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Assessment of liver fibrosis by transient elastography and procollagen III amino terminal propeptide in rheumatoid arthritis patients treated with methotrexate

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Abstract

Background Methotrexate (MTX) is well known as the first-line therapy for rheumatoid arthritis (RA) patients. Its prolonged usage necessitates frequent assessing for adverse impacts, most importantly hepatotoxicity. Since there are no set standards for verifying liver damage in RA patients; transient elastography (TE) is emerged as a non-intrusive technique for identifying and evaluating liver fibrosis, alongside with serum procollagen III amino terminus propeptide (PIIINP). The objective of this study is to investigate liver fibrosis in 60 patients with RA patients on MTX therapy and 30 healthy individuals by TE and PIIINP, in addition, to recognize the prognostic indicators for liver fibrosis.

Results This study compared 60 adult RA patients who had been on MTX for at least 1 year to 30 matched age and sex healthy individuals. Liver fibrosis was measured using TE and PIIINP. A cutoff point of 7.1 kPa was declared abnormal, suggesting substantial liver fibrosis, while PIIINP > 170 ng/ml indicating elevated PIIINP levels. Based on TE results, liver fibrosis was reported in 20 patients (33.3%) with 14 patients (23.3%) who had significant liver fibrosis, 4 patients (6.7%) had advanced liver fibrosis, and 2 patients (3.3%) had liver cirrhosis. Meanwhile, five of the controls had mild liver fibrosis with highly statistically significant difference between patients and controls. The patient group had significantly higher level of PIIINP when compared to the healthy group with a specificity and sensitivity for detecting liver fibrosis of 85% and 82.5%, respectively.

Conclusions MTX usage in RA patients was correlated with an overall increase in liver fibrosis. Cumulative dosage of MTX, the presence of fatty liver and elevated serum PIIINP levels are all significant predictors of liver stiffness in RA. TE is organ specific and could be helpful in assessing true liver status rather than PIIINP level which is not organ specific. TE is superior to serum PIIINP and is recommended as a routine investigation for RA patients on MTX therapy particularly those with fatty liver.

Keywords Rheumatoid arthritis, Transient elastography, PIIINP, Liver fibrosis, Methotrexate

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Background

Methotrexate (MTX) was used as a first-line medication for treating rheumatoid arthritis (RA) for many years [1]. Since the early 1970s, MTX-induced hepatic damage has been a well-documented phenomenon that has been extensively studied, with most of the studies focusing on retrospective cohorts [2, 3].

As a matter of fact, histological abnormalities are not consistent well with conventional liver enzymes [4]. Although hepatic biopsy is still the most reliable method for staging hepatic fibrosis, it poses significant hazards [5] and is associated with serious complications in more than 1% of patients [6, 7]. There is certainly a need for a valid, accurate, and reliable non-intrusive assessment tool to identify early cases with hepatic fibrosis [8]. Transient elastography (TE) or fibroscan, a non-invasive approach, had been identified in numerous chronic hepatic disorders as an alternate to hepatic biopsy [9–11] and associated enormously with histological result [12–14].

Furthermore, it has been suggested that assessing amino terminus levels of type III procollagen (PIIINP) is a useful diagnostic modality for ongoing process of hepatic fibrosis, which may avoid liver biopsies. The vast majority of studies trials and published recommendations regarding its application have been carried out on patients with psoriasis and psoriatic arthritis with a little evidence in RA [15].

The main objective of this work was to determine the frequency of hepatic fibrosis in RA patients treated via MTX by TE and PIIINP, in addition, to recognize the prognostic indicators for liver fibrosis.

Methods

Patients: This study involved 60 patients diagnosed according to 2010 ACR/EULAR classification criteria for RA [16], matched to 30 healthy individuals by age and sex. Patients recruited were either inpatients or outpatients at the Department of Rheumatology and Rehabilitation, Minia University Hospital, between February 2020 and May 2021. Patients were considered eligible if they were over eighteen and had been receiving MTX treatment for at least 1 year. Exclusion was done if there were one or more of the following: current or previous liver disease, congestive heart failure, diabetes mellitus, alcohol intake, malignancy, or use of leflunomide or sulfasalazine. An informed consent was obtained from all participants and approval was obtained from the local research ethics committee (No. 386:1/2020).

Clinical evaluation: Each patient had a full history taking and thorough comprehensive clinical assessment. Examination of joint tenderness was performed by Ritchie articular index [17]. Body weight and height were measured for both patients and controls to calculate the body mass index (BMI). Special consideration was given to the duration of MTX therapy, the precise dose of MTX to calculate the cumulative dose, and the course and form of MTX therapy.

Disease Activity Assessment: Activity of RA was scored using disease activity score 28 (DAS 28-ESR) [18].

Investigations: Complete blood count, 1st-hour erythrocyte sedimentation rate, rheumatoid factor by Latex fixation, serum AST and ALT, total and direct bilirubin, serum albumin, serum gamma glutamyl transferase level, alkaline phosphatase, prothrombin time, serum creatinine, and blood urea. Viral markers for hepatitis B and C (HBsAg, HBcAb, and HCVAb) were performed to exclude cases with hepatitis. Serum PIIINP was measured using the standard ELISA method. A serum level of PIIINP > 170 ng/ml was considered elevated [19].

Abdominal ultrasonography: Abdominal conventional ultrasonography was carried out to all participants to assess liver structure and presence or absence of portal hypertension. Abdominal ultrasonography was performed using ultrasound device Aplio 500 system (Toshiba, Tokyo, Japan) using B-mode and Doppler ultrasonography to evaluate liver structure and portal hypertension. Assessment of portal hypertension was based on assessment of the portal vein caliber, hepatopetal unidirectional flow, velocity, preserved or disrupted pulsatility, splenomegaly, or presence of ascites.

Transient elastography: This was performed by a consultant radiologist with 20 years of experience in ultrasonography. All patients and controls underwent liver stiffness measurement via TE using the Aplio 500 ultrasound system (Toshiba, Tokyo, Japan), which measures the amount of hepatic stiffness between 25 and 65 mm below the skin's surface in the volume of a cylinder that is 1 cm broad and 4 cm long. The examination was performed in the right lobe of the liver in an intercostal space in the midaxillary line, after at least 6 h fasting, while each subject lay supine with his right arm in full abduction and breathing normally, with holding the breath for few seconds during the acquisition. The vibration wave is generated by the using the Extra Large (XL) probe, 2.5 MHz, and a gentle "flick" is felt by the patient each time. The transducer was placed perpendicular to the skin, and the region of interest (ROI) was set between 25 and 65 mm from the surface. Ten readings are taken at the same setting, and the median of these readings was considered to determine the stage. Significant fibrosis, severe fibrosis, and cirrhosis are classified using cutoffs more than or equal to 7.1, 9.5, and 12.5 kPa, respectively [20].

Statistical analysis: Data were analyzed using Statistical Package for the Social Sciences software (SPSS) version 26. The data were presented as numbers, percentage, or mean, range, and standard deviations. Comparison between groups was done by independent sample t test and Chi-square test. Correlation was done using Spearman correlation coefficient. A stepwise logistic regression analysis was carried out to identify predictors of hepatic fibrosis. Additionally, the serum PIIINP's sensitivity,

specificity, accuracy, negative predictive value (NPV), and positive predictive value (PPV) were determined.

Results

Among the 60 studied patients, there were 51 females (85%) and 9 males (15%). Their age ranged between 21 and 65 years with a mean of 46.46 ± 11.97 years versus 43.40 ± 14.18 years of the control ($p=0.285$). The mean age of disease onset was 39.96 ± 11.32 (ranging from 19 to 61 years), and the mean duration of the disease was 6.50 ± 5.51 years ranging from 1 to 25 years. BMI of RA patients ranged from 19.47 to 38.95 kg/m² with a mean of 25.68 ± 4.48 versus 25.49 ± 4.88 in the control group.

All RA patients were treated with MTX for at least 1 year. The cumulative dose of MTX ranged from 600 to 12,960 mg with a mean of $3,199.77 \pm 2,600.57$ mg, and the duration of MTX intake ranged from 1 to 18 years with a mean of 3.80 ± 3.22 years. Fifty patients (83.3%) were receiving MTX through the injection form while 10 patients (16.7%) were receiving it via both injection and oral routes. Its course was continuous in 44 patients (73.3%) and intermittent in 16 patients (26.7%). Fifty-five patients (91.7%) were receiving folic acid, 45 patients (75%) were taking antimalarials, and 12 patients (20%) were on oral corticosteroids at the time of the study.

Abdominal ultrasonography of the RA patients showed fatty liver in 18 patients (30%) with accompanied mild hepatomegaly in 10 patients (16.7%), while cirrhotic liver was detected in only 1 patient (1.7%) with no evidence of portal hypertension in any studied cases.

Based on TE assessment and as it is illustrated in Table 1, liver fibrosis was reported in 20 patients (33.3%) with 14 patients (23.3%) who had significant liver fibrosis (Fig. 1), 4 patients (6.7%) had advanced liver fibrosis (Fig. 2), and 2 patients (3.3%) had liver cirrhosis (Fig. 3).

RA patients who had hepatic fibrosis were significantly older, had a longer disease duration, a higher articular index, and more active disease ($p<0.001$) than RA patients without hepatic fibrosis. In addition, higher BMI

patients tend to have more advanced hepatic fibrosis. Cumulative dose of MTX in the fibrosis group was significantly higher with longer duration ($p<0.001$) than RA patients without hepatic fibrosis, with no significant difference between the two groups regarding age at onset or number of swollen joints (Table 2).

There was no statistically significant difference between the two groups regarding laboratory parameters, except for the serum AST level and serum PIIINP. Moreover, 16 patients (80%) of RA patients who had liver fibrosis were positive for serum PIIINP, while only 8 patients (20%) out of 40 RA patients without hepatic fibrosis were positive for serum PIIINP. The mean level of serum PIIINP was statistically significantly higher (131.69 ± 101.39) ng/ml than mean level of the controls (82.30 ± 76.73) ng/ml ($p<0.05$).

There was a statistically significant correlation between the level of PIIINP and body weight ($r=0.294$; $p=0.023$), duration of the disease ($r=0.646$; $p<0.001$), duration of MTX therapy ($r=0.720$; $p<0.001$), cumulative dosage of MTX ($r=0.708$; $p<0.001$), and disease activity ($r=0.527$; $p<0.001$) (Table 3).

Table 4 demonstrates a positive statistically significant correlation between value of TE, DAS 28-ESR ($r=0.396$, $p<0.001$), AST level ($r=0.281$, $p<0.05$), PIIINP level ($r=0.700$, $p<0.001$), elevated PIIINP > 170 ng/ml ($r=0.634$, $p<0.001$), fatty liver ($r=0.536$, $p<0.001$), MTX cumulative dose ($r=0.714$, $p<0.001$), MTX duration ($r=0.731$, $p<0.001$), and disease duration ($r=0.600$, $p<0.001$).

There was no significant correlation between value of TE, ALT level ($r=0.146$, $p=0.266$), serum albumin level ($r=-0.025$, $p=0.849$), BMI ($r=0.173$, $p=0.186$), age ($r=0.145$, $p=0.287$), sex ($r=-0.225$, $p=0.083$), age at onset ($r=-0.139$, $p=0.291$), antimalarial intake ($r=-0.045$, $p=0.736$), corticosteroid intake ($r=0.152$, $p=0.247$), and folic acid intake ($r=-0.229$, $p=0.078$).

When we applied stepwise logistic regression analysis, cumulative dose of MTX was the highest significant

Table 1 Prevalence of liver fibrosis in RA patients

Variable	RA patients (n = 60)	
	Range (N)	Mean ± SD (%)
Value of TE (kPa)	2.5 to 16.9	6.83 ± 2.33
TE	Normal (TE < 7.1 kPa)	40 (66.7%)
	Fibrosis (TE ≥ 7.1 kPa)	20 (33.3%)
	Significant fibrosis (7.1 ≤ TE < 9.5)	14 (23.3%)
	Advanced fibrosis (9.5 ≤ TE < 12.5)	4 (6.7%)
	Cirrhosis (TE ≥ 12.5)	2 (3.3%)

TE Transient elastography measured by kilopascals (kPa)

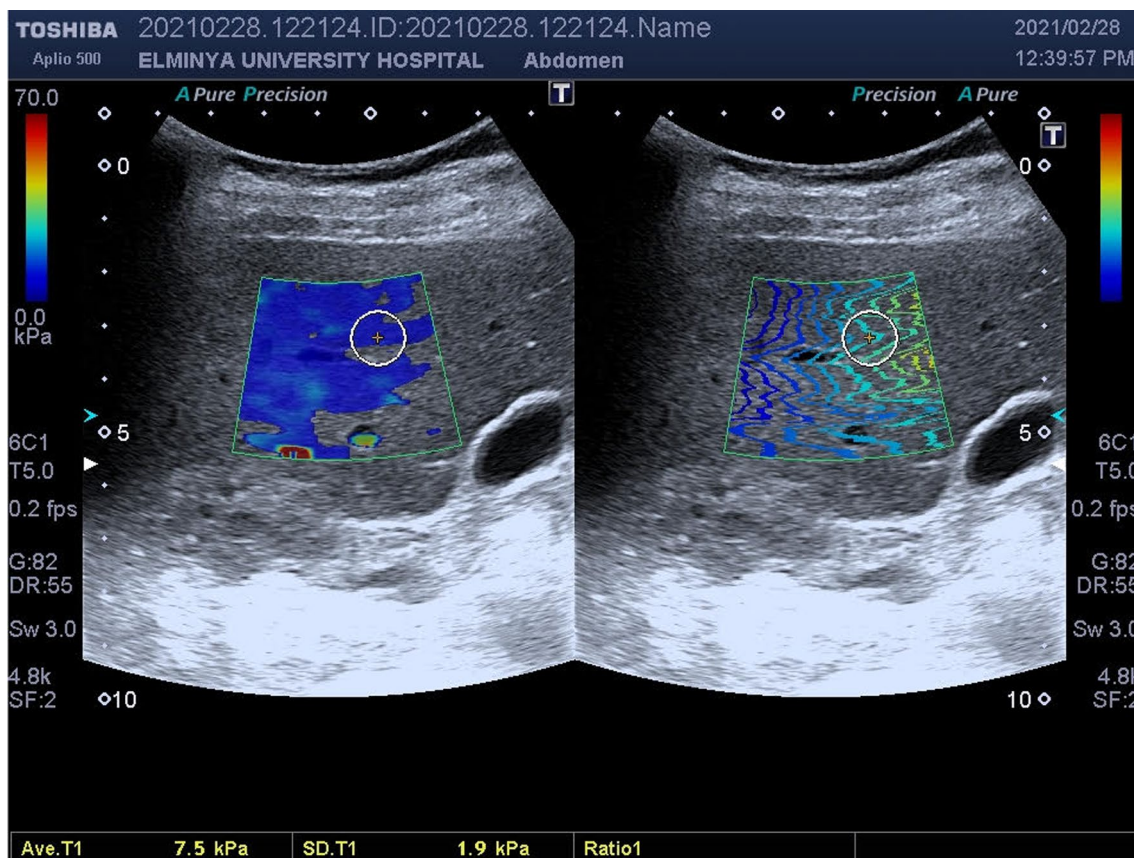


Fig. 1 Transient elastography showing increased liver tissue stiffness in patient with significant liver fibrosis. The patient measures about 7.5 kPa denoting mild fibrosis

predictor ($p < 0.001$) of hepatic fibrosis, followed by fatty liver detected by abdominal sonography ($p < 0.001$), followed by increased serum PIIINP ($p < 0.001$) (Table 5). Neither the duration of MTX nor the duration of the disease was predictive of liver fibrosis.

The ROC curve analysis suggests that PIIINP levels above 170 ng/mL have a relatively high sensitivity (85%) for detecting liver fibrosis risk, while maintaining a reasonably good specificity (82.5%). The PPV and NPV values indicate that a positive test result is moderately predictive of liver fibrosis risk, while a negative result provides a strong indication of the absence of risk. The overall accuracy of 83.33% suggests that the test performs well in correctly classifying individuals based on the chosen cutoff value (Table 6, Fig. 4).

Discussion

MTX is the most often prescribed therapy for RA because of its low cost and effectiveness [21]. In comparison with other DMARDs, it is a long-term safe and effective treatment [22]. One of the most serious adverse effects is hepatotoxicity which is monitored in most cases

by serum aminotransferase levels, which could, but does not always, accurately represent the degree of hepatic damage. Liver fibrosis can progress silently, often without a corresponding increase in serum aminotransferase levels [23, 24]. However, there is a risk of morbidity and even mortality with liver biopsy, which highlights the need for innovative, less invasive methods [25].

TE, a non-invasive approach for evaluating liver stiffness, is commonly used to identify liver fibrosis, particularly in individuals with viral hepatitis [26]. It is comparable to a liver biopsy in a number of studies, and it has a somewhat higher specificity and sensitivity for fibrosis detection [26, 27]. An indicator of the severity of the fibrosis process in humans is assessment of serum PIIINP [15, 28–30]. Its value was found to evaluate liver toxicity of methotrexate in psoriatic patients; however, just a few numbers of studies have been conducted on RA patients [31].

The objective of this work was to determine the frequency of liver fibrosis in RA patients on MTX by both TE and PIIINP, as well as the prognostic indicators for liver fibrosis.

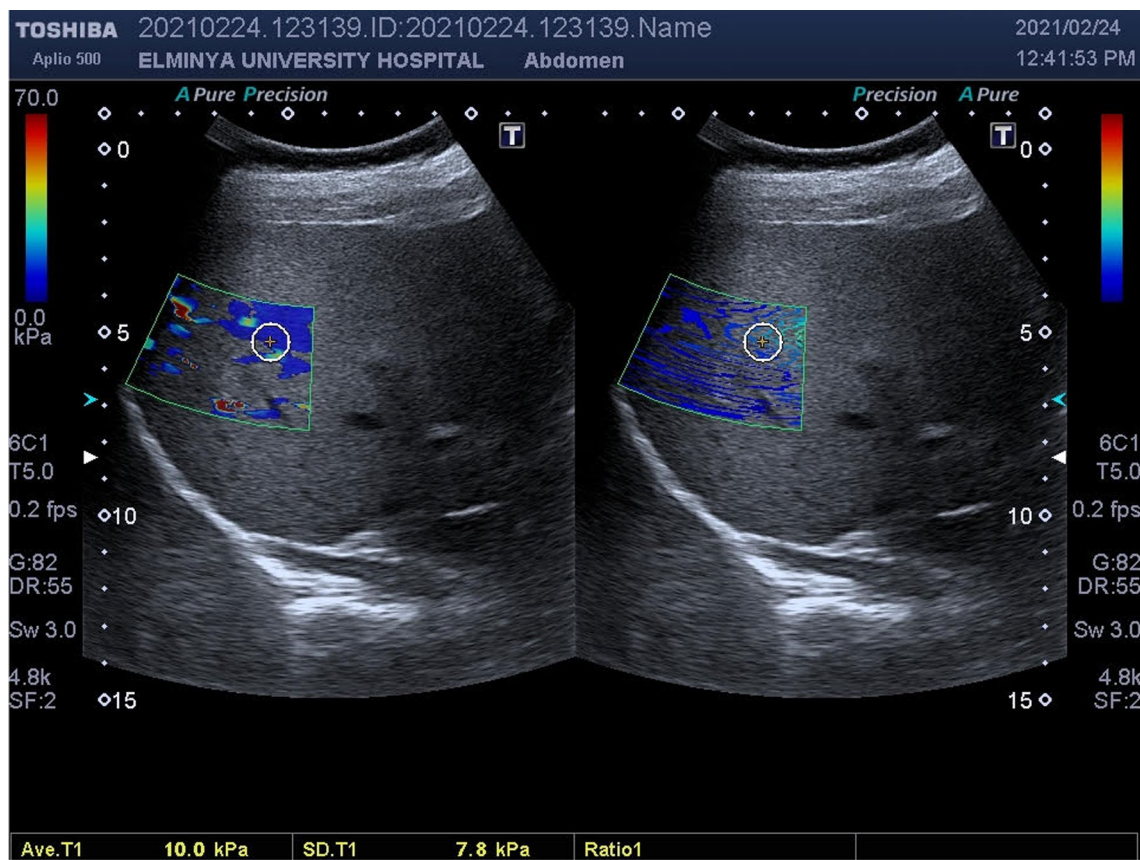


Fig. 2 Transient elastography showing increased liver tissue stiffness in patient with advanced liver fibrosis. The patient measures about 10 kPa denoting severe stiffness

Our study included 60 adult RA patients who all treated with MTX, and 30 age- and sex-matched healthy individuals. The presence of hepatic fibrosis is well-documented in some of RA patients in contrast to general population. In the present work, hepatic fibrosis was detected in 20 RA patients (33.3%) compared with only 5 controls (16.7%) using a 7.1 kPa cutoff. However, in other studies, the prevalence of hepatic fibrosis in RA patients was lower, ranging from 16 to 26.8% [20, 31]. Furthermore, the average hepatic fibrosis as determined by TE was 6.83 ± 2.33 kPa in RA patients and 4.95 ± 2.09 kPa in the healthy group ($p < 0.001$) which is higher compared with other studies. Kumar et al. reported a mean liver stiffness of 4.8 kPa in the RA patients and 4.7 kPa in the healthy individuals [32]. Another study by Laharie et al., which included 149 RA patients, reported the mean FibroScan score was 4.3 kPa [33]. Other study which evaluated liver affection in patients with HCV-related vasculitis using the same cutoff value with 38.5% had severe cases of hepatic fibrosis, and 42.3% had mild-to-moderate cases [34].

The primary reason for this disparity is most likely that other studies excluded obesity based on BMI more than 30 while we did not. Other reasons for such variability that Fibroscan validation studies do not follow the rigorous requirements for applicability as there is variation according to probe position, beside it is an operator dependent [35]. Additionally, measurement disparity between using different probes as the Medium (M) and XL probes, as there might be a basic technological difference, as the two probes differ significantly in terms of energy and ultrasonic frequency [36].

Measurement of BMI in our series is also comparable with other reports, it was ranged from 19.47 to 38.95 kg/m² with a mean of 25.68 ± 4.48 kg/m² in the patient's group versus 25.49 ± 4.88 kg/m² in the control group. Our results came in accordance with Bafna et al. results who studied 75 RA patients on MTX to evaluate the prevalence of hepatic fibrosis and found that the mean of BMI was 24.8 ± 3.9 kg/m² [20]. Obesity is a major predictor of advanced liver fibrosis or cirrhosis, which is linked to more than threefold increase in all causes of liver-related mortality [37, 38]. Liver fibrosis advances in obese

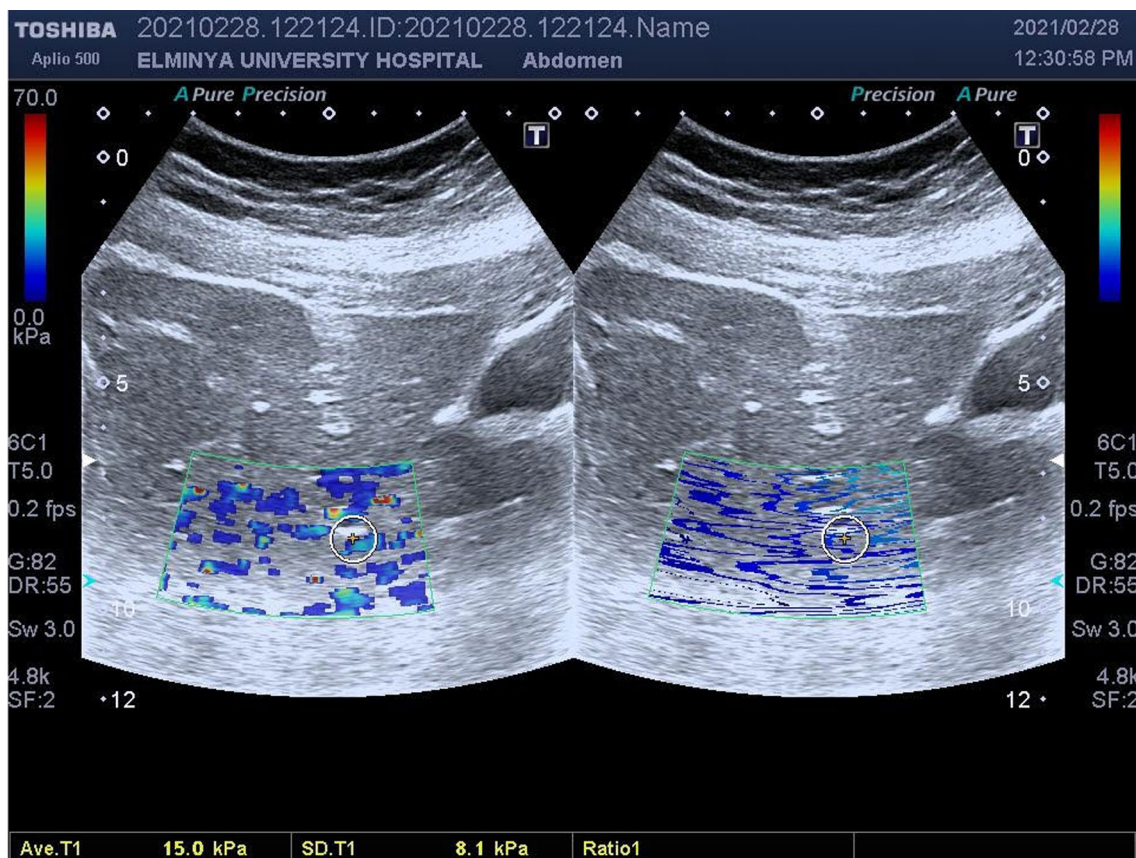


Fig. 3 Transient elastography showing increased liver tissue stiffness in cirrhotic patient. The patient measures about 15 kPa denoting cirrhosis

Table 2 Comparison between RA patients with and without hepatic fibrosis in demographic and RA disease-related variables

	RA patients with hepatic fibrosis (n = 20) Mean ± SD/N (%)	RA patients without hepatic fibrosis (n = 40) Mean ± SD/N (%)	t χ ²	p
Sex				
Female	19 (95%)	32 (80%)	-2.353	0.249
Male	1 (5%)	8 (20%)		
Age (years)	50.75 ± 10.10	44.32 ± 12.37	-2.009	0.049*
Age at onset	38.85 ± 10.15	40.52 ± 11.94	0.537	0.593
Duration of illness	11.90 ± 6.30	3.80 ± 2.06	-7.714	0.001**
BMI	27.36 ± 4.88	24.84 ± 4.07	-2.107	0.039*
DAS 28-ESR	4.24 ± 1.07	3.35 ± 0.50	-4.405	0.001**
Articular index	34.95 ± 13.25	19.5 ± 11.82	-4.582	0.001**
Number of swollen joints	6.94 ± 4.62	7.0 ± 3.70	0.038	0.970
Cumulative dose of MTX (mg)	6,118.0 ± 2642.25	1,740.66 ± 528.29	-10.161	0.001**
Duration of MTX intake (years)	7.27 ± 3.52	2.07 ± 0.68	-9.073	0.001**

BMI Body mass index, DAS Disease activity score, ESR Erythrocyte sedimentation rate, MTX Methotrexate

χ² Chi-square test, *significant p value < 0.05, **highly significant p value < 0.001

Table 3 Correlations between serum PIIINP level and different RA disease parameters

Variables	Serum PIIINP	
	r	p
Age (years)	0.216	0.097
Age at onset of disease (years)	-0.086	0.511
Duration of disease (years)	0.646	0.001**
1st h ESR (mm)	0.166	0.204
Platelet count/mm ³	-0.117	0.375
ALT level (IU/L)	0.082	0.534
AST level (IU/L)	0.173	0.186
Serum albumin g/dl	0.095	0.472
Serum ALP (IU/L)	-0.068	0.607
Serum GGT (IU/L)	-0.064	0.630
Value of DAS 28-ESR	0.527	0.001**
Value of BMI	0.294	0.023*
Value of TE (kPa)	0.700	0.001**
Cumulative dose of MTX (mg)	0.708	0.001**
Duration of MTX (years)	0.720	0.001**

PIIINP Procollagen III amino terminal propeptide, ESR Erythrocyte sedimentation rate, ALT Alanine transaminase, AST Aspartate transaminase, ALP Alkaline phosphatase, GGT Gamma glutamyl transferase, DAS Disease activity score, BMI Body mass index, TE Transient elastography, MTX Methotrexate

By Pearson's correlation test

* significant p value < 0.05

** highly significant p value < 0.001

individuals due to increased adiposity and insulin resistance. It is believed that a profibrotic milieu in the liver is fostered by a rise in the number of dead hepatocytes, an increase in reactive oxygen radicals, and changes in the production of adipokines and cytokines [39].

In this study, serum PIIINP was ranging from 22.0 to 436.0 ng/ml with a mean of 131.69 ± 101.39 ng/ml in RA patients' group which was significantly higher than healthy individuals (82.30 ± 76.73 ng/ml). Our result is in accordance with Amer et al. who conducted a research on 30 RA patients receiving alternative treatments and 60 RA patients receiving MTX in order to assess the validity of PIIINP in the detection of hepatic fibrosis brought on by long-term MTX therapy and found that mean PIIINP on MTX group was 120 ng/ml with the same cutoff point which is more than 170 ng/ml [19]. Our results also showed that serum PIIINP was elevated above threshold of fibrosis (170 ng/ml) in 24 patients (40%), on agreement with Frankowski et al. who studied 96 RA patients aiming to measure hepatic fibrosis in RA patients by evaluating non-invasive diagnostic techniques and discovered that PIIINP was elevated in 44.8% of their patients [25].

In the present work and based on stepwise logistic regression, the cumulative dosage of MTX, fatty liver, and serum PIIINP > 170 ng/ml was found to be

Table 4 Correlations between TE and different RA disease parameters

Variables	TE	
	r	p
rs		
Age	0.145	0.267
Sex	-0.225	0.083
Age at onset of disease	-0.139	0.291
Duration of disease	0.600	0.001**
Value of BMI	0.173	0.186
Value of DAS 28-ESR	0.396	0.002**
Fatty liver	0.536	0.001**
ALT level	0.146	0.266
AST level	0.281	0.030*
serum albumin	-0.025	0.849
Serum PIIINP level	0.700	0.001**
PIIINP > 170 ng/ml	0.634	0.001**
Cumulative dose of MTX	0.714	0.001**
Duration of MTX	0.731	0.001**
Antimalarial intake	-0.045	0.736
Corticosteroid intake	0.152	0.247
Folic acid intake	-0.229	0.078

BMI Body mass index, DAS Disease activity score, ESR Erythrocyte sedimentation rate, ALT Alanine transaminase, AST Aspartate transaminase, PIIINP Procollagen III amino terminal propeptide, MTX Methotrexate

By Pearson's correlation test and Spearman's correlation test

* significant p value < 0.05

** highly significant p value < 0.001

predictor factors for hepatic fibrosis on agreement with Lertnawapan et al. who found the cumulative dosage of MTX and fatty liver as predictors of liver fibrosis [40], Arena et al. who found cumulative dose of MTX as predictor of hepatic fibrosis [23]. On the contrary, laharie et al. noticed no relation between the cumulative dosage of MTX and TE on regression analysis [33].

The current study evaluated the sensitivity and specificity of a single serum PIIINP measurement in patients receiving MTX therapy, with results of 85.0% and 82.5%, respectively. These values are a little higher than those reported by Maybury et al., who evaluated the same parameters and found rates of 74% and 77%, respectively [41], PIIINP is not organ specific, and RA activity as well as other variables may affect its reading.

This study has some limitations: Firstly, exclusion of high BMI could not be done as 43.3% of our patients had BMI above normal value (≥ 25 kg/m²) and obesity is one of the factors that increases liver stiffness, secondly; the cutoff point for measurement of hepatic fibrosis on elastography was not unique in whole studies.

Table 5 Determinants of liver fibrosis by stepwise logistic regression

Dependent	Model	Independent	β	t	p	% of variance
Liver fibrosis	$R^2=0.76$ $F=58.91$ ($P<0.001$)	Included	0.519	6.771	0.001	57%
		Cumulative dose of MTX	0.380	4.987	0.001	11%
		Fatty liver	0.280	4.211	0.001	8%
		Increased serum PIIINP				

MTX Methotrexate, PIIINP Procollagen III amino terminal propeptide

Table 6 Sensitivity, specificity, predictive values, and accuracy for PIIINP in detecting liver fibrosis among RA patients

	Sensitivity	Specificity	PPV	NPV	Accuracy
Liver fibrosis	85.0%	82.5%	70.83%	91.67%	83.33%

PIIINP Procollagen III amino terminal propeptide; PPV Positive predictive value; NPV Negative predictive value

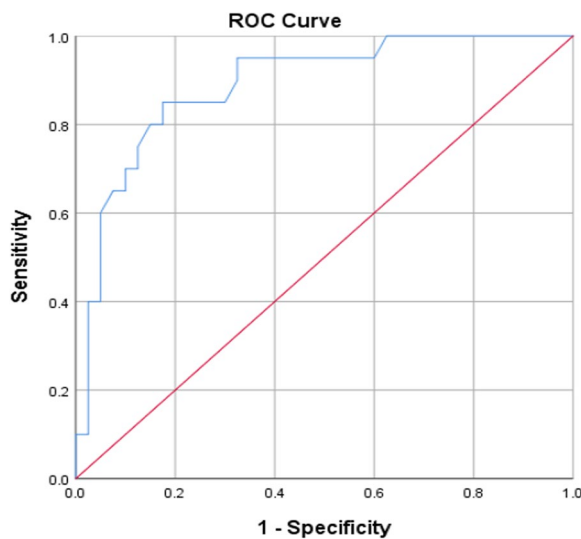


Fig. 4 ROC curve of serum PIIINP level for prediction of liver fibrosis risk. ROC curve of serum PIIINP level with the area under the curve (AUC) of 0.89 where a cut-off PIIINP value of > 170 ng/ml provided 85% sensitivity and 82.5% specificity for predicting liver fibrosis

Conclusions

Transient elastography and PIIINP are recommended for the routine investigations for RA patients on MTX therapy to detect liver fibrosis even if they are asymptomatic. Transient elastography is superior to PIIINP for evaluating the progress of the disease and the effectiveness of treatment. We recommend using of fibroscan as a monitoring for RA patients on MTX therapy, specifically patients with fatty liver. Better control of body weight and RA disease activity is necessary to reduce hepatic fibrosis risk in those patients.

Abbreviations

- ACR American College of Rheumatology
- AUC Area under the curve
- BMI Body mass index
- DAS Disease activity score
- EULAR European alliance of associations for rheumatology
- kPa Kilopascal
- M Medium
- MTX Methotrexate
- NPV Negative predictive value
- PIIINP Serum procollagen III amino terminal propeptide
- PPV Positive predictive value
- RA Rheumatoid arthritis
- ROI Region of interest
- SPSS Statistical Package for the Social Sciences
- TE Transient elastography
- XL Extra large

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Author contributions

Rasha M Ghaleb designed the study and participating in writing the study. Doaa M Mohamed collected the clinical data. Ahmed Hamed analyzed the results. Zaki M Zaki interpreted the laboratory parameters. Nadia El Ameen performed abdominal ultasonography and fibroscan.

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Availability of data and materials

The data are available on request.

Declarations

Ethics approval and consent to participate

The study was approved by the Scientific Ethical Committee of the faculty of medicine, Minia University, Minia, Egypt.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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