Original Article

# Prevalence of Metabolic Dysfunction–Associated Steatotic Liver Disease and Hepatic Fibrosis in Patients with Rheumatoid Arthritis: A Cross-Sectional Case-Control Study

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## ABSTRACT

**Background:**
Hepatic steatosis is commonly associated with rheumatoid arthritis (RA). Methotrexate is the first-line therapy for RA, and its long-term use is linked to hepatic steatosis and fibrosis. We wanted to study the prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and hepatic fibrosis in patients with RA and healthy controls.

**Materials and Methods:**
We conducted a prospective cross-sectional study on 200 individuals with RA who attended the Rheumatology Clinic at Sohag University and 100 matching healthy controls. History, clinical examination, laboratory investigations, and abdominal ultrasonography were performed. Hepatic steatosis was evaluated using abdominal ultrasonography and the Hepatic Steatosis Index (HSI). Liver fibrosis was assessed using the FIB-4, AST to Platelet Ratio Index (APRI), and BMI (Body Mass Index), AST/ALT ratio, and Diabetes (BARD) scores.

**Results:**
We found that the RA was statistically significant in MASLD patients compared with those without MASLD (P=0.04). The APRI score was significantly correlated with the methotrexate (MTX) cumulative dose (r=0.963, P=0.041) and age (r=0.963, P=0.004). FIB-4 score was significantly correlated with MTX dose (r=0.967, P=0.047) and disease duration (r=0.967, P=0.017). APRI score and FIB-4 score were highly significant in patients with a moderate degree of Disease Activity Score (DAS) than other degrees, with P=0.001, and P=0.005. BARD score correlated with MTX dose (r=0.887, P=0.01) and disease duration (r=0.887, P=0.001).

**Conclusion:**
There is an elevated risk of MASLD in patients with RA, particularly those on MTX therapy. APRI, FIB 4, and BARD scoring systems have significance in diagnosing hepatic fibrosis in patients with RA and RA activity (DAS score).

**Keywords:** MASLD, Steatosis, Hepatic fibrosis, Rheumatoid arthritis, Methotrexate, APRI

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## INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that mainly affects the synovial membrane, cartilage, and bone tissue and is associated with progressive disability, systemic complications, and increased mortality (1).

Methotrexate (MTX) is the cornerstone of treatment for RA. The most concerning long-term side effect of MTX is the development of liver fibrosis and steatosis (2).

Steatotic liver disease is one of the conditions known as metabolic dysfunction associated with steatotic liver disease (MASLD), which is characterized by an increase in hepatic fat content. In addition to hepatic steatosis, MASLD includes disorders such as non-alcoholic steatohepatitis, hepatic fibrosis, cirrhosis, and finally hepatocellular carcinoma (3).

In Western nations, MASLD is the most prevalent leading cause of chronic hepatic disease. (4). It is closely linked to cardiometabolic disorders such as type 2 diabetes (T2D) and the metabolic syndrome (MS) (5).

Several studies have shown that identifying MASLD at an early stage decreases the potential risk of developing an advanced form of hepatic fibrosis. It has been demonstrated that MASLD is a reliable indicator of serious cardiovascular diseases (5).

For decades, fatty alterations in the liver have been linked to RA (5). This may be due to the fact that inflammatory mediators, such as tumor necrosis factor (TNF) and interleukin (IL-1, IL-6), play a similar function in the pathophysiology of both RA and MASLD (6).

Patients with RA can have hepatic disease because of treatment with hepatotoxic drugs like MTX or leflunomide (LFN). There is insufficient data to support the hypothesis that the cumulative dose of MTX may independently predict the development of MASLD with transaminitis (7) and may be correlated with liver stiffness determined by transient elastography (5).

In the UK, the National Institute for Clinical Excellence (NICE) recommends MTX as a disease-modifying medication that has been used extensively for several decades to treat RA. (8).

MTX-induced liver damage has been reported since the early 1970s (9). The primary clinical fear emerges from the possibility of substantial hepatic fibrosis with extended MTX consumption. This risk has been predicted to affect 5% of individuals (ranging from 3.5% to 7%), with some findings connecting fibrosis to the total cumulative dose (10).

Liver biopsy is an invasive technique; however, it remains the most accurate method for assessing and staging liver fibrosis. There are serious hazards associated with it, such as bleeding and hospitalization (11). As a result, several non-invasive indicators of hepatic fibrosis have been developed, such as the enhanced liver fibrosis (ELF) blood marker profile and transient elastography (TE) for measuring liver stiffness (12).

In this study, we aimed to study the prevalence of MASLD and fibrosis in a large sample of patients with RA and healthy controls.

## MATERIALS AND METHODS

This cross-sectional study was conducted on a total of 200 patients aged 18 years or older attending the outpatient clinic of the Rheumatology and Rehabilitation Department at Sohag University Hospital with RA diagnosed according to the 2010 ACR/EULAR (European League Against Rheumatism) classification criteria for RA (13). In addition, 100 healthy individual volunteers were recruited from the community as age and sex-matched controls. Written informed consent was obtained from all patients, and approval was obtained from the ethics committee.

**Exclusion criteria:**

History of hepatitis B and C virus infection, receiving hepatotoxic drugs other than RA-specific drugs, alcohol abuse (i30 g/day in men and ≥ 20 g/day in women), diagnosis of Wilson's disease, α1-antitrypsin deficiency or hemochromatosis, autoimmune liver disease, cancer, and pregnancy.

**Patients were subjected to the following:**

**1. Full history and clinical examination** were done with special emphasis on age, sex, presence of DM or hypertension, disease duration, and therapeutic history. The mean weekly MTX dose was multiplied by the number of treatment weeks to determine the patient's MTX exposure. Body mass index (BMI) was calculated as BMI=Weight (kg)/ [Height (m)]2 (14).

**2. Assessment of RA activity** was done using Disease Activity Score (DAS 28) by calculating tender joint numbers in 28 joint sites (bilateral shoulder joint, elbow joint, wrist joint, Metacarpophalangeal (MCPs), Proximal Interphalangeal (PIPs), and knee joint), swollen joint count at the same sites, ESR level (mm/hr), visual analog scale for global health (VAS-GH) (patient assessment of his condition using a 100 scale with 0=best, 100=worst). The results were put into a complex mathematical formula to produce the overall score ranges as: remission (<2.6), mild (2.6- 3.2), moderate (3.2-5.1), or severe disease activity (>5.1) (15).

**3. Laboratory investigations were collected;** Routine investigations of ESR, CRP, serum creatinine, CBC with

differential, lipid profile involving (cholesterol, triglyceride, HDL, VLDL), complete liver functions involving (liver enzymes, albumin, total proteins, total bilirubin), and random blood sugar were done. Immunological investigations such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (Anticcp) were done as well.

**4. Liver steatosis and fibrosis Assessment**

• HSI = 8 x ALT/AST + BMI (+ 2 if type 2 diabetes yes, + 2 if female). HSI values of 39.9 and above indicate that a MASLD-positive diagnosis is highly likely (16).

• The fibrosis-4 (FIB-4) index, as follows FIB-4 index = (age [years] × AST [U/L])/ (platelet [109/L] × p ALT [U/L]) (17).

• APRI (AST to Platelet Ratio Index) was calculated as (AST/upper limit of normal range)/platelet count (109/L) × 100 (18).

• The BARD score was composed of three variables: an AST/ALT ratio ≥0.8, 2 points; a BMI ≥28, 1 point; and the presence of diabetes, 1 point. The possible score ranges from 0 to 4 points (19).

**Abdominal ultrasonography:**

The examination was performed after overnight fasting with the patient in a supine position using a convex-type transducer on an ultrasound device with a 3.5–5-MHz frequency (Mindray DP-2200, made in China).

It was used to assess liver size, the degree of liver brightness (indicating fat content in the liver), and spleen size. The liver size was measured as the span of the right lobe in the mid-clavicular line on an oblique view and classified as shrunken (<11 cm), average (11-15 cm), or enlarged (> 15 cm) (20). Longitudinal spleen length greater than 13 cm was considered enlarged (21).

Steatosis was classified according to enhanced liver echogenicity, portal and hepatic vein clouding, and inadequate diaphragm vision (22) into:

(a) Absent: if the liver echogenicity was normal and there was no vessel clouding.

(b) Mild, with a slight increase of liver echogenicity with regular visualization of the diaphragm and the portal and hepatic veins.

(c) Moderate, with a moderate increase of liver echogenicity with slightly reduced visualization of the portal or hepatic veins and the diaphragm.

(d) Severe, with a severe increase of liver echogenicity with poor appearance of the portal vein and diaphragm.

We classified our participants into MASLD and non-MASLD groups according to MASLD criteria reported in the EASL guideline 2024 (23) that include patients who had hepatic steatosis in conjunction with at least one cardiometabolic risk factor, which includes:

1) Overweight or Obesity: BMI>25 kg/m2, waist circumference >94 cm in men and >80 cm in women.

2) Dysglycaemia or type 2 diabetes: Prediabetes: HbA1c 39-47 mmol/mol (5.7-6.4%) or fasting plasma glucose 5.6-6.9 mmol/L (100-125 mg/dl) or 2-h plasma glucose during oral glucose tolerance test (OGTT) 7.8-11 mmol/L (140-199 mg/dl) or type 2 diabetes: HbA1c >48 mmol/mol (>6.5%) or fasting plasma glucose >7.0 mmol/L (>126 mg/dL) or 2-h plasma glucose during OGTT >11.1 mmol/L (>200 mg/dL) or treatment for type 2 diabetes

3) Plasma triglycerides: >1.7 mmol/L (>−150 mg/dL) or lipid-lowering treatment.

4) HDL-cholesterol: <1.0 mmol/L (<39 mg/dL) in men and <1.3 mmol/L (<50 mg/dL) in women or lipid-lowering treatment.

5) Blood pressure: >130/85 mmHg or treatment for hypertension.

**Ethical consideration:**

The study protocol adheres to the ethical principles outlined in the 1975 Declaration of Helsinki. After approval of the protocol by the Ethical Committee of Research (registration number: Soh-Med-22-11-17), written informed consent was obtained from each participant. Clinical trial registration number: NCT05679648.

**Statistical Analysis Design:**

Data were analyzed using SPSS software version 12.1 for Windows. Quantitative data were presented as mean and standard deviation (mean ± SD). Data were analyzed using a student t-test to compare the means of the two groups. Qualitative data were presented as numbers and percentages and were compared using either the Chi-square ($X^2$) test or the one-way ANOVA. The P value was considered significant if it was less than 0.05.

## RESULTS:

As regard to comparison between the two studied group, age, HTN, ESR, WBCs, ALT, AST, cholesterol, triglyceride, HDL, BMI, liver size, and MASLD were highly statistically significant in RA group than control group with P values of <0.001, 0.002, 0.002, 0.016, <.001, <.001, 0.042, 0.037, <.001, 0.0015, and 0.04, respectively). However, there was a lower statistical significance in the RA group than the control group regarding HB, albumin, protein, and VLDL, with P values of 0.002, <.001, 0.052, and 0.003, respectively. FIB 4 score was highly statistically significant in the RA group than the control group (P=0.044), while the other scoring systems were statistically insignificant as shown in Table 1.

When the participants were classified into MASLD and non-MASLD groups, RA, female sex, age, and serum creatinine were higher statistically significant in patients with MASLD than in non-MASLD ones with P values of

< 0.001, 0.035, 0.001, and < 0.001, respectively, while HB level and serum albumin were lower statistically significant in patients with MASLD than in non-MASLD ones with P values of < 0.001, and < 0.001, respectively, as shown in Table 2.

When patients with RA were classified into MASLD and non-MASLD groups, age, DAS, HB level, serum creatinine, and MTX dose were higher statistically significant in patients with MASLD and RA than patients with RA but without MASLD with r= 0.892 and P values of 0.001, 0.000, 0.000, 0.003, and 0.045, respectively as shown in Table 3.

When we compared patients with MASLD and non-MASLD regarding HIS, female sex, presence of RA, increased age, high ESR, high serum ALT, high serum bilirubin, high serum cholesterol, high serum triglyceride, high HDL, and increased BMI were higher statistically associated with high HIS in MASLD patients than non MASLD ones with P values of 0.001, 0,021, 0,001, 0.001, 0.001, 0.02, 0.001, 0.001, 0.001, and 0.001, respectively) as shown in Table 4.

In this study, we used different scores for detecting hepatic fibrosis in patients with RA, and the following results were found :

APRI score had a positive correlation with the cumulative dose of MTX, age, serum creatinine, ALT, AST, and bilirubin with r=0.963 and P values of 0.041, 0.004, <0.001, <0.001, <0.001, and <0.001, respectively, but had a negative correlation with ESR, HB, platelet, and serum protein with P values of <0.001, <0.001, <0.001, and 0.036 respectively. We also found that the APRI score was highly significant in patients with a moderate degree of DAS score than other degrees (P=0.001) as shown in Table 5.

FIB 4 score had positive correlation with MTX dose, age, disease duration, serum creatinine, ALT, AST, bilirubin, and RBS with r=0.967 and P values of 0.047, <0.001, 0.017, <0.001, 0.014, 0.015, <0.001, and <0.001, respectively, while platelet, serum albumin, serum protein, and VLDL had negative correlation with FIB 4 score with P values of <0.001, <0.001, <0.001, and 0.008, respectively. We also found that the FIB 4 score was highly significant in female patients and patients with a moderate degree of DAS score than other degrees, with P values of 0.003 and 0.005, respectively, as shown in Table 6.

BARD score had a positive correlation with MTX dose, age, disease duration, ESR, WBCs, ALT, bilirubin, RBS, and BMI with r=0.887 and P values of <0.001, 0.014, 0.001, 0.005, <0.001, <0.001, 0.001, <0.001, and <0.001, respectively, while serum protein, and HDL had a negative correlation with BARD score with P values of 0.047, and 0.040 respectively. We also found that the BARD score was highly significant in female patients (P=0.001), as shown in Table 7.

Table 1. The sociodemographic characteristics, laboratory, and ultrasonographic data of both studied groups (A)

| | RA (n=200) | | Control= 100 | | |
|---|---|---|---|---|---|
| | Mean | Std. Deviation | Mean | Std. Deviation | P value |
| Age | 46.50 | 12.657 | 40.32 | 17.288 | <0.001 |
| ESR | 42.930 | 26.1739 | 24.620 | 20.5283 | 0.002 |
| HB | 11.827 | 1.5401 | 12.762 | 2.0940 | 0.002 |
| WBCs | 8.489 | 3.2065 | 7.644 | 2.5234 | 0.016 |
| PLT | 318.530 | 106.8645 | 291.180 | 91.7638 | 0.063 |
| Cr | 0.664 | 0.2118 | 0.622 | 0.2381 | 0.762 |
| ALT | 19.570 | 10.3178 | 15.040 | 8.3193 | <0.001 |
| AST | 22.020 | 8.0251 | 18.460 | 6.0942 | <0.001 |
| Albumin | 3.550 | 0.3374 | 3.826 | 0.4534 | <0.001 |
| Protein | 7.112 | 0.5375 | 7.202 | 0.6962 | 0.052 |
| Bilirubin | 0.319 | 0.0958 | 0.48 | 0.232 | <0.001 |
| RBS | 106.460 | 44.2254 | 91.066 | 42.6198 | 0.203 |
| Cholesterol | 187.771 | 39.9186 | 168.640 | 37.0453 | 0.042 |
| Triglyceride | 124.256 | 55.6490 | 106.602 | 48.8147 | 0.037 |
| HDL | 41.686 | 8.8358 | 35.060 | 12.1113 | <0.001 |
| VLDL | 27.386 | 8.5398 | 28.832 | 27.1216 | 0.003 |
| BMI | 30.7614 | 10.30471 | 26.8604 | 6.18720 | 0.015 |
| liver_size | 15.141 | 2.1406 | 11.844 | 1.3686 | <0.001 |
| PV | 9.699 | 1.4630 | 9.570 | 0.9992 | 0.210 |
| Spleen | 10.720 | 1.8524 | 10.830 | 1.2128 | <0.001 |
| BARD | 2.27 | 0.895 | 2.40 | 0.804 | 0.226 |
| FIB4 | .8588 | 0.49694 | 0.8499 | 1.01823 | 0.044 |
| APRI | 00.1888 | 0.07931 | 0.1788 | 0.10886 | 0.535 |

ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: Wight blood cells, PLT: Platelet, Cr: Creatinine, ALT: Alanine transaminase, AST: Aspartate transaminase, RBS: Randum blood sugar, HDL: High density lipoprotein, VLDL: Very low-density lipoprotein, BMI: Body mass index, PV: Portal vein, FIB4: Fibrosis 4 index, APRI: AST to platelet ratio index

(B)

| | RA (n=200) | | Control (n= 100) | | |
|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | P value |
| Female | 164 | 82.0 | 78 | 78 | 0.44 |
| DM | 26 | 13.0 | 12 | 12 | 0.856 |
| HTN | 56 | 28.0 | 12 | 12 | 0.002 |
| MASLD | 164 | 82 | 46 | 46 | 0.04 |

Table 2. Comparison between MASLD and non-MASLD groups regarding RA disease, age, sex, and laboratory findings among all studied individuals

| n (%) or mean±SD | MASLD (n=210) | | Non-MASLD (n=90) | | P |
|---|---|---|---|---|---|
| RA | 164 (78.1) | | 36 (40) | | <0.001 |
| Control | 46 (21.9) | | 54 (60) | | |
| Female | 176 (83.8) | | 66 | 73.3 | 0.035 |
| Age | 47.5±12.4 | | 37.4 | 16.9 | <0.001 |
| ESR | 39.8 | 25.9 | 29.9 | 24.6 | 0.37 |
| HB | 12.1 | 1.6 | 12.3 | 1.7 | <0.001 |
| WBCs | 8.2 | 3.2 | 8.1 | 2.7 | 0.57 |
| PLT | 307.6 | 99.7 | 313.7 | 109.92 | 0.47 |
| Creatinine | 0.67 | 0.25 | 0.61 | 0.14 | <0.001 |
| Albumin | 3.57 | 0.35 | 3.81 | 0.46 | <0.001 |
| Protein | 7.11 | 0.58 | 7.22 | 0.63 | 0.82 |
| Bilirubin | 0.99 | 0.59 | 0.43 | 0.21 | 0.11 |

RA: Rheumatoid arthritis, ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: White blood cells, PLT: Platelet. Bold values are significant at P<0.05

Table 3. Comparison between MASLD and non-MASLD groups in patients with RA regarding age, laboratory findings, disease duration, and MTX dose

| (%) or mean±SD | MASLD (n=164) | | Non-MASLD (n=36) | | P |
|---|---|---|---|---|---|
| Age | 47.9±11.2 | | 40.06 | 16.670 | 0.001 |
| Female | 136 (82.9) | | 26 | 72.2 | 0.476 |
| DD | 7.951 | 6.3938 | 6.944 | 5.9854 | 0.811 |
| ESR | 42.598 | 26.5084 | 44.444 | 24.8934 | 0.340 |
| DAS | 4.24 | 0.509 | 3.72 | 0.783 | 0.000 |
| HB | 11.899 | 1.3934 | 11.500 | 2.0760 | 0.000 |
| WBCs | 8.510 | 3.2355 | 8.394 | 3.1137 | 0.575 |
| PLT | 316.085 | 103.7747 | 329.667 | 120.9208 | 0.687 |
| Creatinine | 0.681 | 0.2248 | 0.588 | 0.1117 | 0.003 |
| Albumin | 3.532 | 0.3381 | 3.633 | 0.3260 | 0.941 |
| Protein | 7.118 | 0.5644 | 7.083 | 0.3975 | 0.098 |
| Bilirubin | 0.318 | 0.0938 | 0.326 | 0.1057 | 0.087 |
| MTXdose | 0.750 | 0.2535 | 0.695 | 0.3301 | 0.045 |
| Cumulative | 3.427 | 2.5885 | 2.611 | 1.5543 | 0.066 |

ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: White blood cells, PLT: Platelet, DD: Disease duration, DAS: Disease activity score, MTX: Methotrexate. Bold values are significant at P<0.05

Table 4. Relation between HIS and RA disease, age, sex, and laboratory findings in all individuals

| | MASLD (n=166) | | Non-MASLD (n=134) | | P |
|---|---|---|---|---|---|
| RA | 120 | 72.3 | 80 | 60 | 0.021 |
| Female | 152 | 91.6 | 90 | 67.2 | 0.001 |
| Age | 45.42 | 11.489 | 43.22 | 17.744 | 0.001 |
| ESR | 38.880 | 24.7143 | 34.284 | 27.1519 | 0.001 |
| ALT | 19.795 | 10.5919 | 15.910 | 8.5730 | 0.001 |
| AST | 21.024 | 7.6689 | 20.597 | 7.5693 | 0.424 |
| albumin | 3.683 | .3498 | 3.591 | .4528 | 0.001 |
| Protein | 7.198 | .5166 | 7.073 | .6763 | 0.098 |
| bilirubin | 1.130 | .74079 | .445 | .1964 | 0.02 |
| cholesterol | 195.387 | 41.1196 | 164.060 | 30.7324 | 0.001 |
| Triglyceride | 141.289 | 58.8382 | 89.981 | 28.3018 | 0.001 |
| HDL | 39.908 | 9.6840 | 38.943 | 11.4518 | 0.001 |
| VLDL | 27.949 | 9.5345 | 27.767 | 23.3433 | 0.085 |
| BMI | 34.4600 | 9.75169 | 23.2684 | 2.68354 | 0.001 |

RA: Rheumatoid arthritis, ESR: Erythrocyte sedimentation rate, ALT: Alanine transaminase, AST: Aspartate transaminase, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, BMI: Body mass index. Bold values are significant at P<0.05

Table 5. Relation between APRI score and sex, DAS score grades, age, MTX dose, laboratory investigation, and BMI in patients with RA

| | Mean±SD | | r | P |
|---|---|---|---|---|
| MTX dose | 0.705 | 0.3178 | -0.102 | 0.075 |
| cumulative | 3.280 | 2.4519 | 123 | 0.041 |
| Age | 46.50 | 12.657 | 0.186 | 0.004 |
| Sex | Female (164) | | | 0.309 |
| DD | 7.770 | 6.3196 | -0.069 | 0.167 |
| ESR | 42.930 | 26.1739 | -0.293 | <0.001 |
| HB | 11.827 | 1.5401 | -0.235 | <0.001 |
| WBCs | 8.489 | 3.2065 | -0.048 | 0.251 |
| PLT | 318.530 | 106.8645 | -0.605 | <0.001 |
| Creatinine | 0.664 | 0.2118 | 0.374 | <0.001 |
| ALT | 19.570 | 10.3178 | 0.501 | <0.001 |
| AST | 22.020 | 8.0251 | 0.641 | <0.001 |
| Albumin | 3.550 | 0.3374 | -0.108 | 0.064 |
| Protein | 7.112 | 0.5375 | -0.128 | 0.036 |
| Bilirubin | 0.319 | 0.0958 | 0.302 | <0.001 |
| RBS | 106.460 | 44.2254 | 0.091 | 0.100 |
| cholesterol | 187.771 | 39.9186 | -0.042 | 0.276 |
| Triglyceride | 124.256 | 55.6490 | 0.085 | 0.115 |

Table 5. Relation between APRI score and sex, DAS score grades, age, MTX dose, laboratory investigation, and BMI in patients with RA

| | Mean±SD | | r | P |
|---|---|---|---|---|
| HDL | 41.686 | 8.8358 | 0.025 | 0.362 |
| VLDL | 27.386 | 8.5398 | 0.088 | 0.107 |
| BMI | 30.7614 | 10.30471 | -0.054 | 0.223 |
| DAS | No (20) | | | 0.001 |
| | Low (30) | | | |
| | Moderate (130) | | | |
| | High (10) | | | |
| | very high (10) | | | |

MTX: Methotrexate, DD: duration therapy, ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: Wight blood cells, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, RBS: Random blood sugar, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, BMI: Body mass index, DAS: Disease activity score. Bold values are significant at P<0.05

Table 6. Relation between FIB-4 score and sex, DAS score grades, age, MTX dose, laboratory investigation, and BMI in patients with RA

| | mean±SD | | Correlation | P |
|---|---|---|---|---|
| MTX dose | 0.705 | 0.3178 | 0.119 | 0.047 |
| cumulative | 3.280 | 2.4519 | 0.017 | 0.408 |
| Age | 46.50 | 12.657 | 0.674 | <0.001 |
| DD | 7.770 | 6.3196 | 0.150 | 0.017 |
| ESR | 42.930 | 26.1739 | -0.038 | 0.297 |
| HB | 11.827 | 1.5401 | 0.018 | 0.399 |
| WBCs | 8.489 | 3.2065 | -0.104 | 0.072 |
| PLT | 318.530 | 106.8645 | -0.585 | <0.001 |
| Creatinine | 0.664 | 0.2118 | 0.303 | <0.001 |
| ALT | 19.570 | 10.3178 | 0.156 | 0.014 |
| AST | 22.020 | 8.0251 | 0.154 | 0.015 |
| Albumin | 3.550 | 0.3374 | -0.248 | <0.001 |
| Protein | 7.112 | 0.5375 | -0.244 | <0.001 |
| Bilirubin | 0.319 | 0.0958 | 0.269 | <0.001 |
| RBS | 106.460 | 44.2254 | 0.211 | 0.001 |
| cholesterol | 187.771 | 39.9186 | -0.107 | 0.066 |
| Triglyceride | 124.256 | 55.6490 | -0.040 | 0.287 |
| HDL | 41.686 | 8.8358 | 0.079 | 0.132 |
| VLDL | 27.386 | 8.5398 | -0.171 | 0.008 |
| BMI | 30.7614 | 10.30471 | 0.045 | 0.263 |
| | Frequency | | | |
| Sex | 164 females | | | 0.003 |
| DAS28 | No (20) | | | 0.005 |
| | Low (30) | | | |
| | Moderate (130) | | | |
| | High (10) | | | |
| | very high (10) | | | |

MTX: Methotrexate, DD: duration therapy, ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: White blood cells, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, RBS: Random blood sugar, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, BMI: Body mass index, DAS: Disease activity score. Bold values are significant at P<0.05

Table 7. Relation between BARD score and sex, DAS score grades, age, MTX dose, laboratory investigation, and BMI in patients with RA

| | Mean±SD | | Correlation | P value |
|---|---|---|---|---|
| MTX dose | 0.705 | 0.3178 | 0.264 | <0.001 |
| cumulative | 3.280 | 2.4519 | 0.094 | 0.094 |
| Age | 46.50 | 12.657 | 0.155 | 0.014 |
| DD | 7.770 | 6.3196 | 0.226 | 0.001 |
| ESR | 42.930 | 26.1739 | 0.181 | 0.005 |
| HB | 11.827 | 1.5401 | -0.054 | 0.223 |
| WBCs | 8.489 | 3.2065 | 0.254 | <0.001 |
| PLT | 318.530 | 106.8645 | 0.085 | 0.115 |
| Creatinine | 0.664 | 0.2118 | 0.006 | 0.468 |
| ALT | 19.570 | 10.3178 | 0.552 | <0.001 |
| AST | 22.020 | 8.0251 | 0.050 | 0.242 |
| Albumin | 3.550 | 0.3374 | -0.012 | 0.435 |
| Protein | 7.112 | 0.5375 | -0.119 | 0.047 |
| Bilirubin | 0.319 | 0.0958 | 0.228 | 0.001 |
| RBS | 106.460 | 44.2254 | 0.253 | <0.001 |
| cholesterol | 187.771 | 39.9186 | -0.087 | 0.111 |
| Triglyceride | 124.256 | 55.6490 | -.0054 | 00.224 |
| HDL | 41.686 | 8.8358 | -0.124 | 0.040 |
| VLDL | 27.386 | 8.5398 | 0.084 | 0.119 |
| BMI | 30.7614 | 10.30471 | 0.349 | <0.001 |
| | Frequency | | | |
| Females | (n=164) | | | 0.001 |
| DAS28 | No (20) | | | 0.2 |
| | Low (30) | | | |
| | Moderate (130) | | | |
| | High (10) | | | |
| | very high (10) | | | |

MTX: Methotrexate, DD: duration therapy, ESR: Erythrocyte sedimentation rate, HB: Hemoglobin, WBCS: White blood cells, PLT: Platelet, ALT: Alanine transaminase, AST: Aspartate transaminase, RBS: Random blood sugar, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, BMI: Body mass index, DAS: Disease activity score. Bold values are significant at P<0.05

## DISCUSSION:

MASLD has emerged as the most common chronic liver disease. It is characterized by the accumulation of excess triglycerides in the liver in the presence of at least one cardiometabolic risk factor. It encompasses various conditions, such as isolated liver steatosis, metabolic dysfunction associated with steatohepatitis, as well as fibrosis, and cirrhosis (23). Hepatic affection may be part of extra-articular symptoms of RA (24), which may be manifested as autoimmune hepatitis, autoimmune biliary diseases, and MASLD (25)

When we classified our participants into MASLD and non-MASLD, we found that female sex was statistically significant in patients with MASLD. In contrast, Vernon et al. (26) and Chen et al. (27) found that male sex is one of the risk factors for fatty liver. Our result may be due to the fact that 80% of our participants were females.

In our results, we found that the presence of RA was statistically significant in patients with MASLD. This result agrees with Erre and colleagues (3), who found that a high incidence of hepatic steatosis was detected by increased hepatic brightness on ultrasonography in patients with RA compared with the control group.

This finding may be part of the extra-articular manifestation of RA. Ursini and colleagues (5) conducted cross-sectional research in which ultrasonography revealed hepatic steatosis in 25% of patients with RA. Zamani and others (24) revealed that about 36% of their patients with RA had MASLD.

We detected that increased serum creatinine was more significant in patients with MASLD. This result agreed with Kasem et al. (28), who found that the incidence of chronic renal disease was significantly higher in the NAFLD than in the non-NAFLD group (38.1% vs 7.4%). This finding may be explained by the fact that fatty liver disease has been associated with several extrahepatic disorders such as obesity, DM, dyslipidemia, hypertension, and CKD and both diseases were independent risk factors for each other (29).

Our result showed an increased risk of MASLD with age. This agreed with Clayton-Chubb and colleagues (30) who reported an increasing incidence of fatty liver disease among aging Australians.

When we classified patients with RA into MASLD and non-MASLD, we detected that the increase in DAS in patients with RA was statistically significant in patients with MASLD. This may be due to increased BMI in our patients with MASLD, which plays a role in increasing RA activity. This result agreed with Gremese et al. (31), who reported that increased RA disease activity has been associated with high BMI, treatment resistance, and an illness linked to a higher risk of fatty liver disease.

Our result revealed that an increased MTX dose in patients with RA was highly significant with MASLD. This result agreed with Erre and others (3) who detected that increasing MTX-CD is one of the independent risk indicators for the occurrence of hepatic steatosis. Sakthiswary and others (32) revealed that in a cohort of 978 patients with RA, the MTX-CD was the only independent risk factor of MTX-associated liver steatosis with transaminitis. On the other hand, Choi et al. (33) and Mori et al. (34) revealed that there was no significant association between MTX dose and the development of hepatic steatosis.

Our result revealed that HIS was more significant in rheumatoid female patients with MASLD than in males. Erre et al. (3) detected a significant association between RA and hepatic steatosis. But they found that male sex was one of the risk factors for liver steatosis.

Our study found that HIS was highly significant in relation to serum ALT levels in patients with MASLD. This finding was in agreement with Pouwels and colleagues (35), who reported that asymptomatic elevation of ALT and AST levels occurred in up to 90% of cases with hepatic steatosis, once other causes of liver disease were excluded. Chentoufi and others (36) found that the patients with RA and fatty liver had elevated liver enzymes. They explained this result by stating that hepatic injury occurred in patients with RA, and elevated liver enzymes resulted from hepatic cellular damage.

Our study found that HIS was highly significant in relation to serum triglyceride levels and high BMI in patients with MASLD. This finding was in agreement with Mori et al. (34), who reported that increased serum triglyceride levels and BMI were associated with an increased risk of hepatic steatosis.

Our study found that APRI and FIB 4 scores for detecting hepatic fibrosis were statistically significant with the degree of DAS score in patients with RA on methotrexate and had a positive correlation with MTX dose.

This result was in contrast to that of Olsson-White et al.(37). APRI and FIB-4 may be mistakenly increased in patients with inadequate control of their RA since platelets are an acute-phase reactant and are increased in inflammatory conditions and reported that neither APRI nor FIB-4 were found to be sensitive nor specific in their study, so they might not be effective methods for detecting liver fibrosis in patients with RA receiving MTX. Avouac and others (38) detected that patients with RA on prolonged methotrexate treatment had a decreased FIB-4 value. This result indicated that methotrexate was not linked with an increased risk of liver fibrosis.

## CONCLUSION:

There is an elevated risk of MASLD in patients with RA, particularly those on MTX therapy. Female sex, high BMI, and hypertriglyceridemia were the main risk factors for MASLD in RA patients. The APRI and FIB-4 scoring systems have a significant association with RA activity and methotrexate dose.
Clinical trial number: NCT05679648

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None.

## CONFLICTS OF INTEREST:

The authors have no conflicts of interest to declare related to this work.

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