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# Quantitative MRCP and metrics of bile duct disease over time in patients with primary sclerosing cholangitis: A prospective study

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## Summary

**Background:** Imaging markers of biliary disease in primary sclerosing cholangitis (PSC) have potential for use in clinical and trial disease monitoring. Herein, we evaluate how quantitative magnetic resonance cholangiopancreatography (MRCP) metrics change over time, as per the natural history of disease.

**Methods:** Individuals with PSC were prospectively scanned using non-contrast MRCP. Quantitative metrics were calculated using MRCP+ post-processing software to assess duct diameters and dilated and strictured regions. Additionally, a hepatopancreatobiliary radiologist (blinded to clinical details, biochemistry and quantitative biliary metrics) reported each scan, including ductal disease assessment according to the modified Amsterdam Cholangiographic Score (MAS).

**Results:** At baseline, 14 quantitative MRCP+ metrics were found to be significantly different in patients with PSC ( $N=55$ ) compared to those with primary biliary cholangitis ( $N=55$ ), autoimmune hepatitis ( $N=57$ ) and healthy controls ( $N=18$ ). In PSC specifically, baseline metrics quantifying the number of strictures and the number and length of bile ducts correlated with the MAS, transient elastography and serum

Palak J. Trivedi and Katherine Arndtz are joint first author.

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ALP values ( $p < 0.01$  for all correlations). Over a median 371-day follow-up (range: 364–462), 29 patients with PSC underwent repeat MRCP, of whom 15 exhibited quantitative changes in MRCP+ metrics. Compared to baseline, quantitative MRCP+ identified an increasing number of strictures over time ( $p < 0.05$ ). Comparatively, no significant differences in biochemistry, elastography or the MAS were observed between timepoints. Quantitative MRCP+ metrics remained stable in non-PSC liver disease.

**Conclusion:** Quantitative MRCP+ identifies changes in ductal disease over time in PSC, despite stability in biochemistry, liver stiffness and radiologist-derived cholangiographic assessment (trial registration: ISRCTN39463479).

## 1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic, invariably progressive liver disease characterised by multi-focal stricturing throughout the biliary tree.<sup>1</sup> No medical therapy has been shown to slow disease progression, and transplantation remains the only life-extending intervention for patients. Unfortunately, testing the efficacy of new PSC therapies poses several unique challenges, given delays in diagnosis,<sup>2</sup> phenotypic heterogeneity,<sup>3</sup> and the variable rates of progression between individuals.<sup>4</sup> To this end, several risk scores and biomarkers have been developed, either from the date of PSC diagnosis,<sup>5–9</sup> or as a point measure from the moment of testing.<sup>10–17</sup> Most stratification tools rely on liver biochemistry and markers of parenchymal fibrosis.<sup>4</sup> This is despite the fact that ductal disease progression antedates the development of cirrhosis. Moreover, whilst biomarkers of fibrosis can distinguish patients with early versus advanced disease, they do not identify those with early-stage disease that is rapidly progressive.

Cholangiography is the 'gold standard' for PSC diagnosis,<sup>18–22</sup> with non-invasive assessment via magnetic resonance cholangiopancreatography (MRCP) the modality of choice. Whilst MR-based risk scoring systems exist, these largely focus on parenchymal changes rather than ductal involvement.<sup>11,12,23</sup> Indeed, the interpretation of PSC ductal disease is more subjective, and associated with significant inter-reader disagreement.<sup>24,25</sup> To this effect, a position statement from the Imaging Working Party of the International PSC Study Group emphasises the need for detecting complications early, predicting disease progression and limiting variability in MRCP reporting.<sup>26</sup> Patient support groups also highlight the diagnostic and prognostic limitations of current imaging modalities.<sup>27</sup>

The objective of this study was to explore whether quantitative MRCP could identify ductal changes over time, specifically in PSC patients who, according to currently available technology, have stable early-stage liver disease. Additional study goals were to determine the correlation between specific biliary metrics and existing clinical and laboratory indices of disease severity, and further validate the discriminatory capability of quantitative MRCP across immune-mediated liver and biliary diseases.

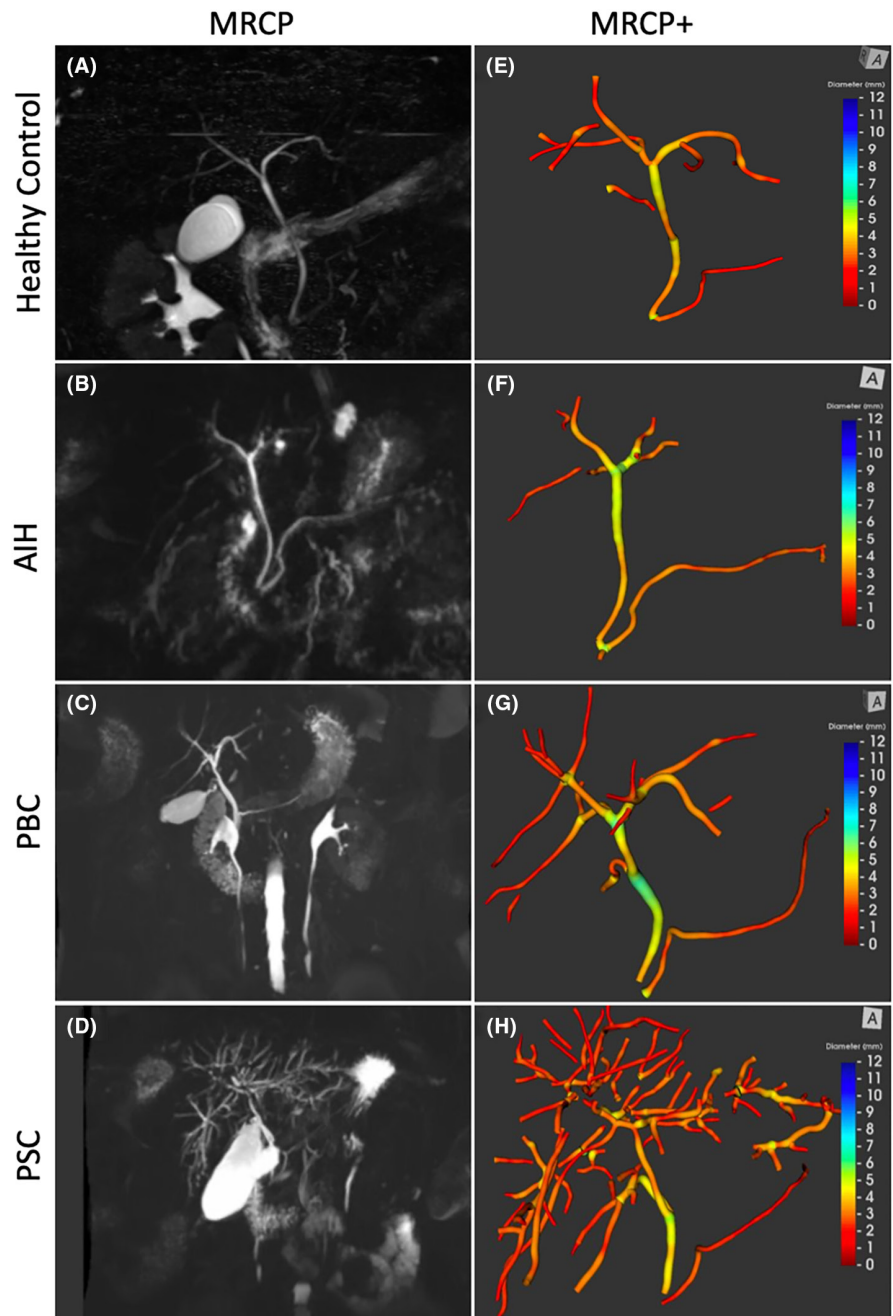
## 2 | METHODS

### 2.1 | Study design and participants

This was a prospective observational cohort study, in which patients were invited to participate in longitudinal imaging. Eligible participants were those over 18 years of age with a diagnosis of PSC,<sup>19–21</sup> and compensated liver disease. For comparator groups, we also recruited individuals with established diagnoses of primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), alongside healthy controls without liver disease (HC). Exclusion criteria were prior transplantation, concomitant viral hepatitis, alcohol-induced liver disease, non-alcoholic/metabolic dysfunction-associated steatotic liver disease (MASLD), other chronic metabolic liver disease, drug-induced liver injury, IgG4-related disease or secondary sclerosing cholangitis, previous or active hepatobiliary malignancy, the presence of biliary stents or external biliary drains, inability or unwillingness to provide informed consent, hepatic decompensation or a contraindication to MRI. All patients provided informed, signed consent.

The study involved the collection of MRCP images, clinical data, vibration-controlled transient elastography readings (FibroScan®; Echosens, France) and routine laboratory measures. In patients with PSC, we also recorded the distribution of ductal disease (isolated intrahepatic or combined intra- and extra-hepatic) and the Modified Amsterdam PSC Cholangiographic Score (MAS) as evaluated centrally by a hepatopancreatobiliary radiologist who was blinded to patient clinical details and readouts from the MRCP+ post-processing step (Table S1). All scans were subsequently exported for digital image post-processing, in which biliary trees were modelled in three dimensions and quantitative metrics produced (MRCP+™ software; Perspectum Ltd.; Oxford, UK), as previously described.<sup>28,29</sup> All analysts performing image post-processing were also blinded to patient clinical details and the quantitative biliary assessments from any other study visits. Full details relating to imaging data acquisition are provided in File S1. Representative MRCP+ images are displayed in Figure 1. All subjects with liver disease were invited for a second MRCP after an interval of 12 months, to monitor for ductal disease change over time.

**FIGURE 1** Example maximum intensity projections of 3D MRCP and corresponding MRCP+- derived biliary tree models. Images of the biliary tree in representative individuals are shown, specifically in (A) a healthy control subject, and individuals with (B) AIH, (C) PBC and (D) PSC. Corresponding MRCP+- derived biliary tree models are also shown for (E) a healthy control subject and individuals with (F) AIH, (G) PBC and (H) PSC.



## 2.2 | Data presentation and statistical analysis

Categorical variables are expressed as raw numbers (and percentages), and continuous data as medians (and interquartile ranges, IQR). Differences between groups of continuous data were assessed using the Kruskal-Wallis test or the Wilcoxon unpaired non-parametric test when drawing comparisons between only two groups. A Bonferroni–Dunn post-hoc correction was made to adjust the alpha in the event of multiple comparisons. Changes over time for continuous sets of data for the same patient group between the first and second scan time points were analysed using linear mixed effects models with a random intercept included for each patient. Spearman's rank correlation coefficients were used

to determine the strength of the association between covariates and individual biliary metrics under evaluation.  $p$  values  $<0.05$  were deemed statistically significant. Statistical analysis was performed using R version 4.0.3.

## 3 | RESULTS

### 3.1 | Study cohort and baseline characteristics

Between August 2015 and August 2017, 186 individuals with immune-mediated liver disease were recruited for the study, of whom 167 had at least 1 MRCP of suitable quality for quantitative processing and were

included in the analysis ( $n=55$ , 57 and 55, with PSC, AIH and PBC, respectively; Table 1 and Figure S1). Additionally, 18 healthy controls were included. The PSC group differed significantly from the PBC and AIH groups in that participants were mostly men, with a greater proportion having concomitant inflammatory bowel disease (IBD). Median liver stiffness was 7.7 kPa in patients with PSC, and was not significantly different from those with PBC or AIH (Table 1). Thirty-one patients with PSC (56%) had isolated intra-hepatic disease. Four patients with PSC had normal biliary trees on imaging with standard MRCP, with the remainder having intra- and extra-hepatic involvement.

### 3.2 | Quantitative biliary metrics in PSC compared to other disease aetiologies

A total of 92 quantitative MRCP+ metrics were calculated for each participant (Table S2). Expert knowledge extracted from an accredited hepatopancreatobiliary radiologist reduced the number of quantitative metrics (for consideration in identifying patients with PSC) from 92 to 24.<sup>30</sup>

We found significant differences between baseline scans of patients with PSC compared to those with PBC, AIH and healthy

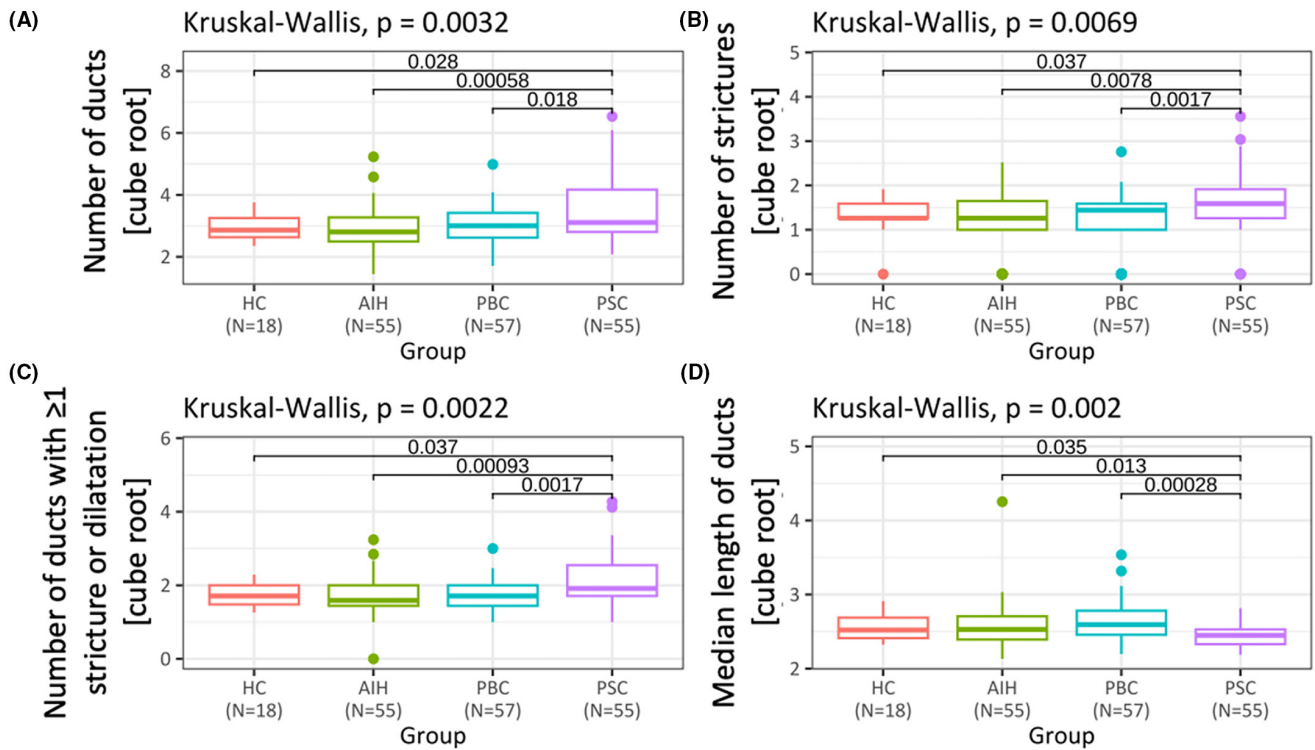
controls, with 14 metrics related to biliary tree volume, the number of MRI apparent ducts, bile duct length, the number of abnormal ducts, the number of strictures and dilatations, the length of strictures and dilatations and the severity of stricturing and dilatations. In agreement with a previous study,<sup>30</sup> we found the following four metrics to be greater in PSC compared to other groups: (1) the total number of modelled ducts; (2) the median duct length; (3) the number of apparent strictures; and (4) the number of ducts with either a stricture or dilatation (Table 1). Additionally, these biliary metrics had good discriminatory value in differentiating patients with PSC from AIH, PBC and healthy controls (Figure 2).

### 3.3 | Correlation of quantitative biliary metrics in with existing markers of disease severity

Of the 55 patients with PSC scanned at baseline, 13 were considered low risk on the MAS (scores 0–1) and 37 were deemed at high risk for intrahepatic disease (scores 2–3) according to standard MRCP-derived images. In turn, 35 patients were considered low risk for extrahepatic disease and 15 were considered high risk. Five patients did not have a recorded intrahepatic or extrahepatic MAS.

TABLE 1 Baseline patient characteristics.

	PSC (n = 55)	PBC (n = 57)	AIH (n = 55)	Healthy volunteers (n = 18)	p value
Age at enrolment (years)	39.6 (18.0–68.9)	53.6 (29.9–81.0)	55.6 (22.4–80.1)	31.0 (21.0–45.0)	<0.001
Male sex (n, %)	33 (60)	5 (9)	10 (18)	9 (50)	<0.001
Laboratory parameters					
ALT (IU/L)	57 (27.5, 109)	32 (22, 58)	19 (13, 29.5)	–	<0.001
AST (IU/L)	44 (26.5, 67.5)	35 (25, 53)	23 (19, 33.5)	–	<0.001
ALP (IU/L)	176 (95, 347.5)	138 (94, 318)	69 (58, 84.5)	–	<0.001
Bilirubin (mmol/L)	11 (8, 17.5)	9 (6, 16)	9 (7, 12.5)	–	0.083
Creatinine (mmol/L)	69 (60.5, 83)	66 (60, 76)	68 (59, 77.5)	–	0.763
Sodium (mmol/L)	141 (140, 143)	141 (139, 142)	142 (141, 143.5)	–	<0.001
Platelet Count ( $\times 10^9/L$ )	254 (212, 295.5)	230 (173.2, 267.8)	219.0 (157.5, 266)	–	0.044
INR	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	–	0.221
Liver stiffness (kPa)	7.7 (6.2, 11.5)	7.1 (5.3, 12.0)	6.8 (4.9, 11.2)	–	0.181
Medications (n, %)					
Corticosteroids	3 (6%)	1 (2%)	30 (55%)	–	<0.001
Azathioprine	6 (11%)	1 (2%)	38 (69%)	–	<0.001
Other immunosuppression	3 (6%)	0 (0%)	16 (29%)	–	<0.001
Ursodeoxycholic acid	22 (40%)	56 (98%)	0 (0%)	–	<0.001
Mayo PSC risk score	-0.88 (-1.28, -0.30)	–	–	–	–
Quantitative MRCP assessments					
Number of ducts	30 (22–73)	22 (16–35)	27 (18–40)	24 (18–35)	0.014
Median duct length (mm)	14.7 (12.7–16.2)	16.2 (13.7–19.8)	17.5 (14.8–21.5)	16.0 (14.0–19.4)	0.049
Number of apparent strictures	4 (2–7)	2 (1–5)	3 (1–4)	2 (2–4)	0.007
Number of ducts with a stricture or dilatation	7 (5–17)	4 (3–8)	5 (3–8)	5 (3–8)	0.002



**FIGURE 2** Inter-group comparisons of quantitative MRCP metrics shown in a cube root scale. (A) the number of ducts; (B) the number of strictures; (C) the number of ducts with either a stricture or dilatation; and (D) the average duct length.

The score for both intrahepatic and extrahepatic disease correlated positively with quantitative MRCP+ metrics, specifically, the total number of modelled ducts (Spearman's  $\rho=0.51$ ;  $p<0.001$  and  $\rho=0.46$ ;  $p<0.001$ , respectively), the number of apparent strictures (Spearman's  $\rho=0.55$ ;  $p<0.001$  and  $\rho=0.46$ ;  $p<0.001$ , respectively), and the number of ducts with either a stricture or a dilatation (Spearman's  $\rho=0.55$ ;  $p<0.001$  and  $\rho=0.48$ ;  $p<0.001$ , respectively).

We found strong associations between the MAS for both intrahepatic and extrahepatic disease and the total number of strictures, number of modelled ducts and number of ducts with a stricture or dilatation on quantitative MRCP (Figure 3); albeit, there was no significant association between Modified Amsterdam Scores and liver biochemical parameters (Figure S2).

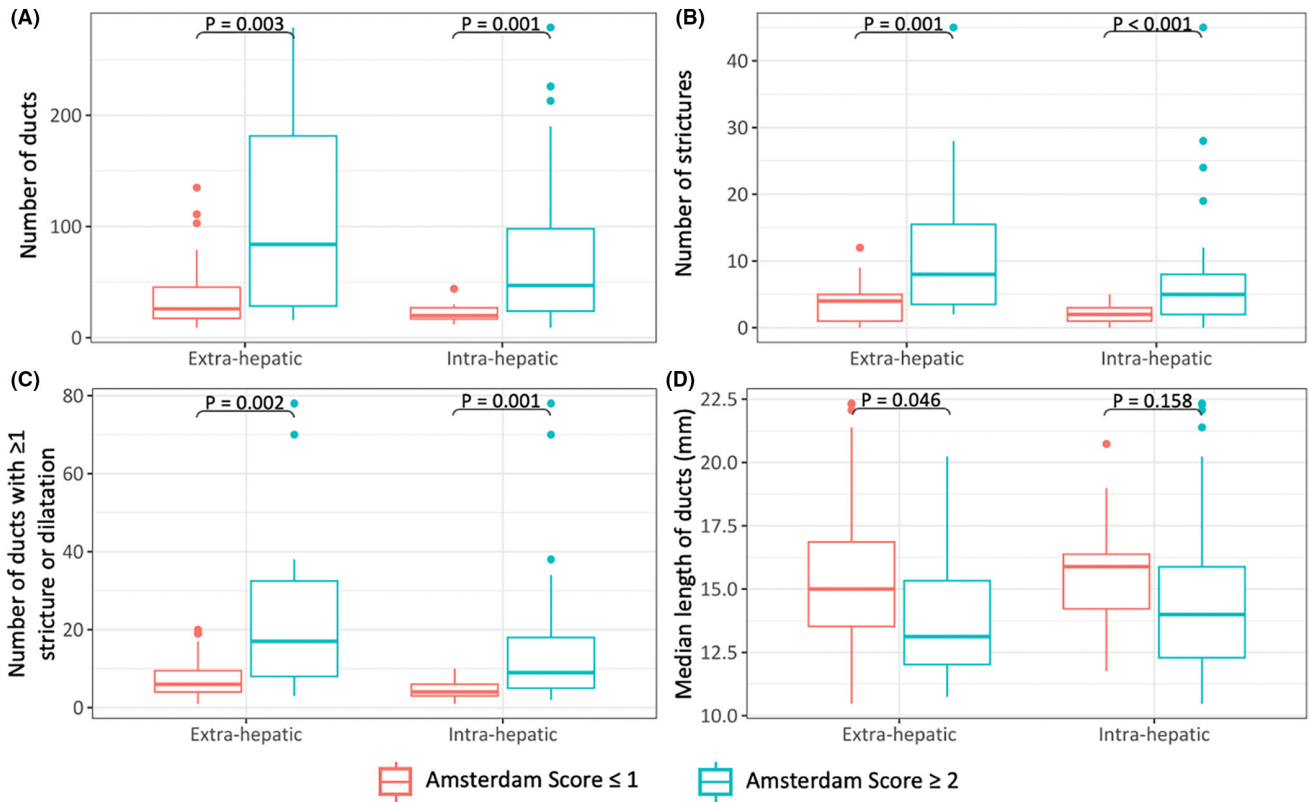
By contrast, the number of apparent strictures identified on quantitative MRCP+ correlated with serum ALP values ( $p<0.01$ ), along with a positive linear association between the number of strictures, number of ducts and number of ducts containing one or more strictures or dilatation and serum bilirubin ( $p<0.01$ ; Figure S3). All quantitative MRCP+ metrics showed strong correlation between each other (Figure S4); and the number of strictures, number of ducts and number of ducts with one or more strictures or dilatation exhibited moderate correlation with median liver stiffness values using transient elastography (Figure S5). Median duct length also exhibited a weak negative correlation with extrahepatic MAS

but no significant correlation with intrahepatic MAS (Spearman's  $\rho=-0.33$ ;  $p=0.018$  and  $\rho=-0.22$ ;  $p=0.130$ ).

### 3.4 | Changes in ductal disease over time

Sixty-three percent of participants ( $N=29$  PSC,  $N=34$  AIH,  $N=42$  PBC) underwent repeat imaging approximately 12 months after the initial scan (Table 2). Fifty-two percent of patients with PSC ( $n=15$ ) showed increasing stricturing of the biliary tree according to quantitative biliary metrics (Figure S6), which was not captured by standard qualitatively reported MRCP. The detected change in an example patient is shown in Figure 4. There was a significant linear increase in the number of strictures over time in those with PSC (slope = +1.6 strictures/year [95% confidence interval: 0.1–3.1],  $p=0.046$ ).

Baseline demographics, liver biochemical markers or MAS were not predictive of the rate of change of the number of strictures (Table S3). No significant changes were observed in markers of ductal disease among individuals without PSC (Figure S6). By contrast, only two and three patients with PSC demonstrated radiological progression in ductal disease according to standard qualitative MRCP reporting for intrahepatic disease and extrahepatic disease, respectively. No significant changes were observed between time-points with regards to liver biochemical markers, the Mayo PSC risk score or liver stiffness scores (Table 2).



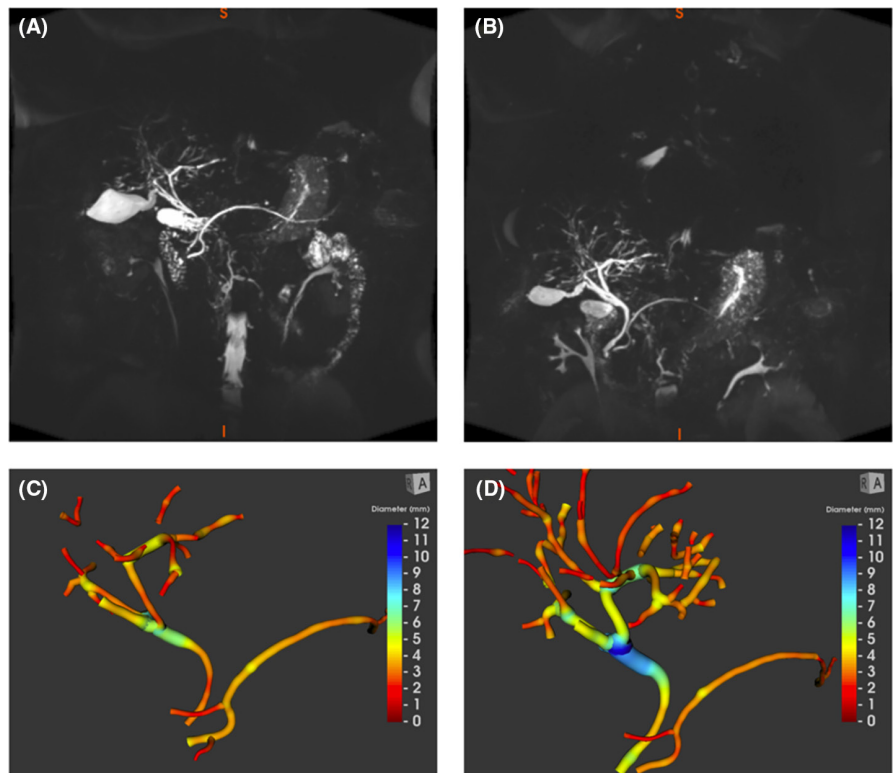
**FIGURE 3** Association between quantitative MRCP+ metrics and the Amsterdam Cholangiographic Score. Box plots demonstrating the (A) association between the total number of ducts and the MAS (Left: extrahepatic ducts; Right: intrahepatic ducts); (B) the number of strictures and the MAS (Left: extrahepatic ducts; Right: intrahepatic ducts); (C) the association between the number of ducts with a stricture or dilatation and the MAS (Left: extrahepatic ducts; Right: intrahepatic ducts); and (D) the association between median duct length and the MAS (Left: extrahepatic ducts; Right: intrahepatic ducts).

**TABLE 2** Changes in disease markers over time according to aetiology.

	PSC (N=29)			AIH (N=34)			PBC (N=42)		
	Baseline	Follow up interval	p value	Baseline	Follow up interval	p value	Baseline	Follow-up interval	p value
Days	0	371 (370-392)	—	0	378 (371-385)	—	0	378 (371-392)	—
Laboratory parameters									
ALT (IU/L)	48 (25-94)	48 (27-78)	0.811	19 (13-27)	17 (14-26)	0.896	29 (22-53)	25 (19-43)	0.070
AST (IU/L)	38 (26-62)	38 (28-55)	0.829	22 (18-31)	22 (19-27)	0.950	33 (25-52)	29 (23-43)	0.116
ALP (IU/L)	149 (88-305)	143 (106-221)	0.963	69 (60-78)	69 (58-85)	0.687	136 (93-228)	121 (97-244)	0.111
Bilirubin (µmol/L)	11 (8-16)	11 (8-13)	0.582	8 (7-11)	8 (7-12)	0.697	8 (6-13)	8 (6-11)	0.319
Platelet count (×10 <sup>9</sup> /L)	249 (210-275)	231 (162-276)	0.160	224 (194-274)	223 (179-293)	0.503	238 (194-272)	236 (193-279)	0.677
Mayo PSC Risk Score	-0.93 (-1.2-0.3)	-0.85 (-1.4 to 0.2)	0.931	—	—	—	—	—	—
Transient elastography reading	7.7 (6.1-10.9)	7.2 (6.5-10.4)	0.321	6.3 (4.7-8.4)	6.3 (5.3-9.5)	0.555	6.8 (5.1-10.2)	6.3 (4.8-10.7)	0.964
Amsterdam PSC Cholangiographic Score									
Intrahepatic disease	2 (2-2)	2 (2-2)	0.279	—	—	—	—	—	—
Extrahepatic disease	0 (0-2)	0 (0-2)	0.589	—	—	—	—	—	—
Quantitative MRCP									
Number of strictures	5 (2-7)	6 (4-12)	0.019*	2 (1-4)	2 (1-3)	0.754	3 (1-4)	2 (1-4)	0.503

\*Indicates a significant change from baseline.

**FIGURE 4** Example MRCP images and MRCP+ models from a patient with PSC showing changes in ductal disease over 1 year. Selected images from a patient with PSC showing disease progression. Maximum intensity projection 3D MRCPs at (A) baseline (intra-hepatic Amsterdam score=2, extra-hepatic Amsterdam score=0) and (B) after 1 year (intra-hepatic Amsterdam score=2, extra-hepatic Amsterdam score=0). Corresponding MRCP+ derived biliary tree models at (C) baseline (number of ducts with strictures or dilatations=6, number of dilatations=5, abnormal length sum=90.3mm, dilatation relative severity sum=295.6) and (D) 1-year follow-up (number of ducts with strictures or dilatations=12, number of dilatations=11, abnormal length sum=214.6mm, dilatation relative severity sum=733.5).



## 4 | DISCUSSION

Primary sclerosing cholangitis represents an important and pressing disease with substantial unmet needs; given its ill-defined aetiology, critical absence of medical therapy, and the fact that more than 50% of patients go on to need transplantation and/or develop cancer.<sup>3</sup> However, rates of progression vary, and accurately predicting disease course is of interest to clinicians, patients and all those committed to developing new therapies. Until now, cholangiographic risk scores have been derived through endoscopic retrograde cholangiopancreatography (ERCP), an invasive tool that is reserved for biliary intervention or sampling of potentially malignant strictures. Qualitative MRI-based risk stratification has been explored,<sup>11,12</sup> albeit with poor-to-moderate inter-reader agreement.<sup>24,31</sup> This presents a challenge when detecting longitudinal changes and when trying to gauge the magnitude of disease progression. Taken together, there is a need for a non-invasive and objective measure of ductal disease change over time.

In this study, we validate correlations between specific quantitative MRCP+ metrics and existing markers of disease severity.<sup>32,33</sup> Most striking, was the ability of quantitative MRCP+ to capture changes in ductal disease over time in a prospective cohort of PSC patients. Temporal changes were apparent despite liver biochemistry, elastography and standard qualitative MRCP readouts being stable. Our studied cohort represents a population of patients with early-stage liver disease as well as low and unchanged fibrosis scores over the course of time. This is important, given that biliary stricture severity and ductal disease changes may be less relevant, prognostically, among patients with moderate-severe fibrosis.<sup>34</sup>

This study is in line with additional efforts in the field to combine biliary imaging, elastography and other biochemical metrics to better characterise the progression, associated risk factors and outcomes of patients with hepatobiliary diseases. Clinical trials increasingly employ MRI prediction models in post-hoc survival analysis,<sup>35</sup> and some studies now formally include imaging scores in their list of secondary outcomes.<sup>36</sup> Medicines' regulators indirectly suggest that trials are performed in patients without advanced fibrosis, with progression to cirrhosis used as part of a composite outcome measure.<sup>37,38</sup> These trends underscore the gaps in our current ability to predict clinical outcomes, quantify changes in disease activity over time and intervene appropriately.

Previous retrospective analyses using quantitative MRCP+ have highlighted intrahepatic dilatation as a key discriminatory metric of high-risk versus low-risk PSC,<sup>28</sup> and provided correlation between biliary metrics and the Mayo Risk Score, magnetic resonance elastography, Modified Amsterdam Cholangiographic Score, the Amsterdam Oxford PSC Score, the paediatric PSC SCOPE Index and the PSC Risk Estimate Tool (PRESTO).<sup>32,33</sup> Additionally, several retrospective studies have reported the prognostic value of quantitative biliary metrics at a single timepoint to predict transplant-free survival or decompensation.<sup>39-41</sup> The data presented herein provides added value, as the first prospective investigation shows an increase in the total number of strictures over time despite stability in other disease parameters. Furthermore, quantitative MRCP+ was able to discriminate PSC from healthy controls and other immune-mediated liver diseases, highlighting its potential as an adjunctive diagnostic tool.

Our study is not without limitations. Although prospective, our cohort derives from a single tertiary centre and is relatively small



in terms of patient numbers compared to retrospective series. Indeed, whilst an investigator-initiated, prospective observational trial, recruitment targets were constrained by grant funding and pre-specified timelines for completion. Additionally, as the study was conducted in a tertiary centre, many eligible patients who attend our clinic opt for MRCP scans to be performed locally, rather than travelling long distances to participate in non-interventional studies. Regardless, baseline participant characteristics are similar to larger, more contemporary cohorts from the United Kingdom,<sup>42</sup> indicating the representative nature of our PSC study population. Additionally, we lack a comparator group of patients with inflammatory bowel disease only, which is important to consider given that a proportion have sub-clinical cholangiographic changes that herald development of PSC in later life.<sup>43,44</sup>

Previous technical validation studies show that the measurement of the number of strictures has excellent scan-rescan repeatability (ICC=0.90), alongside high inter- and intra-reader agreement (ICC=0.83 and 0.85, respectively).<sup>28</sup> However, evaluating additional time points is essential, including over shorter intervals, and by incorporating new and emerging radiological scoring systems such as the newly developed DiStrict score.<sup>45</sup> The magnitude of 'meaningful change' in the number of strictures also requires further study, particularly as it relates to the incidence of adverse events. Of interest, positive correlations have been reported between the overall number of strictures and the risks of liver transplantation/liver-related deaths, with a hazard ratio of 1.05 for each additional stricture.<sup>41</sup> Longer-term studies capturing a breadth of histological and clinical outcomes are needed to validate MRCP+ as a prognostic biomarker for use in routine practice and also to determine if its metrics can be used as a radiological endpoint in future clinical trials. This would include studies of whether MRCP+ can be used to identify progressive, clinically relevant 'dominant' strictures that are in need of intervention at a later stage. Lastly, the development of hepatobiliary cancer is a principal concern for all who live with PSC, and it is of critical interest to assess the ability of quantitative MRCP+ to distinguish benign versus malignant strictures in a suitably powered cohort. Presently, MRCP+ is not at a stage where it is possible to distinguish benign versus malignant biliary lesions, and it is unclear if inclusion of gadolinium-based contrast would add discriminatory value.

In conclusion, we show that metrics derived using MRCP+ correlate well with markers of disease used in routine clinical practice, whilst demonstrating there are quantifiable changes in ductal disease over time in the majority of patients who are not currently captured by existing tools. This study thus supports future prospective use of MRCP+ to capture its performance over time and across diverse settings, as well as its potential to aid clinical decision-making, and support aspirations of improved patient outcomes.

#### AUTHOR CONTRIBUTIONS

**Palak J. Trivedi:** Conceptualization; investigation; methodology; validation; formal analysis; project administration; data curation;

writing – original draft; writing – review and editing. **Katherine Arndt:** Conceptualization; investigation; methodology; validation; project administration; writing – review and editing; data curation; resources. **Nadir Abbas:** Data curation; writing – review and editing. **Alison Telford:** Visualization; investigation; formal analysis; project administration; software; data curation; resources. **Liam Young:** Visualization; writing – review and editing; formal analysis; project administration; software; data curation; resources. **Rajarshi Banerjee:** Funding acquisition; visualization; project administration; software. **Peter Eddowes:** Funding acquisition; visualization; software; project administration; data curation; resources. **Kartik S. Jhaveri:** Visualization; formal analysis; supervision. **Gideon M. Hirschfield:** Conceptualization; investigation; funding acquisition; writing – review and editing; visualization; supervision.

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#### SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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