Detection of significant liver fibrosis in Chinese psoriasis patients receiving methotrexate: a comparison between transient elastography and liver histology

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ABSTRACT

Introduction: Methotrexate (MTX) is effective for treating psoriasis and psoriatic arthritis, but its potential hepatoxicity remains a concern. Liver biopsy, the gold standard for detecting MTX-induced liver injury, is invasive and carries considerable risk. Transient elastography (TE) offers a non-invasive alternative for detecting advanced liver fibrosis. This study investigated the performance of TE in detecting MTX-induced liver fibrosis among Chinese psoriasis patients, compared with liver biopsy.

Methods: This study included adult patients with clinical psoriasis. Liver stiffness measurement using TE was performed in patients receiving MTX. Exclusion criteria were known liver cirrhosis, positive viral hepatitis carrier status, or conditions influencing TE performance. Liver biopsy was performed when liver stiffness was ≥7.1 kilopascals (kPa) or when the total cumulative dose (TCD) of MTX was ≥3.5 g.

Results: A total of 228 patients were screened; among 34 patients who met the inclusion criteria, nine (26.5%) had significant liver fibrosis (Roenigk grade ≥3a). The area under the receiver operating characteristic curve was 0.76 (95% confidence interval=0.59-0.93; P=0.021), indicating that TE had satisfactory performance in detecting liver fibrosis. A cut-off value of 7.1 kPa of liver stiffness yielded 100% sensitivity and 68% specificity. Liver fibrosis was not correlated with the TCD of MTX or the duration of MTX use; it was significantly correlated with obesity and diabetes status (body mass index ≥30 kg/m^2, waist circumference ≥138 cm, and glycated haemoglobin level ≥7.8%).

Conclusion: Transient elastography is reliable and superior to the TCD for detecting liver fibrosis in Chinese psoriasis patients receiving MTX. Liver biopsy should be reserved for high-risk patients or patients with liver stiffness ≥11.7 kPa on TE.

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New knowledge added by this study

- Transient elastography (TE) exhibits satisfactory performance in the detection of methotrexate (MTX)-induced liver fibrosis among Chinese psoriasis patients receiving MTX.
- Although current guidelines state that liver biopsy should be considered if the total cumulative dose of MTX is ≥3.5 g, it is shown that the dose was not correlated with the degree of liver fibrosis in Chinese psoriasis patients. Importantly, liver stiffness (LS) measurement by TE is a more appropriate method for monitoring MTX-induced liver fibrosis.
- Chinese patients with obesity who exhibit a high body mass index and large abdominal circumference have a higher risk of liver fibrosis and should be closely monitored when receiving MTX.

Implications for clinical practice or policy

- Transient elastography can be used to monitor MTX-induced liver fibrosis, whereas liver biopsy should be reserved for high-risk psoriasis patients.
- Yearly TE monitoring is recommended for patients with LS ≥7.1 kilopascals (kPa), while liver biopsy should be considered for patients with LS ≥11.7 kPa.

接受甲氨蝶呤治療的華人銀屑病患者顯著肝纖維化的檢測：瞬時彈性成像與肝臟組織學的比較

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引言：甲氨蝶呤有效治療銀屑病和銀屑病關節炎，但其潛在的肝毒性仍令人擔憂。雖然肝臟活組織檢查是檢測甲氨蝶呤引起的肝損傷的黃金標準，但它是侵入性的，存在相當大的風險。瞬時彈性成像為檢測晚期肝纖維化提供了非侵入性替代方案。本研究調查了瞬時彈性成像在檢測華人銀屑病患者中甲氨蝶呤誘導的肝纖維化方面的表現，並與肝臟活組織檢查比較。

方法：這項研究針對臨床中診斷為銀屑病的成年患者，通過使用瞬時彈性成像技術對接受甲氨蝶呤治療的患者進行肝硬度測量。排除標準包括已知的肝硬化、病毒性肝炎患者或影響瞬時彈性成像測試的各種情況。當肝硬度≥7.1千帕或甲氨蝶呤總累積劑量≥3.5克時，會進行肝臟活組織檢查。

結果：這項研究共篩檢了228名患者；34名患者符合納入標準，其中9名（26.5%）有明顯肝纖維化（Roenigk分級≥3a）。肝硬度的曲線下面積為0.76（95%置信區間=0.59-0.93；P=0.021），顯示瞬時彈性成像在檢測肝纖維化方面具有令人滿意的表現。以7.1千帕作肝硬度臨界值，瞬時彈性成像檢測方法的敏感性為100%，特異性為68%。本研究發現肝纖維化與甲氨蝶呤總累積劑量或甲氨蝶呤治療持續時間不相關，但與肥胖和糖尿病狀況（體重指數≥30 kg/m²、腰圍≥138厘米、糖化血紅素水平≥7.8%）有顯著關聯。

結論：瞬時彈性成像對於檢測使用甲氨蝶呤治療銀屑病的華人患者的肝纖維化情況來說是可靠的，並且優於以總累積劑量作為評估指標。我們建議高風險患者或在瞬時彈性成像檢查中肝硬度數值>11.7千帕的患者才進行肝臟活組織檢查。

Introduction

Methotrexate (MTX) is an effective immunosuppressive drug for moderate to severe psoriasis and psoriatic arthritis.[1,2] It is considered relatively safe and cost-effective for long-term use. However, prolonged used of MTX can potentially cause liver fibrosis and fatty changes without alterations in liver enzymes. The mechanism of MTX-induced liver fibrosis is suspected to involve the production of extracellular adenosine, a pro-fibrotic agent.[3]

Although liver fibrosis can be evaluated by imaging or biochemical parameters, liver biopsy remains the gold standard for diagnosing liver fibrosis.[4] However, it has limitations such as sampling error and poor feasibility for serial assessments. The rates of liver biopsy–associated morbidity and mortality are approximately 1% and 0.01% to 0.1%, respectively.[5,6] The Roenigk scale is generally used to grade MTX-induced liver fibrosis,[7] but other systems (eg, Ishak and METAVIR) have also been used for fibrosis assessment.[8,9]

The measurement of serum level of specific biomarkers such as the amino terminal of type III procollagen peptide can be used as alternative methods to assess liver fibrosis.[10-13] However, these measurements are not widely available in many regions. Therefore, a sensitive and specific non-invasive technique is required to detect MTX-induced liver injury.

Transient elastography (TE) is a non-invasive method for assessing liver 'hardness' or stiffness that involves measuring the velocity of a vibration wave (ie, a shear wave) when travelling to a particular depth inside the liver, based on the principle that the wave velocity is greater in fibrotic tissue than in normal liver tissue. This technique has been used as a screening tool for liver cirrhosis in various conditions.[14-17] In contrast to liver biopsy, TE allows the simultaneous assessment of a larger sampling area, is easily reproducible, and has low inter-observer variability and a low failure rate (<5%).[15] Generally, a liver stiffness (LS) of ≤5 kilopascals (kPa) suggests a low probability of fibrosis, whereas a value of ≥7 kPa suggests a high likelihood of advanced fibrosis in patients with various chronic liver disorders.[14-18] Thus far, there are limited data regarding TE accuracy and cut-off threshold in terms of detecting MTX-induced liver injury among Chinese psoriasis patients.

This study aimed to evaluate the performance (reliability) of TE in detecting significant liver fibrosis among psoriasis patients in the Chinese population, compared with gold-standard liver biopsy assessment using the Roenigk classification.

Methods

This cross-sectional single-centre study was conducted from 1 December 2019 to 31 March 2021. Patients with psoriasis and/or psoriatic arthritis undergoing regular follow-up in the dermatological clinic at a major tertiary hospital in Hong Kong were consecutively screened for inclusion (Fig 1). The inclusion criteria were as follows: age ≥18 years, clinical diagnosis of psoriasis with or without arthritis, and current use of MTX with a cumulative dosage of ≥150 mg or minimum duration of 6 months. Patients were excluded if they had known liver cirrhosis or concomitant chronic liver disease (including chronic hepatitis B or C infection, alcohol use disorder, Wilson's disease, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, and a history of hepatocellular carcinoma), had a condition that could influence TE accuracy (eg, ascites, severe renal disease, peritoneal dialysis, or severe cardiovascular insufficiency),[14-18] refused to give consent, were pregnant, or had not been receiving MTX. After the acquisition of informed consent, all participants provided a thorough history and underwent a comprehensive examination.

Clinical and laboratory data

Upon recruitment, clinical and metabolic

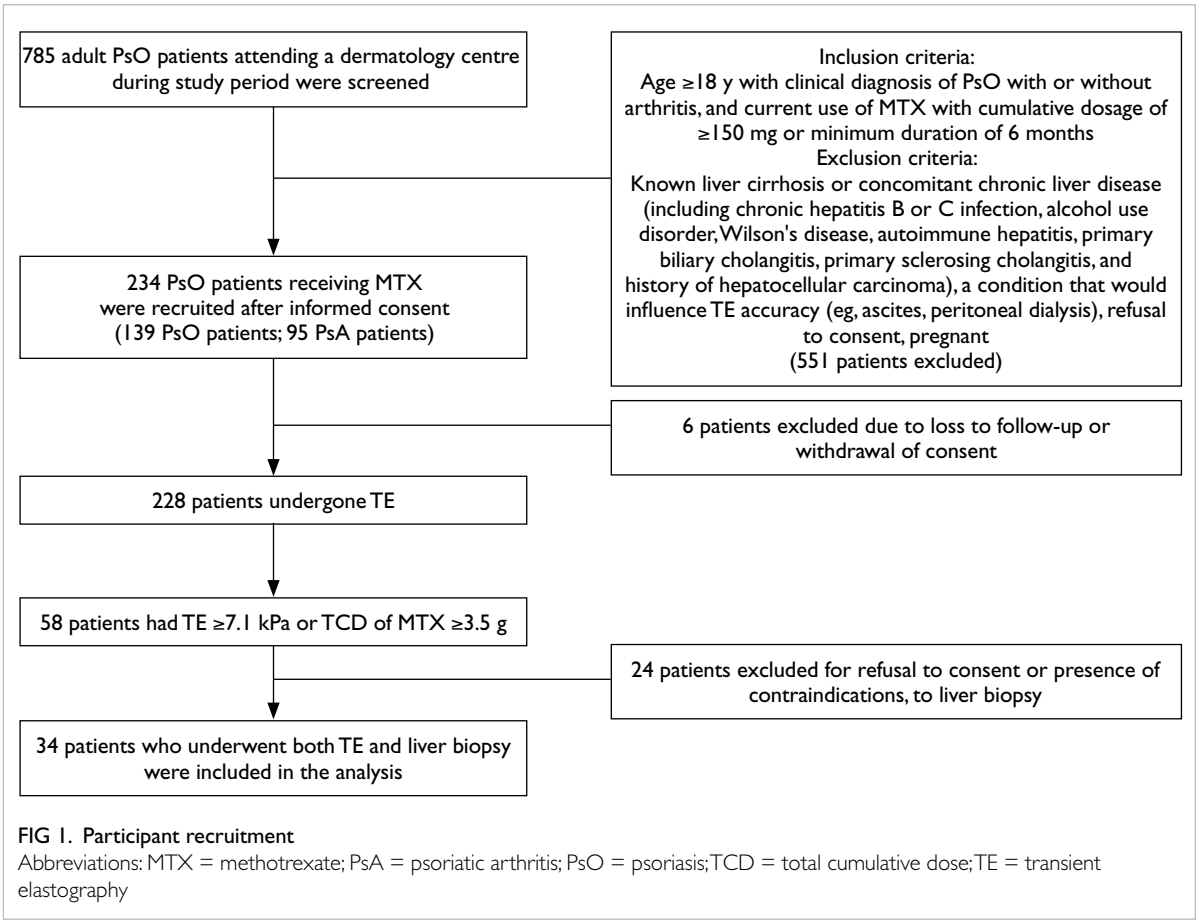

FIG 1. Participant recruitment
Abbreviations: MTX = methotrexate; PsA = psoriatic arthritis; PsO = psoriasis; TCD = total cumulative dose; TE = transient elastography

measurements, including body weight, body mass index (BMI), systolic and diastolic blood pressure, and waist circumference, were recorded. The duration and cumulative dosage of MTX treatment, disease severity (measured by the Psoriasis Area and Severity Index), and body surface area (BSA) were documented. Laboratory parameters assessed included hepatitis B/C infection status, complete blood count, serum fasting glucose level, glycated haemoglobin (HbA1c) level, triglyceride level, low- and high-density lipoprotein cholesterol levels, liver enzyme levels (eg, aspartate aminotransferase and alanine aminotransferase), and renal function. Patient demographic data, co-morbidities (hypertension, diabetes, cardiovascular disease, chronic liver/renal disease, and alcoholic liver disease), and concomitant medications were collected from electronic medical records.

Liver stiffness measurement by transient elastography

Transient elastography assessments were conducted within 1 month after recruitment. Liver stiffness was evaluated using the FibroScan ultrasonic imaging device (Echosens, Paris, France) and expressed as the median value (in kPa) after at least 10 successful acquisitions. Measurements were considered reliable if the success rate was ≥60%, combined with an interquartile range (IQR) of ≤30%.[15,16] For patients with a BMI of <30 kg/m^2, an M probe was used; for those with a BMI of ≥30 kg/m^2, an XL probe was used. The controlled attenuation parameter (CAP) was also recorded to estimate liver steatosis, expressed in decibels per metre (dB/m).[16] The investigators (senior research assistants trained to perform TE) were blinded to the patients' clinical characteristics, MTX dosage, and previous liver ultrasound or biopsy results. Patients were instructed to fast for 4 hours prior to LS measurements. In previous studies involving Asian populations, significant liver fibrosis or cirrhosis was indicated by LS values of ≥7.1 kPa[19] and >14.0 kPa,[20] respectively. Therefore, in our study, significant liver fibrosis on TE was defined as LS ≥7.1 kPa.

Liver biopsy

A liver biopsy (to assess the degree of liver fibrosis by histology) was performed within 3 months after TE in patients who had significant liver fibrosis (ie, LS ≥7.1 kPa on TE) or a total cumulative dose (TCD) of MTX ≥3.5 g, with or without additional risk factors. This protocol was adopted based on international guidelines[1,2,18-22] and previous studies in Asian populations.[21,22] Ultrasound-guided core-

needle liver biopsy procedures were performed by an experienced radiologist using a percutaneous approach.[5,6]

Histological assessments were conducted by a pathologist with expertise in hepatobiliary disorders, who was blinded to the TE results. The Roenigk scale was used to grade liver fibrosis/cirrhosis, defined as grade 1 (no fibrosis, no or mild fatty infiltration, no or mild nuclear variability, and no or mild portal inflammation), grade 2 (no fibrosis, but moderate to severe fatty infiltration, nuclear pleomorphism, and portal inflammation), grade 3a (mild fibrosis, moderate to severe fatty infiltration, portal tract enlargement, and lobular necrosis), grade 3b (moderate to severe fibrosis), and grade 4 (cirrhosis).[7] For patients with MTX-induced liver injury (Roenigk grade 3a), MTX could be continued, with follow-up liver biopsy repeated in 6 months. For those with significant liver fibrosis or cirrhosis (Roenigk grades 3b or 4), MTX was discontinued and alternative treatment was initiated.[2]

Data analysis and statistics

For statistical analysis, continuous variables were expressed as median (range or IQR, as specified) or mean (± standard deviation) values, as appropriate. Receiver operating characteristic (ROC) curves were used to determine the predictive ability of TE-based LS relative to histopathology (Roenigk grade ≥3a), with 95% confidence intervals (CIs). Correlations between two variables were calculated using Pearson or Spearman rank correlation coefficients. The Chi squared test or Fisher's exact test was used for comparisons of categorical variables, as appropriate. Quantitative variables were subjected to normality assessment via the Shapiro–Wilk test; non–normally distributed variables were compared between groups using the Wilcoxon rank-sum test. Statistical analyses were conducted using SPSS software (Windows version 26.0; IBM Corp, Armonk [NY], United States). P values <0.05 were considered statistically significant.

Results

Baseline characteristics

In total, 785 psoriasis patients were recruited into the study; 234 fulfilled the screening criteria and were included in the analysis. Six patients subsequently withdrew their consent (Fig 1).

Among 228 patients who underwent TE evaluation, 140 were diagnosed with psoriasis and 88 were diagnosed with psoriatic arthritis (Table 1). Fifty-eight patients, who either had LS ≥7.1 kPa or received a TCD of MTX ≥3.5 g, were advised to undergo liver biopsy; 24 patients who refused or had contraindications to liver biopsy were excluded from the study (Fig 1). Thus, 34 patients (24 fulfilling

TABLE 1. Demographic and clinical characteristics of patients who underwent transient elastography and those who underwent liver biopsy assessments*

	Patients with TE (n=228)	Patients with liver biopsy (n=34)
Age, y [mean ± SD (range)]	56.0 ± 19.0 (18-85)	50.8 ± 12.3
Male sex	140 (61.4%)	22 (64.7%)
Chinese ethnicity	228 (100%)	34 (100%)
Diagnosis and co-morbidities		
Psoriatic arthritis	88 (38.6%)	16 (47.1%)
Psoriasis without arthritis	140 (61.4%)	18 (52.9%)
Hypertension	102 (44.7%)	23 (67.6%)
Diabetes mellitus	64 (28.1%)	21 (61.8%)
Dyslipidaemia	79 (34.6%)	13 (38.2%)
Measurements†		
Aspartate aminotransferase, U/L	28.9 ± 16.0	32.3 ± 15.5
Alanine aminotransferase, U/L	31.1 ± 27.1	43.4 ± 23.0
Creatinine, μmol/L	97.1 ± 20.1	79.3 ± 19.3
eGFR, mL/min	77.0 ± 19.1	82.8 ± 11.5
Fasting glucose, mmol/L	5.82 ± 1.87	6.35 ± 2.40
HbA1c, %	5.96 ± 0.94	6.29 ± 1.31
≥6.5	42 (18.4%)	13 (38.2%)
>5.6-6.4	98 (43.0%)	8 (23.5%)
Cholesterol, mmol/L	4.53 ± 1.00	4.67 ± 0.90
HDL cholesterol, mmol/L	1.41 ± 0.53	1.29 ± 0.31
LDL cholesterol, mmol/L	2.52 ± 0.87	2.58 ± 0.77
Triglyceride, mmol/L	1.43 ± 0.88	1.77 ± 1.21
BMI, kg/m^2	25.7 ± 5.5	29.73 ± 6.01
<18.5 (underweight)	12 (5.3%)	0
18.5-24.9 (normal)	95 (41.7%)	8 (23.5%)
25-29.9 (overweight)	78 (34.2%)	11 (32.4%)
≥30 (obese)	43 (18.9%)	15 (44.1%)
Body weight, kg	69.5 ± 18.9	82.9 ± 19.9
Waist circumference, cm	92.0 ± 15.0	104.5 ± 21.91
Waist circumference >102 cm (men) or >89 cm (women)		18 (52.9%)
Disease activity		
PASI score	8.13 ± 6.35	10.9 ± 9.20
BSA, %	12.3 ± 10.5	10.1 ± 6.91
Methotrexate use [median (range)]		
Total cumulative dose, g	1.44 (0.5-17.2)	3.58 (0.15-12.7)
Duration, y	3.46 (0.5-21.9)	9.33 (0.5-21.6)
TE [median (interquartile range)]		
Liver stiffness, kPa‡	6.91 (4.5-7.1)	8.80 (7.1-12.4)
Steatosis (CAP), dB/m§	263.5 (214-310)	321.0 (262-357)
Liver stiffness ≥7.1 kPa	58 (25.4%)	24 (70.6%)
CAP ≥268 dB/m	92 (40.4%)	24 (70.6%)
Liver histology, Roenigk grade		
1	N/A	11 (32.4%)
2	N/A	14 (41.2%)
≥3a	N/A	9 (26.5%)

Abbreviations: BMI = body mass index; BSA = body surface area; CAP = controlled attenuation parameter; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N/A = not applicable; PASI = Psoriasis Area and Severity Index; SD = standard deviation; TE = transient elastography

* Data are shown as No. (%) and mean ± SD, unless otherwise specified

† Metabolic syndrome (3 of 5 criteria): (1) elevated fasting blood glucose (≥5.6 mmol/L); (2) reduced HDL cholesterol level (men: <1.04 mmol/L; women: <1.3 mmol/L); (3) high triglyceride level (≥1.7 mmol/L or 150 mg/L); (4) waist circumference (men: >102 cm; women: >89 cm); (5) high blood pressure (≥130/85 mm Hg) [no data]

‡ Liver stiffness[17,18]: F0-1 = absent/mild (<7.1 kPa); F2-3 = moderate to severe (≥7.1 to 14 kPa); F4 = advanced liver scarring/cirrhosis (≥14.1 kPa)

§ Liver steatosis according to CAP values[16]: mild = ≥248 to 267 dB/m; moderate to severe = ≥268 dB/m

the TE criteria and 15 fulfilling the TCD criteria of MTX) who had undergone both TE and liver biopsies were included in further analyses. The clinical and demographic details of the study participants are summarised in Table 1.

Among the 34 patients, the median values of LS and CAP were 8.80 kPa (IQR, 7.1-12.4; range, 3.5-30.4) and 321.0 dB/m (IQR, 262-357; range, 200-400), respectively. Furthermore, 24 patients (70.6%) had a high LS value (ie, ≥7.1 kPa, indicative of significant fibrosis); 24 patients (70.6%) had a CAP value of ≥268 dB/m, indicative of moderate to severe steatosis.

Histology evaluation revealed liver fibrosis in nine of 34 (26.5%) patients: six had Roenigk grade 3a, three had Roenigk grade 3b, and none had Roenigk grade 4 (cirrhosis).

Correlations of liver stiffness with clinical and laboratory parameters

Liver stiffness measurements via TE showed moderate correlations with BMI (r=0.441; P=0.009), waist circumference (r=0.437; P=0.01), and body weight (r=0.456; P=0.007); there were no correlations with the TCD of MTX or duration of MTX use (Table 2).

Patients with LS ≥7.1 kPa had a higher BMI (P=0.01), body weight (P=0.01), and waist circumference (P=0.03). They also exhibited greater disease severity with a higher Psoriasis Area and Severity Index score (P=0.02) and more extensive BSA involvement (P=0.03). Furthermore, patients with LS ≥7.1 kPa had higher fasting glucose (P=0.03) and HbA1c levels (P=0.02), but they did not show significant differences in serum lipid levels (Table 3).

In terms of histology findings, patients with a Roenigk grade ≥3a had significantly greater BMI (P=0.01), waist circumference (P=0.04), BSA (P=0.04), and HbA1c values (P=0.03), compared with those who exhibited lower stages of histological fibrosis. Notably, there were no significant differences in the TCD of MTX, lipid profiles, or liver and renal biochemistries between the two groups. Patients with Roenigk grade ≥3a (LS: 11.7 kPa; range, 7.8-15.7) had higher LS values than those with Roenigk grade <3a (LS: 8.6 kPa; range, 5.9-11) [P=0.018] (Table 3).

TABLE 2. Correlation of liver stiffness values with clinical and laboratory parameters (n=34)

	TE-based LS (Pearson correlation)	P value
BMI	0.441	0.009
Body weight	0.456	0.007
Waist circumference	0.437	0.01
TCD of MTX	0.202	0.25
Duration of MTX use	0.004	0.98
HbA1c level	0.310	0.08
Fasting glucose	0.281	0.11

Abbreviations: BMI = body mass index; HbA1c = glycated haemoglobin; LS = liver stiffness; MTX = methotrexate; TCD = total cumulative dose; TE = transient elastography

Performance characteristics of transient elastography for diagnosing significant/advanced liver fibrosis

Comparison of TE-based LS values (in kPa) with histopathology revealed an area under the ROC curve of 0.76 (95% CI=0.59-0.93; P=0.021) [Fig 2], which demonstrated the satisfactory performance of TE in detecting significant liver fibrosis. An LS cut-off value of 7.1 kPa yielded 100% sensitivity and 68% specificity for diagnosing Roenigk grade ≥3a.

In a subgroup analysis of patients with LS ≥7.1 kPa, excluding patients who only met the TCD criteria of MTX (n=24), the area under the ROC curve with reference to Roenigk grade ≥3a was 0.702 (95% CI=0.47-0.94); an LS cut-off value of 10.7 kPa yielded 86% sensitivity and 59% specificity. In contrast, when ROC analysis was focused on the subgroup of patients with a TCD of MTX ≥3.5 g (n=14, excluding patients who only met the TE criteria), the area under the ROC curve was 0.622 (95% CI=0.31-0.94); an LS cut-off value of 8.2 g yielded 60% sensitivity and 67% specificity.

Discussion

Use of transient elastography to monitor liver fibrosis in psoriasis patients receiving methotrexate

International guidelines recommend using TE for routine monitoring of MTX therapy.[2,4] According to the Australasian position statement, TE monitoring is recommended every 3 years if initial LS is <7.5 kPa and yearly if LS is ≥7.5 kPa; liver biopsy is recommended if LS is >9.5 kPa.[23]

Currently, there is no guideline for monitoring MTX-induced liver fibrosis among Chinese psoriasis patients in Hong Kong. On the basis of previous studies,[2,4,23] the present study utilised a modified approach that reflects our department's routine practice of conducting liver biopsy for patients who have TE-based LS ≥7.1 kPa or a TCD of MTX ≥3.5 g, with or without abnormal liver biochemistry.

Our study confirmed the robust performance of TE in detecting significant liver fibrosis among Chinese psoriasis patients receiving MTX; the LS cut-off value of 7.1 kPa yielded 100% sensitivity and 68% specificity. These findings are consistent with a recent review and studies in other countries (Table 4).[7,19,20] According to these published data, TE demonstrated fair to good performance in detecting

TABLE 3. Comparison of psoriasis patients with and without liver fibrosis according to transient elastography and liver histology (n=34)*

	Liver stiffness, kPa			Liver histology, Roenigk grade		
	≥7.1 (n=24)	<7.1 (n=10)	P value	≥3a (n=9)	<3a (n=25)	P value
BMI, kg/m²	31.5 ± 6.17	25.4 ± 2.41	0.01	33.5 ± 0.68	29.4 ± 6.18	0.01
Body weight, kg	88.4 ± 20.7	69.8 ± 11.6	0.01	80.5 ± 26.1	83.6 ± 25.9	0.57
Waist circumference, cm	109.6 ± 24.1	92.2 ± 6.26	0.03	138.0 ± 52.0	101.2 ± 14.9	0.04
PASI score	13.5 ± 11.4	4.71 ± 3.73	0.02	11.5 ± 10.7	6.55 ± 4.17	0.29
BSA, %	27.01 ± 19.4	6.10 ± 3.98	0.03	22.4 ± 17.1	6.00 ± 5.65	0.04
Fasting glucose, mmol/L	6.71 ± 2.74	5.50 ± 1.15	0.03	7.60 ± 1.40	6.23 ± 2.49	0.22
HbA1c, %	6.53 ± 1.45	5.72 ± 0.64	0.02	7.86 ± 2.02	6.15 ± 1.16	0.03
Cholesterol, mmol/L	4.74 ± 0.91	4.50 ± 0.90	0.76	4.43 ± 0.97	4.69 ± 0.91	0.63
HDL cholesterol, mmol/L	1.27 ± 0.33	1.34 ± 0.23	0.12	1.23 ± 0.21	1.20 ± 0.32	0.29
LDL cholesterol, mmol/L	2.25 ± 0.29	2.24 ± 0.69	0.48	2.43 ± 0.61	2.01 ± 0.84	0.97
Triglyceride, mmol/L	1.81 ± 0.99	1.68 ± 1.00	0.22	1.30 ± 0.46	1.81 ± 1.26	0.31
Aspartate aminotransferase, U/L	35.7 ± 16.7	24.1 ± 7.41	0.03	43.0 ± 11.3	31.3 ± 15.6	0.20
Alanine aminotransferase, U/L	52.2 ± 37.2	25.4 ± 10.6	0.02	50.0 ± 31.5	43.8 ± 34.6	0.77
Creatinine, μmol/L	80.5 ± 19.3	76.4 ± 21.4	0.85	84.3 ± 5.85	78.8 ± 20.6	0.30
eGFR, mL/min	82.3 ± 12.0	83.9 ± 11.0	0.52	79.3 ± 10.1	83.1 ± 11.8	0.58
TCD of MTX, g	3.21 ± 0.92	5.56 ± 0.89	0.08	5.23 ± 3.58	4.79 ± 3.87	0.47
Duration of MTX use, y	5.99 ± 1.49	11.7 ± 2.13	0.06	7.42 ± 4.75	9.15 ± 7.65	0.16
Liver stiffness, kPa				13.3 ± 7.90	8.5 ± 4.70	0.018
Median (interquartile range)	N/A	N/A	N/A	11.7 (7.8-15.7)	8.6 (5.9-11)	
CAP, dB/m	321 ± 57.5	284 ± 57.4	0.11	311.6 ± 55.3	310.5 ± 60.3	0.59

Abbreviations: BMI = body mass index; BSA = body surface area; CAP = controlled attenuation parameter; eGFR = estimated glomerular filtration rate; HbA1c = glycated haemoglobin; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MTX = methotrexate; N/A = not applicable; PASI = Psoriasis Area and Severity Index; TCD = total cumulative dose

* Data are shown as mean ± standard deviation, unless otherwise specified

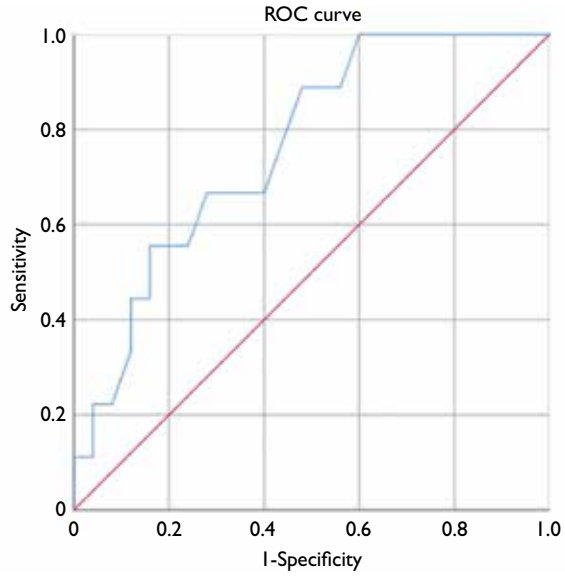

FIG 2. Performance of transient elastography as reflected by area under the receiver operating characteristic (ROC) curve comparing liver fibrosis detection between liver stiffness measurement (in kilopascals) and liver biopsy (Roenigk grade ≥3a)*

* Diagonal segments are produced by ties

liver fibrosis, with high negative predictive values (NPVs) [83% to 96%] but generally low positive predictive values (PPVs),[19-24] which might be explained by the overall low prevalence of significant liver fibrosis in this population and the higher rate of TE failure among patients with obesity. Obesity might also influence diagnostic performance; a recent review noted that obesity could substantially reduce TE accuracy.[19] Lee et al[25] showed that, compared with control participants, independent risk factors for liver fibrosis included diabetes mellitus (odds ratio [OR]=30.4), obesity with high BMI (OR=8.3), and overweight (OR=6.3). Our results supported previous observations that TE-based LS measurements were not correlated with the TCD of MTX, although they were associated with BMI, diabetes mellitus, and obesity.[19,24] Rongngern et al[19] analysed 41 Asian psoriasis patients receiving MTX; they demonstrated that TE had good performance in detecting MTX-induced liver injury, with an area under the ROC curve of 0.78.[19]

In this same study,[19] using an LS cut-off value of 7.1 kPa, for detecting MTX-induced liver injury, defined as Roenigk grade ≥3a, TE provided

TABLE 4. Comparison of studies about the diagnostic performance of transient elastography in detecting methotrexate-induced liver fibrosis among psoriasis patients, compared with liver histology

	Current study	Rongngern et al[19]	Khandpur et al[20]	Berends et al[7]
Ethnicity	Chinese	Asian	Indian	Caucasian
Study design	Prospective	Retrospective	Prospective	Retrospective
No. of patients	34	41	19*	24
TE-based LS, kPa [median (range)]	8.8 (3.5-30.4)	5.8 (3.4-11.8)	5.3 (2.7-17.8)	6.4 (3.3-18.4)
AUROC curve of TE (95% CI)				
LS	0.76 (0.59-0.93)	0.78 (0.63-0.93)	0.41 (0.16-0.80)[a]	N/A
CAP	0.78 (0.61-0.95)	NA	0.70 (0.45-0.94)†	N/A
Cut-off value				
LS, kPa	7.1	7.1	7.1	7.1
CAP, dB/m	254	N/A	203	N/A
Sensitivity	100%‡	50%[b,c]	80%†	50%[b]
Specificity	68%‡	76.9%[b] to 83.9%[c]	55%†	88%[b]
PPV	26.7%	10%[b] to 50%[c]	N/A	33%
NPV	100%	83.9%[c] to 96.8%[b]	N/A	86%
Accuracy	68%	N/A	N/A	70%

Abbreviations: 95% CI = 95% confidence interval; AUROC = area under the receiver operating characteristic curve; CAP = controlled attenuation parameter; LS = liver stiffness; N/A = not available; NPV = negative predictive value; PPV = positive predictive value; TE = transient elastography

* 19 patients had liver biopsy; No. of patients who underwent TE = 5

† Sensitivity and specificity refer to CAP performance

‡ Sensitivity and specificity refer to LS alone

Comparisons with histopathology in terms of detecting significant liver fibrosis:

[a] According to Ishak stage ≥F1

[b] For determining METAVIR stage ≥F2

[c] For predicting Roenigk grade ≥3a

a sensitivity and specificity of 50% and 83.9%, respectively, and a PPV of 50% and a NPV of 84%; in addition, the use of TE values ≥7.1 yielded 50% sensitivity and 76.9% specificity for detecting significant liver fibrosis, defined as METAVIR stage ≥F2; and giving a PPV of 10% and a NPV of 96.8%. Similarly, our study showed a PPV of 26.7% and a NPV of 100%. In the study of 53 psoriasis patients receiving MTX, Khandpur et al[20] identified median LS values of 5.3 kPA (range, 2.7-17.8); TE could only detect 4 (21%) of 19 patients with liver fibrosis (Ishak stage ≥F1).[20]

Because the median LS for our patients with significant liver fibrosis (Roenigk grade ≥3a) was 11.7 kPa (IQR, 7.8-15.7), we recommend yearly TE monitoring for patients with LS ≥7.1 kPa. Liver biopsy should be considered for patients with LS ≥11.7 kPa, instead of a TCD ≥3.5 g or LS ≥7.1 kPa; earlier biopsy is suggested for high-risk patients (eg, patients with high BMI, abdominal obesity, or diabetes mellitus).

Associations of body mass index, abdominal obesity, and glycated haemoglobin level with liver fibrosis

The median LS in this study (n=228) was 6.91 kPa (IQR, 4.5-7.1). Among the 34 patients who underwent liver biopsy, the median LS was 8.80 kPa (IQR, 7.1-12.4). Overall, 9 of 34 patients (26.5%) had Roenigk grade 3a (mild)/3b (moderate to severe) liver fibrosis, whereas 14 (41.2%) patients had moderate to severe fatty infiltration (Roenigk grade 2) [Table 1]. The prevalences of liver fibrosis and steatotic changes in our study were higher than the rates reported in a 2015 review, where histology showed that only 5% of patients (range, 0%-33%) receiving MTX had developed significant liver fibrosis.[14]

Impacts of body mass index and coexisting non-alcoholic steatohepatitis or fatty liver disease on liver stiffness measurement

The aetiology of liver fibrosis can be multifactorial. Previous studies have shown that obesity, combined with other metabolic risk factors, is associated with liver fibrosis in non-alcoholic fatty liver disease (NAFLD) patients and psoriasis patients.[26-28] The potential contributions of coexisting non-alcoholic steatohepatitis or NAFLD and metabolic syndrome to liver fibrosis have been suggested. In our cohort, >40% of psoriasis patients had a CAP of ≥268 dB/m, indicative of moderate to severe steatosis. The liver fibrosis could be attributed to coexisting non-

alcoholic steatohepatitis or NAFLD, in addition to MTX-induced changes. The work of Wong et al[26] demonstrated that NAFLD patients with BMI ≥30 kg/m^2 had higher LS compared with normal healthy individuals. Our findings corroborate these observations; we found that BMI, body weight, and waist circumference were moderately correlated with TE-based LS measurements (all r>0.40; all P<0.05) [Table 2]. Intriguingly, although 70.6% of our biopsy cohort had moderate to severe hepatic steatosis (Table 1), CAP values were not significantly associated with LS >7.1 kPa or Roenigk grade ≥3a (Table 3). Therefore, the adverse effect of BMI on LS cannot be explained by concomitant hepatic steatosis alone.

In our study, patients with clinically significant liver fibrosis more frequently displayed characteristics of metabolic syndrome compared with patients lacking histologically confirmed liver fibrosis, as evidenced by significantly greater BMI (33.5 ± 0.68 kg/m^2 vs 29.4 ± 6.18 kg/m^2; P=0.01), waist circumference (138.0 ± 52.0 cm vs 101.2 ± 14.9 cm; P=0.04), and HbA1c values (7.86 ± 2.02% vs 6.15 ± 1.16%; P=0.03) [Table 3]. Sub-analysis showed that all patients with histologically confirmed liver fibrosis had a BMI ≥25 kg/m^2 (Table 5), suggesting that psoriasis patients should maintain a normal BMI to decrease the risk of liver fibrosis.

Role of transient elastography: liver stiffness measurements to guide liver biopsy considerations

Despite the recommendation to perform a screening liver biopsy for exclusion of possible liver cirrhosis among patients receiving long-term MTX therapy (with a TCD >3.5 g),[1,2] our study did not identify a positive correlation between significant liver fibrosis and the TCD of MTX. Similarly, a study involving 420 patients with inflammatory arthritis receiving MTX revealed no significant correlation between cumulative MTX dosage and TE-based LS measurements.[24] In the present study, although

TABLE 5. Liver stiffness values according to body mass index, psoriasis severity, and liver histology among psoriasis patients receiving methotrexate

BMI (regardless of psoriasis severity)		**Normal***	**Overweight***	**Obese***	**P value**
No. of patients (n=34)		8	11	15	
LS, kPa	Mean ± SD	7.6 ± 5.1	9.2 ± 3.9	12.5 ± 7.21	0.10
	Median (IQR)	5.9 (4.3-9.2)	8.8 (5.6-11.7)	10.7 (7.8-14.3)	
Psoriasis severity (regardless of BMI)		**Mild†**		**Moderate to severe†**	
No. of patients (n=34)		21		13	
LS, kPa	Mean ± SD	8.9 ± 3.9		12.4 ± 8.1	
	Median (IQR)	8.4 (5.2-11.9)		10.7 (6.7-15.7)	
Mild†		Normal*	Overweight*	Obese*	
No. of patients (n=21)		6	7	8	
LS, kPa	Mean ± SD	5.8 ± 2.7	8.8 ± 4.2	11.4 ± 3.1	0.027
	Median (IQR)	4.8 (3.8-7.7)	8.4 (5.6-10.2)	11.9 (8.3-14.3)	
Moderate to severe†		Normal*	Overweight*	Obese*	
No. of patients (n=13)		0	5	8	
LS, kPa	Mean ± SD	N/A	9.2 ± 3.5	14.4 ± 9.7	0.28
	Median (IQR)	N/A	8.4 (5.6-12.1)	10.9 (7.5-22.9)	
Liver histology (Roenigk scale)					
Fatty changes without fibrosis (Roenigk grade 1 or 2)		Normal*	Overweight*	Obese*	
No. of patients (n=25)		7	7	11	
LS, kPa	Mean ± SD	6.1 ± 3.8	8.6 ± 3.2	12.1 ± 5.7	0.039
	Median (IQR)	4.8 (3.8-7.1)	7.7 (6.3-10.6)	10.2 (8.8-12.4)	
Liver fibrosis (Roenigk grade ≥3a)		Normal*	Overweight*	Obese*	
No. of patients (n=9)		0	5	4	
LS, kPa	Mean ± SD	N/A	13.1 ± 9.8	13.7 ± 2.7	0.29
	Median (IQR)	N/A	8.8 (7.8-21.5)	13.4 (11.6-15.7)	

Abbreviations: BMI = body mass index; IQR = interquartile range; LS = liver stiffness; N/A = not available; SD = standard deviation

* BMI: normal = 18.5 to <25 kg/m^2; overweight = 25 to <30 kg/m^2; obese = ≥30 kg/m^2

† Psoriasis Area and Severity Index score: mild = <10; moderate = 10 to <25; severe = ≥25

the TCD of MTX was higher in patients with liver fibrosis (5.23 g vs 4.79 g in those without), the difference was not statistically significant. In this context, LS measurements may be superior to the TCD of MTX when considering the need for liver biopsy to rule out advanced liver fibrosis.

Contrary to concerns about hepatotoxicity during long-term MTX therapy, we did not find a correlation between LS values and the duration of MTX use. The duration of MTX use in patients without liver fibrosis was nearly 10 years, indicating that the drug is generally well-tolerated in psoriasis patients. Patients who tended to continue MTX treatment belonged to an MTX-responsive group without significant adverse events, such as liver derangement identified via blood tests. In contrast, patients experiencing liver derangement or other adverse events might have discontinued MTX treatment earlier and were thus excluded from the study. Although we excluded patients with chronic hepatitis B, TE-based LS measurement is a widely validated non-invasive tool for real-world assessments of liver fibrosis in such patients; it allows the prediction of advanced fibrosis and disease progression.[29] Therefore, TE should also be considered a valuable tool in guiding treatment for psoriasis patients with chronic hepatitis B who are receiving MTX.

In addition to LS measurement, TE can assess the degree of steatosis through CAP. This assessment was beneficial among patients with psoriasis in the present study; 26.5% (9 of 34) of the patients had metabolic syndrome and were predisposed to concomitant hepatic steatosis, regardless of MTX use. The median CAP value in our study was 321 ± 95 dB/m (range, 200-400). The area under the ROC curve of TE was 0.783 (95% CI=0.61-0.95; P<0.01); the cut-off of 254 dB/m for detecting steatosis yielded 91% sensitivity and 60% specificity. However, the presence of simple hepatic steatosis alone does not warrant liver biopsy, and management decisions should follow appropriate clinical guidelines.[30-32]

Limitations

This study had some limitations. Notably, its sample size was small. Although liver fibrosis is generally uncommon in patients with psoriasis receiving MTX therapy, a larger sample size may be required for more definitive conclusions. Additionally, sampling error and inter- and intra-observer variabilities in histological assessment of liver tissue may have influenced the findings.

Conclusion

Transient elastography is a reliable screening tool for detecting significant liver fibrosis in Chinese psoriasis patients receiving MTX. When considering liver biopsy to rule out the possibility of clinically significant liver fibrosis, TE-based LS measurements provide superior reference information, compared with the TCD of MTX. Patients with high BMI, body weight, and abdominal obesity have a higher risk of liver fibrosis. Therefore, these factors should be considered when monitoring MTX-related liver fibrosis in psoriasis patients.

Author contributions

Concept or design: CSM Wong, LLY Mak, CK Yeung, HHL Chan, MF Yuen.
Acquisition of data: CSM Wong, MMH Chung, LLY Mak.
Analysis or interpretation of data: CSM Wong, MMH Chung, LLY Mak.
Drafting of the manuscript: CSM Wong, LLY Mak, F Chu, VKH Lee, RCL Lo.
Critical revision of the manuscript for important intellectual content: CK Yeung, HHL Chan, MF Yuen.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Ethics approval

This study was approved by the Institutional Review Board of The University of Hong Kong and Hong Kong West Cluster, Hospital Authority, Hong Kong (Ref No.: UW19-390) and was conducted in full compliance with the International Council for Harmonisation E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki. Patient consent has been obtained for all clinical information and images reported in this article. All participant information has been deidentified and remains anonymous.

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