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Using FibroScan to Assess for the Development of Liver Fibrosis in Patients With Arthritis on Methotrexate: A Single-center Experience

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ABSTRACT. ***Objective.*** Methotrexate (MTX) is often the primary medication to treat various rheumatic diseases (RDs) because of its low cost and its demonstrated efficacy in controlling disease activity. However, a concern has been the potential for hepatic fibrosis associated with long-term MTX usage. This study investigated the association between cumulative MTX intake and development of liver fibrosis by utilizing noninvasive transient elastography (FibroScan).

Methods. All patients with inflammatory arthritis treated with MTX were offered screening with FibroScan. A certified technician measured liver stiffness after patients adhered to a fast. Relevant clinical information was obtained by patient survey and medical records review. The population was divided into quartiles based on participants' cumulative dosage of MTX.

Results. Five hundred twenty patients with RD were included in this study. The prevalence of stages F3 or F4 liver fibrosis was 13.3% in the control group and 12.7% in the entire sample. Compared with subgroup 1 (control with cumulative MTX exposure of ≤ 499 mg), MTX subgroups 2 to 4 were not significantly correlated with higher FibroScan scores (P = 0.82, 0.59, and 0.18, respectively). In multivariable linear regression analysis, statistically significant factors for liver stiffness were BMI, waist circumference, male sex, and age.

Conclusion. No significant correlation between the cumulative MTX dosage and liver stiffness, even at high MTX doses, was observed. The analyses showed significant correlations between the FibroScan score and BMI. These findings were reassuring in that current rheumatology practice appears to be safe and effective in screening for liver fibrosis in patients on long-term low-dose MTX therapy.

Key Indexing Terms: FibroScan, liver fibrosis, medication safety, methotrexate, transient elastography

Methotrexate (MTX) has been the cornerstone in the treatment of inflammatory arthritis since the 1980s.[1,2,3] While MTX is generally well tolerated in most patients,[4,5,6] hepatic fibrosis with long-term usage is a potential safety concern.[7,8,9] A number of clinical guidelines have been published to monitor for MTX-associated hepatotoxicity in clinical practice. The American College of Rheumatology (ACR) recommends monitoring patients receiving MTX by testing liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as albumin every 4–8 weeks.

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ACR guidelines from the 1990s recommended performing pretreatment liver biopsy in patients with underlying liver problems such as excessive alcohol consumption, positive viral markers (hepatitis B virus [HBV] and hepatitis C virus [HCV]), and persistently elevated liver enzymes.[10] Although liver biopsy remains the gold standard technique for detecting liver fibrosis,[11,12,13] its invasive nature and its potential for procedure-related complications make it impractical for the routine screening of patients on MTX.[14,15,16] Noninvasive techniques, including transient elastography (TE; FibroScan),[17,18] have emerged as an alternative to liver biopsy for estimating hepatic fibrosis. FibroScan is a reliable, noninvasive, ultrasound (US)-based method[19] that has been used to assess hepatic fibrosis in a number of different conditions, including HBV and HCV infection, alcoholic liver disease, and autoimmune disease.[20,21,22,23,24]

Although there are widely discussed concerns surrounding liver toxicity in rheumatology patients treated with MTX, there is paucity of data regarding the prevalence of hepatic fibrosis in this patient population.[25,26,27] Therefore, we aimed to estimate the prevalence of liver fibrosis in rheumatology patients receiving low-dose MTX, and to assess for any linkage between cumulative

MTX dosage (total amount of MTX intake by the participant during the course of treatment) and hepatic fibrosis in patients followed by rheumatologists in a Canadian rheumatology practice. The secondary objective was to identify correlates of hepatic fibrosis in patients with rheumatological disorders receiving MTX therapy.

METHODS

Study population. Institutional ethics committee clearance was obtained (University of British Columbia, H18-01684). Between June 2019 and July 2020, patients in a large rheumatology clinic were eligible to participate in this prospective study. All adult patients treated with MTX who met study criteria and provided informed consent to participate in this study were included.

Patients with inflammatory arthritis were included if they had been prescribed at least 1 dose of MTX during the course of their treatment at the clinic. All eligible patients were offered a FibroScan; however, participation in the study was entirely voluntary. There were some patients who were prescribed MTX but never started the medication. These patients were included in the study within the control group, with their cumulative MTX dosage = 0 mg.

Exclusion criteria included patients with known chronic liver diseases such as acute or chronic HBV or HCV, autoimmune hepatitis, chronic cholestatic diseases (such as primary biliary cirrhosis or primary sclerosing cholangitis), or with a history of alcoholic liver disease or alcohol abuse (> 12 oz of wine or equivalent per week). Patients currently receiving or previously exposed to disease-modifying antirheumatic drugs (DMARDs) azathioprine (AZA), leflunomide (LEF), and sulfasalazine (SSZ) were excluded because of the drugs' known risk of hepatotoxicity. Patients with known or suspected history of fatty liver disease (FLD) or nonalcoholic steatohepatitis (NASH) were not excluded from the study.

Table 1. Demographics and characteristics of all participants.

	N = 520
Age, yrs, mean (SD)[a]	58.6 (13.3)
Female sex	327 (62.9)
Weight, kg, mean (SD)[a]	78.2 (21.3)
Waist circumference, cm, mean (SD)[a]	91.7 (16.8)
BMI, kg/m^2, mean (SD)[a]	27.6 (6.8)
Cumulative dose of MTX, mg, mean (SD)[a]	3142.4 (4051.6)
Alcohol > 12 oz/wk (yes/no)[a], n	255/258
Ethnicity	
White	317 (61.0)
Asian	115 (22.1)
South Asian	50 (9.6)
First Nation	12 (2.3)
Hispanic	11 (2.1)
Middle Eastern	9 (1.7)
African	6 (1.2)
Rheumatic disease	
RA, PMR, and other inflammatory polyarthritis	283 (54.4)
PsA, AS, IBD, and other seronegative arthritis	163 (31.4)
Noninflammatory arthritis	74 (14.2)

Values are n (%) unless otherwise indicated. [a] Covariate missingness: age, n = 2 (0.38%); weight, n = 5 (0.96%); waist circumference, n = 89 (17%); BMI, n = 5 (0.96%); cumulative MTX dose, n = 18 (3.46%); alcohol consumption, n = 7 (1.34%). AS: ankylosing spondylitis; IBD: inflammatory bowel disease; MTX: methotrexate; PMR: polymyalgia rheumatica; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

Demographic information (age, sex), ethnicity, medical history (liver disease, diabetes mellitus), and alcohol consumption information were obtained through direct questioning (Table 1). Rheumatic disease (RD) diagnoses (rheumatoid arthritis [RA], psoriatic arthritis [PsA], or other immune diseases) were based on established classification criteria and clinical judgment provided by the treating rheumatologist. Height, weight, and waist circumference were measured in a standard format by the study technician at the time of FibroScan. BMIs were calculated using a standard online BMI calculator (weight in kilograms divided by height in meters squared). MTX cumulative dosages were calculated using information from patient electronic medical records.

FibroScan test. We used TE (FibroScan, Echosens), which is an established and validated method for the assessment of liver fibrosis by measuring liver stiffness. All FibroScan measurements were carried out by 1 of 2 trained technicians at the Artus Health Centre. Patients were asked to fast for at least 2 hours prior to the FibroScan test. Liver stiffness scores were reported in kilopascal (kPa). Liver stiffness outcome was represented both as a continuous variable, and as an ordinal classification from F0 to F4, as the following: F0 = no fibrosis; F1 (0.0 kPa ≤ FibroScan score < 7.1 kPa) = portal fibrosis without septa; F2 (7.1 kPa ≤ FibroScan score < 8.7 kPa) = portal fibrosis with few septa; F3 (8.7 kPa ≤ FibroScan score < 10.4 kPa) = numerous septa without cirrhosis; and F4 (FibroScan score ≥ 10.4 kPa) = cirrhosis.

These values have been proposed in the study by Wong et al on liver stiffness measurement in nonalcoholic FLD (NAFLD).[28] All patients with FibroScan scores ≥ 7.1 were classified as F2+, and all patients with score ≥ 8.7 were classified as F3+.

A scatterplot of the FibroScan score vs the cumulative MTX dosage among all participants in the study is shown in Figure 1A.

Statistical analysis. In order to investigate the effect of each independent variable individually on the FibroScan score of participants, we first performed a univariable linear analysis on each factor. In linear regression, the outcome variable is continuous. It can have any one of an infinite number of possible values. In this case, the outcome variable was the measured FibroScan score expressed in kPa, that in theory could range from 0 to infinity. A multivariable analysis was performed, taking into account the effect on the outcome variable, which in this case is the FibroScan score.

The liver stiffness continuous outcome was modeled in linear regression models, whereas the ordinal outcome was first dichotomized as F3+, then modeled in binary logistic models. Explanatory variables included age, sex, weight, waist circumference, BMI, MTX cumulative dose in mg (as 0–499, 500–2999, 3000–5999, or ≥ 6000); RD (RA, PsA, ankylosing spondylitis, other), and alcohol consumption (yes or no). Each outcome was fit against each explanatory variable in initial univariable regression models, then step-wise model selection was employed to find the significant multivariable model at $\alpha = 0.05$, as well as $\alpha = 0.15$. The latter significance level was also used because this somewhat looser criterion may reveal borderline significant findings that can direct future research. The selected linear models are presented with regression coefficients (and 95% CIs) representing additive effects on liver stiffness. The selected logistic models are presented with odds ratios (and 95% CIs) representing multiplicative effects on the odds of liver stiffness levels F3+. Linear model fit was assessed by normal quantile-quantile plots of the residuals, whereas logistic model fit was assessed using the Hosmer and Lemeshow goodness-of-fit test.[29]

RESULTS

There were 547 patients who met the inclusion criteria and consented to participate in the study. In 22 subjects, it was not possible to obtain accurate FibroScan readings because of technical reasons typically because of large body habitus. There were 5 subjects who reported having an underlying liver disease and

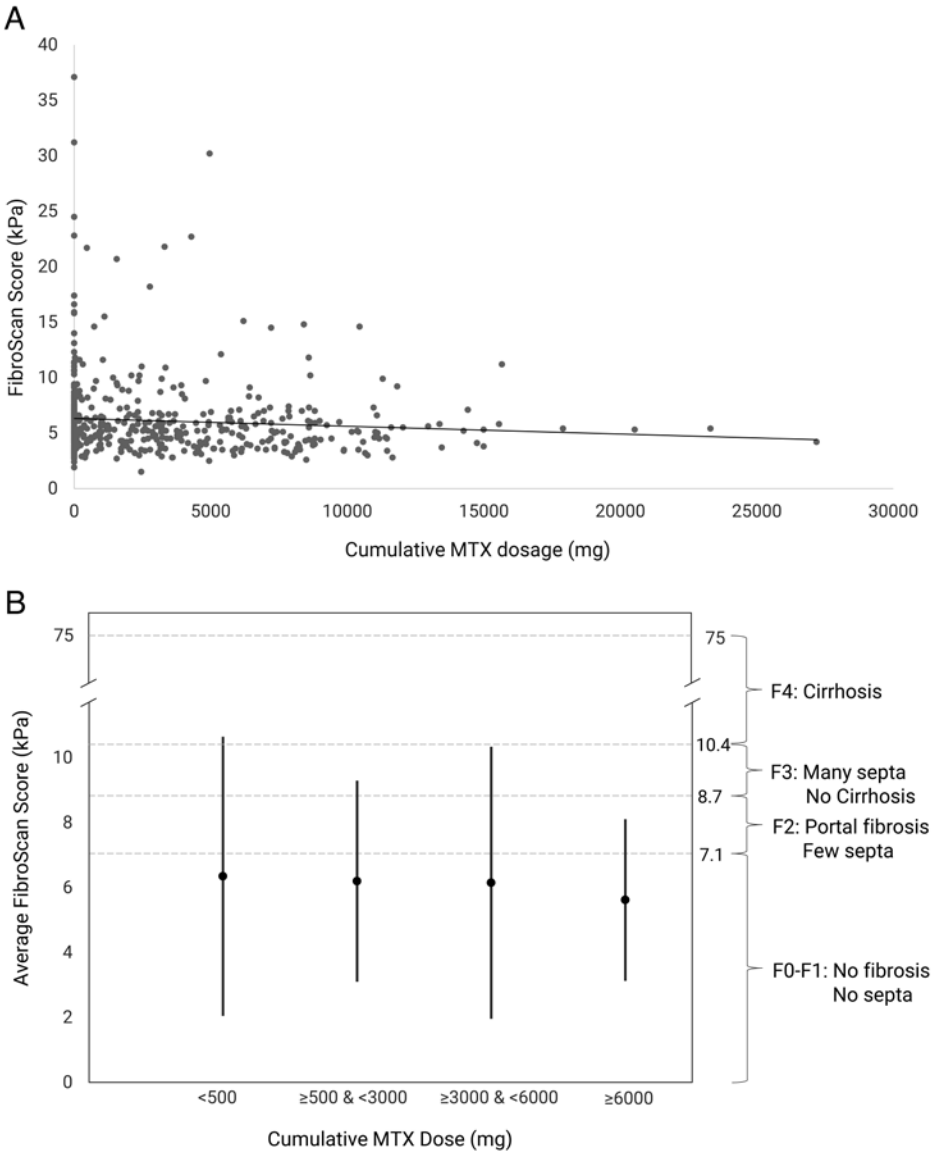

Figure 1. (A) Scatterplot of the FibroScan score vs the cumulative MTX dosage among all participants. The plot shows there is no significant correlation between the cumulative MTX dosage and the FibroScan score. The line is the best linear fit to the data and that it is almost horizontal indicates the 2 variables (the cumulative MTX dosage and the FibroScan score) are almost independent from each other. Minimum cumulative MTX dosage = 0 mg, maximum cumulative MTX dosage = 27,200 mg, minimum FibroScan score = 1.5 kPa, and maximum FibroScan score = 37.1 kPa. (B) Average liver stiffness score per cumulative MTX dosage subgroup. No significant difference between subgroups of different cumulative MTX dosage has been observed. kPa: kilopascal; MTX: methotrexate.

were excluded. A total of 520 patients were included in the primary analysis.

Baseline characteristics of the study population. The demographics and characteristics of all 520 participants are summarized in Table 1. The range of cumulative dose of MTX for all participants was 0 mg to 27,200 mg, with a mean of 3142.6 mg (SD 4051.6). The mean age among all participants was 58.6 years (SD 13.3), and 327 were female. Alcohol consumption was considered yes if the participant declared drinking > 12 ounces of wine (or equivalent) per week, and no otherwise. With this criterion, 258 out of 513 responses were alcohol nonconsumers, which was nearly an even split. Other characteristics included in this study were mean (± SD) weight (78.2 ± 21.3 kg), waist circumference (91.7 ± 16.8 cm), and BMI (27.6 ± 6.8).

Demographics and characteristics of participants were then calculated for 4 different subgroups based on participants' cumulative dosage of MTX as the following: group 1, 0–499 mg; group 2, 500 mg–2999 mg; group 3, 3000 mg–5999 mg; and group 4, ≥ 6000 mg.

Table 2 shows participant characteristics in each subgroup. There were no significant differences between the average age, sex ratio, weight, waist circumference, or BMI among the 4

Table 2. Demographics and characteristics of all participants for 4 different subgroups based on the CD of MTX.

	Group 1 CD = 0–499 mg	Group 2 500 mg < CD ≤ 2999 mg	Group 3 3000 mg < CD ≤ 5999 mg	Group 4 CD ≥ 6000 mg
No. of participants	211	95	104	110
Age, yrs	55.77 ± 14.09	59.20 ± 11.07	61.26 ± 13.40	61.24 ± 12.35
Sex (F/M)	124/87	61/34	66/38	76/34
Weight, kg	80.27 ± 21.45	77.45 ± 20.42	75.90 ± 22.56	76.87 ± 20.51
BMI, kg/m^2	27.74 ± 5.99	27.64 ± 6.64	27.17 ± 7.51	27.59 ± 7.90
Waist circumference, cm	91.94 ± 16.08	92.52 ± 14.95	90.45 ± 17.02	91.61 ± 19.99
Cumulative MTX dose, mg	45.36 ± 111.87	1682.67 ± 709.72	4220.6 ± 904.36	9500.46 ± 3495.27
Alcohol consumption (yes/no)	122/87	34/59	51/53	48/59
Liver stiffness, kPa	6.35 ± 4.30	6.20 ± 3.10	6.15 ± 4.19	5.62 ± 2.49

Values shown represent mean ± SD unless otherwise indicated. CD: cumulative dose; kPA: kilopascal; MTX: methotrexate.

subgroups. Subgroup 1 (cumulative MTX dosage ≤ 499 mg) was the only group in which the alcohol consumers were the majority (122/209 responses). Alcohol consumers were the minority in the other 3 subgroups (group 2: 34/93; group 3: 51/104; group 4: 48/107).

Population FibroScan scores. Using FibroScan to measure liver stiffness, the scores in the total population ranged between 1.5 kPa and 37.1 kPa, with an average of 6.13 kPa ± 3.76 kPa. Figure 1A is a scatterplot of the liver stiffness (FibroScan scores) in kPa vs the cumulative dosage of MTX in mg. The dotted line is the best linear fit to the data and shows no significant correlation between the 2 variables.

In order to assess interobserver agreement, intraclass correlation coefficient (ICC) estimates were calculated on 177 subjects. Based on a mean rating, absolute agreement, 2-way mixed effects model, the overall ICC was 0.93 (95% CI 0.91–0.95; data not shown).

In order to further investigate the effect of cumulative MTX intake on liver stiffness, we calculated the FibroScan score distribution among the 4 individual subgroups of cumulative MTX dosage (Table 2). As shown in Figure 1B, which plots the average FibroScan score vs cumulative MTX dosage, there was no significant difference between the 4 subgroups.

FibroScan scores were also converted to ordinal categories, from stage F0 to stage F4, according to the criteria reported by Wong et al.[28] Whereas stage F0 and F1 may be considered normal, stage F3 or F4 indicate high liver stiffness, with possible presence of numerous septa with or without cirrhosis.

Table 3 shows the FibroScan scores, classified into 1 of 4 possible stages: F0/1, F2, F3, and F4, in each of the 4 study subgroups and in the total population. The majority of the study participants (79.6%) had a FibroScan score of < 7.1 (stage F0/1), indicating no liver fibrosis. The prevalence of FibroScan score ≥ 7.1 kPa (F2+) was 20.4%, and that of FibroScan score ≥ 8.7 kPa (F3+) was 12.7% in the entire study population. In the cumulative MTX dosage ≥ 6000 mg (group 4), the prevalence was 15.5% and 9.1% for F2+ and F3+, respectively. The observed prevalence of F2+ or F3+ liver fibrosis was similar in the 4 subgroups.

Univariable linear analysis. The results of the univariable linear analysis suggested that the characteristics that were associated with higher FibroScan scores included male sex, weight, waist circumference, and BMI (Table 4). Age, alcohol consumption, and the cumulative MTX dosage were not found to be significantly correlated with the FibroScan score in the univariable linear models.

Multivariable linear analysis. In this study, multivariable linear analysis (selected at $\alpha = 0.15$) revealed that factors that had a significant correlation with liver stiffness included age, male sex, waist circumference, and BMI (Table 4).

Table 3. Number of participants in cumulative MTX dosage subgroups and FS (F0–F4) subgroups.[a]

MTX Subgroup	F0–F1	F2	F3	F4	F2+	F3+
Group 1, n = 211	159 (75.4)	24 (11.4)	8 (3.8)	20 (9.5)	52 (24.6)	28 (13.3)
Group 2, n = 95	73 (76.8)	6 (6.3)	10 (10.5)	6 (6.3)	22 (23.2)	16 (16.8)
Group 3, n = 104	89 (85.6)	3 (2.9)	5 (4.8)	7 (6.7)	15 (14.4)	12 (11.5)
Group 4, n = 110	93 (84.5)	7 (6.4)	4 (3.6)	6 (5.5)	17 (15.5)	10 (9.1)
Total, N = 520	414 (79.6)	40 (7.7)	27 (5.2)	39 (7.5)	106 (20.4)	66 (12.7)

Values are n (%) unless otherwise indicated. [a] The prevalence of participants with corresponding FS scores (F0–F4) in 4 cumulative MTX dosage subgroups. Also demonstrated are prevalence of participants with stages F2+ and F3+ liver stiffness according to FibroScan measurements. FS subgroups according to severity of fibrosis are as follows: F0–F1: FS < 7.1 kPa; F2: 7.1 kPa ≤ FS < 8.7 kPa; F3: 8.7 kPa ≤ FS < 10.4 kPa; F4: 10.4 kPa ≤ FS; F2+: 7.1 kPa ≤ FS; F3+: 8.7 kPa ≤ FS. Cumulative MTX exposure subgroups are as follows: group 1: cumulative dose of MTX ≤ 499 mg; group 2: 500 mg ≤ cumulative dose of MTX < 3000 mg; group 3: 3000 mg ≤ cumulative dose of MTX < 6000 mg; group 4: cumulative dose of MTX > 6000 mg. F2+: FS ≥ 7.1; F3+: FS ≥ 8.7; FS: FibroScan score; MTX: methotrexate.

Table 4. Linear regression analysis.

	Regression Coefficient[a]	95% CI	Pr ≥ |t|
Univariable analysis			
Age (div 10)	0.02	–0.01 to 0.05	0.23
Sex (male)	0.13	0.06–0.21	0.0006
Weight (div 10)	0.06	0.04–0.08	< 0.0001
Waist circumference (div 10)	0.09	0.06–0.11	< 0.0001
BMI (div 5)	0.09	0.07–0.12	< 0.0001
Alcohol consumption	–0.02	–0.09 to 0.06	0.66
Cum MTX dose: 500–2999 mg	0.01	–0.09 to 0.12	0.82
Cum MTX dose: 3000–5999 mg	–0.03	–0.13 to 0.07	0.59
Cum MTX dose: ≥ 6000 mg	–0.07	–0.17 to 0.03	0.18
Multivariable analysis			
Intercept	0.91	0.64–1.18	< 0.0001
Age (div 10)	0.03	–0.0004 to 0.05	0.05
Sex (male)	0.11	0.04–0.18	0.004
Waist circumference (div 10)	0.04	0.008–0.07	0.02
BMI (div 5)	0.06	0.02–0.10	0.002

Univariable and multivariable linear analysis selected at $\alpha = 0.15$. [a] In linear regression, the regression coefficient represents how much the dependent variable increases when the corresponding predictor variable is increased by 1 unit and the other predictors are held constant. cum: cumulative; div: divided by; MTX: methotrexate; Pr ≥ |t|: probability of observing any value equal or larger than t.

Table 5. Logistic regression analysis.

	Regression Coefficient[a]	OR	OR Range	$P(\chi^2)$
Univariate analysis				
Age (div 10)	0.16	1.18	0.96–1.44	0.12
Sex (male)	0.26	1.291	0.76–2.18	0.34
Weight (div 10)	0.28	1.323	1.18–1.48	< 0.0001
Waist circumference (div 10)	0.38	1.467	1.24–1.73	< 0.0001
BMI (div 5)	0.46	1.578	1.33–1.88	< 0.0001
Alcohol consumption	–0.17	0.848	0.51–1.42	0.53
Cum MTX dose: 500–2999 mg	0.28	1.324	0.68–2.58	0.41
Cum MTX dose: 3000–5999 mg	–0.16	0.852	0.41–1.75	0.66
Cum MTX dose: ≥ 6000 mg	–0.43	0.654	0.31–1.40	0.27
Multivariate analysis				
Intercept	–5.91	—	—	< 0.0001
Age (div 10)	0.21	1.23	0.99–1.52	0.06
BMI (div 5)	0.47	1.60	1.34–1.92	< 0.0001

Univariable and multivariable logistic regression analysis selected at $\alpha = 0.15$. EST type is MLE. [a] In logistic regression, the regression coefficient is the ln of the OR. More precisely, if "b" is the regression coefficient, exp(b) is the OR corresponding to a 1 unit change in the dependent variable. cum: cumulative; div: divided by; EST: estimate; MLE: maximum likelihood estimation; MTX: methotrexate; OR: odds ratio; $P(\chi^2)$: probability of chi-square.

Univariable logistic analysis. The outcome variable was the measured FibroScan score converted into 1 of 4 possible stages: F0/1, F2, F3, or F4. Using the univariable logistic models, factors that were associated with higher FibroScan stages included weight, waist circumference, and BMI (Table 5). Sex, age, alcohol consumption, and the cumulative MTX dosage were not found to be significantly correlated with the stages of liver stiffness.

Multivariable logistic analysis. Last, we performed multivariable logistic analysis (Table 5) to model the probability of a positive

correlation between our explanatory variables and higher stages of liver stiffness. Logistic regression modeling (at $\alpha = 0.15$) revealed that only age and BMI had a significant correlation with higher liver stiffness. Other characteristics, including the cumulative MTX dosage, did not have significant correlation with the stages of liver stiffness in our models.

DISCUSSION

Previous guidelines from the ACR defer to the American Association for the Study of Liver Disease (www.aasld.org) for monitoring in patients with additional risk factors for liver disease, and hepatologists are increasingly using noninvasive strategies such as FibroScan to detect fibrosis. We present the largest prospective study to date, to our knowledge, evaluating liver stiffness in patients with inflammatory arthritis treated with MTX, using FibroScan.

While the majority of patients in our study had normal FibroScan scores, 20.4% of patients had FibroScan scores > 7.1 kPa (ie, stages F2, F3, or F4), compared to 16% of MTX-treated patients with RA reported by Bafna et al.[25] In our cohort, 12.7% of patients had FibroScan scores > 8.7 kPa (ie, stages F3 or F4) indicating advanced fibrosis. This number is higher than the 4.0% rate in Bafna's study,[25] and the 8.5% rate of severe liver fibrosis among patients with various benign inflammatory disorders on MTX reported by Laharie et al.[27]

In our study, factors that significantly correlated with an increase in liver stiffness in multivariable linear analysis included age, male sex, waist circumference, and BMI. In our logistic models, the only factors that correlated with higher stages of liver stiffness were age and BMI.

According to the literature, the relationship between MTX treatment and the development of liver fibrosis is determined by multiple factors, including patient-related and disease-related characteristics.[30–38] Patient-related factors associated with MTX-induced hepatotoxicity include high alcohol consumption, history of liver disease, persistently abnormal AST/ALT levels, diabetes, obesity, NAFLD, hepatotoxic drugs (other than MTX), and hyperlipidemia.[30]

With respect to disease-related characteristics, although historical reports suggest that nearly all patients with RA who have been treated with MTX have some liver biopsy abnormalities,[31] serious liver disease is believed to be uncommon in RA.[32] Some observational studies have suggested that patients with psoriasis (PsO) may be more likely than patients with RA to develop severe fibrosis.[33,34,35] This might be a result of higher incidence of obesity, diabetes, alcoholism,[36] and NASH[37,38] among patients with PsO. Interestingly, in a separate univariable analysis of subgroups in our study (analysis not shown here), patients with PsA had significantly greater ($P = 0.001$) stiffness scores compared to patients with RA on FibroScan. However, the difference disappeared completely in multivariable models after adjusting for waist circumference, weight, and age.

As shown in Table 3, surprisingly, patients in the higher MTX cumulative dosage subgroups had lower prevalence of liver fibrosis (stages F3 or F4). The observed findings did not seem to be a result of patients with more longstanding disease having less obesity and lower BMI, as these variables were similar between all MTX dosage subgroups. An explanation could be that patients on longstanding MTX treatment are being closely monitored with serial blood tests by their rheumatologist, appropriate action (eg, reduction in dosage or stoppage of MTX, consideration of liver biopsy, and/or referral to hepatology) is taken with abnormal liver enzymes, and those with abnormal findings are selected out.

In other words, it would be logical to assume that those patients who developed liver complications during the course of their treatment had their treatment MTX discontinued. Conversely, those patients who were able to remain on MTX for extended periods presumably did not have cause to have MTX discontinued and they stayed on the medication. This is a subject that needs to be investigated further in future research. However, while cumulative MTX is known to be associated with liver damage in the absence of monitoring and appropriate intervention,[8] the findings are reassuring in that current rheumatology practice appears to be safe and effective in screening for liver fibrosis in patients on long-term low-dose MTX therapy.

In the present study, patients were managed routinely by their rheumatologist. This was both a strength and a limitation. It was a strength in that the outcomes could be said to reflect standard rheumatology practice as it pertains to management of patients receiving MTX. However, it was also a limitation in that there was a potential for bias, given that the treating rheumatologist would presumably lower the dose of MTX or stop the medication altogether in the event of clinical complications such as elevated liver enzymes or other side effects attributable to MTX.

FibroScan is fast, noninvasive, and can reliably differentiate steatohepatitis from fibrosis in patients with NAFLD, unlike ALT levels, US, computed tomography, and magnetic resonance imaging. While FibroScan was technically not possible in 22 patients, results in > 500 patients in our study show that FibroScan can successfully be implemented to assess liver stiffness in the majority of MTX-treated patients with inflammatory arthritis.

In our study population, 12.7% had stage 3 or 4 (F3+) liver fibrosis (Table 3). Among subjects in group 1 (MTX ≤ 499 mg), 13.3% had F3+ fibrosis, whereas in group 4 (MTX > 6000 mg) the rate of fibrosis was 9.1%. While standard practice at our center appeared to have been effective in screening out some patients with liver fibrosis, there still remained a certain proportion who would have remained unidentified without the use of FibroScan. Whether and how often to screen patients on long-term MTX therapy with FibroScan remains a topic for future research.

One potential issue to consider is that waist circumference and high BMI appeared to have a high correlation with elevated FibroScan scores. This makes it more difficult to detect changes in FibroScan scores, due to MTX or other risk factors, in patients who are obese. Moreover, the high prevalence of metabolic syndrome in patients with PsO may also confound utility of TE for monitoring of MTX toxicity in this subgroup. In

general, patients who are overweight may need to be monitored more closely (eg, with more frequent FibroScans or with liver specialist involvement).

Although patients receiving DMARDs with potential risk of hepatotoxicity (AZA, LEF, and SSZ) were excluded, a limitation of this study was that we did not look at other hepatotoxic drugs such as acetaminophen and nonsteroidal antiinflammatory drugs.

Another possible limitation relates to the distribution of alcohol consumers within the 4 groups. In subgroup 1, the alcohol consumers were the majority, whereas in the other 3 subgroups, alcohol consumers were the minority. This is not surprising as patients on long-term MTX therapy would be advised by their clinicians to stop or minimize alcohol intake. Nevertheless, it could be argued that alcohol consumption in group 1 was a confounder in this study. However, results of both univariable and multivariable regression analyses revealed no significant correlation between alcohol consumption and FibroScan scores.

Finally, this was a cross-sectional study. A prospective study with FibroScan scores at baseline and subsequent measurements (eg, at 1- to 3-year intervals depending on level of risk such as older male patients with high BMI and waist circumference) could better answer questions about potential change in scores in individual patients and relate it to different baseline variables.

In summary, in the present study, liver fibrosis measured with FibroScan was not associated with cumulative MTX dosage. Significant factors for liver stiffness were BMI, waist circumference, male sex, and age. While cumulative MTX is known to be associated with liver damage in the absence of monitoring and appropriate intervention,[8] the findings are reassuring in that current rheumatology practice appears to be safe and effective in screening for liver fibrosis in patients with inflammatory arthritis on long-term low-dose MTX therapy.

Given the strong associations found in this study, we recommend that clinicians pay especially close attention to patients with higher BMI, greater waist circumference, male sex, and older age when monitoring for liver fibrosis in the setting of long-term MTX therapy.

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