Survey uncovering variations in the management of primary sclerosing cholangitis across Europe

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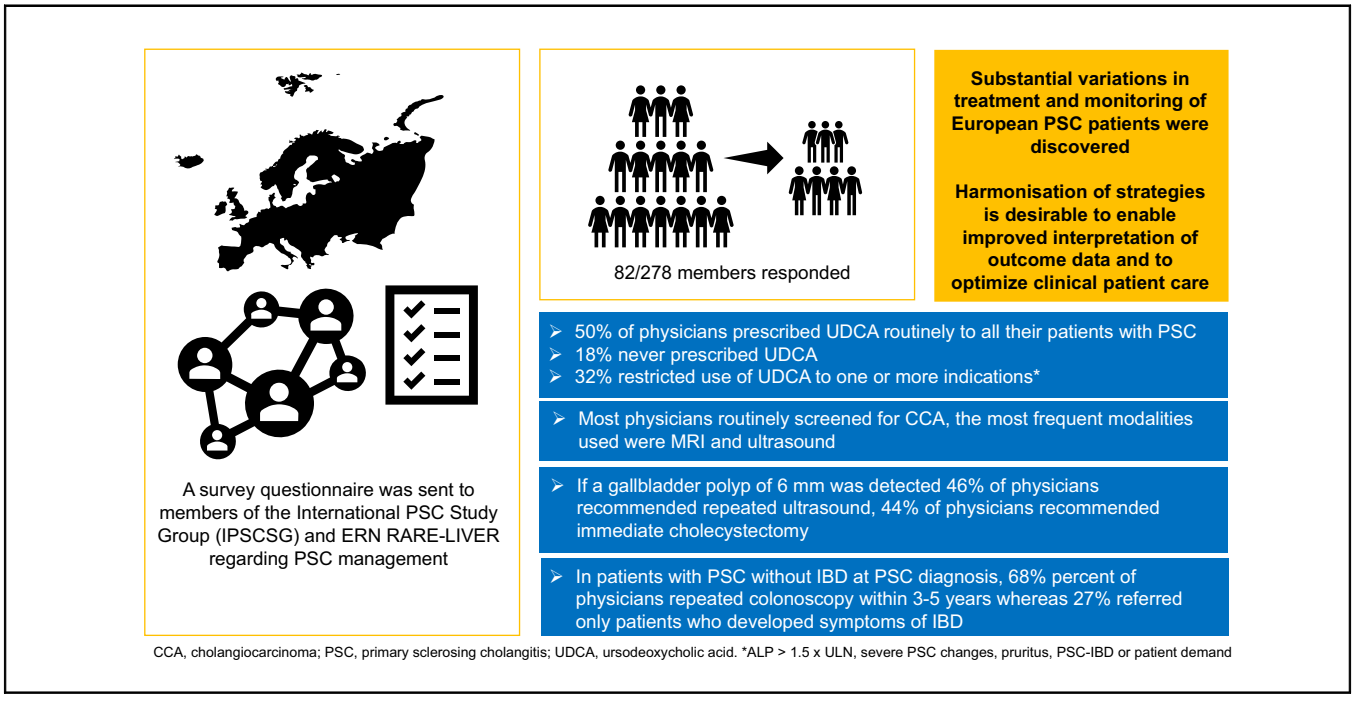
Graphical abstract



Highlights

- Substantial variations in the treatment and monitoring of patients with PSC was seen across Europe.
- Considerable discrepancies between practice and published guidelines in the management of patients with PSC existed.
- Despite no robust evidence or clear recommendations, most physicians treated all their patients with UDCA.
- Regular screening for cholangiocarcinoma was performed by 90% of physicians. A variety of screening methods were used.
- In PSC without IBD detected at diagnosis of the bile duct disease, most physicians would repeat colonoscopy on a regular basis.

Lay summary

In this study, we explored how different centres in Europe manage primary sclerosing cholangitis (PSC), a rare inflammatory disease of the bile ducts. We collected information through a questionnaire sent to specialist physicians who were part of a European network for rare liver diseases. We found several differences in how patients with PSC were monitored and treated. This includes differences in surveillance for bile duct cancer, gallbladder polyps and inflammatory bowel disease. By pointing out these differences, we hope that management of PSC will be standardized, which could aid clinical research and benefit patients.

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Research article

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Survey uncovering variations in the management of primary sclerosing cholangitis across Europe

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Background & Aims: Data on the management of primary sclerosing cholangitis (PSC) in European expert centres are sparse. In this study, a PSC group from the ERN RARE-LIVER surveyed European hepatologists to uncover differences in real-life clinical practices.

Methods: In April 2020 a survey questionnaire was sent to members of the International PSC Study Group and ERN RARE-LIVER. Participants were asked about the size of their PSC cohort, use of medical treatments including ursodeoxycholic acid (UDCA) and surveillance for cholangiocarcinoma, gallbladder polyps and inflammatory bowel disease (IBD). Data were presented descriptively.

Results: Eighty-two of 278 members responded. Fifty percent of physicians prescribed UDCA routinely to all their patients with PSC, whereas 12% never prescribed UDCA. UDCA was used for one or more indications including: alkaline phosphatase >1.5x the upper limit of normal, severe PSC changes, pruritus, PSC-IBD or patient demand. Few physicians offered other medical treatments than UDCA. The use of medical treatments was generally comparable in small (<99 patients) and large (≥99 patients) cohorts, as well as for adult and paediatric physicians. Most physicians routinely screened for cholangiocarcinoma and the most frequent modalities used were MRI and ultrasound. At detection of a gallbladder polyp of 6 mm, 46% of physicians recommended repeated ultrasound after 3-6 months, whereas 44% of physicians recommended immediate cholecystectomy. In patients with PSC without IBD at PSC diagnosis, 68% of physicians repeated colonoscopy within 3-5 years whereas 27% referred only patients who developed symptoms of IBD.

Conclusion: Substantial variations in treatment and monitoring of European patients with PSC were discovered. Harmonisation of strategies is desirable to enable improved interpretation of outcome data and to optimise clinical patient care.

Lay summary: In this study, we explored how different centres in Europe manage primary sclerosing cholangitis (PSC), a rare inflammatory disease of the bile ducts. We collected information through a questionnaire sent to specialist physicians who were part of a European network for rare liver diseases. We found several differences in how patients with PSC were monitored and treated. This includes differences in surveillance for bile duct cancer, gallbladder polyps and inflammatory bowel disease. By pointing out these differences, we hope that management of PSC will be standardized, which could aid clinical research and benefit patients.

Introduction

The management of primary sclerosing cholangitis (PSC) offers many challenges due to an unknown disease aetiology, potentially life-threatening complications and the absence of effective medical treatments.[1] PSC is characterised by progressive destruction and stricturing of the biliary system, typically leading to cirrhosis and end-stage liver disease. The disease is mainly diagnosed in young adults with median age at diagnosis of 40 years, but can also be diagnosed in children.[2] Inflammatory bowel disease (IBD) and PSC are closely associated disease entities, and roughly 70% of patients with PSC have IBD, mainly ulcerative colitis.[3] Patients with PSC are at considerably increased risk of developing hepatobiliary and colorectal malignancies.[4–6]

There are limited randomised controlled trials that address the best monitoring and treatment of patients with PSC. International guidelines differ in their recommendations, reflecting

Keywords: Primary sclerosing cholangitis; surveillance; inflammatory bowel disease; cholangiocarcinoma; gallbladder polyp.

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the weak evidence basis of patient care in PSC.[7–10] There is a scarcity of data that consistently support the use of medical therapy to prevent disease progression and prolong transplant-free survival in PSC.[11–13] Ursodeoxycholic acid (UDCA) has traditionally been prescribed for PSC, but its use remains controversial.[7–10] Potentially beneficial effects of treatment with immunosuppressive agents and antibiotics, primarily vancomycin, have likewise been reported in case series. However, there is currently insufficient evidence to support treatment recommendations. Owing to the lack of medical treatments with proven long-term efficacy, liver transplantation remains the only treatment option for decompensated cirrhosis, recurrent cholangitis or disabling symptoms. Cholangiocarcinoma (CCA) is the most common hepatobiliary malignancy in PSC[6] and cancer surveillance, prevention, and diagnosis are among the most challenging issues.

There is little evidence on how the challenges of PSC are addressed in European expert centres and what regimens are offered to patients. Identifying differences in physicians' approaches to disease management is essential for treatment optimisation. In this study, a PSC working group from the ERN RARE-LIVER surveyed European hepatologists to uncover differences in real-life clinical practices.

Materials and methods

In April 2020 a survey questionnaire was sent to 278 hepatologists who were members of the International PSC Study Group and ERN RARE-LIVER group. Members were from 17 different European countries. Participants were asked about the size of their PSC cohort, use of UDCA and other medical treatments, and surveillance for CCA, gallbladder polyps, and IBD. The questionnaire consisted of 15 questions:

1. Are you an adult or paediatric physician?
2. How many PSC patients are cared for at your department?
3. To which PSC patients do you recommend UDCA treatment?
4. If starting UDCA treatment, which dosing do you choose?
5. If starting UDCA treatment, do you evaluate treatment response?
6. In the rare PSC patients with normal liver enzymes and bilirubin, would you start UDCA treatment?
7. If evaluating treatment response, when do you do that?
8. Do you use vancomycin as long-term treatment?
9. Do you use immunosuppression for PSC?
10. Do you carry out routine biochemical and imaging screening for CCA (on a regular basis)?
11. If yes, which method of diagnosis?
12. If screening on a regular basis, what is the time interval?
13. In a non-cirrhotic PSC patient with a gall bladder polyp of 6 mm size detected on ultrasound, would you either recommend controlling in 3 months, 6 months, refer to surgery for cholecystectomy or if confirmed in short-term ultrasound control refer for cholecystectomy?
14. In patients without IBD at screening colonoscopy after diagnosis of PSC, is colonoscopy repeated?
15. Can or do you refer patients with biliary high-grade dysplasia for liver transplantation?

Data presentation and analysis

Data were obtained using a survey created in REDcap (Research Electronic Data Capture). Data were analysed using Microsoft Excel. Results were presented as means (SD) or total counts (%). To explore whether management strategies differed depending on cohort size and if the respondent was an adult or paediatric physician, results were also presented according to cohort size and physician type (adult or paediatric). No formal statistical comparison was performed due to the small number of patients in each subgroup.

Ethical considerations

This study was conducted according to the Declaration of Helsinki.

Results

A total of 82 (29.5%) hepatologists managing between 3 and 800 patients with PSC responded to the survey. Fifteen (18.3%) responders were paediatricians. The sizes of the patient cohorts are shown in Table 1.

Medical treatments

Fifty percent of physicians answered that they prescribed UDCA to all patients with PSC, whereas 12% never prescribed UDCA (Table 1). UDCA was used for one or more of the following indications: alkaline phosphatase >1.5 x the upper limit of normal, severe PSC changes on imaging, pruritus, PSC-IBD or patient demand. Most physicians (68%) used a dosage of UDCA of 13-15 mg/kg/day. Sixty-five percent of physicians continued UDCA

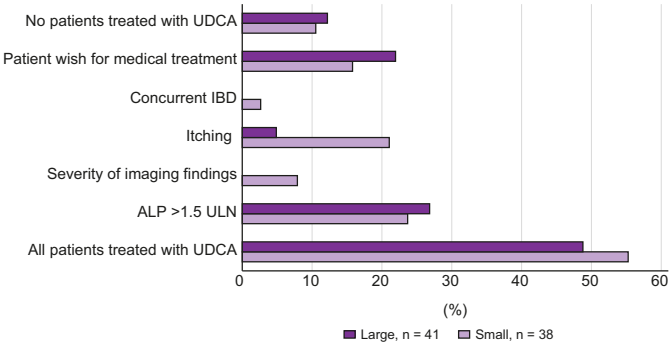

Fig. 1. UDCA indication in small (<99 patients) and large (≥99 patients) centres. ALP, alkaline phosphatase; IBD, inflammatory bowel disease; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

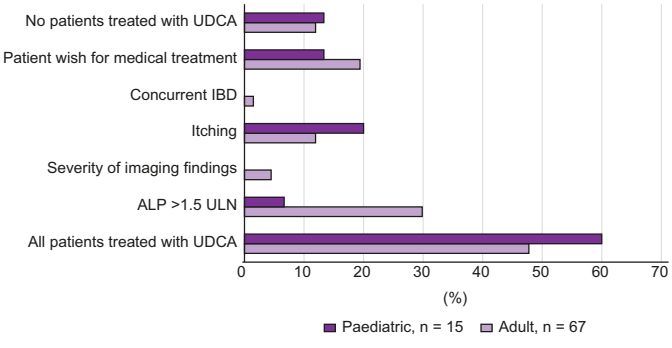

Fig. 2. UDCA indication in adult and paediatric physicians. ALP, alkaline phosphatase; IBD, inflammatory bowel disease; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

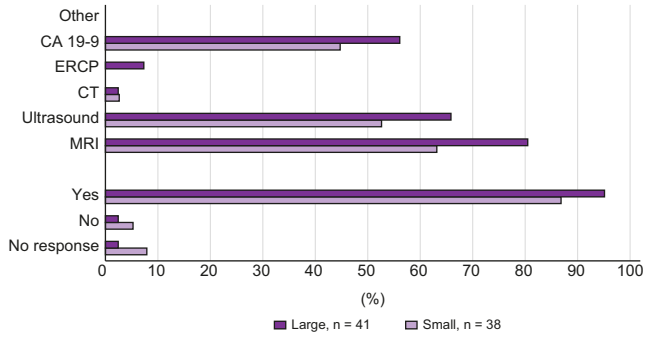

Fig. 3. CCA screening in small (<99 patients) and large (≥99 patients) centres. CA19-9, cancer antigen 19-9; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography.

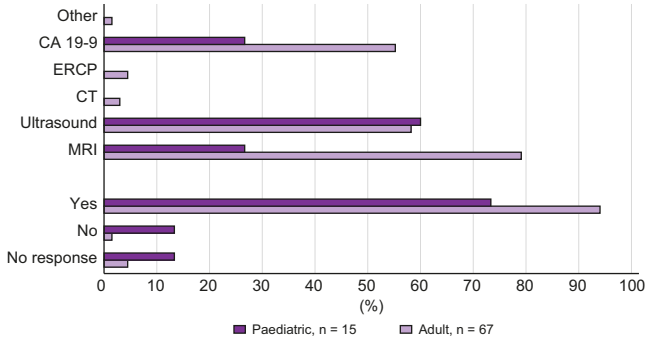

Fig. 4. CCA screening in adult and paediatric physicians. CA19-9, cancer antigen 19-9; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography.

treatment regardless of treatment response, while 23% of physicians discontinued UDCA if no biochemical or clinical response was observed. Eleven percent assessed the response after 1 month, 32% after 2 months, and 29% after 6 months of UDCA therapy, respectively. Thirty-two percent of physicians initiated UDCA in patients with normal serum liver enzymes and bilirubin. As for other medical treatments, 16% of physicians treated selected patients with vancomycin, while most physicians (76%) never prescribed long-term oral vancomycin to patients with PSC (Table S1). Immunosuppression was used by 37% of physicians to treat selected patients with PSC, while 60% never used immunosuppression. The use of medical treatments and evaluation of treatment effect was generally comparable in small *vs.* large cohorts as well as in adult *vs.* paediatric physicians (Figs. 1 and 2, Table 1, Table S1).

Surveillance for CCA and gallbladder polyps

Ninety percent of physicians routinely screened for CCA with imaging and/or biochemical markers (Table 2). Adult physicians more frequently screened for CCA than paediatric physicians (Fig. 4, Table 2). The most frequent screening modalities were (answers not mutually exclusive) MRI (70%), followed by ultrasound (59%), serum cancer antigen 19-9 (CA19-9: 50%), endoscopic retrograde cholangiopancreatography (4%) and CT (2%) (Table 2). Paediatricians did not use CT and endoscopic retrograde cholangiopancreatography, and MRI was used less frequently by paediatricians than by adult physicians Fig. 4, Table 2). Large centres screened more often for CCA (Fig. 3). Sixty-five percent of physicians performed annual CCA screening, 5% screened at 2-year intervals, and 22% used another time interval (Table 2). Four percent did not perform any CCA surveillance. Overall, the screening intervals were similar in small and large cohorts and in adult and paediatric physicians. If a gallbladder polyp of 6 mm was detected on ultrasound in a non-cirrhotic patient with PSC, 46% of physicians recommended repeated ultrasound after 3 or 6 months (26% and 21%, respectively), whereas 44% of physicians directly referred the patient to a cholecystectomy. In larger cohorts, a higher percentage of physicians referred patients directly for cholecystectomy.

Screening for IBD in patients without IBD

In patients with PSC without IBD at PSC diagnosis, 34% of physicians repeated colonoscopy every 5 years and another 34% only once within 3-5 years (Table S2). Twenty-seven

Table 1. UDCA treatment strategies.

	Total	Small centres (<99 patients)	Large centres (≥99 patients)	Adult physicians	Paediatric physicians
Responders, n (%)	82	38 (46)	41 (50)	67 (93)	15 (18)
Size of PSC cohort, mean (SD)	147 (160)	36 (25)	251 (163)	177 (165)	23 (15)
UDCA indication, n (%)					
All patients treated with UDCA	41 (50)	21 (55)	20 (49)	32 (48)	9 (60)
Patients with ALP >1.5x ULN	21 (26)	9 (24)	11 (27)	20 (30)	1 (7)
Depending on severity of imaging findings	3 (4)	3 (8)	0	3 (4)	0
Itching	11 (13)	8 (21)	2 (5)	8 (12)	3 (20)
Concurrent IBD	1 (1)	1 (3)	0	1 (1)	0
Patients with a strong wish for medical treatment	15 (18)	6 (16)	9 (22)	13 (19)	2 (13)
No patients treated with UDCA	10 (12)	4 (11)	5 (12)	8 (12)	2 (13)
UDCA treatment dosing, n (%)					
>15 mg/kg/day	13 (16)	5 (13)	8 (20)	9 (13)	4 (27)
13-15 mg/kg/day	56 (68)	24 (63)	30 (73)	50 (75)	6 (40)
<13 mg/kg/day	6 (7)	4 (11)	1 (2)	4 (6)	2 (13)
No response	7 (9)	5 (13)	2 (5)	4 (6)	3 (20)
Do you start UDCA treatment in patients with PSC and normal liver enzymes and bilirubin? n (%)					
Yes	26 (32)	12 (32)	14 (34)	20 (30)	6 (40)
No	52 (63)	24 (63)	25 (61)	45 (67)	7 (47)
No response	4 (5)	2 (5)	2 (5)	2 (3)	2 (13)

(*continued on next page*)

Table 1 (*continued*)

	Total	Small centres (<99 patients)	Large centres (≥99 patients)	Adult physicians	Paediatric physicians
UDCA treatment response evaluation, n (%)					
No evaluation	3 (4)	2 (5)	1 (2)	2 (3)	1 (7)
Stop treatment if no clinical/biochemical response	19 (23)	6 (16)	10 (24)	17 (25)	2 (13)
Continue treatment regardless of clinical/biochemical response	53 (65)	25 (66)	28 (68)	44 (66)	9 (60)
No response	7 (9)	5 (13)	2 (5)	4 (6)	3 (20)
Evaluation of UDCA treatment response, n (%)					
After 1-3 months	38 (46)	19 (50)	17 (41)	31 (46)	7 (47)
After 6 months	24 (29)	13 (34)	10 (24)	23 (34)	1 (7)
After 12 months	4 (5)	2 (5)	2 (5)	4 (6)	0
At no regular time frame	8 (10)	4 (11)	4 (10)	4 (6)	4 (27)
Other	1 (1)	0	1 (2)	1 (1)	0
No response	7 (9)	5 (13)	2 (5)	4 (6)	3 (20)

IBD, inflammatory bowel disease; UDCA, ursodeoxycholic acid.

Table 2. CCA surveillance.

	Total	Small centres (<99 patients)	Large centres (≥99 patients)	Adult physicians	Paediatric physicians
Responders, n (%)	82	38 (46)	41 (50)	67 (93)	15 (18)
Do you carry out routine biochemical and imaging screening for CCA? n (%)					
Yes	74 (90)	33 (87)	39 (95)	63 (94)	11 (73)
No	3 (4)	2 (5)	1 (2)	1 (1)	2 (13)
No response	5 (6)	3 (8)	1 (2)	3 (4)	2 (13)
Which modality do you use for CCA screening? n (%)					
MRI	57 (70)	24 (63)	33 (80)	53 (79)	4 (27)
Ultrasound	48 (59)	20 (53)	27 (66)	39 (58)	9 (60)
CT	2 (2)	1 (3)	1 (2)	2 (3)	0
ERCP	3 (4)	0	3 (7)	3 (4)	0
CA19-9	41 (50)	17 (45)	23 (56)	37 (55)	4 (27)
Other	1 (1)	0	0	1 (1)	0
Time interval for CCA screening, n (%)					
Annually	53 (65)	27 (71)	24 (59)	44 (66)	9 (60)
Other	18 (22)	4 (11)	14 (34)	4 (6)	14 (93)
With 2-year intervals	4 (5)	3 (8)	1 (2)	3 (4)	1 (7)
No response	7 (9)	4 (11)	2 (5)	3 (4)	4 (27)
In a non-cirrhotic PSC patient with a gallbladder polyp of 6 mm size detected on ultrasound would you? n (%)					
Refer to cholecystectomy	36 (44)	15 (39)	19 (46)	30 (45)	6 (40)
Recommend controlling in 3-6 months	38 (46)	17 (45)	21 (51)	33 (49)	5 (33)
No response	8 (10)	6 (16)	1 (2)	4 (6)	4 (27)

CA19-9, cancer antigen 19-9; CCA, cholangiocarcinoma; ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis.

percent of physicians only referred patients who developed symptoms of IBD to repeated colonoscopy. Adult physicians more frequently performed regular colonoscopy than paediatric physicians.

Liver transplantation and biliary dysplasia

In most centres (68%), physicians were able to refer patients with high-grade biliary dysplasia for liver transplantation (Table S3).

Discussion

PSC management offers many challenges, and a well-documented optimal strategy does not exist. Accordingly, in this survey study among European hepatologists, we found substantial variations in the treatment and monitoring of patients with PSC across Europe. For some of the issues in management, there were considerable discrepancies between practice and published guidelines. Thus, for medical treatment, despite no robust evidence or clear recommendations,[10] most physicians treated all their patients with UDCA. Whereas the American Association for the Study of Liver Diseases (AASLD)[9] and the British Society of Gastroenterology[7] do not endorse the use of UDCA for patients with PSC, the European Association for the Study of the Liver (EASL) guidelines 2009 stated that "UDCA (15–20 mg/d) improves serum liver tests and surrogate markers of prognosis (I/B1), but does not reveal a proven benefit on survival (III/C2)" and that "the limited data base does not yet allow a specific recommendation for the general use of UDCA in PSC". Further, the EASL guideline suggests considering UDCA treatment for prevention of colorectal cancer (CRC) in high-risk groups (patients with strong family history of CRC, previous colorectal neoplasia or longstanding extensive colitis).[10] We found that the real-life use of UDCA was motivated by a general treatment decision or indications such as elevations in alkaline phosphatase, itching and/or patient demand. Immunosuppressants are not recommended for PSC treatment unless there are features of co-occurring autoimmune hepatitis, so-called PSC-AIH (autoimmune hepatitis) overlap or variant syndrome.[10] However, small studies and case series report a significant effect of immunosuppressive drugs, such as azathioprine and tacrolimus, on liver biochemistry in patients with PSC.[14,15] This has not been investigated in

randomised placebo-controlled studies but the results may explain our finding that 37% of physicians would consider immunosuppressants for PSC in selected patients. Vancomycin was prescribed for selected patients by 16% of physicians. Long-term vancomycin has recently been identified as a potential therapeutic agent for PSC, with small case series showing modest improvement in liver biochemistry in adult patients[16] whereas no effects were detected in a recent, large retrospective study on children.[17] Randomised placebo-controlled clinical trials are needed to investigate the effect of vancomycin and there are concerns about the emergence of multidrug-resistant bacteria. Treatment is at present not recommended in guidelines.[9]

Current guidelines on CCA surveillance are vague and do not recommend routine CCA screening, although they discuss the option of using different imaging techniques and CA19-9.[10] Nevertheless, we found that regular CCA screening was performed by 90% of physicians. CCA remains an enormous challenge in PSC, with an estimated lifetime risk of around 20%[18] and inadequate imaging techniques and biomarkers for early detection.[1] This concern probably explains why physicians screen for CCA despite insufficient evidence and hence no firm recommendations in current guidelines. As early detection of CCA is challenging, the survival benefit of surveillance is not fully clarified. On the other hand, the detection of high-grade biliary dysplasia may in some countries lead to liver transplantation and thereby affect survival. Furthermore, we found that physicians applied various screening methods for CCA. Current recommendations are ambiguous regarding which screening method to ideally use, and there is no evidence to suggest that a single screening method can effectively detect CCA at an early stage.[7,8,10] In recent large, retrospective studies, including a population-based British study and an American single-centre study, surveillance for hepatobiliary cancers is reported to increase survival.[19,20] In contrast, no survival benefit was detected in a 5-year prospective, population-based Swedish study recently presented orally (Villard C *et al.* Oral presentation of 5 years of surveillance and follow-up of 512 PSC patients. The Liver Meeting AASLD Nov 2021). EASL guidelines commented in 2009 that the use of CA19-9 for surveillance needed further evaluation,[10] whereas UK-PSC guidelines in 2019 did not recommend CA19-9 as routine CCA surveillance due to its low diagnostic accuracy.[7]

We also found a considerable difference in the management of gallbladder polyps. On finding a gallbladder polyp of 6 mm, approximately 50% of physicians applied a control regimen with repeated ultrasound within 3 or 6 months, whereas 44% directly referred the patient for cholecystectomy. The management of gallbladder polyps remains problematic. Gallbladder neoplasms in patients with PSC were reported in a single-centre study to often be malignant at sizes above 8 mm with cancer found in around 30% of polyps from 8-15 mm, and in 50% of polyps from 16-23 mm.[21] EASL guidelines in 2009 recommend considering annual abdominal ultrasound to screen for gallbladder polyps and cholecystectomy even for polyps with a diameter of less than 10 mm.[10] UK-PSC guidelines 2019 state that if polyps are identified, treatment should be directed by a specialist hepatopancreatobiliary multidisciplinary meeting.[7] AASLD in its 2010 guidelines recommends cholecystectomy as a treatment regardless of lesion size if the underlying liver disease permits.[8]

In PSC without IBD detected at diagnosis of the bile duct disease, most physicians would repeat colonoscopy in the patients on a regular basis. However, a significant percentage of physicians only referred patients to colonoscopy if they developed symptoms of IBD. Although most patients with PSC have IBD, clinically silent bowel disease is not uncommon, and a fair proportion of patients will be asymptomatic.[22] It is unclear if the risk for CRC is similar in symptomatic and asymptomatic patients with PSC-IBD and whether annual colonoscopy surveillance is equally important. UK-PSC guidelines suggest that patients with PSC may benefit from a 5-year colonoscopy or earlier in the advent of new symptoms.[7]

The European Society of Gastrointestinal Endoscopy/EASL suggest that if no IBD is documented, the next ileocolonoscopy should be considered at 5 years or whenever bowel complaints suggestive of IBD occur.[23] Other guidelines do not endorse colonoscopic re-evaluation in patients with PSC without known IBD.[8–10]

Since PSC is a rare disease, a possible concern is that the size of the patient cohort may affect management decisions. However, we found no data to support that management differed between cohort sizes. A possible selection bias is that participants were invited by the membership of an international PSC network and thus were more likely to apply the same strategies. Hence, strategies may be even more variable in the broader hepatology community. There are presently no published recommendations for the management of children with PSC.[24] Our study suggests that adult and paediatric physicians generally manage their patients the same way. A possible explanation is that paediatric physicians treat their patients based on adult research since paediatric data are very limited. A smaller proportion of paediatric physicians routinely screened for CCA, possibly reflecting the rarity of CCA in children. Furthermore, paediatric physicians preferentially performed a colonoscopy in non-IBD PSC patients in the case of symptoms and not on regular basis. A likely reason for this practice is that colonoscopy is a more invasive procedure in children, and that CRC is rare in paediatric patients.

An important limitation of this study was the lack of information on physician non-responders to the survey. Furthermore, some responders may have been from the same centre, which was not depicted in the data. Data on which countries responded was also not collected. The responder rate was approximately 30%. The low responder rate may be explained by the fact that not all International PSC Study Group and ERN RARE-LIVER members routinely manage patients with PSC. Disease management according to geographical region is another interesting aspect we did not explore. Another important limitation of this study was that the survey did not address biliary endoscopic treatment of PSC and management of dominant strictures. Uncovering such practices would be of great importance since both a unified definition of dominant strictures and threshold for intervention is lacking. Given the complexity of this area, we believed tackling it in the questionnaire would extend the survey to a degree by which participants were less likely to answer. We considered this a trade-off, and prioritized keeping the survey length short instead of exploring this area further.

Our study highlights some of the crucial issues within the management of patients with PSC including use of medical treatments and surveillance for PSC-associated malignancies. Overall, we found apparent uncertainties and discrepancies between practice and published guidelines and our results confirm that existing data and recommendations for clinicians are inadequate for uniform patient management, as shown by the overt heterogeneity in responses. Guideline recommendations remain a

challenge, mainly due to the lack of proper comparative studies. Harmonisation of strategies is desirable to enable improved interpretation of outcome data and to optimise clinical patient care. Already established international networks and research associations should work to coordinate guideline recommendations in order to generate a better basis for developing clinical trials and to improve the daily management of patients with PSC.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; CA19-9, cancer antigen 19-9; CCA, cholangiocarcinoma; CRC, colorectal cancer; EASL, European Association for the Study of the Liver; IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis; UDCA, ursodeoxycholic acid.

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This study received no financial support.

Conflict of interest

The authors declare that they have no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

HY and co-authors UB, CS and OC designed the study and HY collected data. BL, HY and JE conducted data analyses and JE and HY wrote the manuscript. All authors reviewed and edited the manuscript. All authors contributed substantially to the interpretation of data and the drafting or critical revision of the manuscript for important intellectual content. All authors assume full responsibility for analyses and interpretation of these data. The corresponding author attests that all listed authors meet authorship criteria and that those not meeting the criteria have been omitted.

Data availability statement

The datasets generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2022.100553.

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