Assessment of Liver Fibrosis Markers in People with Rheumatoid Arthritis on Methotrexate

Liver Fibrosis Screening in RA

1. Debbie A. Olsson-White (https://orcid.org/0000-0002-4799-1783), MBBS FRACP

2. John K. Olynyk (https://orcid.org/0000-0003-0417-3411), MBBS FRACP MD FAASLD AGAF

3. Oyekoya T. Ayonrinde (https://orcid.org/0000-0002-0598-151X), MBBS FRACP PhD

4. Shereen Paramalingam (https://orcid.org/0000-0001-6401-4530), MBBS FRACP

5. Helen I. Keen (https://orcid.org/0000-0002-8469-2424), MBBS FRACP PhD

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iv) Author to whom correspondence about the manuscript should be sent:

Helen I. Keen

Department of Rheumatology, Fiona Stanley Hospital, 11 Robin Warren Drive, Murdoch WA 6150, Australia.

Email: helen.keen@health.wa.gov.au

Phone: 08 6152 2222

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b) The authors all satisfy all 4 points below
1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
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ABSTRACT

**Background**: Up to 3% of methotrexate (MTX)-treated rheumatoid arthritis (RA) patients may develop liver fibrosis or cirrhosis, requiring effective screening algorithms.
**Aims:** To assess the utility of non-invasive liver fibrosis assessment in RA patients on MTX.

**Methods:** 56 patients were recruited from rheumatology outpatient clinics in a public tertiary centre from July 2017 to October 2018. Clinical data was collected. Screening for hepatic fibrosis was performed utilising transient elastography (TE), aminoaspartate transaminase to platelet ratio index (APRI), Hepascore, and Fibrosis-4 index (FIB-4). Those with suspected significant liver fibrosis based on these screening tests were assessed by a hepatologist.

**Results:** 27 patients were suspected to have liver fibrosis on screening, including 10/56 (18%) by TE, 20/56 (36%) by Hepascore, 2/56 by APRI (4%) and 1/56 by FIB-4 (2%). Of these 27 patients, 11 were reviewed by a hepatologist and 1 diagnosed with significant liver fibrosis. TE, but not APRI, Hepascore or FIB-4, was found to have 100% sensitivity and 84% specificity (p=0.029) for hepatologist-diagnosed liver fibrosis.

**Conclusion:** Liver fibrosis develops in a minority of MTX-treated RA patients. This study suggests that TE is a more sensitive screening test than APRI, FIB-4 or Hepascore in the identification of people with RA at risk of hepatic fibrosis.

Key Indexing Terms (MeSH terms):

- Rheumatoid arthritis
- Methotrexate
Liver Cirrhosis

Chemical and Drug Induced Liver Injury

Elasticity Imaging Techniques

**Introduction**

For over 25 years, Methotrexate (MTX) has been the cornerstone of treatment of rheumatoid arthritis (RA). It is recommended as first-line therapy by both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) in both early and established RA.\(^1\)

MTX inhibits dihydrofolate reductase and reduces intracellular stores of folic acid, affecting its role in the synthesis of purine and pyrimidine.\(^1,2\) It’s mechanism of action is responsible for its clinical efficacy, but also many of its toxicities, including liver fibrosis and cirrhosis.\(^1,2\) The risk of liver fibrosis has been extensively described and variably reported, with an incidence of up to 3% in patients taking methotrexate.\(^3-5\) Known independent risks for liver fibrosis include obesity, hypercholesterolaemia, high alcohol intake, diabetes and the metabolic syndrome.\(^6-7\) However, to date, published evidence suggests that neither dose nor duration of methotrexate therapy are associated with liver fibrosis.\(^2,5,7,8\)

Whilst the risk of MTX induced liver fibrosis remains low, given its seriousness, and the current widespread use of methotrexate, reliable screening for MTX induced liver
fibrosis is required. Current ACR guidelines recommend regular 1-3 month monitoring of liver function tests (LFTs). However, published evidence suggests liver enzyme levels are not sensitive in the detection of liver fibrosis, thus current recommendations may be suboptimal and are worthy of review.

The gold standard for diagnosing liver fibrosis is by liver biopsy. However, liver biopsy is invasive, expensive and associated with procedural risks such as pain, bleeding and pneumothorax, with a low reported rate of death. In addition, the accuracy of results is influenced by the quality and length of the specimen, aetiology of liver disease, and experience of the histopathologist, which may lead to over- or under-staging of disease. Given these considerations, non-invasive tests have been investigated in patients with liver disease of varying aetiology for assessment and screening for fibrosis.

Conventional B-mode ultrasound is a well-established imaging modality for detecting morphological parenchymal liver changes and overt cirrhosis, but is highly operator dependant and has limited ability to assess the presence or severity of fibrosis. Other non-invasive liver fibrosis screening tests include Hepascore, aminoaspartate transaminase (AST) to platelet ration index (APRI), Fibrosis-4 index (FIB-4) and transient elastography (TE) – which have been validated in patients with a variety of liver diseases but not MTX-induced liver fibrosis complicating treatment of RA.

The APRI is calculated by: (AST in IU/L) / (AST upper limit of normal in IU/L) / (platelets in 10⁹/L), which generates a value used to estimate the risk of significant fibrosis. One study has assessed the utility of the APRI in RA and suggested that APRI scores
correlated with liver fibrosis in RA patients.\textsuperscript{2} However, as elements of the APRI are acute phase reactants, the APRI score has the potential to be affected by disease activity in RA.

Hepascore is a serum model generated by a computer algorithm that uses age, sex, and the serum levels of total bilirubin, $\delta$-glutamyl transferase, $\alpha_2$-macroglobulin, and hyaluronic acid to generate a score that predicts the risk of significant liver fibrosis.\textsuperscript{29} Hepascore has not been studied or validated in the RA population, and may have limited utility given hyaluronic acid, a key component of cartilage and synovial fluid, is elevated in the serum of people with RA.\textsuperscript{30}

The FIB-4 index is a non-invasive biomarker that has been validated to detect or exclude significant liver fibrosis in chronic liver diseases such as HIV/Hepatitis-C co-infection, Hepatitis B and NAFLD.\textsuperscript{23,26,31,32} FIB-4 is calculated by: \((\text{Age in years} \times \text{AST in IU/L}) / (\text{platelet count} \times 10^9 \times \sqrt{\text{ALT in IU/L}})\). Age has been shown to affect the accuracy of the FIB-4 test, and subsequently age-group appropriate cut-off values have been recommended.\textsuperscript{25,33} A single study examining FIB-4 in RA patients taking MTX found it to be useful in detecting liver fibrosis when compared to liver biopsy.\textsuperscript{25}

Transient elastography (TE) uses a non-invasive transducer that emits low amplitude, low frequency vibrations which essentially propagate an elastic shear wave through the liver.\textsuperscript{14,28} The velocity of these are measured and generate a continuous score in kilopascals (kPa), which has been extensively studied in a range of liver diseases\textsuperscript{2} where it correlates with the ordinal Metavir staging score from F0 (absent fibrosis) to F4 (cirrhosis). The specificity is decreased in those with abdominal obesity, congestive...
cardiac failure, acute hepatitis or cholestasis.\textsuperscript{14} There have been several studies performed assessing the use of TE in RA patients, with some of these showing that results correlate well with liver biopsy findings, supporting a role for TE as a useful modality to screen for liver fibrosis in RA patients.\textsuperscript{2,5,8,34} TE has never been compared to the Hepascore, APRI or FIB-4 in RA patients treated with MTX.

This study aims to compare APRI, Hepascore, FIB-4 and TE in the assessment of liver fibrosis in MTX-treated RA patients, and to assess if disease activity levels of RA affect these markers.

**Materials and Methods**

**Study Participants**

Participants were recruited from outpatient general rheumatology and inflammatory arthritis clinics at a single tertiary centre, from July 2017 to October 2018. Inclusion criteria were a clinical diagnosis of RA, age $\geq$18 years, and current MTX therapy of any duration. Exclusions from the study included current leflunomide therapy (due to associated independent increased risk of liver fibrosis from dual therapy with MTX\textsuperscript{35}); body mass index (BMI) $\geq$30; known liver disease including chronic viral hepatitis B or C, liver fibrosis or cirrhosis from any other cause; history of chronic kidney disease, diabetes, congestive cardiac failure and heavy alcohol intake. The study protocol was approved by the South Metropolitan Health Service Health Research Ethics Committee (approval number EC00265), and all patients signed informed consent prior to inclusion.
Study Method

The data collected included disease activity score-28 for RA (DAS-28 (ESR)), BMI calculated by weight (kg)/ height (m)^2, number of weekly alcoholic drinks and dose and duration of methotrexate. TE was performed on the same day as venepuncture for full blood count (FBC), urea and electrolytes (UEC), liver function test (LFT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and aspartate transaminase (AST). Hepascore, APRI and FIB-4 were determined as previously described. The APRI Hepatitis C threshold of ≥0.7 was selected to indicate significant fibrosis. Since hepascore is not validated in MTX monitoring, we applied the NAFLD threshold of ≥0.45 as a cut-off to indicate significant fibrosis in this study. As FIB-4 is not validated in MTX monitoring, we applied the generally accepted threshold of ≥2.67 to indicate significant fibrosis.

TE liver stiffness raw scores were measured in kilopascals (kPa) and converted to an ordinal “Metavir score” of F0-F4 to indicate the degree of likely fibrosis, as previously described. As TE has not been validated in MTX monitoring, we applied the NAFLD threshold of ≥7 kPa and F2 or greater to indicate significant fibrosis in this study. This approach was taken because methotrexate-induced liver injury has histopathological similarities to non-alcoholic steatohepatitis (NASH), in which TE has been validated with good negative predictive value to exclude liver fibrosis.

For the purpose of this study, we consider a patient to have a definitive diagnosis of liver fibrosis when clinically diagnosed by the treating hepatologist. If concern regarding fibrosis arose from the screening tests undertaken in the study, further clinical
investigation was undertaken on the basis of expert review by a hepatologist. Liver biopsy was only performed if required on clinical grounds and a diagnostic or therapeutic consequence of biopsy was expected. Patient diagnoses were also reviewed by a second hepatologist.

**Statistical Analysis**

Statistical analysis was performed using SPSS version 25: non-parametric statistics for non-normally distributed data and parametric for normally distributed data. Data are presented as mean +/- SD or median and range. Comparisons between groups were made using Spearman rank correlation for continuous variables and Chi-square test for ordinal variables. Sensitivity and specificity for the screening test, using the clinical diagnosis of fibrosis as the gold standard were calculated. Statistical significance was assigned at p<0.05.

**Results**

A total of 56 subjects were recruited over 16 months, with mean age 61.6 years (Table 1). The population was predominantly female, with long-standing methotrexate use, in DAS-28 remission (Table 2).

Utilising the predetermined thresholds considered to indicate potential liver fibrosis, 27 subjects were identified with potential significant fibrosis: 2/56 subjects (4%) by APRI, 1/56 (2%) by FIB-4, 20/56 (36%) by Hepascore and 10/56 (18%) by TE. Four subjects (7%) had ≥2 positive screening tests.
13 participants (Table 3) had results that clinically warranted further investigations with referral for conventional liver ultrasound (US), shear wave elastography, comprehensive biochemical workup for liver disease and specialist hepatology review. The decision to investigate further was made based on the presence of a TE result alone predicting liver fibrosis, and/or ≥2 positive screening tests. 11 participants had hepatologist review as 1 patient deferred review, and 1 patient declined review. Only 1 patient was considered to have significant clinical fibrosis following hepatologist review. This was Patient 3 (see Table 3), with 3 out of 6 non-invasive liver fibrosis screening tests returning results suggestive of at least moderate liver fibrosis.

Patient 1 initially had conflicting results (see Table 3). Original TE, Hepascore and APRI was suggestive of advanced fibrosis or cirrhosis, and a follow-up ultrasound suggested morphological changes could be consistent with cirrhosis, however shear wave elastography performed at the same time did not support that, indicating at most mild fibrosis. TE, APRI and Hepascore were repeated on follow-up by the hepatologist, showing at most mild fibrosis. A liver biopsy was offered but the patient declined. Overall the reviewing hepatologist concluded there was no evidence of cirrhosis or significant fibrosis, and this was agreed by a second hepatologist.

The other 9 patients reviewed by a hepatologist were deemed not to have significant fibrosis based on further testing. Notably repeat TE on several patients by the reviewing hepatologist revealed lower scores than the original TE performed.

*Correlation between APRI, Hepascore, FIB-4 and TE*
APRI was found to have moderate correlation with FIB-4 ($r=0.492$, $p=0.000$) and Hepascore ($r=0.412$, $p=0.001$), but not TE ($r=-0.080$, $p=0.555$) (Table 4). TE exhibited 100% sensitivity and 84% specificity ($p=0.029$) for detecting hepatologist-diagnosed significant liver fibrosis, with APRI, Hepascore and FIB-4 performing less well (Table 5).

**Correlation between RA disease activity, APRI, Hepascore, FIB-4 and TE**

RA disease activity, as assessed by the DAS-28, did not correlate with any of the screening tests (Table 4). Hyaluronic acid levels were found to be high in all patients with suspected liver fibrosis by Hepascore (see Table 3), and 45/56 (80%) participants overall.

**Discussion**

The risk of liver fibrosis in patients treated with methotrexate has been extensively studied, and the incidence reported to be less than 3%. In our small cohort of patients with varying durations of methotrexate therapy, we found a high prevalence of suspected liver fibrosis using non-invasive screening, that was not confirmed on hepatologist assessment. Only one patient (2% of overall study population) had a hepatologist diagnosis of liver fibrosis after further assessment. The majority of study participants had ALT and AST levels within the reference range, including the participant clinically assessed as having significant fibrosis (see Table 3). These findings suggest that current ACR recommendations for screening by LFTs alone are inadequate. This is consistent with literature indicating liver function tests are insensitive to detect liver fibrosis and serum ALT levels reduce with age.
Our primary aim in this study was to compare APRI, Hepascore, FIB-4 and TE in assessing liver fibrosis in RA patients on methotrexate. To our knowledge, this is the first direct comparison of these screening tests for liver fibrosis together in RA subjects treated with methotrexate. Hepascore values had moderate correlation with APRI and FIB-4, but not with TE in this population of patients with RA. 36% of participants had a Hepascore value indicating liver fibrosis, though Hepascore was found to lack sensitivity and specificity for detecting liver fibrosis in RA patients. This suggests that Hepascore may not be a reliable indicator of fibrosis in RA patients treated with methotrexate and may be falsely elevated, since the Hepascore algorithm includes hyaluronic acid in its calculation. A similar observation was reported in MTX-treated patients with psoriasis. In our study, all of the participants with raised Hepascore were found to have high hyaluronic acid levels, as did 80% of study participants overall. RA disease activity may have contributed to the elevation of hyaluronic acid, limiting the validity of Hepascore in the RA population.

Only 1 participant had suspected liver fibrosis based on FIB-4, and 2 by APRI. None of these patients were ultimately diagnosed with clinically significant fibrosis by expert opinion. APRI and FIB-4 also have the potential to be falsely elevated in patients with poor RA control due to platelets being an acute phase reactant and elevated in inflammation. Furthermore, given neither APRI nor FIB-4 were found to be sensitive nor specific in this study, they may not be useful screening tools for liver fibrosis in RA treated with methotrexate.

Several studies have suggested TE is a useful modality to screen for liver fibrosis for people with RA taking methotrexate. In our study, 10 participants had TE results
alone that clinically warranted further investigation and were referred to hepatology. Several of those reviewed had repeat TE or SWE, that returned lower scores than their original scan. There are several factors that can influence liver stiffness measurement by TE, some of which were accounted for in our exclusion criteria (hepatic congestion, acute hepatitis, cholestasis, alcoholic hepatitis). However, food ingestion up to 180 minutes prior to TE can also increase readings\textsuperscript{37}, and our participants were not routinely fasted prior to their original scan (as they were for subsequent ones) as these were performed in the outpatient clinic at the time of recruitment, which may have affected our results. In our study population, TE did not correlate with Hepascore, FIB-4 or APRI. However, TE was the only test that demonstrated sensitivity and specificity for liver fibrosis (100\% sensitivity and 84\% specificity, p=0.029). Our findings are consistent with the current literature and suggest TE is a useful screening tool in RA patients on methotrexate.

Our study does have limitations. We specifically excluded patients with BMI>30, history of diabetes or high alcohol intake (as they may have a higher likelihood of non-alcoholic or alcohol-related steatohepatitis), or on leflunomide, as these variables and the features of the metabolic syndrome have been shown to increase the risk of liver fibrosis in MTX-treated individuals.\textsuperscript{6,7,12,35} However, we excluded obese patients in order to minimise the effect of confounders in assessing liver fibrosis in methotrexate as a screening tool. Our patients were not routinely fasted prior to TE, which may have reduced the accuracy of these results on initial assessment. Our study is also a single centre study which reduces the generalisability of results. Since all subjects did not undergo liver biopsy, we cannot know the true underlying prevalence of liver fibrosis in
our cohort. Pragmatically, there is likely to be growth in the use of non-invasive liver fibrosis screening tests and it is important to understand the limitations of these in the assessment of subjects with RA.\textsuperscript{20,21,38} Our study found that in people with RA treated with MTX, TE is a better screening tool than Hepascore, FIB-4 or APRI.

**Conclusion**

Our cross-sectional study found that only TE and Hepascore identified participants who were subsequently clinically assessed as having significant liver fibrosis. The high number of positive Hepascore screening tests, in the context of high serum hyaluronic acid levels in people with RA, suggests high false positive detection may result from joint pathology rather than liver pathology, limiting the utility of Hepascore in RA. TE appeared to have the best utility for screening for liver fibrosis in people with RA treated with MTX. Further and larger studies would be useful to confirm these findings, ideally considering comparison against the gold standard of liver biopsy.

**Acknowledgement**

The authors would like to thank the hepatology nurses involved in performing TE/Fibroscan\textsuperscript{®}: Crystal Connelly and Marcelle Perrin. The authors would also like to thank the rheumatology team involved in recruiting patients: Nicola Cook, Janet Roddy, Ai Tran, Pauline Habib, Helen Marsden and Graeme Carroll.

**References**


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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean +/- SD, or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.64 +/- 12.78</td>
</tr>
<tr>
<td>BMI</td>
<td>24.23 +/- 2.97</td>
</tr>
<tr>
<td>Alcohol drinks/week</td>
<td>4.42 +/- 5.31</td>
</tr>
<tr>
<td>Weekly Methotrexate Dose (mg)</td>
<td>16.79 +/- 4.74</td>
</tr>
<tr>
<td>Methotrexate Duration (months)</td>
<td>108.34 +/- 93.15</td>
</tr>
</tbody>
</table>
Female gender 38 (68%)

Additional DMARD †

- Sulphasalazine 2 (4%)
- Hydroxychloroquine 10 (18%)

Prednisolone 6 (11%)

Biologic DMARD 26 (46%)

† DMARD = Disease Modifying Anti-Rheumatic Drug

Table 2: Results for Baseline Parameters and Liver Fibrosis Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Mean</th>
<th>Median</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE liver stiffness (kPa)</td>
<td>6.65</td>
<td>4.95</td>
<td>9.59</td>
<td>0.9-75</td>
</tr>
<tr>
<td>TE Metavir (F)</td>
<td>0.58</td>
<td>0.00</td>
<td>1.17</td>
<td>0-4</td>
</tr>
<tr>
<td>Parameter</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>Hepascore</td>
<td>0.40</td>
<td>0.36</td>
<td>0.30</td>
<td>0.04-1</td>
</tr>
<tr>
<td>APRI</td>
<td>0.32</td>
<td>0.30</td>
<td>0.19</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td>FIB-4</td>
<td>1.40</td>
<td>1.34</td>
<td>0.55</td>
<td>0.39-2.94</td>
</tr>
<tr>
<td>HA† (ug/ml)</td>
<td>84.71</td>
<td>71.00</td>
<td>62.40</td>
<td>8-295</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>12.39</td>
<td>8.50</td>
<td>11.82</td>
<td>2-58</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>7.76</td>
<td>2.90</td>
<td>11.91</td>
<td>1-58</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>29.21</td>
<td>27.50</td>
<td>9.11</td>
<td>18-74</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>28.55</td>
<td>23.50</td>
<td>15.98</td>
<td>10-82</td>
</tr>
<tr>
<td>SJC‡ (no)</td>
<td>0.21</td>
<td>0.00</td>
<td>0.68</td>
<td>0-3</td>
</tr>
<tr>
<td>TJC § (no)</td>
<td>1.05</td>
<td>0.00</td>
<td>2.14</td>
<td>0-10</td>
</tr>
<tr>
<td>DAS-28</td>
<td>2.12</td>
<td>2.06</td>
<td>0.86</td>
<td>0.49-3.63</td>
</tr>
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</table>

† HA = Hyaluronic Acid level
‡ SJC = Swollen joint count
§ TJC = Tender joint count
Table 3: Results for Participants with Abnormal Liver Fibrosis Markers and Suspected Liver Fibrosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>DAS-28 (kPa)</th>
<th>TE (Metavir)</th>
<th>Hepascore</th>
<th>APRI</th>
<th>FIB-4 (ug/L)</th>
<th>AST (U/L)</th>
<th>ALT (U/L)</th>
<th>PLT (x10^9/L)</th>
<th>ESR (mm/hr)</th>
<th>CRP (mg/L)</th>
<th>Liver Imaging</th>
<th>Biochemical Work-up</th>
<th>Hepatologist Review</th>
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<tr>
<td>1</td>
<td>1.92</td>
<td>14.3</td>
<td>4</td>
<td>1</td>
<td>1.5</td>
<td>188</td>
<td>224</td>
<td>47</td>
<td>26</td>
<td>68</td>
<td>US§: Lobulated contour – cirrhosis, SWE¶ 6.0kPa (F0-F1).</td>
<td>Not significant. 5.9kPa, APRI 0.279, FIB-4 2.44 and Hepascore 0.99.</td>
<td>Declined liver biopsy.</td>
</tr>
</tbody>
</table>
Conclusion: conflicting results, but overall no significant liver fibrosis.

First US: nodular surface - likely cirrhosis. Repeat US 3 months later:

Liver biopsy performed = Deranged lipids, no other significant results. Liver biopsy performed = mild non-specific changes.
Conclusion: No significant fibrosis.

Results consistent with significant fibrosis. Liver biopsy not necessary. Repeat fibroscan

US: Liver morphology normal. SWE 4.8kPa (F0).

Not significant. US: No cirrhosis. Deranged lipids, no other

<table>
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<tr>
<th>3</th>
<th>2.36</th>
<th>7.3</th>
<th>2</th>
<th>0.55</th>
<th>0.3</th>
<th>1.61</th>
<th>123</th>
<th>27</th>
<th>21</th>
<th>262</th>
<th>13</th>
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<td>4</td>
<td>0.5</td>
<td>8</td>
<td>2</td>
<td>0.44</td>
<td>0.3</td>
<td>1.17</td>
<td>89</td>
<td>25</td>
<td>26</td>
<td>206</td>
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<td>&lt;1</td>
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<tr>
<td>SWE 5.8kPa (F0-F1)</td>
<td>significant results.</td>
<td>indicates nil fibrosis.</td>
<td></td>
<td></td>
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</tbody>
</table>

Conclusion:
no significant fibrosis.

Repeat fibroscan
3.5kPa (F0) – no significant fibrosis.

US: Normal morphology, 2x hyperechoic lesions.
Follow-up CT liver: no
<table>
<thead>
<tr>
<th>No</th>
<th>BMI</th>
<th>ALT</th>
<th>AST</th>
<th>ALP</th>
<th>CHOL</th>
<th>TRIG</th>
<th>HDL</th>
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<td>0</td>
<td>2.8</td>
<td>7.5</td>
<td>2</td>
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<td>0.3</td>
<td>0.69</td>
<td>53</td>
<td>40</td>
<td>82</td>
<td>388</td>
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<td>7</td>
<td>3.1</td>
<td>6.7</td>
<td>1</td>
<td>0.99</td>
<td>0.3</td>
<td>1.31</td>
<td>255</td>
<td>32</td>
<td>50</td>
<td>262</td>
<td>9</td>
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<tr>
<td></td>
<td>1.48</td>
<td>10.2</td>
<td>3</td>
<td>0.05</td>
<td>0.2</td>
<td>0.71</td>
<td>8</td>
<td>19</td>
<td>16</td>
<td>288</td>
<td>8</td>
<td>4.9</td>
</tr>
</tbody>
</table>
Conclusion: no fibrosis.

Increased hepatic echogenicity (?fatty infiltration vs. chronic liver disease) SWE 4.6kPa (F0).

Repeat fibroscan 4.5kPa with CAP 305 – no evidence liver fibrosis but does have fatty liver.
<table>
<thead>
<tr>
<th>10</th>
<th>1.5</th>
<th>75</th>
<th>4</th>
<th>0.46</th>
<th>0.3</th>
<th>1.88</th>
<th>72</th>
<th>29</th>
<th>25</th>
<th>219</th>
<th>6</th>
<th>1.6</th>
</tr>
</thead>
</table>

US: Mildly increased echogenicity, SWE 8.9kPa (F2).

Repeat fibroscan 3.5kPa with CAP 252 suggests mild fatty liver.

Conclusion: no significant fibrosis.
<table>
<thead>
<tr>
<th>US</th>
<th>ANA</th>
<th>Repeat fibroscan</th>
<th>Conclusion: no evidence fibrosis.</th>
<th>Patient referred to hepatology, appointment deferred.</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>13</td>
<td>3.2kPa with CAP 100.</td>
<td>Not done by patient.</td>
<td>Not recorded.</td>
</tr>
<tr>
<td>15</td>
<td>2.29</td>
<td>8.1</td>
<td>3</td>
<td>0.22</td>
</tr>
</tbody>
</table>

† HA = Hyaluronic acid levels (ug/L) (normal = 6-40 ug/L)
‡ PLT = Platelets
§ US = Ultrasound
¶ SWE = shear wave elastography

AST normal = <45 U/L, ALT normal = <40 U/L, PLT normal = 150-400 x 10⁹/L, ESR normal = 1-15mm/hr, CRP normal = <5.0mg/L
Table 4: Statistical Correlations Between APRI, Hepascore, FIB-4 and TE and RA Disease Activity

<table>
<thead>
<tr>
<th></th>
<th>Spearman Rank</th>
<th>Hepascore</th>
<th>APRI</th>
<th>FIB-4</th>
<th>TE</th>
<th>DAS-28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepascore</strong></td>
<td>Correlation Coefficient</td>
<td>1</td>
<td>0.412**</td>
<td>0.531**</td>
<td>0.049</td>
<td>-0.002</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>-</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>0.717</td>
<td>0.986</td>
</tr>
<tr>
<td><strong>APRI</strong></td>
<td>Correlation Coefficient</td>
<td>0.412**</td>
<td>1</td>
<td>0.492**</td>
<td>-0.080</td>
<td>-0.185</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.001</td>
<td>-</td>
<td>0.000</td>
<td>0.555</td>
<td>0.168</td>
</tr>
<tr>
<td><strong>FIB-4</strong></td>
<td>Correlation Coefficient</td>
<td>0.531**</td>
<td>0.135</td>
<td>1</td>
<td>-0.115</td>
<td>-0.072</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.000</td>
<td>0.318</td>
<td>-</td>
<td>0.394</td>
<td>0.595</td>
</tr>
<tr>
<td><strong>TE</strong></td>
<td>Correlation Coefficient</td>
<td>0.049</td>
<td>-0.080</td>
<td>-0.115</td>
<td>1</td>
<td>0.008</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.717</td>
<td>0.555</td>
<td>0.394</td>
<td>-</td>
<td>0.950</td>
</tr>
<tr>
<td><strong>DAS-28</strong></td>
<td>Correlation Coefficient</td>
<td>-0.002</td>
<td>-0.185</td>
<td>-0.072</td>
<td>0.008</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td>0.986</td>
<td>0.168</td>
<td>0.595</td>
<td>0.950</td>
<td>-</td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.05 level (2-tailed)

**Correlation is significant at the 0.01 level (2-tailed).
Table 5: Sensitivity and Specificity of TE, Hepascore, FIB-4 and APRI

<table>
<thead>
<tr>
<th></th>
<th>TE</th>
<th>Hepascore</th>
<th>FIB-4</th>
<th>APRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Specificity</td>
<td>84%</td>
<td>64%</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>P value</td>
<td>0.029</td>
<td>0.187</td>
<td>0.847</td>
<td>0.847</td>
</tr>
</tbody>
</table>