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# Transient Elastography for Detecting Liver Fibrosis in Methotrexate-Treated Patients with Inflammatory Disorders: A Systematic Review

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## Abstract

**Objective**: Methotrexate (MTX) is used for the treatment of inflammatory disorders but can cause liver enzyme abnormalities. Liver enzyme elevations are neither specific nor sensitive for detecting liver fibrosis. Liver biopsy is an imperfect gold standard with its own limitations. Fibroscan is a non-invasive technique used to evaluate liver fibrosis. The objective of this study was to review the literature to characterize the utility of Fibroscan for detection of liver fibrosis compared to biopsy in patients with inflammatory conditions treated with MTX.

**Methods**: A systematic literature search was carried out of all English publications. The search was limited to studies involving subjects greater than 18 years of age, meeting criteria for the diagnosis of Crohn's Disease (CD), Rheumatoid Arthritis (RA), psoriasis (Ps) or psoriatic arthritis (PsA).Studies where liver biopsy was not performed were excluded.

**Results**: Among 18 references identified, three publications met the criteria. The selected studies were prospective, cross-sectional studies (n=21-518).The cutoffs for significant or severe fibrosis based on Fibroscan score (FSS) differed amongst the studies (7kPA-8.7kPa).FSS did not reflect biopsy findings in a large portion of patients (40%-69%).The accuracy of Fibroscan for the detection of no or mild fibrosis (F<2) ranged from 0%-88%.The accuracy of Fibroscan for the detection of significant fibrosis or cirrhosis (F2-4) ranged from 0%-30%.

**Conclusions**: There is insufficient evidence to support the use of Fibroscan for detecting liver fibrosis in a MTX-taking population with inflammatory disorders.

**Keywords**: Fibroscan; Liver fibrosis; Crohn's Disease; Psoriatic Arthritis; Rheumatoid Arthritis; MTZ

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## Introduction

Methotrexate (MTX) is frequently used for the induction and maintenance of disease remission in a number of inflammatory conditions, including Psoriasis (Ps), Psoriatic Arthritis (PsA), Rheumatoid Arthritis (RA) as well as Crohn's Disease (CD) [1-4]. Long term MTX has been associated with a number of side effects including interstitial lung disease, myelosuppression and acute and chronic liver disease [5]. Liver biopsy of patients taking low-dose MTX may range from normal to steatosis to hepatic fibrosis and cirrhosis [6]. Whether MTX directly induces hepatotoxicity is unclear.

Current guidelines set forth by the American Colleges of Gastroenterology and Rheumatology suggest that patients on MTX be monitored monthly for abnormalities in their AST or ALT. Liver biopsy should be performed if the majority of a patient's liver enzymes are abnormal over a one year period [7, 8]. However, liver enzyme elevations are neither specific nor sensitive for the detection of underlying liver fibrosis [9]. Furthermore, liver biopsy is an imperfect gold standard with its own limitations; this includes sampling error due to the heterogeneous distribution of fibrosis and inter-observer variability with biopsy reporting as well as risks including bleeding and pain [10].

Fibroscan (transient elastography of the liver) is a new, non-invasive technique used to evaluate liver fibrosis. Fibroscan Score (FSS) is based on the measurement of the velocity (kPa) of an elastic shear wave as it travels through hepatic tissue providing an estimate of liver stiffness [10]. It has been validated in the Hepatitis C population in comparison to the METAVIR. The METAVIR staging system is a five-point scale used in the assessment of the degree of liver fibrosis seen on liver biopsy. A score of 0 to 4 is made based on the following criteria: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with septa; F3, numerous septa without cirrhosis; F4, cirrhosis. FSS correlates with METAVIR in the following way: F0-1, <7kPa; F2, 7.1-9.5; F3, 9.6-12.5; F4, >12.5 [11]. Given its use in assessing and monitoring liver disease in the setting of Hepatitis C infection, this raises the question if this technology could be applied for monitoring other liver diseases, specifically MTX-induced liver disease.

The objective of this study was to systematically review the literature to characterize the utility of transient elastography (Fibroscan) for the detection of liver fibrosis compared to biopsy in a MTX-taking population.

## Materials and Methods

### Literature Search

We performed a search of the following bibliographic data-bases: PubMed (1950 to July 2009), EMBASE (1980 to July 2009) and the Cochrane Library (up to July 2009).Abstracts from the annual scientific meetings of the ACR(2005–08), European League Against Rheumatism (EULAR) (2004–09), American Gastroenterology Association (AGA) (2005-2011), Canadian Association of Gastroenterology (CAG) (2005-2011), American College of Gastroenterology (ACG) (2005-2011), and European Crohn's and Colitis Organization (ECCO) (2005-2011) were also searched. The search strategy is described in Supplementary **Figure 1**. Our search combined terms for ‘Fibroscan®’, ‘ Inflammatory bowel disease’, ‘Inflammatory arthritis’, ‘Psoriatic arthritis’, ‘Seronegative inflammatory arthritis’, ‘Fibro test‘, ‘Hepatic fibrosis’, ‘ Liver fibrosis’, ‘Liver biopsy’, ‘Methotrexate’, ‘ Transient elastography’, ‘ Elastography and Liver’.

**Figure: 1**

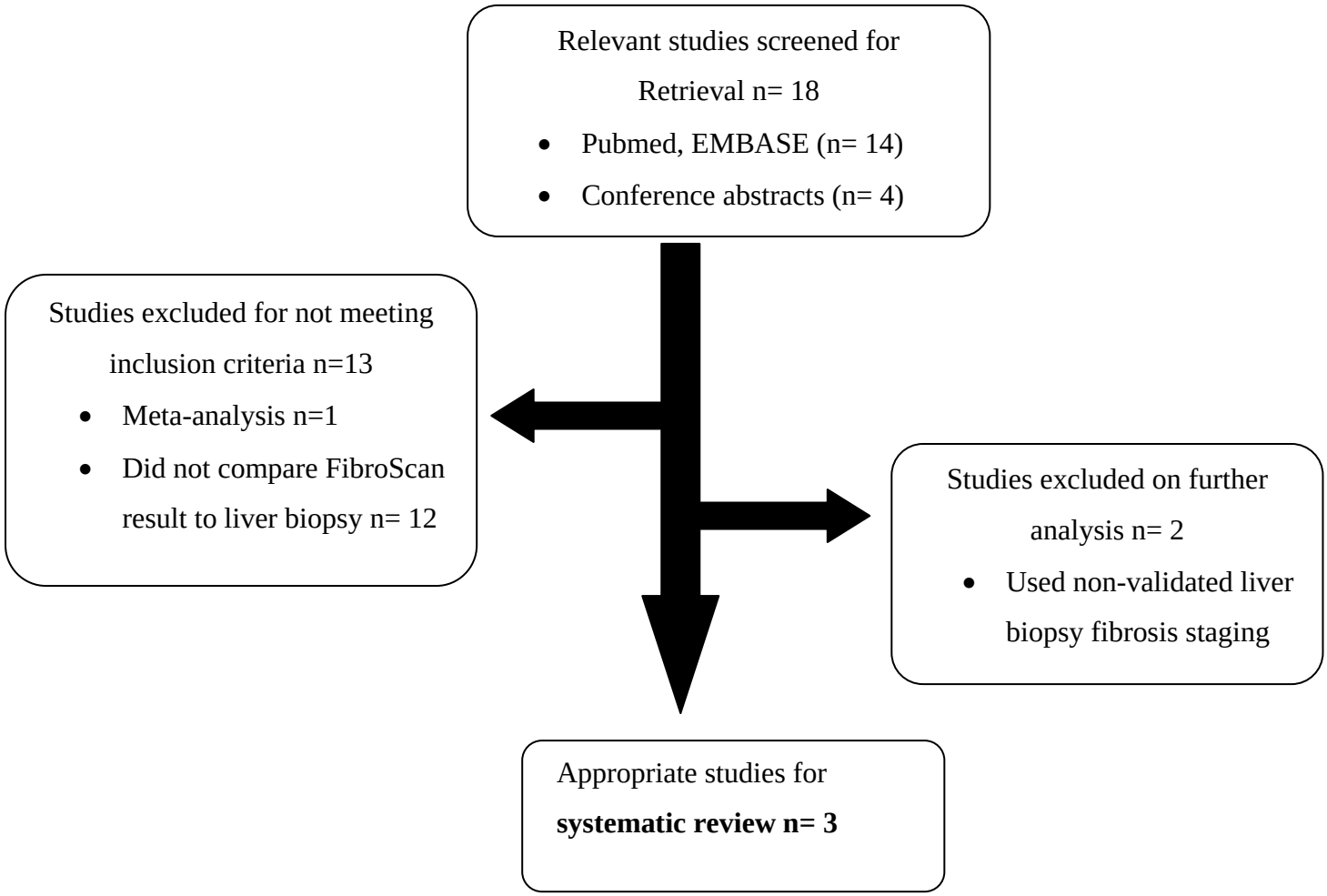


**Figure 1:** Transient elastography for the assessment of liver fibrosis in methotrexate-taking patients with inflammatory disorders: flow-chart of study selection

## Study Selection

Citations were first screened by title and abstract to retrieve relevant articles. The retrieved articles were then reviewed in full. A hand search of the references in relevant papers was also conducted to identify any additional articles addressing our objective. The inclusion criteria were: articles including patients over the age of 18 with a diagnosis of RA or PsA by ACR criteria or a histological diagnosis of CD who received a cumulative dose of ≥1.5g of MTX at the time of enrollment [12] and had a Fibroscan performed in addition to liver biopsy. Exclusion criteria included the following: studies involving patients with known chronic liver disease from other causes (viral hepatitis, hemochromatosis, primary biliary cirrhosis, auto-immune hepatitis, alcohol-induced hepatitis); patients with a body mass index > 35 kg/m2. Case reports, reviews and articles in languages other than English were excluded.

## Data Extraction and Quality Appraisal

From the included papers, we extracted the publication details, patient characteristics, MTX exposure, evidence of liver fibrosis as documented on transient elastrography and correlation with liver biopsy for each patient [Table 1]. Included studies underwent methodological quality assessment using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist [13, 14]. Based on this tool, articles were given a quality assessment rating of "low", "moderate" or "high" [Table 2].

**Table 1 Study Characteristics** (data for patients with liver biopsy shown)

| Characteristic | Berends et. al. 2007 | Bray et. al. 2012 | Laharie et. al. 2010 |
|---|---|---|---|
| **No. of patients** | 24 | 21 (10 with valid FSS) | 518 (10 with liver biopsy) |
| **Type of study** | Cross-sectional study | Cross-sectional study | Cross-sectional study |
| **Quality of study (STROBE Scale)** | Moderate | Moderate | Moderate |
| **Mean age (range), years** | 55 (34 -73) | 59 (41 - 83) | 62 (48-73) |
| **Percent diabetes** | 17 | 19 | N/A |
| **Percent alcohol use** | 42 | 48 | 40 |
| **Percent male** | 46 | 57 | 46 |
| **BMI, kg/m2** | 26 (20-38) | 33 (25-41) | 29.7 (21.9-41.8) |
| **Inflammatory disease** | Ps (n= 24) | Ps (n= 10), RA (n= 1) | RA (n=2), CD (n= 2), Ps (n= 5), Bullous Pemphigoid (n= 1) |
| **Mean cumulative dose of MTX, mg** | 3352 (314-20235) | 5420 (1250-18695) | 2189 (300-5460) |
| **FSS indicating significant liver fibrosis, kPa** | >7.1 | >7.1 | >7.9 |
| **Mean FSS (range), kPa** | 6.4 (3.3-18.4) | 7.2 (3.3-21.5) | 11.4 (8.8-16.6) |
| **Metavir score (no. of patients)** | F0(5)/F1(13)/F2(4)/F3(1)/F4(1) | F0(9)/F1(0)/F2(0)/F3(1)/F4(0) | F0(1)/F1(1)/F2(4)/F3(2)/F4(2) |
| **Percent liver fibrosis on FSS** | 42 | 40 | 100 |
| **Percent ≥F2 Metavir score** | 25 | 10 | 80 |
| **Positive Predictive Value of FSS for significant fibrosis, %** | 33 | 25 | 90 |
| **Negative Predictive Value of FSS for significant fibrosis, %** | 86 | 100 | N/A |

MTX=Methotrexate; FSS=FibroScan Score; BMI: Body Mass Index; Ps=Psoriasis; RA: Rheumatoid Arthritis; CD=Crohn's Disease; kPa=kilopascals

**Table 2. The STROBE Statement**: methodological quality assessment of cross-sectional studies (13, 14)

| Study Variable | Item | Recommendation | Berends 2007 | Laharie 2010 | Bray 2012 |
|---|---|---|---|---|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract<br>(b) Provide in the abstract an informative and balanced summary of what was done and what was found | *<br>*** | ***<br>*** | ***<br>* |
| **Introduction** | | | | | |
| Background | 2 | Explain the scientific background and rationale for the investigation being reported | *** | ** | ** |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | ** | * | ** |
| **Methods** | | | | | |
| Study design | 4 | Present key elements of study design early in the paper | *** | *** | * |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | ** | ** | ** |
| Participants | 6 | Give the eligibility criteria, and the sources and methods of selection of participants | *** | *** | ** |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | *** | ** | ** |
| Data sources | 8 | For each variable of interest, give sources of data and details of methods of assessment (measurement) | *** | ** | *** |
| Bias | 9 | Describe any efforts to address potential sources of bias | ** | ** | ** |
| Study size | 10 | Explain how the study size was arrived at | * | ** | * |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | ** | ** | * |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) If applicable, describe analytical methods taking account of sampling strategy<br>(e) Describe any sensitivity analyses | **<br>***<br>***<br>n/a<br>n/a | ***<br>***<br>***<br>n/a<br>n/a | *<br>*<br>*<br>n/a<br>n/a |
| **Results** | | | | | |
| Participants | 13 | (a) Report the numbers of individuals at each stage of the study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram | ***<br>***<br>* | ***<br>***<br>*** | ***<br>***<br>* |
| Descriptive data | 14 | (a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate the number of participants with missing data for each variable of interest<br>(c) Report numbers of outcome events or summary measures | ***<br>***<br>n/a | ***<br>***<br>n/a | **<br>*<br>n/a |
| Outcome data | 15 | Report numbers of outcome events or summary measures | *** | *** | *** |

| | | | | | |
|---|---|---|---|---|---|
| Main results | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | **<br>**<br>n/a | ***<br>**<br>n/a | **<br>**<br>n/a |
| Other analyses | 17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | * | *** | * |
| **Discussion** | | | | | |
| Key results | 18 | Summarize key results with reference to study objectives | *** | *** | * |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | *** | *** | *** |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | *** | *** | *** |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | ** | * | * |
| **Other information** | | | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | * | * | *** |
| Overall Rating | | | ** | *** | * |

*low quality; **moderate quality; ***high quality

## Results

### Search Results

In order to determine if transient elastography is a valid measure of liver fibrosis in individuals taking MTX for inflammatory conditions, a total of 14 full-length articles and 4 conference abstracts were identified. Figure 1 outlines the study selection process. Most of the studies did not meet the inclusion criteria for this review. Specifically, they did not compare the study participants' FSS to a liver biopsy taken from the same participant. Five of the full-length articles met the inclusion criteria for this review; however, 2 studies were excluded on further analysis as they did not use a validated liver fibrosis staging system when comparing FSS to liver biopsy results. In total, 3 studies were included and 15 studies were excluded.

### Study Characteristics

Table 1 highlights the characteristics of each study included in the systematic review. All included studies were cross-sectional studies that were not randomized. None of the studies included data on a control population. A total of 40 Ps, 5 RA, 2 CD and 1 "other inflammatory condition" subjects were evaluated in the included studies. Sample size ranged from 21-518; however, Laharie et al. [15] provided liver biopsy data on only 13 subjects and therefore, data on only those 13 subjects were included in this review.

Baseline patient characteristics were variable: mean age 55-59 years, BMI 26-33kg/m$^2$, 46-57% male, and 6.6-17% diabetics. Absolute alcohol exposure was also variable (38-48% of subjects), though data on the degree of exposure per subject was not disclosed.

## Methodological Quality of Studies

Studies were evaluated for methodological quality using the STROBE checklist [13, 14]. Laharie et al. [15] was deemed to be of high quality overall; however, for our outcome of interest, it was of moderate quality due to selection bias (large proportion of patients eligible for biopsy did not undergo biopsy) and analyses in this subgroup were under-powered. Berends et al. [16] was found to be of moderate quality on account of failure to report which confounders were included in their analyses. Bray et al. [17] was of poor quality because the study design was not explicitly stated in the paper, and handling of quantitative variables in the study was not well described. Statistical analysis did not account for missing data on patients with invalid scores, BMI as a cofounder was not statistically accounted for and a subgroup analysis was not included.

## Fibroscan Score and METAVIR Liver Fibrosis Score

All studies included a data set (cumulative dose of MTX, FSS, and METAVIR score) on subjects who had been exposed to MTX. There was no standardized time within or between studies at which subjects were evaluated with transient elastography. Transient elastography was carried out at whatever point each subject was captured for the study. Both Berends et al. [16] and Bray et al. [17] used a FSS cutoff of >7.1kPa to indicate significant or severe liver fibrosis while Laharie et al. [15] used a FSS cutoff of >7.9kPa.Mean cumulative MTX dose ranged from 2189mg-5420mg.Mean FSS ranged from 4.6-7.2kPa. The majority of the subjects in the Berends et al. [16] and the Bray et al. [17] studies had a METAVIR score of F0-F1 (24 subjects, 53% ), while the majority of the subjects included in the Laharie et al. [15] study had a METAVIR score of F3-F4 (11 subjects, 84.6%).

The incidence of significant liver fibrosis detected by liver biopsy was highest in the Laharie et al. [15] study (84.6%) with much lower incidences seen in the other 2 studies respectively [10% [17], 20% [16] ]. Based on FSS, Berends et al. [16], Bray et al. 2012 [17] and Laharie et al. [15] reported a liver fibrosis incidence of 35%, 40% and 100% respectively. Overall, the specificity and sensitivity for Fibroscan compared to biopsy was 69% and 50% for Berends et al. [16], 66% and 100% for Bray et al. [17] and 0% and 100% for Laharie et al. [15] respectively. No association was seen in either the Berends et al. study [16] or the Laharie et al. study [15] between a higher cumulative dose of MTX and the degree of liver fibrosis based on biopsy. None of the studies included data on patients' liver enzyme serologies.

## Discussion

Liver fibrosis has been reported as an important complication identified with the long-term use of MTX in patients with inflammatory disease. Given its success in monitoring for the development of liver fibrosis in patients with Hepatitis C, transient elastography of the liver is a less invasive way of monitoring for the development of liver fibrosis in MTX-exposed individuals in comparison to the combination of serology, imaging and liver biopsy. This is the first systematic review reporting on the utility of fibroscan for detecting liver fibrosis in patients treated with MTX.

We found that the available literature does not support Fibroscan as an accurate indicator of biopsy-proven liver fibrosis in patients on low-dose MTX. There is a relative lack of studies evaluating the use of transient elastography for the assessment of liver fibrosis in this population. Furthermore, there are even fewer studies of sound methodological quality that compare the FSS to the gold standard of liver biopsy.

The evaluation of transient elastography of the liver has been mainly carried out in the Hepatitis C patient population [18, 19]. In Hepatitis C patients, Fibroscan specificity was reported as 93% for cirrhosis (F4) and 96% for advanced fibrosis (F3). Sensitivity was < 50% for both groups [11]. A meta-analysis examined the overall performance of transient elastography for the diagnosis of liver fibrosis in a multitude of liver diseases [18]. Transient elastography was found to be an excellent modality for the diagnosis of cirrhosis independent of the cause of liver disease. Its diagnostic accuracy was much more variable for the diagnosis of lesser degrees of fibrosis with Area Under

the Receiver Operating Curve (AUROC) for **F>2** of 0.72 to 0.88; **F>3**, 0.90 to 0.91; and **F>4**, 0.95 to 0.99. This is significant because F2 is a threshold for initiating treatment of the underlying condition [18]. Test performance was also dependent on the cause of liver fibrosis; less accuracy was seen in liver fibrosis not caused by Hepatitis C, for example Autoimmune Hepatitis or Primary Biliary Cirrhosis [18].

Studies looking at low dose MTX use in patients with inflammatory conditions suggest that the prevalence of liver fibrosis is highly variable and is dependent on other risk factors for liver fibrosis such as BMI and alcohol exposure [20, 21]. When such factors are controlled for, the incidence of liver fibrosis in this patient population is low [9, 12]. In our systematic review, liver fibrosis was variable. It was reported in 10-85% of subjects. Although the included studies had a high degree of alcohol use (38-48%)and the mean BMIs ranged from overweight to obese (26-33 $kg/m^2$), these potential confounders were not accounted for in the analyses. Furthermore, in previous studies, of those patients who do develop liver fibrosis, the majority develop low stage fibrosis [9, 12]. This was also shown by Berends et al. [16] and Bray et al. [17], where the majority of subjects developing liver fibrosis (n=24) had METAVIR scores less than F2.Unfortunately, FIbroscan has been shown to be less accurate in low stage liver fibrosis [11, 18, 22]. It is unclear why the Laharie et al. [15] study had a higher mean FSS; potential confounding factors, such as diabetes, alcohol consumption, obesity, cumulative MTX dose and Ps, were not different in this study compared to the other included studies. The FSS in both the Berends et al. [16] study and the Laharie et al. [15] study do not correlate with the degree of liver fibrosis found on liver biopsy. Bray et al. [17] had reported slightly better diagnostic accuracy, but still only correlated 60% of the time with biopsy. All included studies showed a trend towards overestimating the degree of liver fibrosis based on FSS [Table 1]. Based on these findings there is insufficient evidence to support the utility of liver transient elastography for assessing liver fibrosis in patients with inflammatory conditions taking MTX.

The studies included in this systematic review had many limitations. Sample size was small and there was either a significant time delay between the Fibrscan and biopsy or the timing was not reported. There were limitations of the biopsy procedure itself, which may have led to issues with sampling error and inter-observer variability. In addition, these studies involved multiple diseases, which have different risk factors for fibrosis; for example, patients with PsA have a higher incidence of metabolic syndrome [23]. There were insufficient subjects to analyze the different diseases separately. Confounders were mentioned in the studies, but not statistically accounted for.In the Bray et al. study [17], five operators performed scans with varying experience, which may have led to issues with inter-reporting reproducibility. Moreover, the very high exclusion rate of subjects because of failed Fibroscan questions the validity of the results. In Laharie et al. [15], biopsy results were obtained in a small proportion of enrolled patients with possible selection bias. In addition, the study design was not explicitly stated in the paper, and handling of quantitative variables in the study was not well described. Statistical analysis did not account for missing data on patients with invalid scores, BMI as a cofounder was not statistically accounted for and a subgroup analysis was not included. In the Berends et al. study [16], again the study population was small. There was up to 18 months between scan and biopsy.

## Conclusion

Fibroscan may be useful for ruling out fibrosis in a MTX-taking population with inflammatory diseases; however, further studies of better design are needed to conclusively address the use of this technology for surveillance in this population.

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