hospitals. Across the six hospitals, 138 of 483 (28.6%) patients were diagnosed with cirrhosis. Variceal screening was undertaken on 63 of 138 (45.7%) patients. There was significant variation observed between hospitals in proportions of cirrhotic patients screened for varices, ranging from 0% (Hospital 4) to 80% (Hospital 7) ($p < 0.0001$) (**Supplementary Figure 2A**).

Data on HCC screening was available in five hospitals, consisting of 93 cirrhotic patients. HCC screening was undertaken on 68 of 93 (73.1%) patients with no significant variation observed between hospitals. Proportions of cirrhotic patients screened for HCC ranged from 56% (Hospital 11) to 100% (multiple hospitals) ($p = 0.1256$) (**Supplementary Figure 2B**).



Supplementary Figure 2. Screening for Cirrhotic Complications

(A) Bar chart showing the percentages of cirrhotic patients undergoing screening for varices. Data was available from six hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

(B) Bar chart showing the percentages of cirrhotic patients undergoing screening for HCC. Data was available from five hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

PBC REVIEW TOOL

The proposed 3-page PBC Review tool. Pages 1 and 2 contain questions based on EASL and BSG/UK-PBC guidelines. Page 3 contains the PBC-10 screening questionnaire.

Clinical diagnosis:		Year of diagnosis	Year of biopsy (or n/a)
Cholestatic LFTs		AMA/ANA (titre)	Histology
Treatment:		Weight	kg
1. Ursodeoxycholic Acid	mg/day	mg/kg/day	
Was UDCA discontinued or was the dose reduced? (Circle, if applicable)		DISCONTINUED	REDUCED
Reason (e.g. not tolerated) and updated dose:			
Response: If ALP >1.67 ULN, has there been any decrease in ALP? (Circle yes or no)		YES	NO
(to be assessed following 1 year of UDCA treatment) Has ALP become <1.67 ULN?		YES	NO
2. Obeticholic Acid	mg/day		
3. Fibrate	mg/day		
4. Other (specify)			
Trial participation:	YES	NO	If yes, which drug(s):
Symptom management:			
Pruitus	YES	NO	Fatigue
			YES
			NO
Treatment:		Treatment:	
		Other (sicca, autonomic dysfunction, sleep difficulties):	
		Treatment(s):	

*May not apply to all patients. Sicca syndrome = dry/gritty eyes or mouth; Autonomic dysfunction = postural hypotension; Sleep difficulties may include daytime somnolence.

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PBC Review

Bone density:		Hip T-score:		Lumbar T-score:	
Year of last scan:		Is the patient osteoporotic?		YES	NO
		If osteoporotic, was appropriate treatment prescribed?		YES	NO
Details:					
Date of last elastography:				Result:	
Is this patient high risk? Defined as bilirubin >50 µmol/L OR decreasing albumin OR signs of decompensation (variceal bleed, ascites or encephalopathy)				YES	NO
Details:					
If yes, has transplant been considered?				YES	NO
Details:					
Is this patient cirrhotic?	YES	NO			
Date of last HCC screening:			Date of last OGD:		
If co-existing Autoimmune Hepatitis, is there a record of diagnostic biopsy?				YES	NO
Year of biopsy:					
Other concerns:			Other medications:		
Follow up time:					months

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REFERENCES

PBC Review

PBC-10 QUESTIONNAIRE (circle the appropriate answer for all questions 1-10)

IN THE LAST FOUR WEEKS, how often did you experience any of the following?						
1. I have felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
2. If I eat or drink a small amount, I still feel bloated	Never	Rarely	Sometimes	Most of the time	Always	
3. My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
4. Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
5. I had to force myself to do the things I needed to do	Never	Rarely	Sometimes	Most of the time	Always	
6. If I was busy one day, I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always	
7. Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
Now some more general statements about how PBC may be affecting you as a person. How much does the following statement apply to you?						
8. I feel guilty that I can't do what I used to be able to do because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Not applicable
These statements relate to the possible effects of PBC on your social life and your life overall. Thinking of your own situation, how much do you agree or disagree with them?						
9. My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	
10. PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	

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- 1 Hirschfield GM, Beuers U, Corpechot C, *et al.* EASL Clinical Practice

- Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145–72. doi:10.1016/j.jhep.2017.03.022
- 2 Komori A, Tanaka A, Takikawa H, *et al.* Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan. *Hepatol Res* 2014;**44**:71–90. doi:10.1111/hepr.12270
 - 3 Younossi ZM, Stepanova M, Golabi P, *et al.* Factors Associated with Potential Progressive Course of Primary Biliary Cholangitis: Data from Real-world US Database. *J Clin Gastroenterol* 2019;**53**:693–8. doi:10.1097/MCG.0000000000001120
 - 4 Hirschfield GM, Dyson JK, Alexander GJM, *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;**0**:1–27. doi:10.1136/gutjnl-2017-315259
 - 5 Van De Meeberg PC, Houwen RHJ, Sinaasappel M, *et al.* Low-dose versus high-dose ursodeoxycholic acid in cystic fibrosis-related cholestatic liver disease. Results of a randomized study with 1-year follow-up. *Scand J Gastroenterol* 1997;**32**:369–73. doi:10.3109/00365529709007686
 - 6 Angulo P, Dickson ER, Therneau TM, *et al.* Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: A randomized trial. *J Hepatol* 1999;**30**:830–5. doi:10.1016/S0168-8278(99)80136-6

SUPPLEMENTARY MATERIAL

Manuscript Title: Widespread Gaps in the Quality of Care for Primary Biliary Cholangitis in the United Kingdom

Authors: Mathuri Sivakumar¹, Akash Gandhi², Eathar Shakweh³, Yu Meng Li³, Niloufar Safinia³, Belinda Smith³, Aileen Marshall⁴, Lucy Turner⁵, Ashis Mukhopadhy⁶, Hasan Haboubi⁷, Rebecca Vincent⁷, Huey Tan⁸, Laith Alrubaiy^{1,2}, David Jones^{9,10}.

Affiliations:

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3. In the past 12 months, record of presence/absence of:		
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b. Fatigue?		

PBC Audit

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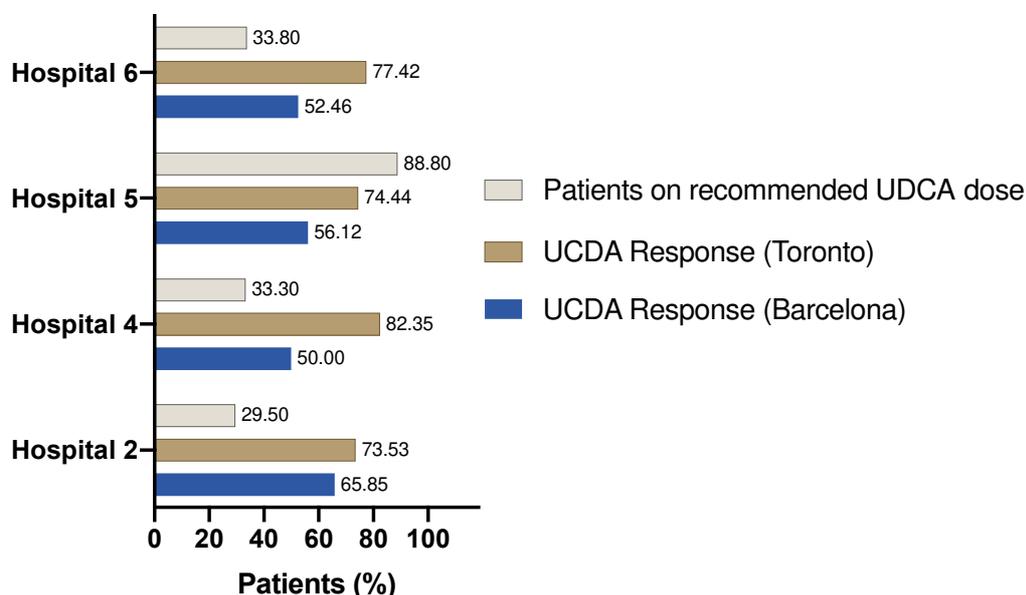
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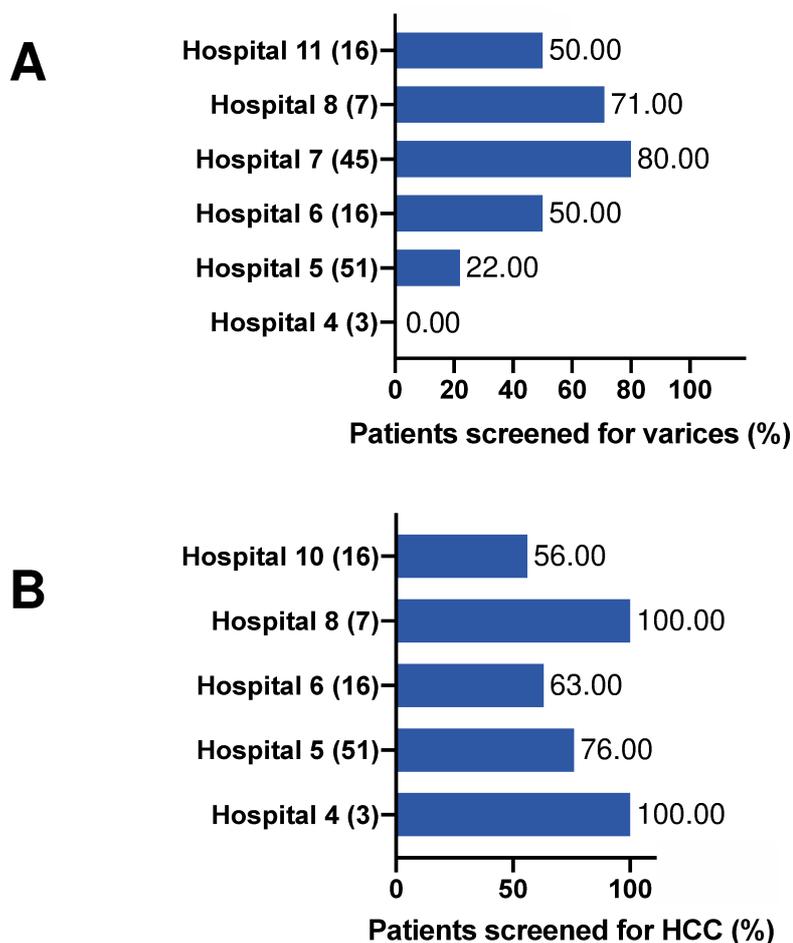
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Hospital 2 (75)	-	-	-	13.33% (10)	46.67% (35)	-	-	-
Hospital 4 (19)	100% (19)	42.11% (8)	5.26% (1)	0% (0)	73.68% (14)	31.58% (6)	7 (1)	48.33 (3.215)
Hospital 5 (166)	90% (149)	36.14% (60)	4.22% (7)	2.41% (4)	86.75% (144)	7.23% (12)	7.31 (1.545)	45.67 (3.617)
Hospital 6 (69)	78% (54)	30.43% (21)	-	1.45% (1)	-	-	-	-

Screening for Cirrhotic Complications

Data on cirrhotic patients was available from six hospitals. Across the six hospitals, 138 of 483 (28.6%) patients were diagnosed with cirrhosis. Variceal screening was undertaken on 63 of 138 (45.7%) patients. There was significant variation observed between hospitals in proportions of cirrhotic patients screened for varices, ranging from 0% (Hospital 4) to 80% (Hospital 7) ($p < 0.0001$) (**Supplementary Figure 2A**).

Data on HCC screening was available in five hospitals, consisting of 93 cirrhotic patients. HCC screening was undertaken on 68 of 93 (73.1%) patients with no significant variation observed between hospitals. Proportions of cirrhotic patients screened for HCC ranged from 56% (Hospital 11) to 100% (multiple hospitals) ($p = 0.1256$) (**Supplementary Figure 2B**).



Supplementary Figure 2. Screening for Cirrhotic Complications

(A) Bar chart showing the percentages of cirrhotic patients undergoing screening for varices. Data was available from six hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

(B) Bar chart showing the percentages of cirrhotic patients undergoing screening for HCC. Data was available from five hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

PBC REVIEW TOOL

The proposed 3-page PBC Review tool. Pages 1 and 2 contain questions based on EASL and BSG/UK-PBC guidelines. Page 3 contains the PBC-10 screening questionnaire.

Clinical diagnosis:		Year of diagnosis	Year of biopsy (or n/a)
Cholestatic LFTs		AMA/ANA (titre)	Histology
Treatment:		Weight	kg
1. Ursodeoxycholic Acid	mg/day	mg/kg/day	
Was UDCA discontinued or was the dose reduced? (Circle, if applicable)		DISCONTINUED	REDUCED
Reason (e.g. not tolerated) and updated dose:			
Response: If ALP >1.67 ULN, has there been any decrease in ALP? (Circle yes or no)		YES	NO
(to be assessed following 1 year of UDCA treatment) Has ALP become <1.67 ULN?		YES	NO
2. Obeticholic Acid	mg/day		
3. Fibrate	mg/day		
4. Other (specify)			
Trial participation:	YES	NO	If yes, which drug(s):
Symptom management:			
Pruitus	YES	NO	Fatigue
			YES
			NO
Treatment:		Treatment:	
		Other (sicca, autonomic dysfunction, sleep difficulties):	
		Treatment(s):	

*May not apply to all patients. Sicca syndrome = dry/gritty eyes or mouth; Autonomic dysfunction = postural hypotension; Sleep difficulties may include daytime somnolence.

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PBC Review

Bone density:		Hip T-score:		Lumbar T-score:	
Year of last scan:		Is the patient osteoporotic?		YES	NO
		If osteoporotic, was appropriate treatment prescribed?		YES	NO
Details:					
Date of last elastography:				Result:	
Is this patient high risk? Defined as bilirubin >50 µmol/L OR decreasing albumin OR signs of decompensation (variceal bleed, ascites or encephalopathy)				YES	NO
Details:					
If yes, has transplant been considered?				YES	NO
Details:					
Is this patient cirrhotic?	YES	NO			
Date of last HCC screening:			Date of last OGD:		
If co-existing Autoimmune Hepatitis, is there a record of diagnostic biopsy?				YES	NO
Year of biopsy:					
Other concerns:			Other medications:		
Follow up time:			months		

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REFERENCES

PBC Review

PBC-10 QUESTIONNAIRE (circle the appropriate answer for all questions 1-10)

IN THE LAST FOUR WEEKS, how often did you experience any of the following?						
1. I have felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
2. If I eat or drink a small amount, I still feel bloated	Never	Rarely	Sometimes	Most of the time	Always	
3. My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
4. Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
5. I had to force myself to do the things I needed to do	Never	Rarely	Sometimes	Most of the time	Always	
6. If I was busy one day, I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always	
7. Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
Now some more general statements about how PBC may be affecting you as a person. How much does the following statement apply to you?						
8. I feel guilty that I can't do what I used to be able to do because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Not applicable
These statements relate to the possible effects of PBC on your social life and your life overall. Thinking of your own situation, how much do you agree or disagree with them?						
9. My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	
10. PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	

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- 1 Hirschfield GM, Beuers U, Corpechot C, *et al.* EASL Clinical Practice

- Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145–72. doi:10.1016/j.jhep.2017.03.022
- 2 Komori A, Tanaka A, Takikawa H, *et al.* Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan. *Hepatol Res* 2014;**44**:71–90. doi:10.1111/hepr.12270
 - 3 Younossi ZM, Stepanova M, Golabi P, *et al.* Factors Associated with Potential Progressive Course of Primary Biliary Cholangitis: Data from Real-world US Database. *J Clin Gastroenterol* 2019;**53**:693–8. doi:10.1097/MCG.0000000000001120
 - 4 Hirschfield GM, Dyson JK, Alexander GJM, *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;**0**:1–27. doi:10.1136/gutjnl-2017-315259
 - 5 Van De Meeberg PC, Houwen RHJ, Sinaasappel M, *et al.* Low-dose versus high-dose ursodeoxycholic acid in cystic fibrosis-related cholestatic liver disease. Results of a randomized study with 1-year follow-up. *Scand J Gastroenterol* 1997;**32**:369–73. doi:10.3109/00365529709007686
 - 6 Angulo P, Dickson ER, Therneau TM, *et al.* Comparison of three doses of ursodeoxycholic acid in the treatment of primary biliary cirrhosis: A randomized trial. *J Hepatol* 1999;**30**:830–5. doi:10.1016/S0168-8278(99)80136-6

SUPPLEMENTARY MATERIAL

Manuscript Title: Widespread Gaps in the Quality of Care for Primary Biliary Cholangitis in the United Kingdom

Authors: Mathuri Sivakumar¹, Akash Gandhi², Eathar Shakweh³, Yu Meng Li³, Niloufar Safinia³, Belinda Smith³, Aileen Marshall⁴, Lucy Turner⁵, Ashis Mukhopadhy⁶, Hasan Haboubi⁷, Rebecca Vincent⁷, Huey Tan⁸, Laith Alrubaiy^{1,2}, David Jones^{9,10}.

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Authorship Footnotes:

- Mathuri Sivakumar¹ and Akash Gandhi² should be considered joint first author.
- Laith Alrubaiy^{1,2} and David Jones^{9,10} should be considered joint senior author.
- Huey Tan's⁸ current institution is University Hospitals Plymouth NHS Trust, Plymouth, UK.
- Mathuri Sivakumar's¹ current institution is University of Birmingham College of Medical and Dental Sciences, Birmingham, UK

KEYWORDS: Standards; Liver Cirrhosis, Biliary; Liver Diseases; Hepatitis, Autoimmune; Guideline; Ursodeoxycholic Acid.

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- Supplementary Table 2

Page 7 Supplementary Data Collection

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- Screening for Cirrhotic Complications (Supplementary Figure 2) (**page 10**)

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PBC AUDIT PROFORMA

The 2-page supporting proforma provided to hospitals for data collection.

PBC Audit

Patient #	Age
M/F	Weight kg
Year of Diagnosis	
Date patient last weighed / /	

	Y	N
1. Clinical diagnosis:		
Accurate diagnosis with ≥ 2 of diagnostic criteria (ANA/AMA > 1 in 40, cholestatic LFTs, consistent histology)?		
2. Treatment:		
a. Is there ongoing treatment with Ursodeoxycholic Acid 13-15mg/kg/day? <i>[If YES go to question 'f', if NO go to question 'b']</i>		
b. Is there treatment with Ursodeoxycholic Acid at an alternative dose? <i>[If YES go to question 'f' if NO go to question 'c']</i>		
c. Is the patient on UDCA at an unspecified dose? <i>[If YES go to question 'f', if NO go to question 'd']</i>		
d. Has the patient had treatment with UDCA and discontinued? <i>[If YES please give the reason if known, if NO go to question 'e']</i>		
e. The patient has no recorded treatment with UDCA? <i>[If YES go to question 'f']</i>		
f. Is there a record of assessing response at 1 year? (ALP < 1.67 ULN)	Full	Part
	None	No record
3. In the past 12 months, record of presence/absence of:		
a. Pruritus?		
b. Fatigue?		

PBC Audit

	Y	N
4. Bone density:		
a. Assessment within the last 5 years <input type="text"/>		
b. If abnormal (T ≤ -score 2.5), record of appropriate action plan in notes? <input type="text"/>		
5. Is patient high risk? Defined as bilirubin > 50 µmol/L OR dropping albumin <input type="text"/> OR patient is decompensating (variceal bleed, ascites or encephalopathy?)		
6. If high risk, has patient been considered for transplant in the past 3 months? <input type="text"/>		
7. If cirrhotic, record of screening for:		
a. HCC within the last year? (or offered and patient declined) <input type="text"/>		
b. Varices within the last year? (or offered and patient declined) <input type="text"/>		
c. If No: Is there record of varices screening in the last 2 years? <input type="text"/>		
8. If co-existing Autoimmune Hepatitis, record of diagnostic biopsy? <input type="text"/>		

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Supplementary Table 1. Summary of the performance in England, Wales and Scotland.

Standard	Target (%)	Number of patients treated according to guidelines/total number patients [†] (%)			p-value
		England	Wales	Scotland	
Prescription of the recommended UCDA dose of 13-15mg/kg daily	90	164/277 (59.2)	97/218 (44.5)	31/110 (28.2)	<0.0001
Assessment of biochemical response to UDCA following one year of treatment	80	243/277 (87.7)	86/218 (62.8)	83/110 (75.5)	<0.0001
Recorded symptom assessment of pruritus	90	108/293 (36.9)	66/181 (36.5)	35/118 (29.7)	0.3566
Recorded symptom assessment of fatigue	90	74/293 (25.3)	65/181 (35.9)	32/118 (27.1)	0.0406
Assessment of bone density within five years of diagnosis	80	217/326 (66.6)	79/178 (44.4)	62/117 (53.0)	<0.0001
Assessment of liver transplant eligibility in high risk patients	90	25/39 (64.1)	5/13 (38.5)	9/9 (100.0)	0.0127

Footnotes:

[†] Total number of patients where data was available.

Supplementary Table 2. Summary of the performance in hospitals with general gastroenterology clinics and hospitals with dedicated hepatology clinics.

Standard	Target (%)	Number of patients treated according to guidelines/total number of patients [†] (%)		p-value [‡]
		GGC Centres	DHC Centres	
Prescription of the recommended UCDA dose of 13-15mg/kg daily	90	17/45 (37.8)	275/560 (49.1)	0.1640
Assessment of biochemical response to UDCA following one year of treatment	80	38/45 (84.4)	374/479 (78.1)	0.4461
Recorded symptom assessment of pruritus	90	19/57 (33.3)	190/535 (35.5)	0.7731
Recorded symptom assessment of fatigue	90	37/139 (36.8)	176/535 (32.9)	0.5565
Assessment of bone density within five years of diagnosis	80	22/55 (40.0)	336/566 (59.4)	0.0065
Assessment of liver transplant eligibility in high risk patients	90	3/10 (30.0)	36/51 (70.6)	0.0272

Footnotes:

GGC: general gastroenterology clinic, DHC: dedicated hepatology clinic.

[†]Total number of patients where data was available.

[‡]Fisher's exact test was used to test independence between secondary and tertiary centres.

SUPPLEMENTARY DATA COLLECTION

Methods

Supplementary data collection was optional and varied between hospitals according to the decision of the local audit lead. Additional data collection included the presence of steatosis, obeticholic acid (OCA) prescription, autoantibody status, biochemical profile at one year of UDCA treatment, transient elastography, and records of the following: oesophago-gastro-duodenoscopy (OGD) for varices screening and abdominal ultrasound for HCC screening. Supplementary data was used for further descriptive analysis and to assess UDCA response according to established criteria where possible.[1,2]

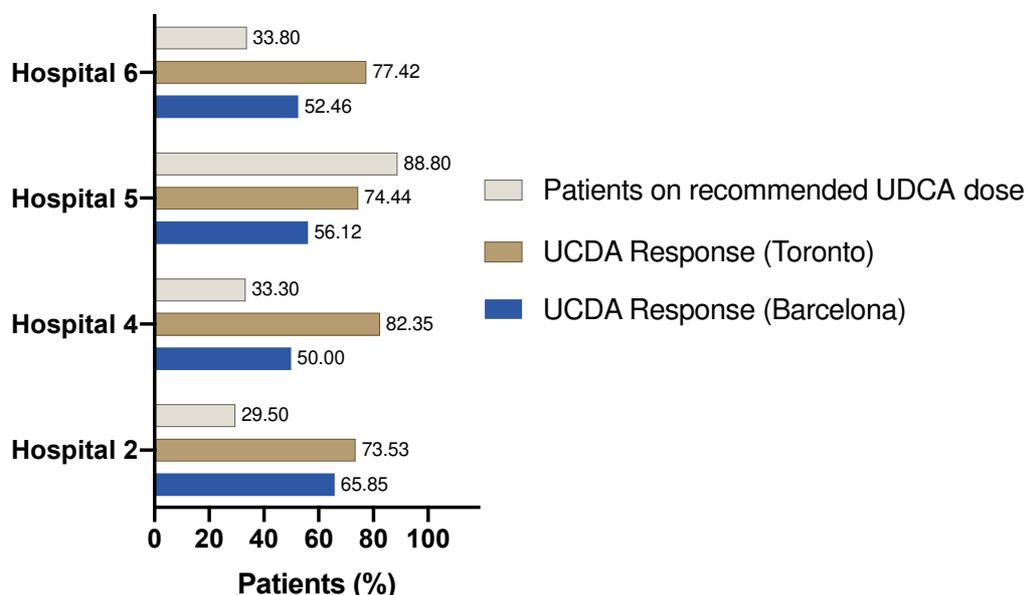
Sub-analyses were undertaken on supplementary data provided by York, London North West, Royal Free London and Imperial College NHS Trusts as they provided further data on the biochemical profile of patients. Determination of UDCA response status following one year of treatment was undertaken for each applicable patient according to the two sets of following criteria: Barcelona criteria, defined as decrease in ALP $\leq 40\%$ and ALP $\geq 1 \times$ upper limit of normal (ULN); and Toronto criteria, defined as ALP $\leq 1.67 \times$ ULN.[1,3,4] Pearson's correlation coefficient (r) was calculated to assess the correlation between proportion of patients on correct UDCA dosing with the proportion of patients demonstrating a) UDCA response according to Barcelona criteria and b) UDCA response according to Toronto criteria.

UDCA Treatment Response

The percentages of patients classified as demonstrating UDCA response according to the Barcelona criteria were 65.9% (Hospital 2), 50.0% (Hospital 4), 56.1% (Hospital 5) and 52.5% (Hospital 6). No significant correlation was observed between the percentage of patients prescribed the correct UDCA dose and the percentage of patients demonstrating UDCA response ($p=0.4678$) (**Supplementary Figure 1**).

In the same four sites, percentages of patients classified as demonstrating UDCA response according to the Toronto criteria were 75.5% (Hospital 2), 82.4% (Hospital 4), 74.4% (Hospital 5) and 77.4% (Hospital 6). No significant correlation was observed between the percentage of patients prescribed the correct UDCA dose and the percentage of patients demonstrating UDCA response ($p=0.3147$)

(**Supplementary Figure 1**).



Supplementary Figure 1. Bar chart showing the percentages of PBC patients classified with UDCA treatment response according to Barcelona criteria and Toronto criteria. Percentages of patients on the recommended UDCA dose are shown for comparison. Four hospitals provided the necessary data on ALP profile for this analysis, as displayed on the y-axis.

Interpretation of UDCA Treatment Response

Although we expected to observe a significant relationship between the percentage of patients prescribed the appropriate UDCA dose and the percentage of patients exhibiting treatment response, as suggested by guidelines and existing literature[1,5,6] – we did not observe a statistically significant relationship. Our analysis of the UDCA treatment response was mostly based on ALP due to the limited collection of biochemical test results and our inability to use other criteria, such as Paris-I or Rotterdam.[1] Interestingly, the observed biochemical response, according to the Toronto criteria, was slightly higher than that measured using the Barcelona criteria. Prospective research is needed to validate the different biochemical response criteria in PBC patients.

Supplementary Table 3. Supplementary Patient Data

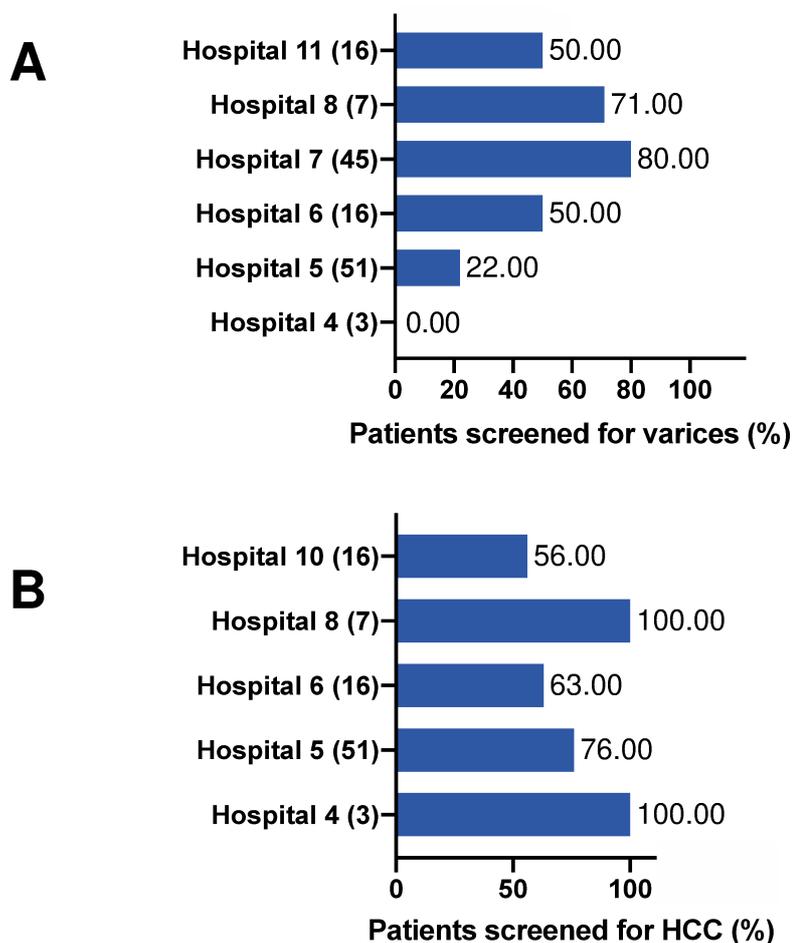
Additional descriptive data obtained from York, London North West, Royal Free and Imperial College NHS Trusts is presented.

Trust (number of PBC patients)	% of patients with positive antibody titre (number)			% of patients currently prescribed obeticholic acid (number)	% of patients who underwent liver elastography (number)	% of patients with steatosis (number)	Mean MELD of cirrhotic patients (SD)	Mean UKELD of cirrhotic patients (SD)
	AMA	PBC- specific ANA	ASMA					
Hospital 2 (75)	-	-	-	13.33% (10)	46.67% (35)	-	-	-
Hospital 4 (19)	100% (19)	42.11% (8)	5.26% (1)	0% (0)	73.68% (14)	31.58% (6)	7 (1)	48.33 (3.215)
Hospital 5 (166)	90% (149)	36.14% (60)	4.22% (7)	2.41% (4)	86.75% (144)	7.23% (12)	7.31 (1.545)	45.67 (3.617)
Hospital 6 (69)	78% (54)	30.43% (21)	-	1.45% (1)	-	-	-	-

Screening for Cirrhotic Complications

Data on cirrhotic patients was available from six hospitals. Across the six hospitals, 138 of 483 (28.6%) patients were diagnosed with cirrhosis. Variceal screening was undertaken on 63 of 138 (45.7%) patients. There was significant variation observed between hospitals in proportions of cirrhotic patients screened for varices, ranging from 0% (Hospital 4) to 80% (Hospital 7) ($p < 0.0001$) (**Supplementary Figure 2A**).

Data on HCC screening was available in five hospitals, consisting of 93 cirrhotic patients. HCC screening was undertaken on 68 of 93 (73.1%) patients with no significant variation observed between hospitals. Proportions of cirrhotic patients screened for HCC ranged from 56% (Hospital 11) to 100% (multiple hospitals) ($p = 0.1256$) (**Supplementary Figure 2B**).



Supplementary Figure 2. Screening for Cirrhotic Complications

(A) Bar chart showing the percentages of cirrhotic patients undergoing screening for varices. Data was available from six hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

(B) Bar chart showing the percentages of cirrhotic patients undergoing screening for HCC. Data was available from five hospitals, as displayed on the y-axis. The number of patients with cirrhosis are shown in brackets for individual hospitals.

PBC REVIEW TOOL

The proposed 3-page PBC Review tool. Pages 1 and 2 contain questions based on EASL and BSG/UK-PBC guidelines. Page 3 contains the PBC-10 screening questionnaire.

Clinical diagnosis:		Year of diagnosis	Year of biopsy (or n/a)
Cholestatic LFTs		AMA/ANA (titre)	Histology
Treatment:		Weight	kg
1. Ursodeoxycholic Acid	mg/day	mg/kg/day	
Was UDCA discontinued or was the dose reduced? (Circle, if applicable)			DISCONTINUED REDUCED
Reason (e.g. not tolerated) and updated dose:			
Response: If ALP >1.67 ULN, has there been any decrease in ALP? (Circle yes or no)			YES NO
(to be assessed following 1 year of UDCA treatment) Has ALP become <1.67 ULN?			YES NO
2. Obeticholic Acid	mg/day		
3. Fibrate	mg/day		
4. Other (specify)			
Trial participation:	YES	NO	If yes, which drug(s):
Symptom management:			
Pruitus	YES	NO	Fatigue
			YES NO
Other (sicca, autonomic dysfunction, sleep difficulties):			
Treatment:		Treatment:	
Treatment(s):			

*May not apply to all patients. Sicca syndrome = dry/gritty eyes or mouth; Autonomic dysfunction = postural hypotension; Sleep difficulties may include daytime somnolence.

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Bone density:		Hip T-score:		Lumbar T-score:	
Year of last scan:		Is the patient osteoporotic?		YES	NO
		If osteoporotic, was appropriate treatment prescribed?		YES	NO
Details:					
Date of last elastography:				Result:	
Is this patient high risk? Defined as bilirubin >50 µmol/L OR decreasing albumin OR signs of decompensation (variceal bleed, ascites or encephalopathy)				YES	NO
Details:					
If yes, has transplant been considered?				YES	NO
Details:					
Is this patient cirrhotic?	YES	NO			
Date of last HCC screening:			Date of last OGD:		
If co-existing Autoimmune Hepatitis, is there a record of diagnostic biopsy?				YES	NO
Year of biopsy:					
Other concerns:			Other medications:		
Follow up time:			months		

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PBC Review

PBC-10 QUESTIONNAIRE (circle the appropriate answer for all questions 1-10)

IN THE LAST FOUR WEEKS, how often did you experience any of the following?						
1. I have felt embarrassed because of the itching	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
2. If I eat or drink a small amount, I still feel bloated	Never	Rarely	Sometimes	Most of the time	Always	
3. My mouth was very dry	Never	Rarely	Sometimes	Most of the time	Always	
4. Fatigue interfered with my daily routine	Never	Rarely	Sometimes	Most of the time	Always	Not applicable
5. I had to force myself to do the things I needed to do	Never	Rarely	Sometimes	Most of the time	Always	
6. If I was busy one day, I needed at least another day to recover	Never	Rarely	Sometimes	Most of the time	Always	
7. Because of PBC, I found it difficult to concentrate on anything	Never	Rarely	Sometimes	Most of the time	Always	
Now some more general statements about how PBC may be affecting you as a person. How much does the following statement apply to you?						
8. I feel guilty that I can't do what I used to be able to do because of having PBC	Not at all	A little	Somewhat	Quite a bit	Very much	Not applicable
These statements relate to the possible effects of PBC on your social life and your life overall. Thinking of your own situation, how much do you agree or disagree with them?						
9. My social life has almost stopped	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	
10. PBC has reduced the quality of my life	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree	

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REFERENCES

- 1 Hirschfield GM, Beuers U, Corpechot C, *et al.* EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;**67**:145–72. doi:10.1016/j.jhep.2017.03.022
- 2 Komori A, Tanaka A, Takikawa H, *et al.* Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan Guidelines for the management of primary biliary cirrhosis: The Intractable Hepatobiliary Disease Study Group supported by the Ministry of Health, Labour and Welfare of Japan. *Hepatol Res* 2014;**44**:71–90. doi:10.1111/hepr.12270
- 3 Younossi ZM, Stepanova M, Golabi P, *et al.* Factors Associated with Potential Progressive Course of Primary Biliary Cholangitis: Data from Real-world US Database. *J Clin Gastroenterol* 2019;**53**:693–8. doi:10.1097/MCG.0000000000001120
- 4 Hirschfield GM, Dyson JK, Alexander GJM, *et al.* The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;**0**:1–27. doi:10.1136/gutjnl-2017-315259
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