ORIGINAL ARTICLE

Assessment of Liver Fibrosis by FibroScan in Rheumatology Patients Treated with Conventional Synthetic Disease-Modifying Antirheumatic Drugs.

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Abstract

Background: Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) are widely used in the management of inflammatory rheumatic diseases. Long-term exposure, particularly methotrexate, raises concerns regarding hepatotoxicity and liver fibrosis. **Objective:** To determine the frequency of liver fibrosis among rheumatology patients treated with csDMARDs using transient elastography (FibroScan). **Methods:** This retrospective study included rheumatology patients receiving csDMARDs therapy (monotherapy or combination) who had undergone FibroScan assessment. Liver fibrosis was defined as METAVIR stage of F2 or higher. **Results:** Among 60 patients, liver fibrosis (F2–F4) was detected in 18 (30.0%), while 42 (70.0%) had no or mild fibrosis (F0–F1). Mean age did not differ significantly between groups; however, patients with fibrosis had a younger age at rheumatic disease diagnosis. Triglyceride levels were significantly lower in the fibrosis group. csDMARDs type, combination therapy, and cumulative drug doses did not differ significantly between groups. Multivariate logistic regression analysis identified no independent predictors of liver fibrosis. **Conclusion:** Liver fibrosis was detected in nearly one-third of rheumatology patients treated with csDMARDs using FibroScan. No significant associations were observed between liver fibrosis and csDMARDs type, combination therapy, or cumulative drug exposure. These findings suggest that liver fibrosis in csDMARD-treated patients may not be solely attributable to conventional clinical or treatment-related factors, underscoring the potential value of non-invasive liver assessment in routine rheumatology practice.

Keywords: *Conventional synthetic disease-modifying antirheumatic drugs, Fibroscan, liver fibrosis,*

Introduction

Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) constitute a diverse class of agents used for the treatment of several inflammatory arthritides, including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and various connective tissue diseases [1,2]. Commonly used csDMARDs include methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine. These agents may be administered as monotherapy or in combination to prevent progressive joint damage and structural deterioration [3].

Long-term use of csDMARDs, particularly methotrexate has been associated with potential hepatotoxicity, including the development of liver fibrosis and, less commonly, cirrhosis [4]. Although methotrexate is highly effective, the literature regarding its association with liver fibrosis remains inconsistent. Serious hepatic adverse events such as hepatitis have been documented [5], whereas the occurrence of methotrexate induced cirrhosis appears to be relatively rare [6]. Leflunomide, a newer csDMARD frequently used in combination with methotrexate, has also been implicated in hepatotoxicity, with reports indicating increased liver enzyme levels and, in severe cases, the development of liver fibrosis [7].

Earlier guidelines recommended serial liver biopsies for monitoring liver fibrosis. However, this approach is no longer favoured as a routine screening tool due to its invasive nature and associated procedure-related risks [8]. More recently, non-invasive liver stiffness measurement using transient elastography, such as FibroScan, has been introduced as an alternative method for assessing the severity of liver fibrosis and for screening the general population to identify individuals at risk of chronic liver disease [9]. Transient elastography has been recognized as a reliable alternative to liver biopsy across a wide range of chronic hepatic conditions [10].

The objective of this study is to determine the frequency of liver fibrosis among rheumatology patients treated with csDMARDs using Fibroscan technique.

Materials and Methods

This retrospective study included rheumatology patients who were treated with csDMARDs for underlying rheumatologic conditions such as RA, PsA, ankylosing spondylitis, and connective tissue diseases at Hospital Raja Permaisuri Bainun. All patients had previously undergone FibroScan assessment. They received either csDMARD monotherapy or combination therapy. The study was approved by the Malaysian Medical Research and Ethics Committee (NMRR ID: NMRR ID-25-03949-XJW). Clinical data were extracted from medical records, including ethnicity, sex, age at disease onset, comorbidities, body mass index (BMI), laboratory findings, and treatment history. Obesity was defined as a BMI greater than 30 kg/m^2. Cumulative doses of methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine were calculated.

All patients had undergone liver stiffness measurement using FibroScan , which assesses hepatic stiffness at a depth of 25–65 mm below the skin surface. Liver fibrosis was staged by converting FibroScan results (kPa) into the METAVIR scoring system: F0 (no fibrosis), F1 (mild fibrosis without septa), F2 (moderate fibrosis with few septa), F3 (severe fibrosis with numerous septa without cirrhosis), and F4 (cirrhosis or advanced hepatic scarring) [11]. In this study, F0 and F1 were grouped as no significant fibrosis. Hepatic steatosis was graded as follows: no steatosis (<11%, S0), mild steatosis (11–34%, S1), moderate steatosis (34–67%, S2), and severe steatosis (>67%, S3) [12].

Data analysis was performed using SPSS version 28 (IBM Corp., Armonk, NY, USA). Continuous variables are presented as means with standard deviations, or medians with interquartile ranges

(IQRs), depending on distribution normality. Categorical variables are summarised as counts and percentages. For group comparisons, the independent t-test was applied to normally distributed continuous data, while the Mann–Whitney U test was used for non-normally distributed variables. The chi-square test was used for categorical variables. .Binary logistic regression was performed to identify independent predictors of liver fibrosis (METAVIR F2–F4). Variables with $p < 0.10$ in univariate analysis (age at diagnosis and triglyceride level) were entered into the multivariate model, together with methotrexate use and clinically relevant covariates (obesity, diabetes mellitus, viral hepatitis, and autoimmune hepatitis). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant.

Results

Among the 60 rheumatology patients treated with csDMARDs, liver fibrosis assessed by FibroScan was detected in 18 patients (30.0%; stages F2–F4), while 42 patients (70.0%) had no or mild fibrosis (F0–F1). The mean age of the cohort was 55.2 ± 12.9 years, with no significant difference between patients with and without liver fibrosis. However, patients with fibrosis had a significantly younger age at disease diagnosis compared with those without fibrosis (42.2 ± 15.8 vs. 45.2 ± 12.1 years, $p = 0.044$). Gender distribution, disease duration, body mass index, obesity prevalence, ethnicity, lifestyle factors, inflammatory markers, and most laboratory parameters were comparable between groups. Notably, triglyceride levels were significantly lower in the fibrosis group compared with the non-fibrosis group (0.80 vs. 1.16 mmol/L, $p = 0.010$), while other lipid parameters did not differ significantly. (Table 1)

Disease characteristics and treatment

Rheumatoid arthritis was the most common diagnosis in both groups. The type of csDMARDs, combination therapies, and cumulative drug doses did not differ significantly between groups. (Table 2)

Figure 1 demonstrates varying degrees of steatosis across fibrosis stages, with moderate to severe steatosis observed even among patients with minimal fibrosis.

Multivariate analysis

After adjusting for obesity, diabetes mellitus, viral hepatitis, and autoimmune hepatitis, binary logistic regression analysis revealed no independent association between age at diagnosis, triglyceride levels, and methotrexate use with the presence of liver fibrosis. (Table 3).

Discussion

Over the years, csDMARDs have continued to serve as the primary treatment option for a range of immune-mediated inflammatory conditions, including RA and PsA [13,14]. Agents such as methotrexate and leflunomide are known to carry a risk of hepatotoxicity [15]. Reported rates of liver fibrosis among patients receiving methotrexate range from approximately 2–16% in RA and 0–4% in PsA [16,17]. In contrast, sulfasalazine has been reported to exert a protective effect against the development of liver fibrosis, and the addition of hydroxychloroquine to RA therapy may similarly help reduce the risk of methotrexate-related liver injury [18,19].

Methotrexate induced liver injury is a multifactorial process involving inflammation, oxidative stress, endothelial damage, and the subsequent progression of hepatic fibrogenesis, particularly with higher cumulative doses of methotrexate [20,21]. In contrast, the precise mechanisms underlying leflunomide-associated hepatotoxicity remain incompletely understood, although cumulative exposure has been linked to the development of hepatic fibrosis in patients with rheumatoid arthritis, highlighting the need

for hepatic monitoring during long term therapy [22].

Liver fibrosis may progress insidiously and is often not accompanied by a parallel elevation in serum aminotransferase levels, making early detection challenging [23]. Although liver biopsy remains the gold standard for evaluating the extent of hepatic fibrosis, its invasive nature, potential complications, and limited feasibility for repeated assessments restrict its routine use [24]. These limitations underscore the need for reliable, non-invasive alternatives for fibrosis assessment. Transient elastography (FibroScan) has emerged as a practical and reproducible noninvasive technique for measuring liver stiffness, demonstrating reliable and clinically acceptable results. Its diagnostic performance has been well validated in patients with chronic hepatitis C infection, where FibroScan has shown good accuracy in assessing the presence and severity of hepatic fibrosis, supporting its utility in both clinical practice and research settings [25].

In our study, lower triglyceride levels were observed among patients with liver fibrosis. Consistent with this finding, Chen TP et al. reported that hypertriglyceridemia was associated with a reduced risk of advanced hepatic fibrosis [26]. Triglyceride accumulation within the cytoplasm of hepatocytes is a defining feature of metabolic dysfunction-associated steatotic liver disease (MASLD). Consequently, greater hepatic steatosis has been shown to be inversely associated with the severity of liver fibrosis [27]. Moreover, the concept of a "burnt-out" liver in advanced fibrosis or cirrhosis reflects diminished hepatic fat content, accompanied by reduced serum triglyceride levels. This inverse relationship between triglyceride levels and fibrosis severity has been described in MASLD and other chronic liver diseases and is generally considered a marker of poor prognosis [28].

We were unable to demonstrate a significant association between the cumulative dose of methotrexate and the presence of liver fibrosis in our study, a finding that is consistent with the study by Barbero-Villarís et al. Using transient elastography (FibroScan) to assess liver stiffness in 46 patients with various conditions receiving long-term MTX therapy, they similarly reported no correlation between cumulative MTX dose and liver stiffness [29]. In contrast, Curtis et al. reported a direct association between cumulative MTX exposure and the severity of hepatotoxicity, highlighting ongoing inconsistency in the existing literature [30].

Excess body weight and adipose tissue accumulation play a central role in the development of metabolic dysfunction associated steatohepatitis, which typically evolves from simple steatosis and may progress to fibrosis, cirrhosis, and, in some cases, hepatocellular carcinoma [31]. Obesity is a strong predictor of advanced liver fibrosis and cirrhosis and is associated with increase in liver related mortality [32]. In obese individuals, liver fibrosis progression is driven by increased adiposity and insulin resistance, creating a profibrotic hepatic environment characterized by enhanced hepatocyte apoptosis, elevated oxidative stress, and dysregulated adipokine and cytokine production [33]. However, in our study, no significant difference in obesity status was observed between the two groups.

Our study has several limitations. First, its retrospective design and relatively small sample size limit the ability to infer causal relationships. In addition, baseline FibroScan measurements prior to the initiation of csDMARD therapy were unavailable. A prospective study incorporating serial FibroScan assessments would be more appropriate for identifying and controlling potential risk factors contributing to liver fibrosis. Furthermore, liver fibrosis detected by FibroScan was not confirmed by histopathology through liver biopsy.

Conclusion

Liver fibrosis assessed by FibroScan was identified in 30% of rheumatology patients

treated with csDMARDs. No significant differences were observed in most demographic, metabolic, disease-related, or treatment factors between patients with and without fibrosis, and no independent associations were found after multivariate adjustment. These findings suggest that liver fibrosis in csDMARD treated patients may not be solely attributable to conventional clinical or treatment-related factors, underscoring the potential value of noninvasive liver assessment in routine rheumatology practice.

Ethical approval

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID 25-03949-XJW).

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Conflict of interest

None.

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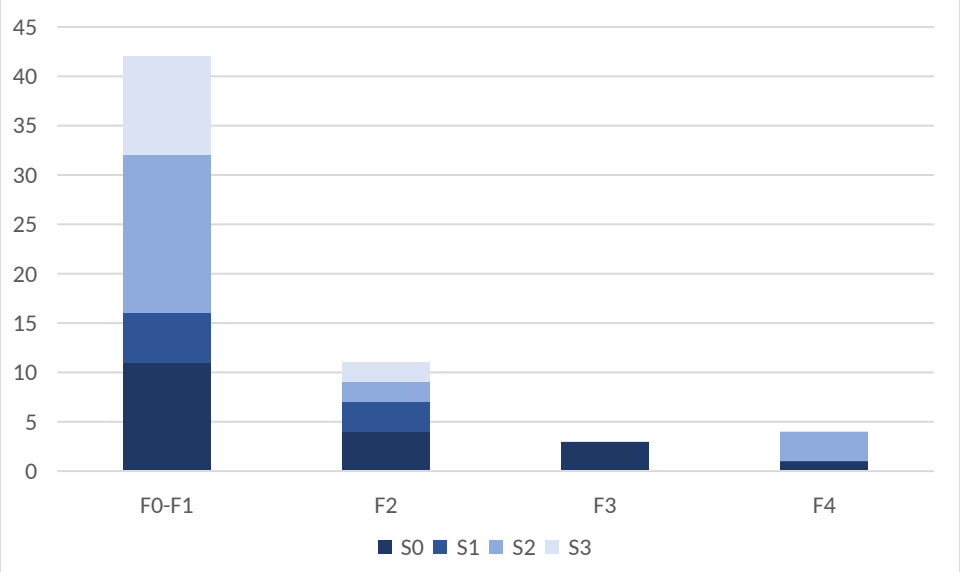
Authors' contributions

OPS, WM, MB, KCG responsible for conceptualizing, collecting clinical data; OPS for report writing, and finalizing the manuscript; LPJ for statistical analysis.

Figure 1. Distribution of hepatic fibrosis and steatosis grades



Abbreviation: F, fibrosis; S, steatosis.

Note: Distribution of fibrosis (F) and steatosis (S) grades among 60 rheumatology patients treated with csDMARDs. Fibrosis was assessed by FibroScan using METAVIR criteria; steatosis was graded using controlled attenuation parameter (CAP).

Table 1. Baseline characteristics and laboratory variables of patients with and without fibrosis

	Total (n=60)	Fibrosis group (F2-F4) (n=18)	Non-fibrosis group (F0-F1) (n=42)	P value
Age, yr, mean±SD	55.2±12.9	55.7±14.5	55.0±12.4	0.259[a]
Age at diagnosis, yr, mean±SD	44.3±13.3	42.2±15.8	45.2±12.1	**0.044[a]**
Gender				
Male, n (%)	14 (23.3)	4 (22.2)	10 (23.8)	0.894[b]
Female, n (%)	46 (76.7)	14 (77.8)	32 (76.2)	
Disease duration, yr, median (IQR)	8.0 (12)	8.0 (11)	8.0 (13)	0.502[c]
Weight (kg), median (IQR)	61.7 (24.6)	52.5 (30.5)	63.3 (20.2)	0.202[c]
BMI (kg/m2), median (IQR)	24.5 (8.1)	22.7 (11.2)	24.7 (7.0)	0.273[c]
Obese, n (%)	20 (33.3)	6 (33.3)	14 (33.3)	1.000[b]
Ethnicity, n (%)				
Malay	25 (41.7)	7 (38.9)	18 (42.9)	0.127[b]
Chinese	22 (36.7)	10 (56.6)	12 (18.6)	
Indian	11 (18.3)	1 (5.6)	10 (23.8)	
Others	2 (3.3)	0 (0.0)	2 (4.8)	
Comorbidities, n (%)				
Diabetes mellitus	12 (20.0)	6 (33.3)	6 (14.3)	0.091[b]
Hypertension	22 (36.7)	7 (38.9)	15 (35.7)	0.815[b]
Hyperlipidaemia	20 (33.3)	6 (33.3)	14 (33.3)	1.000[b]
Ischemic heart disease	3 (5.0)	1 (5.6)	2 (4.8)	0.897[b]
MASLD	7 (11.7)	2 (11.1)	5 (11.9)	0.930[b]
Thyroid disease	3 (5.0)	0 (0.0)	3 (7.1)	0.245[b]
Lifestyle				
Alcohol, n (%)	3 (5.0)	1 (5.6)	2 (4.8)	0.897[b]
Smoking, n (%)	2 (3.3)	1 (5.6)	1 (2.4)	0.530[b]
Laboratory variables				
ESR, median (IQR)	34.5 (41)	35.0 (49)	33.5 (42)	0.358[c]
CRP, median (IQR)	3.0 (7.2)	2.9 (3.3)	4.2 (9.1)	0.680[c]
WBC, mean±SD	7.2±2.2	6.5±2.6	7.4±2.1	0.264[a]
HB, mean±SD	12.0±1.9	11.7±1.9	12.2±1.8	0.889[a]
Platelet, mean±SD	306.5±87.1	292.7±111.5	312.5±75.1	0.080[a]
Glucose, median (IQR)	5.4 (1.6)	5.1 (1.4)	5.4 (1.5)	0.333[c]
Urea, median (IQR)	4.4 (2.4)	4.6 (2.7)	4.3 (1.8)	0.583[c]
Creatinine, median (IQR)	65.0 (31.5)	68.5 (54.5)	64.0 (29.3)	0.640[c]
AST, IU/L, median (IQR)	23.5 (10.3)	24.5 (14.8)	23.0 (8.0)	0.728[c]
ALT IU/L, median (IQR)	20.5 (16.8)	20.5 (24.3)	20.5 (13.3)	0.949[c]
Total protein, mg/dL, mean±SD	78.3±5.9	77.3±6.3	78.7±5.8	0.885[a]
Serum albumin, mg/dL, mean±SD	42.1±3.6	41.3±3.8	42.4±3.5	0.526[a]
Total bilirubin, mg/dL, median (IQR)	11.9 (5.0)	11.1 (4.5)	12.0 (5.5)	0.512[c]
Alkaline phosphatase, IU/L, mean±SD	85.5±19.8	81.8±21.8	87.1±18.9	0.619[a]
Triglyceride, mmol/L, median (IQR)	0.96 (0.79)	0.80 (0.50)	1.16 (0.83)	**0.010[c]**
High density cholesterol, mg/dL, Median (IQR)	1.50 (0.60)	1.55 (0.94)	1.45 (0.50)	0.257[c]
Low density cholesterol, mg/dL, Median (IQR)	2.88 (0.98)	3.00 (1.05)	2.83 (1.07)	0.467[c]

Abbreviations: yr, year; MASLD, Metabolic dysfunction associated steatotic liver disease; CKD: chronic kidney disease; ESR, Erythrocyte sedimentation rate; CRP, C-reactive protein; BMI, body mass index; WBC, white blood cell; HB, hemoglobin; AST, Aspartate aminotransferase; ALT, Alanine aminotransferase. Bold values are significant at $p<0.05$; [a] Independent t-test; [b] Chi-square test; [c] Mann-Whitney U test

Table 2. Disease and Treatment in patients with or without liver fibrosis

	Total (n=60)	Fibrosis group (F2-F4) (n=18)	Non-fibrosis group (F0-F1) (n=42)	P value
Type of disease, n (%)				
RA	36 (60.0)	11 (61.1)	25 (59.5)	0.554[b]
PsA	11 (18.3)	2 (11.1)	9 (21.4)	
Other*	13 (21.7)	5 (27.8)	8 (19.0)	
Medications, n (%)				
Statin	19 (31.7)	5 (27.8)	14 (33.3)	0.672[b]
NSAIDs	2 (3.3)	1 (5.6)	1 (2.4)	0.530[b]
csDMARDs				
Monotherapy				
MTX	18 (30.0)	3 (16.7)	15 (35.7)	0.071[b]
SSZ	11 (18.3)	6 (33.3)	5 (11.9)	
HCQ	8 (13.3)	4 (22.2)	4 (9.5)	
2 csDMARDS				
MTX and LEF	6 (10.0)	1 (5.6)	5 (11.9)	0.453[b]
MTX and SSZ	5 (8.3)	2 (11.1)	3 (7.1)	0.610[b]
LEF and SSZ	4 (6.7)	1 (5.6)	3 (7.1)	0.821[b]
HCQ and SSZ	2 (3.3)	0 (0.0)	2 (4.8)	0.346[b]
>2 csDMARDs	6 (10.0)	1 (5.6)	5 (11.9)	0.453[b]
Accumulative dose, Median (IQR)				
MTX,mg	3610 (7670)	4585 (4045)	3510 (8287.5)	0.123[c]
SSZ,g	1460 (3569)	2407.5 (2801.8)	1277.5 (2190)	0.201[c]
LEF,mg	29200 (43800)	58400 (51100)	25550 (38325)	0.622[c]
HCQ,g	401.5 (365)	511 (438)	365 (328.5)	0.959[c]

Abbreviations: RA: Rheumatoid arthritis; PsA: psoriatic arthritis; csDMARDs: conventional synthetic disease-modifying antirheumatic drugs; MTX: methotrexate; LEF: leflunomide; SSZ: Sulphasalazine; HCQ: Hydroxychloroquine. * Other inflammatory diseases such as ankylosing spondylitis

[b] Chi-square test; [c] Mann-Whitney U test

Table 3. Multivariate analysis of independent predictors of liver fibrosis.

	Odds ratio	95% CI	P value
Age of diagnosis	0.981	0.938,1.026	0.411
Triglyceride	0.281	0.069,1.141	0.076
Methotrexate	2.727	0.794, 9.363	0.111

Note: Model adjusted for: obesity (BMI > 30 kg/m2), diabetes mellitus, viral hepatitis, and autoimmune hepatitis. Abbreviations: CI, confidence interval

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