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Quantitative spleen and liver volume changes predict survival of patients with primary sclerosing cholangitis

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AIM: To assess the value of quantitative spleen and liver volume changes in predicting the survival of patients with primary sclerosing cholangitis (PSC).

MATERIALS AND METHODS: This institutional review board-approved single-centre study included 89 PSC patients with baseline and follow-up liver imaging studies and laboratory data between 2000 and 2018. Change in spleen, total and lobar liver volumes, and lobar-to-total liver volume ratio was compared between patients with and without adverse outcome (liver transplantation, transplant waiting list, and death). Receiver operating characteristic (ROC) and Kaplan–Meier analysis were performed to identify the volumetric threshold for prediction of outcome and show how these thresholds predict survival, respectively. A p-value of <0.05 was considered statistically significant.

RESULTS: The present cohort included 53 men (60%), with mean age of 42 years at baseline. The only volumetric parameters with significant differences in change between patients with and without adverse outcome were spleen volume ($p<0.001$) and left-to-total liver volume ratio (L/T; $p=0.025$). The probability of transplant-free survival at 36 months was 59.1% versus 11.9% for patients with spleen volume change <50 ml versus ≥ 50 ml, respectively (AUC=0.731); and 61.3% versus 13.8% for patients with L/T change <0.04 versus ≥ 0.04, respectively (AUC=0.638). The patients with changes below the cut-off in both spleen volume and L/T, had a higher probability of transplant-free survival at 36 months (76.8%), compared to those with change at or below the cut-offs in one or both of these two parameters (36.7%, 15%, respectively; $p=0.001$).

CONCLUSION: Spleen volume change and L/T change might be useful biomarkers for prediction of transplant-free survival in patients with PSC.

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Introduction

Primary sclerosing cholangitis (PSC) is a chronic progressive liver disease of unknown aetiology which ultimately causes fibrosis of the extrahepatic and intrahepatic biliary system. The progressive nature of PSC includes development of biliary strictures, fibrosis, cirrhosis, and end-stage liver disease.[1,2] Liver transplantation is the only available definite treatment option for PSC patients with end-stage liver disease. This highlights the importance of disease progression assessment to decide on the need for liver transplantation.[1,3]

A number of prognostic models have been proposed to predict disease progression and survival in PSC patients. The model for end-stage liver disease (MELD) score is the most common clinically used model to determine the need for liver transplantation in most liver diseases, while the Mayo risk score is a specific model for PSC that is most commonly used in clinical trials to predict survival. These models are based on biochemical tests including serum total bilirubin[4,5]. Fluctuation of liver biochemical test results due to biliary strictures, cholangitis, or calculi result in significant variations in the laboratory-based prognostic models.[6,7] This underscores the significance of finding more stable quantifiable parameters that can be used more reliably to predict survival and the need for liver transplantation in PSC patients. There are typical hepatic morphological changes such as lobar or segmental atrophy and hypertrophy in PSC patients which have been described on cross-sectional imaging.[8,9] Qualitative assessment of changes in liver and spleen size over time has been investigated.[9] A recently published study with quantitative measurement of the liver and spleen has shown that left lobe-to-total liver volume ratio (L/T) correlates with severity of PSC as identified by the Mayo risk score[10]; however, the value of quantitative liver and spleen volume changes in predicting survival and outcome of PSC has not been assessed. The objective of the present study was to evaluate whether quantitative changes in spleen and liver volume can predict survival and outcome in patients with PSC.

Materials and methods

Study design

This study was performed as a Health Insurance Portability and Accountability Act (HIPAA)-compliant, institutional review board (IRB)-approved retrospective single-centre study. Patient informed consent was waived by the IRB. A retrospective database search of patients with hepatobiliary diseases between January 2000 and June 2018 identified 204 patients with the confirmed diagnosis of PSC. Diagnosis was confirmed by typical imaging findings (magnetic resonance cholangiopancreatography [MRCP] or endoscopic retrograde cholangiopancreatography [ERCP]) showing characteristic bile duct changes and/or histology in patients with or without cholestatic liver function test results after ruling out other diagnosis and secondary causes of cholangitis. Patients were excluded if they did not have at least two cross-sectional pre-liver transplantation MRCP or computed tomography (CT) studies with at least a 6-month interval (n=73), or if they lacked hepatic function tests within 6 months of the imaging studies, at baseline and/or follow-up (n=42). The cohort included 89 patients with imaging studies and laboratory data at baseline or the time of referral to the institution, and follow-up at last clinic visit (Fig 1). Patients' electronic medical records were reviewed, including demographic data (age, gender, body mass index, race), associated conditions (inflammatory bowel disease including ulcerative colitis and Crohn's disease, colectomy, and immune-mediated overlaps [autoimmune hepatitis, IgG4 disease]), complications of the disease (variceal bleeding, encephalopathy, hepatorenal syndrome, cholangitis, pancreatitis, splenectomy, cholangiocarcinoma), medical treatment (beta blocker, ursodeoxycholic acid), survival status (alive, deceased), and transplantation history (non-transplanted, on the transplant waiting list, or transplanted). Patient records were censored in June 2018 for the clinical endpoints of liver transplantation or all-cause mortality.

Laboratory data (serum total bilirubin [total bilirubin], albumin, aspartate aminotransferase [AST], alanine aminotransferase, alkaline phosphatase [ALP], gamma glutamyl transferase, C-reactive protein, platelet, sodium, creatinine [Cr], and international normalised ratio [INR]) and history of variceal bleeding were recorded at the date closest to the imaging study, up to 6 months.

MELD and Mayo risk score calculation

MELD score was calculated by using the following formula:

$$\text{MELD score} = 3.78\,\text{LN}(\textit{total bilirubin}\ [\text{mg/dl}]) + 11.2\,\text{LN}(\textit{INR}) + 9.75\,\text{LN}(\textit{Cr}\ [\text{mg/dl}]) + 6.43$$

where LN indicated the natural logarithm.

Mayo risk score was calculated by using the following formula:

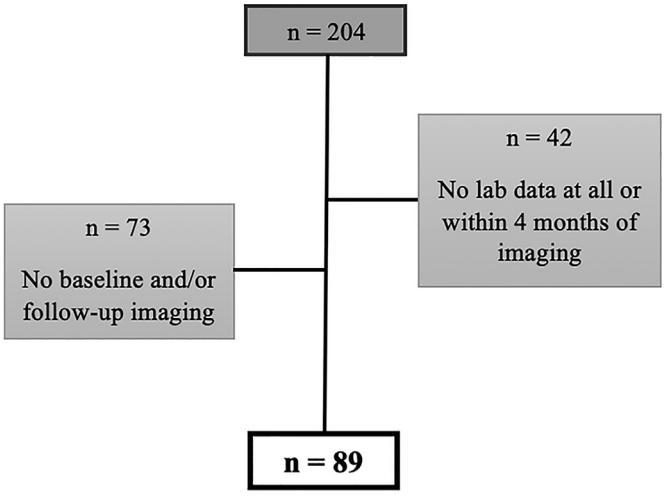

Figure 1 Flow chart of the inclusion and exclusion of the cases.

Mayo risk score = 0.0295 (*age* [years]) + 0.5373 LN (*total bilirubin* [mg/dl]) + 0.5380 LN (*AST* [U/l])–0.8389 (*albumin* [g/dl]) + 1.2426 (*variceal bleeding history* [0; if none, 1; if present])

wherein LN indicated the natural logarithm.

Imaging protocol

Magnetic resonance imaging (MRI) was performed using a 1.5 T MRI system (Siemens Avanto and GE Signa HDx) using a phased-array torso coil. The protocol included axial T2-weighted fat-saturated images (4–6 mm, 4,000–6,000 ms repetition time [TR], 90–100 ms echo time [TE]), and at least six thick slab (40–50 mm, 4,500 ms TR, 500–700 ms TE) heavily T2-weighted MRCP images obtained in the straight coronal plane. Breath-hold unenhanced and contrast-enhanced (0.1 mmol/kg intravenous gadopentetate; Magnevist; Bayer, Wayne, NJ, USA) T1-weighted three-dimensional fat-suppressed spoiled gradient-echo images (320–400 mm field of view, 192×160 matrix, 2.5 mm section thickness, 5.77 ms TR, 2.77 ms TE, 64 kHz bandwidth, 10° flip angle) in the arterial (20 seconds), portal venous (70 seconds), and delayed phase (3 minutes) were also obtained.

CT imaging was performed by using a multidetector CT system (Sensation 64-section, Siemens) with 120 kV(p), 250 mAs, 0.6 mm detector collimation, 0.75 mm section thickness, and 0.5 mm section interval. Arterial and portal venous phase images were obtained 25–30 and 60 seconds after the initiation of intravenous contrast material injection, respectively. The amount of 100–120 ml iodinated contrast (Visipaque 320 or Omnipaque 350, GE healthcare, Waukesha, WI, USA) was administered intravenously.

Volumetric assessment

Volumetric assessment was performed at two different time-points (baseline and follow up) for each case on MRI. Where MRI was unavailable, CT images were used instead (n=17). Measurements were performed using Advantage Workstation Volume Viewer Software (GE Healthcare, Milwaukee, WI, USA).

Measurements were performed by one observer with 2 years of experience (P. K.) during volumetric image analysis. This observer was blinded to the clinical information, scan time (baseline versus follow-up), and PSC disease severity. To assess inter- and intra-observer agreements in the volumetric measurements, 17 patients (11 with MRI and six with CT studies) were selected randomly from the severe PSC patients of this cohort. Then, one radiologist (I. K.) with 21 years of experience in volumetric image analysis measured the total and lobar liver volumes in these 17 PSC patients to assess the interobserver agreement. This radiologist was blinded to the measurements performed by the primary observer. The primary observer (P. K.) with 2 years of experience also measured the total and lobar liver volumes in these 17 PSC patients for a second time, 8 weeks after the first measurements, to minimise recall bias. These measurements were used to assess intra-observer agreement.

Portal venous phase images were used for volumetric measurements as they had high parenchymal enhancement and venous opacification. The total liver volume was measured by hand-tracing the liver outlines on axial images. Hand-tracing was not performed on all adjacent axial images. The frequency was determined by change in liver contour on axial images. Generally, hand-tracing was performed on every third image in the upper half of the liver, and every fifth image in the lower half. Automatic interpolation between the hand-traced images was allowed and corrections were made if necessary. Care was taken to exclude major vessels including the inferior vena cava and extrahepatic portal vein, in addition to major fissures such as the fissure for the ligamentum teres for measuring total liver volume. A three-dimensional model of the liver was created by the software using the hand-traced axial images. Right lobe volume was measured using the same hand-tracing technique along the Cantlie's line using the gallbladder fossa and the middle hepatic vein as anatomical landmarks. The portal vein and inferior vena cava were used as anatomical landmarks for caudate volumetry. Left lobe volume was calculated indirectly by subtracting the measured right liver lobe volume from total liver volume. The left lobe-to-total liver volume ratio (L/T), right lobe-to-total liver volume ratio (R/T), and caudate-to-total liver volume ratio (C/T) were calculated. Spleen volume was measured using the same method, if the spleen was present at baseline and follow-up (n=79).

Statistical analysis

IBM SPSS Statistics for Windows, version 22.0 (IBM, Armonk, NY, USA) was used for data analysis. The Lin concordance correlation coefficient (ρ_c) was used to assess the inter- and intra-observer agreement in volumetric measurements of the total and lobar liver volumes. The observers' volumetric measurements were also compared using the paired t-test or Wilcoxon signed rank test where applicable. The differences in biochemical and volumetric parameters between the baseline and follow-up studies were assessed using the paired t-test or Wilcoxon signed rank test where applicable. The changes in MELD score, Mayo risk score, total bilirubin, ALP, and volumetric parameters over time between patients with and without adverse outcome were compared using the Mann–Whitney U-test. Receiver operating characteristic (ROC) curve analyses were performed to identify the validity of the volume change in detection of outcome for volumetric parameters that showed significant differences. Kaplan–Meier analysis was performed for survival analysis. A p-value of <0.05 was considered statistically significant.

Results

Patient demographics

The present cohort included 36 (40.4%) females and 53 (59.6%) males with a mean age of 42 years at baseline (range 9–84 years) and 45 years at follow-up (range 14–85 years).

There was no significant difference in mean age between males and females ($p>0.05$). Table 1 provides demographic and clinical information of the study cohort. There was history of variceal bleeding in 14.6% ($n=13$) at baseline and 40.4% ($n=36$) at follow-up. MELD and Mayo risk scores were significantly higher at follow-up compared to baseline ($p<0.001$ for both; Table 2).

Inter- and intra-observer agreement for liver volume quantification

There was no statistically significant difference between the observers' measurements and both measurements of the main observer in volumetric quantification of the total liver, right liver lobe, and caudate ($p>0.05$ for all). Excellent interobserver and intra-observer agreement was observed for volumetric analysis of the total and lobar liver ($\rho_c>0.994$ for all). Table 3 provides the detailed measurements and agreement analysis results.

Liver and spleen volumetrics and laboratory values

Baseline and follow-up comparison

The detailed median values of the absolute volumes of the spleen, total liver, left liver lobe, right liver lobe, and caudate, and volume ratios including L/T and C/T at baseline and follow-up are summarised in Table 2. Spleen and caudate volume, L/T (Fig 2), and C/T were significantly increased at follow-up ($p<0.05$). Total liver volume, and right liver lobe volume were significantly smaller at follow-up (Fig 2). The baseline and follow-up laboratory values and volumetric parameters are provided and compared in Table 2. The median interval between imaging study and laboratory data was 9 days at baseline, and 6 days at follow-up (range 0–99 days, range 0–125 days, respectively). The median interval between baseline and follow-up imaging was 61 months (range 6–192 months).

Comparison based on outcome

Forty-two (47.2%) patients suffered an adverse outcome in the present cohort. Among these patients, 24 (57.2%) were transplanted, eight (19%) were on the transplant waiting list, and 10 (23.8%) were deceased by June 2018.

No gender difference was observed based on the occurrence of adverse outcome ($p=0.298$). Of all measured volumes and volume ratios, only L/T change and spleen volume change were significantly different between those who suffered an adverse outcome and those with no adverse outcome ($p=0.025$ and $p<0.001$, respectively). Detailed comparison of the volumetric measurements between patients with and without adverse outcome is provided in Table 4. Mayo risk score change and MELD score change were also significantly different based on adverse outcome ($p=0.016$ and $p<0.001$, respectively). Total bilirubin and ALP changes are summarised in Table 4.

Survival analysis based on change in spleen volume

Spleen volume change could predict outcome (liver transplant, liver transplant waiting list, or mortality) with accuracy of AUC=0.731 ($p<0.001$). Sensitivity and specificity of spleen volume change at a threshold of 50 ml was 68% and 73%, respectively.

The accuracy of Mayo risk score change was AUC=0.648 for detection of outcome with sensitivity of 62% and specificity of 62% at the level of 0.6 ($p=0.016$). MELD score change had an accuracy of AUC=0.717, with sensitivity of 71% and specificity of 63%, respectively, at a threshold of 0.50 ($p<0.001$).

Adverse outcomes were significantly ($p<0.001$) more common in PSC patients with spleen volume change $\geq$50 ml (36 patients with 24 adverse outcome, 66.6%) compared to PSC patients with spleen volume change <50 ml (43 patients with 11 adverse outcomes, 25.5%).

Table 1
Demographics and clinical data of the whole cohort.

Variable	Subcategories	Frequency (%) ($n=89$)	Without event (%) ($n=47$)	With event (%) ($n=42$)	p-Value
Age (year), mean±SD		47±17	45±17	49±17	0.258
BMI (kg/m^2), mean±SD		27.8±6.1	27.6±4.9	28.0±7.6	0.819
Gender	Male	53 (60)	27 (57)	26 (62)	0.829
	Female	36 (40)	20 (43)	16 (38)	
Race	Caucasian	61 (68)	35 (75)	26 (62)	0.167
	African American	23 (26)	10 (21)	13 (31)	
	Others	5 (6)	2 (4)	3 (7)	
IBD	Ulcerative colitis	42 (47)	19 (40)	23 (55)	0.076
	Crohn's disease	20 (23)	15 (32)	5 (12)	
	Colectomy	23 (26)	14 (30)	9 (21)	0.469
Immune-mediated overlap	Autoimmune hepatitis	6 (7)	2 (4)	4 (10)	0.415
	IgG4 disease	3 (3)	2 (4)	1 (2)	1.000
Complications	Variceal bleeding	13 (15)	8 (17)	5 (12)	0.559
	Cholangitis	11 (12)	5 (11)	6 (14)	0.750
	Pancreatitis	5 (6)	4 (9)	1 (2)	0.365
	Cholangiocarcinoma	5 (6)	0 (0)	5 (12)	0.020
Treatment	Beta blocker	26 (29)	7 (15)	19 (45)	0.002
	Ursodeoxycholic acid	53 (60)	24 (51)	29 (69)	0.129

BMI, body mass index; IBD, inflammatory bowel disease; IgG4, immunoglobulin G4.

Table 2
Laboratory data and detailed volume measurements in all patients at baseline and follow-up (n=89).

Variable		Baseline		Follow-up		p-Value
		Median	IQR	Median	IQR	
Biochemical Findings						
Total bilirubin (mg/dl)		0.9	0.5–2.2	1.4	0.6–4.9	<0.001
Serum albumin (g/dl)		3.9	3.3–4.3	3.8	3.0–4.3	0.050
AST (U/l)		62.0	38.0–107.5	56.0	27.5–125.5	0.842
ALT (U/l)		70.0	37.5–120.0	56.0	29.5–94.5	0.002
ALP (IU/l)		305.0	176.0–577.5	245.0	115.0–377.0	<0.001
Platelet (×1,000/μl)		243.0	166.0–353.0	204.0	104.5–259.0	<0.001
Creatinine (mg/dl)		0.70	0.68–0.88	0.80	0.65–0.80	0.072
INR		1.0	1.0–1.1	1.1	1.0–1.3	<0.001
Sodium (mEq/l)		140.0	138.0–141.0	139.0	137.0–141.0	0.278
Risk scores						
MELD score		7.00	6.00–11.00	9.00	6.00–14.00	<0.001
Mayo risk score		0.34	-0.56–1.87	1.29	-0.11–2.63	<0.001
Volumetric findings						
Absolute volume (ml)	Spleen (n=79)	359.9	231.4–658.6	402.8	217.2–764.9	0.002
	Total liver	1885.8	1474.6–2340.4	1810.1	1370.4–2401.8	0.016
	Left lobe	768.6	615.3–1100.8	799.3	620.3–1036.0	0.553
	Right lobe	1027.8	813.3–1348.7	934.4	680.6–1253.4	0.001
	Caudate	46.4	29.9–90.6	48.3	32.8–129.4	0.051
Volume ratio	Left lobe to total liver	0.42	0.36–0.53	0.48	0.36–0.57	0.003
	Caudate to total liver	0.025	0.01–0.04	0.027	0.02–0.05	0.002
Imaging and lab date interval (days)		9	1–48	6	0–40	0.203

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; INR, international normalised ratio.

Table 3
Inter- and intra-observer agreement analysis.

Variables	Observer 1 (mean±SD)	Observer 2 (mean±SD)	p-Value	ρ_c value	95% CI
Interobserver agreement					
Total liver volume (ml)	2210.7±752.0	2253.5±730.9	0.263	0.989	0.971–0.996
Right lobe volume (ml)	1024.2±544.8	1058.9±566.3	0.220	0.989	0.971–0.996
Caudate volume (ml)	217.2±245.4	218.5±235.2	0.843	0.997	0.992–0.999
Intra-observer agreement					
Total liver volume (ml)	2199.7±721.7	2253.5±730.9	0.051	0.994	0.980–0.998
Right lobe volume (ml)	1082.4±576.5	1058.9±566.3	0.112	0.997	0.992–0.999
Caudate volume (ml)	220.2±239.1	218.5±235.2	0.504	0.999	0.999–1.000

CI, confidence interval; ρ_c, Lin concordance correlation coefficient.

Patients with spleen volume change <50 ml had significantly longer transplant-free survival compared to PSC patients with spleen volume change ≥50 ml (p=0.002). Based on Kaplan–Meier analysis, the probability of transplant-free survival at 12, 24, and 36 months follow-up were 89.9%, 81.8%, and 59.1% for patients with spleen volume change <50 ml and 69.2%, 48.1%, and 11.9% for PSC patients with spleen volume change ≥50 ml (Fig 3).

Survival analysis based on change in L/T ratio

L/T change demonstrated an accuracy of AUC=0.638 for detection of outcome (liver transplant, liver transplant waiting list, or mortality; p=0.025). Sensitivity and specificity of L/T change at the level of 0.04 were 57% and 68%, respectively.

L/T change ≥0.04 was significantly more common in patients with adverse outcome as compared to patients without adverse outcome (p=0.02). Twenty-four of 42 patients with adverse outcome (57.1%) developed L/T change ≥0.04. In contrast, among 47 patients without adverse outcome, 15 patients (32%) developed L/T change <0.04.

Patients with L/T change <0.04 had significantly longer transplant-free survival compared to those with L/T change ≥0.04 (p=0.009). Kaplan–Meier analysis estimates for the probability of transplant-free survival at 12, 24, and 36 months follow-up were 64.8%, 61.3%, and 61.3% for patients with L/T change <0.04 and 48.5%, 27.5%, and 13.8% for patients with L/T change ≥0.04 (Fig 4).

Survival analysis based on change in L/T ratio and spleen volume

Out of 79 patients without splenectomy, 22 (27.8%) patients had both spleen volume change ≥50 ml and L/T volume change ≥0.04 (group 1). Twenty-nine (36.7%) patients had one of the spleen volume change ≥50 ml, or L/T volume change ≥0.04 (group 2). Twenty-eight (35.5%) patients had both spleen volume change <50 ml, and L/T volume change <0.04 (group 3).

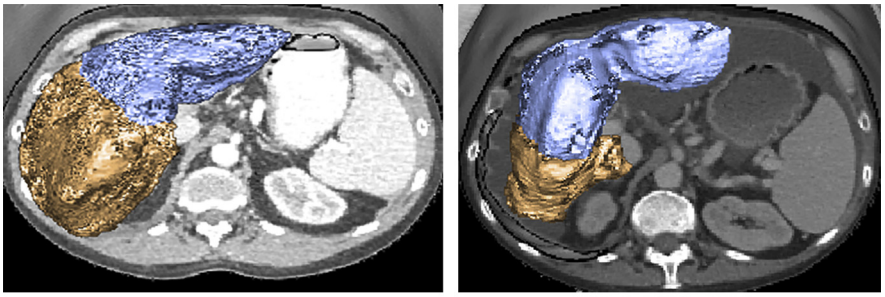

Figure 2 Three-dimensional reconstruction on CT of the liver of a male patient with PSC showing the morphological and volumetric lobar liver changes: (a) at the age of 37 years, with Mayo risk score of 0.65 (<2), MELD score of 10, total liver volume =1782 ml, right lobe (orange) volume =892 ml, left lobe (blue) volume =890 ml, and L/T ratio of 0.50; (b) at the age of 45 years, with Mayo risk score of 4.89 (>2), MELD score of 27, total liver volume =932 ml, right lobe (orange) volume =265 ml, left lobe (blue) volume =666 cc, and L/T ratio of 0.72.

Table 4
Demographics and laboratory data, risk scores, and detailed volume changes based on outcome (n=89).

Variable		Outcome negative (n=47)		Outcome positive (n=42)		p-Value
		Median	IQR	Median	IQR	
Demographics, risk scores, and laboratory results						
Age (year)		38.0	25.0–53.0	38.5	32.5–55.0	0.298
Gender (male/female)		27/20		26/16		0.829
MELD change		0.00	-2.00–2.00	3.00	-1.00–10.25	<0.001
Mayo risk score change		0.45	-0.19–1.16	1.03	0.11–2.04	0.016
Bilirubin change		0.10	-0.20–0.70	1.30	-0.20–6.82	0.006
ALP change		-41.00	-119.00-10-00	-92.00	-276.75–57.5	0.143
Volumetric Findings						
Volume change (ml)	Spleen (n=79)	-16.5	-45.0–71.7	129.0	24.0–534	<0.001
	Total liver	-108.7	-259.6–118.5	-112.6	-491.1–148.7	0.532
	Left lobe	3.9	-106.4–91.0	76.1	-102.8–243.8	0.165
	Right lobe	-0.50	-151.7–66.0	-138.5	-470.5–1.4	0.054
	Caudate	3.5	-3.5–10.2	2.2	-14.6–38.4	0.997
Volume ratio change	Left lobe to total liver	0.02	-0.02–0.06	0.06	-0.02–0.15	0.025
	Caudate to total liver	0.003	-0.001–0.009	0.003	-0.005–0.26	0.902

ALP, alkaline phosphatase; IQR, interquartile range.

Kaplan–Meier analysis estimates for the probability of transplant-free survival at 12, 24, and 36 months follow-up were 42%, 30%, and 15% in group 1; 62.9%, 36.7%, and 36.7% in group 2; and 76.8%, 76,8%, and 76.8% in group 3 (p=0.001; Fig 5).

Discussion

The present study demonstrated that liver and spleen volumetric changes correlate with clinical progression of PSC. Over time, L/T change and spleen volume change correlate with outcome and can predict transplant-free survival in PSC patients. L/T change at 0.04 and spleen volume change at 50 ml were cut-off points, below which PSC patients demonstrate significantly longer transplant-free survival.

Liver transplantation is the only available definite treatment option for patients with PSC. It is of upmost importance to assess progression of liver disease accurately in PSC patients for better timing of liver transplantation. Accurate assessment of disease progression and treatment response is also crucial for assessment of the clinical efficacy of new treatment options in clinical trials.

Prognostic models used for the assessment of PSC activity have been modified over time for different reasons. To exclude invasive and/or less objective variables from the original Mayo risk score, histological staging was removed

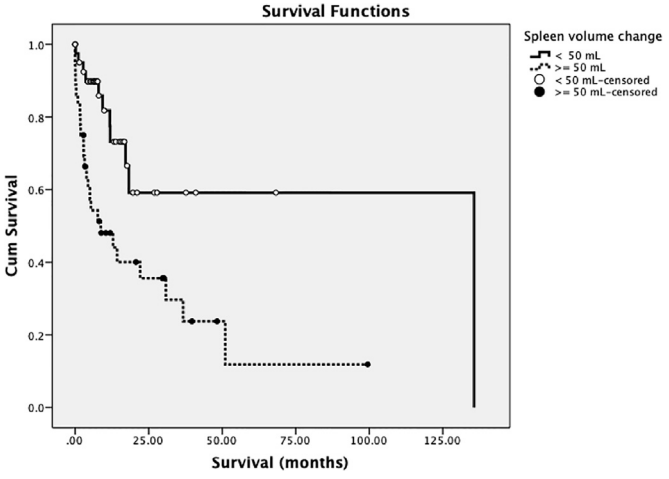

Figure 3 Kaplan–Meier curves demonstrating survival differences based on spleen volume change at 50 ml.

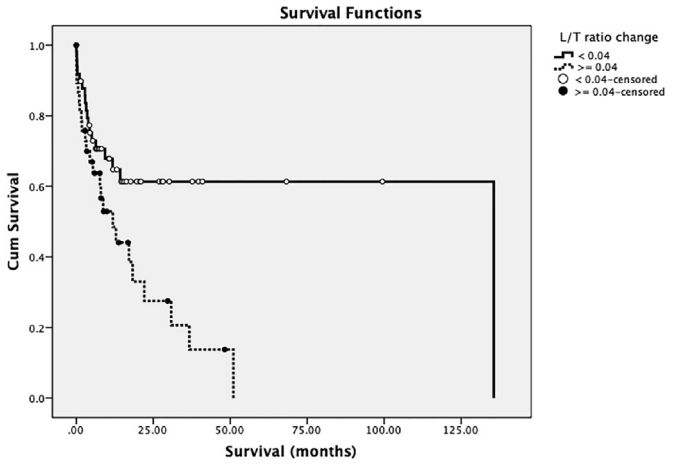

Figure 4 Kaplan–Meier curves demonstrating survival differences based on left lobe to total liver volume ratio change at 0.04.

in the modified Mayo risk score. This could decrease the potential risk of complications from liver biopsy and decrease errors in Mayo risk score calculation secondary to the variability of liver sampling.[11–14] Use of invasive ERCP to assess the cholangiographic classification of intra- and extrahepatic biliary duct lesions also limited the clinical usage of the Amsterdam score[15]; however, laboratory-based prognostic models are prone to significant error in risk stratification secondary to fluctuations in liver biomarkers in the course of PSC. After a comprehensive review of the literature on all biomedical, imaging, and genetic biomarkers for disease progression of primary sclerosing cholangitis, De Vries *et al.* concluded that there is a strong need for development of novel non-invasive and truthful biomarkers for assessing progression of PSC.[4]

Attempts have been made to introduce more robust prognostic models, which are less dependent on fluctuating laboratory variables. Liver or spleen volume has been used in two models assessing PSC severity. In the model presented by Farrant *et al.*[12] splenomegaly and hepatomegaly were used and in the model presented by Dickson *et al.*[13] splenomegaly was included; however, volumetric assessment in those studies were subjective and therefore difficult to standardise. In a recently published report on PSC patients, the authors showed that quantitative liver and spleen volumes correlate with the severity of PSC. They found that L/T is the best quantifiable volumetric biomarker to correlate with disease severity in patients with PSC.[10] The authors did not report correlation of liver or spleen volumetry with outcome. They also did not assess whether over time change in liver or spleen volumetry correlates with disease progression and outcome.

It has been shown that L/T is the best volumetric ratio and spleen volume is the best absolute volume for assessment of disease severity in PSC patients.[10] In the present study, the L/T change and spleen volume change showed the best correlation with disease severity and outcome. The L/T change at 0.04 and spleen volume change at 50 ml predicted outcome with comparable accuracy, sensitivity, and specificity as Mayo risk score and MELD score. Patients with L/T change $\geq$0.04 or spleen volume change $\geq$50 ml had significantly lower liver transplant-free survival probability at 36 months follow-up.

The present study has some limitations including the limitations of a single-centre retrospective study. This study included a fairly large cohort of PSC patients with available laboratory and imaging follow-up. A single reader performed all volumetric measurement. Inter-reader agreement was measured on a subset of 15 cases not included in this cohort. Another limitation of this study is use of both CT and MRI studies for volumetry. Both modalities has shown to provide acceptable reproducibility in liver volumetric measurements.[16–20] The present results may need to be validated by studies with larger sample size.

In conclusion, disease progression correlated with spleen volume and L/T change on long-term follow-up of PSC patients. L/T change and spleen volume change could predict

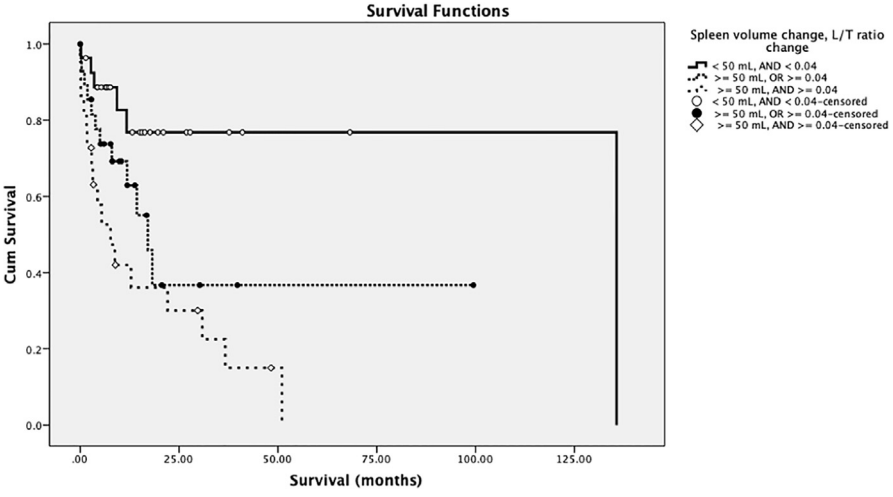

Figure 5 Kaplan–Meier curves demonstrating survival differences based on spleen volume change at 50 ml and left lobe to total liver volume ratio change at 0.04.

outcome with comparable validity to the Mayo risk score and MELD score. L/T change and spleen volume change could also predict liver transplant-free survival in PSC patients.

Conflicts of interest

Authors have no conflict of interest.

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