Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Study of Methotrexate-induced Chronic Hepatotoxicity in Patients of Rheumatoid Arthritis

Pooja Londhe[1], **Juhi Kawale**[2]

[1]MD, Department of General Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India, [2]Assistant Professor, Department of General Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

Abstract

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disease with a high morbidity rate. Methotrexate (MTX) is effective in reducing disease activity but can cause liver injury. Liver biopsy is the gold standard to assess fibrosis, but it is an invasive procedure. FibroScan is a validated non-invasive tool to detect and quantify liver fibrosis. The present study aimed to assess the prevalence of liver fibrosis caused by FibroScan in patients with RA on long-term MTX therapy. A study conducted at Seth GS Medical College, KEM Hospital.

Materials and Methods: Observational prospective cohort study. The study included patients (≥18 years of age) with RA who had been on MTX for more than 2 years/cumulative dose of 1.5 g. Liver fibrosis was assessed by the TE method and biochemical parameters. For FibroScan, the cutoff value of 7.0 kPa was considered abnormal.

Results: A total of 140 patients were enrolled, of which 120 were female (85.7%). TRA patient with consumption of methotrexate for more than 2 year or with cumulative dose of 1.5 gm were enrolled. The mean age was 50.5 year. Liver fibrosis was assessed by the Fibrosacan and biochemical parameter. The mean liver stiffness was 5.0± 1.2 kPa. Seven patients had mild fibrosis (7.1–9.5 kPa), and only one had severe fibrosis, defined as a score > 9.5 kPa. FibroScan scores significantly correlated with cumulative dose of MTX (P = 0.001) and obesity (P = 0.009), but no correlation was found with age, gender, serum glutamic oxaloacetic transaminase, or serum glutamic pyruvic transaminase.

Conclusion: MTX-induced hepatotoxicity can present with normal/mildly elevated liver enzymes, so biochemical markers should not be used for early detection of liver fibrosis. FibroScan is a useful tool for monitoring MTX-induced liver fibrosis. Liver fibrosis, as evidenced by increased liver stiffness on FibroScan, is prevalent among patients on long-term MTX therapy for RA.

Key words: FibroScan, Methotrexate, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease that affects 0.5–1% of the general population. The condition has a significant morbidity rate since it mostly affects the tiny joints of the hands. Early identification and the creation of disease-modifying antirheumatic medications (DMARDs) have significantly improved the long-term prognosis.[1] The preferred DMARD for both early and advanced RA is still methotrexate (MTX). The European League Against Rheumatism and the American College of Rheumatology both support it as a first-line treatment. 23–40% of patients show a notable improvement with MTX treatment.[2]

MTX decreases purine and pyrimidine synthesis by blocking folate metabolism and dihydrofolate reductase, which suppresses the synthesis of DNA and RNA.[3] With significant decreases in morbidity and mortality, it is the recommended agent due to its effectiveness, cost, and capacity to minimize disease activity and damage.[2]

Estimates of the liver's involvement in RA patients taking MTX range from 1 to 10 g cumulative dosage. Until obvious liver damage develops, patients are frequently asymptomatic, requiring careful observation. One accessible and non-invasive tool that can be used for this is FibroScan.[4] Although MTX is usually well tolerated, it has

Access this article online

www.ijss-sn.com

Month of Submission : 04-2026
Month of Peer Review : 05-2026
Month of Acceptance : 06-2026
Month of Publishing : 06-2026

Corresponding Author: Dr. Pooja Londhe, Department of General Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.

been linked to several negative hepatic outcomes, including fatty liver, fibrosis, and, infrequently, cirrhosis, as well as asymptomatic transaminase increases.[4,5]

Although previous guidelines suggested recurrent liver biopsies, their use is restricted due to procedural hazards, and conventional liver enzymes have a poor correlation with histological alterations. As a substitute for biopsy in chronic liver disorders, FibroScan has been proven to have a strong correlation with histology results. With little information about RA, the majority of research has been on psoriasis and psoriatic arthritis.[6] The current study sought to determine the frequency of liver fibrosis linked to long-term MTX treatment in RA and how it correlated with cumulative dosage.

MATERIALS AND METHODS

This is an observational prospective cohort study conducted in the Department of Medicine, Seth GS Medical College and KEM Hospital, Parel, Mumbai, for a duration of 18 months.

Patients of RA with an age of more than 18 years and on MTX for more than 2 years or a cumulative dose of 1.5 g were recruited. Those with liver involvement, mainly due to other causes such as hepatitis B, hepatitis C, or those taking leflunomide, were excluded from the study. Furthermore, significant alcohol consumption, i.e., more than 30 g for men and 20 g for women, was not excluded.

Aims and Objectives

- To study the prevalence of MTX-induced hepatotoxicity in patients with RA
- To study the clinical profile of RA in those on MTX for more than a 2-year cumulative dose of 1.5 g
- To determine risk factors for MTX-induced hepatotoxicity
- To determine the stage of liver damage and correlate it with the dose of MTX by non-invasive tests such as FibroScan.

Methodology

Written informed consent of study participants was taken after approval from the institutional ethical committee. The patient's history and general and systemic examination findings were noted with the help of a standard, pre-validated, semi-structured case record proforma. Detailed history and previous records were reviewed for all patients. Details regarding the duration of the disease, hepatotoxic medications used, and details of all relevant previous investigations were noted. All patients underwent FibroScan and blood tests.

The patients thus would be screened and selected as per the MTX dose of >1.5 g or more than 2 years.

FibroScan – All patients were subjected to TE after overnight fasting, using the ECHOSENS FIBROSCAN 530 COMPACT model. With the patient in the supine position and the right upper limb abducted, an ultrasound-like probe was placed at the right mid-axillary area between the 9th and 10th or 11th intercostal space over the skin. The vibration wave was generated by the probe, and a gentle "flick" was felt by the patient each time. A total of 8–10 valid measurements were taken, with each having a success rate of >60% and an interquartile range of <30%. The median of 8–10 valid measurements expressed in kPa was taken as representative of liver stiffness. The cutoff of ≥7.0 was taken for fibrosis. The above cutoff for fibrosis was from studies of TE in RA, psoriatic arthritis, and non-alcoholic fatty liver disease patients. We used the Metavir scoring system.

Statistical Analysis

The data were entered with the help of MS Excel sheets. Analysis was done with the help of the Statistical Package for the Social Sciences 23.0 software. The data were represented in the form of tables and charts for frequency analysis. Mean, mode, and median were considered to study the central tendency of the quantitative parameters. Moreover, for standard deviation for assessing the degree of variation for comparing quantitative data, the Student's *t*-test was used, and for qualitative data, Pearson's Chi-square (Fisher's exact test) was used. For the representation of MTX cumulative dose and E value, the Spearman rank test was used.

$P < 0.05$ was considered statistically significant.

Hepatic Assessment

All patients underwent FibroScan. Routine blood tests were analyzed with a focus on liver function tests, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), prothrombin time, and albumin. A cutoff ≥7.0 kPa was taken for significant fibrosis. The mean liver stiffness was 5.0 ± 1.2 kPa. Eight patients (5.7%) had liver stiffness ≥7.0 kPa. Seven had mild fibrosis (7.1–9.5 kPa), and one had severe fibrosis defined as >9.5 kPa. Twenty-five (17.9%) had transaminitis in the form of mild SGOT/SGPT elevation. Patients with fibrosis had a significant positive relation with obesity. Distribution by fibrosis stage showed F0 in 74 (52.9%), F1 in 62 (44.3%), F2 in 2 (1.4%), and F3 in 1 (0.7%). The mean FibroScan score was 5.0 ± 2.0 kPa, with fibrosis prevalence of 16%. Kumar *et al.* and Arena *et al.* reported 7.5% and 11%, respectively.

DISCUSSION

In this study, 8 patients i.e 5.7% patients had positive FibroScan values ≥ 7 kPa. Twenty (14.3%) had borderline values (6–7 kPa), requiring repeat FibroScan after 6 months.

The present study was conducted in the Department of Medicine, Seth GS Medical College and KEM Hospital, Parel, Mumbai, Maharashtra. Out of 140 cases, 120 (85.7%) were female, and 20 (14.3%) were male. The majority of subjects belonged to the 36–50 years age group, with 70 (50%), followed by 61 (43.6%) in the 51–70 years age group. Only 2 (1.4%) were older than 70 years. The average age was 50.5 ± 9.9 years. A similar gender distribution was reported by Kumar *et al*.[7] The distribution of cases in age groups <35 years, 36–50 years, 51–70 years, and >70 years was 7 (9.8%), 70 (50%), 61 (43.6%), and 2 (1.4%). In the study by Bafna *et al*.,[8] the mean age was 47.2 ± 11.3 years, compared to the elderly population in Arena *et al*.,[9] In this study, the second largest group was 51–70 years.

Patients were divided based on body mass index (BMI) into four groups. 68 (48.6%) had normal BMI, 44 (31.4%) were overweight, and the remainder were underweight or obese. A significant positive correlation was observed between obesity, deranged OT/PT values, and FibroScan scores. The cumulative dose of MTX correlated with FibroScan values, but this was not statistically significant, similar to Kumar *et al*.[7] The duration of MTX use was 271 weeks in our study compared to 317.5 weeks in Kumar *et al*.,[7] likely explaining the absence of correlation. In Bafna *et al*.,[8] the cumulative duration was 336 weeks, and a positive correlation was found.

Comorbidities included diabetes mellitus in 6 (4.3%), diabetes with hypertension in 8 (5.7%), hypertension in 14 (10%), chronic kidney disease in 1 (0.7%), and thyroid disorder in 7 (5%).

All patients underwent FibroScan and baseline ultrasonography. Routine blood tests included liver function tests, SGOT, SGPT, prothrombin time, and albumin. A cutoff ≥7.0 kPa was taken for significant fibrosis. The mean liver stiffness was 5.0 ± 1.2 kPa. Eight patients (5.7%) had liver stiffness ≥7.0 kPa. Seven had mild fibrosis (7.1-9.5 kPa), and one had severe fibrosis (>9.5 kPa). Twenty-five (17.9%) had transaminitis, and 24 (17.1%) had altered liver echotexture on ultrasonography.

Patients with fibrosis had a significant association with obesity. Distribution by fibrosis stage showed F0 in 74 (52.9%), F1 in 62 (44.3%), F2 in 2 (1.4%), and F3 in 1 (0.7%). The mean FibroScan score was 5.0 ± 2.0 kPa, with a fibrosis prevalence of 16%. Kumar *et al*.[7] and Arena *et al*.[9] reported 7.5% and 11%, respectively.

Eight patients (5.7%) had positive FibroScan values ≥7.0 kPa. Fourteen (14.3%) had borderline values (6–7 kPa), requiring a repeat FibroScan after 6 months. Five of eight patients consumed >4 g MTX, showing a correlation with cumulative dose. Out of 8 positive fibroscan patients , 1 patient had consumed cumulative dose of 1.56 g only and had normal BMI which suggest underlying possible genetic predisposition to develop methotrexate induced hepatotoxicity. Six of eight were obese, showing a significant association with hepatotoxicity. Five of eight had altered echotexture on ultrasonography. Only one had mild SGPT elevation, showing no significant biochemical correlation.

Interpretation and Comparison

The observed prevalence of clinically significant stiffness is 5.7 %. Six of eight were obese, showing a significant association with MTX exposure, comorbidity burden, and FibroScan cutoffs. The mean FibroScan score of 5.0 ± 2.0 kPa and the predominance of F0-F1 stages suggest that most patients on long-term MTX do not develop advanced fibrosis within the exposure durations captured here. The lack of a statistically significant correlation between cumulative MTX dose and FibroScan score in this cohort may be explained by the relatively shorter median duration of exposure compared with studies that reported a positive association, by differences in cumulative dose distributions, or by confounding from metabolic risk factors.[3]

Risk Factors and Mechanistic Considerations

Obesity emerged as the most consistent correlate of fibrosis in this cohort: Six of eight FibroScan-positive patients were obese, and BMI was higher in the fibrosis group (25.4 ± 4.3) than in the no-fibrosis group (23.4 ± 2.6), with a p value at the threshold of significance.[10] This pattern supports the hypothesis that metabolic liver disease and steatosis potentiate MTX -related hepatotoxicity, either by additive injury or by increasing susceptibility to fibrogenesis.[11] The frequent concurrence of altered ultrasonography (five of eight FibroScan-positive patients) reinforces the role of steatosis or parenchymal change as a cofactor. Biochemical markers were poorly sensitive: Only one FibroScan-positive patient had mild SGPT elevation, underscoring that normal transaminases do not exclude significant stiffness and that reliance on liver enzymes alone may miss subclinical fibrosis.[12]

CONCLUSION

FibroScan is a practical, non-invasive screening tool for patients on long-term MTX, particularly for those with obesity or abnormal liver imaging. Using a conservative cutoff of ≥7.0 kPa identified a small but clinically relevant subgroup (8 of 140, 5.7%) who warrant closer followup and potential modification of therapy. Patients with borderline E values (6–7 kPa; 20

of 140, 14.3%) should be reevaluated at 6 months to detect progression.[7] Routine monitoring strategies that combine clinical risk stratification (BMI, metabolic comorbidities), periodic FibroScan, and selective biochemical testing may be more effective than serial liver enzymes alone.[13]

For clinical practice, consider baseline FibroScan for patients initiating long-term MTX who have obesity or abnormal liver imaging, and repeat assessment for those with borderline values or rising clinical risk. Future research should prioritize longitudinal followup to determine the temporal relationship between MTX exposure, metabolic risk factors, and fibrosis progression, and should explore genetic and environmental modifiers of hepatotoxicity. In this cohort, most patients on MTX had no advanced fibrosis, but a small subset, predominantly those with obesity or altered ultrasonography-demonstrated clinically relevant stiffness, supported targeted surveillance strategies.[14]

Limitations

A larger, longer study is warranted with follow-up FibroScan to better define the values defining irreversibility in rheumatological disorders, which would possibly better correlate with histopathology. Other causes, such as non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and autoimmune hepatitis, were not ruled out. Patients with an underlying old fatty liver may be included. Other factors, like genetic were not ruled out.

ACKNOWLEDGMENT

We acknowledge the support extended by the Department of General Medicine for their invaluable support in managing these patients. There are no financial disclosures to be made on our part.

COMPLIANCE WITH ETHICAL STANDARDS

The study work has been approved by the Institutional Ethics Committee II. Project number – EC/125/2021 on June 18, 2021.

CONSENT

Informed consent was taken prior to the start of the study.

REFERENCES

1. Mustafa SH, Ahmad T, Balouch M, Iqbal F, Durrani T. Safety profile of methotrexate therapy in patients with rheumatoid arthritis. Cureus 2022;14:27047.
2. Shinde CG, Venkatesh MP, Kumar TM, Shivakumar HG. Methotrexate: A gold standard for treatment of rheumatoid arthritis. J Pain Palliat Care Pharmacother 2014;28:351-8.
3. (PDF) Methotrexate-Induced Organ Toxicity in Patients with Rheumatoid Arthritis: A Review Article. Available from: https://www.researchgate.net/publication/343892562_methotrexate/induced_organ_toxicity_in_patients_with_rheumatoid_ar [Last accessed on 2025 May 01].
4. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda, MD; p. 2012. Available from: https://www.ncbi.nlm.nih.gov/books/nbk547852 [Last accessed on 2025 May 01].
5. Gaies E, Jebabli N. Methotrexate side effects: Review article. J Drug Metab Toxicol 2012;4:2157-7609.
6. Malekzadeh R, Poustchi H. Fibroscan for assessing liver fibrosis: An acceptable alternative for liver biopsy. Hepat Mon 2011;11:157-8.
7. Kumar A, Vasdev V, Manrai M, Bhayana A, Hegde A, Arjun MN, *et al*. (PDF) Assessment of hepatic fibrosis in patients with rheumatoid arthritis on long-term methotrexate therapy using transient elastography. Indian J Rheumatol 2018;13:246-51.
8. Bafna P, Sahoo RR, Hazarika K, Manoj M, Rungta S, Wakhlu A. Prevalence of liver fibrosis by Fibroscan in patients on long-term methotrexate therapy for rheumatoid arthritis. Clin Rheumatol 2021;40:3605-13.
9. Arena U, Vizzutti F, Abraldes JG, Corti G, Stasi C, Moscarella S, *et al*. Reliability of transient elastography for the diagnosis of advanced fibrosis in chronic hepatitis C. Gut 2008;57:1288-93.
10. Erre G, Luisa C, Meloni P, Castagna F, Mangoni AA, Piga M, *et al*. Methotrexate therapy is not associated with increased liver stiffness and significant liver fibrosis in rheumatoid arthritis patients: A cross-sectional controlled study with real-time two-dimensional shear wave elastography. Eur J Intern Med 2019;69:57-63.
11. Qadri S, Ahlholm N, Lønsmann I, Pellegrini P, Poikola A, Luukkonen PK, *et al*. Obesity modifies the performance of fibrosis biomarkers in nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2021;31:e2008-20.
12. Kamali L, Adibi A, Ebrahimian S, Jafari F, Sharifi M. Diagnostic performance of ultrasonography in detecting fatty liver disease in comparison with fibroscan in people suspected of fatty liver. Adv Biomed Res 2019;27:69.
13. Lee HW, Lee JS, Kim MN, Kim BK, Park JY, Kim DY, *et al*. Risk stratification by noninvasive tests in patients with metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31:1018-31.
14. Bichenapally S, Khachatryan V, Muazzam A, Hamal C, Velugoti LS, Tabowei G, *et al*. Risk of liver fibrosis in methotrexate-treated patients: A systematic review. Cureus 2022;14:e30910.

How to cite this article: Londhe P, Kawale J. Study of Methotrexate-induced Chronic Hepatotoxicity in Patients of Rheumatoid Arthritis. Int J Sci Stud 2026;14(3):1-4.

Source of Support: Nil, **Conflicts of Interest:** None declared.