

Non-Alcoholic Fatty Liver Disease, Liver Stiffness, and Subclinical Cardiorenal and Neurological Involvement in Patients with Rheumatoid Arthritis: A Multicenter Multidisciplinary Study

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ABSTRACT

Introduction/Objectives: Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disease characterized by long-standing inflammation and extraarticular manifestations. Non-alcoholic fatty liver disease (NAFLD) is common in metabolic and inflammatory conditions, and it may be involved in increased prevalence of cardiovascular, renal and neurological abnormalities. The present work aimed to assess the associations between fatty liver grades, liver stiffness and subclinical involvement of the cardiorenal and neurological systems in RA patients, as well as evaluating the possible role of liver stiffness as an indicator of multiple system abnormalities.

Methods: total of 180 subjects were selected and divided equally into three groups: Group 1 (control group) without NAFLD or RA; Group 2 with NAFLD but without RA; and Group 3 with both RA and NAFLD.

Clinical and laboratory assessments were conducted, alongside evaluations of liver, cardiovascular, renal, and neurological status.

Hepatic steatosis and liver stiffness were assessed using ultrasound and transient elastography, utilizing the Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM). Cardio-renal and neurological assessments were conducted using estimated glomerular filtration rate (eGFR), left ventricular ejection fraction (LVEF), the Neurological Symptom Score (NSS), the Neurological Deficit Score (NDS), and the Modified Neurological Deficit Score (MSDS). Analyses included inter-group comparisons, correlation analysis, and multivariable regression models adjusted for age, sex, and body mass index.

Results : The three study groups showed an upward trend in mean liver stiffness, with values ranging from 4.58 ± 0.63 kPa in the control group to 8.16 ± 1.39 in patients with NAFLD without RA, and 11.15 ± 2.71 in patients with both NAFLD and RA. Correlation analyses revealed positive associations between liver stiffness measurement (LSM) and inflammatory markers, the urinary albumin-to-creatinine ratio, and neurological assessment scores, as well as negative associations with eGFR and LVEF; however, these correlations did not remain consistent in the adjusted regression analyses. The results

demonstrated a positive association between liver stiffness (LSM) and the MSDS score (regression coefficient $B = 0.309$, 95% CI: 0.274–0.344; $p < 0.001$); however, adjusted associations of liver stiffness with estimated glomerular filtration rate (eGFR) ($p = 0.829$), left ventricular ejection fraction (LVEF) ($p = 0.264$), the Neurological Symptom Score (NSS) ($p = 0.424$), and the Neurological Deficit Score (NDS) ($p = 0.060$) were not statistically significant.

Both the non-alcoholic fatty liver disease (NAFLD) grade and the Controlled Attenuation Parameter (CAP) were positively associated with the MSDS score, yet neither showed a statistically significant adjusted association with eGFR or LVEF.

Conclusions: Preliminary results indicate increased liver stiffness in patients with overlapping NAFLD and rheumatoid arthritis (RA) and suggest a role for liver markers in certain outcome measures. Unadjusted analyses of other parameters revealed relationships with renal and cardiac function metrics; however, these relationships were not confirmed in the final models presented. Liver stiffness may warrant further attention as an indicator of extrahepatic pathologies, despite questions regarding its independent association and potential role as an intermediate variable.

Keywords: Rheumatoid arthritis; non-alcoholic fatty liver disease; liver stiffness; transient elastography; controlled attenuation parameter; renal function; cardiac function; peripheral neuropathy; multisystem involvement.

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1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease characterized by persistent synovial inflammation, progressive joint damage, and a range of extra-articular manifestations (Kurtul et al., 2019). Beyond its articular manifestations, RA is associated with metabolic disturbances, endothelial dysfunction, accelerated atherosclerosis, and multisystem involvement. Non-alcoholic fatty liver disease (NAFLD) is a common metabolic liver disorder associated with chronic inflammation, insulin resistance, oxidative stress, and immune dysregulation. Increasing evidence suggests that NAFLD may coexist with inflammatory disorders and may be associated with cardiovascular, renal, and neurological complications (Rahman et al., 2022).

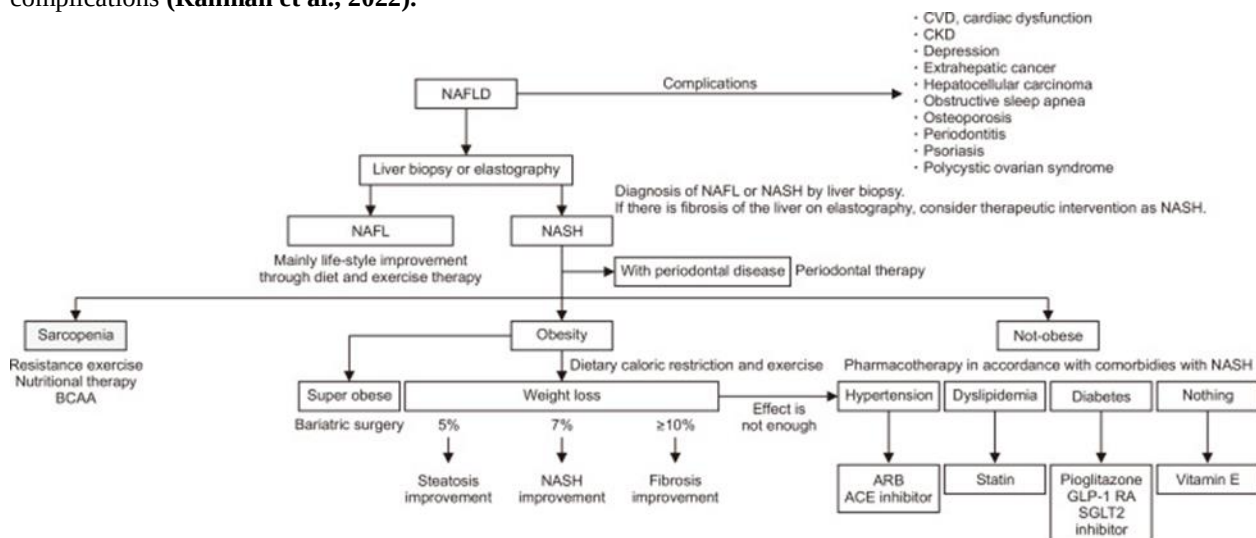


Figure 1. Flowchart illustrating the management and diagnostic approach to non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), including associated complications and treatment strategies (Yoneda et al., 2023).

Figure 1 illustrates a diagnostic and management pathway for NAFLD and NASH. Assessment of hepatic steatosis and fibrosis may involve imaging-based methods and, when clinically indicated, liver biopsy. The figure also summarizes recognized extrahepatic and hepatic complications and emphasizes lifestyle modification, including dietary intervention and weight management, as an important component of treatment (Yoneda et al., 2023).

The association between NAFLD and rheumatoid arthritis has received increasing attention because both conditions are characterized by inflammatory and metabolic abnormalities. NAFLD may progress from hepatic steatosis to more advanced fibrosis and cirrhosis and is associated with an increased risk of extrahepatic complications. In patients with chronic inflammatory disease, the coexistence of NAFLD may therefore be associated with a greater burden of cardiovascular, renal, and neurological abnormalities (Muzurović et al., 2022).

Although the relationship between RA and NAFLD has been investigated, the association between the severity of hepatic disease and subclinical cardiac, renal, and neurological involvement remains incompletely characterized, particularly in Middle Eastern and North African populations. Previous studies have often focused on disease prevalence or overt cardiovascular outcomes rather than a combined assessment of hepatic fibrosis and subclinical multisystem involvement (Alomari et al., 2023).

The primary objective of the study is to examine the relationship between non-alcoholic fatty liver disease (NAFLD) and liver fibrosis and the occurrence of subclinical cardiovascular, renal, and neurological involvement in patients with rheumatoid arthritis. Additionally, the study includes several secondary objectives: determining the relationship between the severity of liver fibrosis and cardiovascular function; determining the relationship between the severity of liver fibrosis and renal function; and determining the relationship between the severity of liver fibrosis and peripheral neuropathy.

2. MATERIALS AND METHODS

2.1. Sample and Grouping

This study was designed as an exploratory, cross-sectional secondary analysis based on patient data from various hospitals collected between May 2021 and April 2022 at Al-Azhar University (Assiut). It aimed to investigate the associations between liver stiffness—as an independent factor—and clinical, cardiac, renal, and cerebral parameters linked to various presentations of non-alcoholic fatty liver disease (NAFLD) and rheumatoid arthritis (RA). The dataset comprised 180 participants, evenly distributed across three study groups: Group 1 (G1, $n = 60$; control group), Group 2 (G2, $n = 60$; NAFLD without RA), and Group 3 (G3, $n = 60$; NAFLD with RA). All data were derived from the primary dataset source.

2.2. Study Variables

Demographic and anthropometric characteristics included age, sex, body weight, waist circumference, and body mass index (BMI). Metabolic and biochemical assessments included fasting blood glucose, glycated hemoglobin (HbA1c), fasting blood lipids, liver enzymes, serum albumin, serum creatinine, blood urea, and estimated glomerular filtration rate (eGFR). Hematological and inflammatory markers included red and white blood cell counts, platelet count, erythrocyte sedimentation rate (ESR), and the systemic immune-inflammation index (SII).

Key independent variables included the grade of hepatic steatosis (S0–S3), Controlled Attenuation Parameter (CAP, in dB/m), and liver stiffness measurement (LSM, in kPa); both CAP and LSM were assessed using transient elastography (FibroScan). The Fibrosis-4 (FIB-4) index was also included as an additional non-invasive marker of liver fibrosis. Non-alcoholic fatty liver disease (NAFLD) status and rheumatoid arthritis (RA) status were incorporated into the classification of study groups and relevant comparative analyses.

Dependent variables consisted of cardiac, renal, and neurological outcomes. Cardiac assessment included left ventricular ejection fraction (LVEF), mitral inflow velocity ratio (E/A), E/e' ratio, and left ventricular mass index (LVMI), where such data were available. Renal function was primarily assessed using the estimated glomerular filtration rate (eGFR), supplemented by serum creatinine and blood urea measurements. Neurological assessment comprised the Neurological Symptom Score (NSS), the Neurological Deficit Score (NDS), and the MSDS variable (subject to confirmation of its full definition and scoring methodology).

Age, sex, and body mass index (BMI) were considered key covariates in the adjusted analyses. Additional clinically relevant factors—including diabetes status, hypertension, inflammatory activity, rheumatoid arthritis duration, and medication use—were also considered for statistical adjustment, provided there was sufficient documentation and the factors were suitable for the statistical model. Associations between liver markers and cardio-renal or neurological outcomes were evaluated using multivariable models specific to each outcome, with particular attention paid to the potential impact of rheumatoid arthritis status.

2.3. Inclusion and Exclusion Criteria

Inclusion criteria covered adult patients aged 18 years or older for whom demographic, anthropometric, biochemical, and clinical data were available. This included Liver Stiffness Measurement (LSM) data obtained via transient elastography (FibroScan), as well as renal, cardiac, and neurological assessment data relevant to the study outcomes.

Exclusion criteria included patients with chronic viral hepatitis, autoimmune hepatitis, or other confirmed causes of chronic

liver disease; patients with a confirmed diagnosis of decompensated cirrhosis or malignant liver tumors; and patients with end-stage cardiac or renal disease. Also excluded were patients consuming alcohol or taking medications associated with severe neurological disorders or hepatotoxicity (Yki-Järvinen, 2014).

2.4. Outcome Measures

Liver stiffness measurement (LSM) via FibroScan was considered the primary independent variable. The dependent variables evaluated were: renal function, cardiac function, and neurological assessments.

Exploratory regression analyses were based on the following six primary outcomes: eGFR, LVEF, NSS, NDS, MSDS, and Albumin-to-Creatinine ratio (UACR)

2.5. Non-Alcoholic Fatty Liver Disease Diagnostic Criteria

According to the new clinical validation protocol, non-alcoholic fatty liver disease (NAFLD) is diagnosed in a patient with evidence of fatty liver as confirmed by abdominal ultrasound or another imaging technique if the patient does not have a history of alcohol abuse or other causes of fatty liver. In accordance with the 2016 international guidelines from learned societies (EASL-EASD-EASO), heavy drinking is defined as 30 g a day for men and 20 g for women. The presence of other conditions, such as chronic hepatitis (B or C), autoimmune liver diseases, or suspected drug-induced liver toxicity, is confirmed by reviewing past medical history and performing laboratory and other relevant investigations. (Miyamori et al., 2023).

Controlled Attenuation Parameter (CAP), which is measured using transient elastography, is used as a measuring device for fatty liver based on the available data. Liver Stiffness Measurement (LSM) is considered separately as an indicator for liver fibrosis, rather than a diagnostic criterion for NAFLD (Leoni et al, 2018).

2.6. Diagnostic and Classification Criteria for Rheumatoid Arthritis

Under the actual clinical validation protocol, rheumatoid arthritis (RA) was diagnosed by a rheumatologist, based on the 2010 classification criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR). These criteria stipulate the following: Synovitis must be present in at least one joint, with no alternative explanation for arthritis, and the overall score according to the set of classification criteria must be 6 out of 10 or more. The scoring system consists of four domains: number and distribution of affected joints (0-5), rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP/ACPA) antibodies (0-3), acute phase response indicators (eg, CRP and ESR; 0-1), and duration of symptom onset (0-1). RA disease activity was also assessed independently (eg, using the DAS28-ESR scale or pre-specified DAS28-CRP), and the scale used (DAS28-ESR or DAS28-CRP) and related measures were noted for each participant (Kourilovitch et al, 2014).

2.7. Liver Stiffness Measurement (Transient Elastography)

In the proposed clinical validation protocol, vibration-controlled transient elastography (FibroScan) was used to assess both hepatic steatosis and liver stiffness. All participants were undergone the procedure at least three hours after their last meal. Measurements were taken from the right lobe of the liver, with the participant in the supine position and the right arm abducted away from the examination area. An M or XL probe were used in accordance with the manufacturer's recommendations and the participant's body habitus; at least 10 valid liver stiffness measurements were obtained, and the median value were recorded in kilopascals (kPa). Measurement reliability was assessed using the interquartile range-to-median ratio (IQR/median), with a target quality criterion of $\leq 30\%$ and results reviewed against established reliability standards. The CAP value was also recorded in dB/m to assess steatosis, distinguishing it from the LSM used to assess liver stiffness. To ensure quality, data regarding the device, probe, number of measurements, LSM and CAP values, and reliability indicators were documented (Wong et al, 2013)

2.8. Statistical analysis

The statistical analysis was planned to determine whether there were differences between three groups (healthy controls, NAFLD without RA, NAFLD with RA) in the term of demographic, anthropometrical, biochemical, hepatic, cardiac, renal and neurological parameters.

Variables were to be summarized as means and standard deviations or medians with interquartile range or 95% confidence intervals for continuous variables and as number and percentages for categorical variables. Normality was to be confirmed through visual inspection and testing with the Shapiro-Wilk method. For nonparametrically distributed variables, comparison among groups was to be performed with the Kruskal-Wallis test, while for normally distributed variables, one-way analysis of variance (ANOVA) was to be used; if normality was confirmed with the ANOVA test, post hoc analysis with Bonferroni correction was to be carried out to confirm the origin of any significant differences. For categorical variables, the chi-square or Fisher exact test was to be used.

correlation analyses would perform correlation analyses to explore associations of hepatic parameters (NAFLD grade,

CAP, and LSM) with cardiovascular, renal, and neurological outcomes by use of either Pearson's or Spearman's correlation coefficients, according to the measurement scale and distributional assumptions.

Multivariable regression models would be used to evaluate the independent relationship of hepatic measures with LVEF, eGFR, NSS, NDS and other validated neurological measures. Age, sex and BMI were deemed as central adjustment variables. Other clinically relevant variables would have been included where data, sample size and model assumptions allowed. If data indicated, for example, that hepatic variables were highly correlated there would have been consideration of including these independently within separate models, and analysis of potential multicollinearity among hepatic variables would have been conducted. (Targher et,2018).

2.9. Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Al-Azhar University (Assiut), under the Institutional Review Board (IRB). The committee operates in accordance with international ethical guidelines, including the Declaration of Helsinki, the guidelines of the Islamic Organization for Medical Sciences, and applicable World Health Organization and International Council for Harmonisation–Good Clinical Practice principles. The study, entitled “Non-Alcoholic Fatty Liver Disease as a Predictor of Subclinical Cardiorenal and Neurological Involvement in rheumatoid arthritis Patients: A Multicenter Multidisciplinary Clinical Study,” received ethical approval under Code No. **RESEARCH/AZ.AST./MED018/4/223/6/2021 on 10 June 2021.**

3. RESULTS

Table 1. Baseline Demographic and Anthropometric Characteristics of the Study Groups (n = 180)

Variable	Statistic	Overall (n=180)	Control (G1) (n=60)	NAFLD_No_RA (G2) (n=60)	NAFLD_With_RA (G3) (n=60)	p-value
Age (years)	Mean ± SD	49.37 ± 11.65	47.17 ± 12.02	50.92 ± 11.51	50.02 ± 11.26	0.18
	Median (IQR)	49.50 (39.00–59.25)	45.50 (36.00–57.50)	53.00 (40.75–60.25)	50.00 (40.75–59.50)	
	Min–Max	28.00–68.00	28.00–68.00	28.00–68.00	28.00–68.00	
Weight (kg)	Mean ± SD	86.65 ± 16.57	86.59 ± 17.58	88.62 ± 16.12	84.75 ± 16.01	0.421
	Median (IQR)	85.95 (74.42–96.25)	85.30 (74.07–94.45)	89.20 (76.00–97.25)	83.45 (72.90–94.77)	
	Min–Max	52.60–123.80	52.60–123.80	56.30–121.10	57.70–118.20	
Waist Circumference (cm)	Mean ± SD	104.09 ± 14.71	104.90 ± 14.45	104.54 ± 14.43	102.83 ± 15.40	0.778
	Median (IQR)	105.65 (91.70–118.00)	107.85 (92.70–116.50)	103.55 (93.47–118.47)	105.45 (88.75–118.03)	
	Min–Max	78.50–125.90	78.50–125.90	78.60–124.70	79.10–125.90	
BMI (kg/m ²)	Mean ± SD	29.80 ± 5.09	29.52 ± 4.93	30.58 ± 5.05	29.29 ± 5.29	0.364
	Median (IQR)	30.10 (25.88–34.23)	30.00 (25.98–33.50)	31.40 (26.38–35.20)	29.65 (24.00–34.00)	
	Min–Max	21.20–37.90	21.20–37.90	21.40–37.90	21.40–37.80	

Notes: Continuous variables are presented as mean ± standard deviation (SD), median (interquartile range [IQR]), and minimum–maximum values. Group 1 (G1) represents controls without NAFLD or RA; Group 2 (G2) represents participants with NAFLD but without RA; and Group 3 (G3) represents participants with both NAFLD and RA. The p-values represent overall comparisons across the three groups. Statistical significance was defined as $p < 0.05$. An asterisk (*) indicates a statistically significant difference.

Baseline demographic characteristics shown in table (1) were broadly comparable across the study groups. Mean age ranged from 47.17 to 50.92 years, while weight, waist circumference, and BMI showed relatively similar distributions. The reported sex distribution was also broadly balanced across the groups. Age showed a statistically significant difference among groups ($p = 0.041$), although the absolute difference in mean age was relatively small.

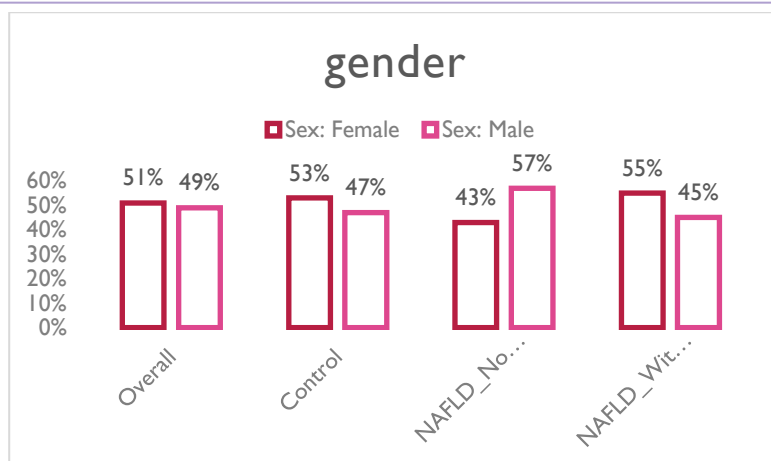


figure 2: illustrates Demographic characteristics according to sex

Figure 2 shows the sex distribution across the study groups. Females represented 51% of the total study population and males 49%. The reported proportions were broadly balanced across the groups, with a higher proportion of males in the NAFLD_No_RA group and a higher proportion of females in the NAFLD_With_RA group. No marked imbalance in sex distribution was observed.

Table 2. Laboratory, Inflammatory, Hepatic, Renal, and Cardiac Parameters Across the Study Groups

Variable	Overall (n=180)	Control (G1) (n=60)	NAFLD_No_RA (G2) (n=60)	NAFLD_With_RA (G3) (n=60)	p-value
RBC ($\times 10^6/\mu\text{L}$)	4.78 $\pm$ 0.51	4.76 $\pm$ 0.47	4.78 $\pm$ 0.50	4.81 $\pm$ 0.58	0.869
WBC ($\times 10^3/\mu\text{L}$)	7.60 $\pm$ 1.68	7.79 $\pm$ 1.71	7.43 $\pm$ 1.75	7.57 $\pm$ 1.57	0.486
Platelets ($\times 10^3/\mu\text{L}$)	305.15 $\pm$ 70.68	305.62 $\pm$ 70.34	302.30 $\pm$ 67.41	307.53 $\pm$ 75.17	0.92
Lymphocytes ($\times 10^3/\mu\text{L}$)	2.57 $\pm$ 0.71	2.61 $\pm$ 0.72	2.47 $\pm$ 0.71	2.64 $\pm$ 0.70	0.401
Neutrophils ($\times 10^3/\mu\text{L}$)	4.33 $\pm$ 1.11	4.30 $\pm$ 1.10	4.36 $\pm$ 1.12	4.33 $\pm$ 1.13	0.964
SII	758.30 $\pm$ 459.03	749.86 $\pm$ 461.98	836.83 $\pm$ 485.90	688.20 $\pm$ 435.15	0.184
ESR (mm/hr)	35.49 $\pm$ 17.12	33.50 $\pm$ 16.42	37.99 $\pm$ 18.49	34.99 $\pm$ 16.44	0.326
Fasting Glucose (mg/dL)	103.76 $\pm$ 12.99	104.62 $\pm$ 13.31	102.59 $\pm$ 13.84	104.08 $\pm$ 11.86	0.733
HbA1c (%)	5.66 $\pm$ 0.47	5.70 $\pm$ 0.48	5.63 $\pm$ 0.48	5.66 $\pm$ 0.46	0.688
ALT (U/L)	55.44 $\pm$ 23.05	54.00 $\pm$ 24.94	55.17 $\pm$ 21.79	57.14 $\pm$ 22.60	0.755
AST (U/L)	48.86 $\pm$ 20.17	47.77 $\pm$ 21.39	49.18 $\pm$ 19.92	49.62 $\pm$ 19.53	0.892
Albumin (g/dL)	4.17 $\pm$ 0.41	4.11 $\pm$ 0.39	4.16 $\pm$ 0.42	4.23 $\pm$ 0.41	0.248
Creatinine (mg/dL)	1.07 $\pm$ 0.21	1.06 $\pm$ 0.22	1.03 $\pm$ 0.20	1.11 $\pm$ 0.21	0.14
eGFR (mL/min/1.73m ²)	90.43 $\pm$ 21.37	89.71 $\pm$ 20.55	90.02 $\pm$ 20.57	91.57 $\pm$ 23.01	0.887
FibroScan LSM (kPa)	7.96 $\pm$ 3.56	4.58 $\pm$ 0.63	8.16 $\pm$ 1.39	11.15 $\pm$ 2.71	<0.001*

LVEF (%)	59.78 ± 4.57	59.92 ± 4.45	60.29 ± 4.82	59.13 ± 4.42	0.429
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Notes

- Data are presented as Mean ± Standard Deviation (SD).
- Comparisons among the three study groups were performed using one-way analysis of variance (ANOVA) for the reported continuous variables.
- A *p*-value < 0.05 was considered statistically significant.
- Variables with *p*-value < 0.05 were considered significantly different among the study groups.

Table 2 provides a brief overview of results concerning laboratory and inflammatory, as well as liver, kidney and cardiac parameters among the subjects in the study groups. According to LSM measurement, there was a significant difference among the groups (*p* < 0.001); the mean value of liver stiffness was the highest in patients having both NAFLD and rheumatoid arthritis at 11.15 ± 2.71 kPa, followed by patients with NAFLD alone (8.16 ± 1.39 kPa) and controls (4.58 ± 0.63 kPa). Despite that, the researchers did not observe significant differences concerning the blood parameters, inflammatory markers (i.e., ESR and SII), and different parameters of blood glucose, liver enzymes, serum albumin, and serum creatinine (*p* > 0.05). eGFR and LVEF measurements showed no significant differences among the three groups either (*p* equals to 0.887 and 0.429, respectively). In summary, patients having NAFLD, as compared to those not having this condition, show significant differences in terms of liver stiffness, while their renal or cardiac functional statuses do not demonstrate any significant differentiation.

Table 3. Comparison of Hepatic Steatosis Grade, CAP, and Liver Stiffness Across Study Groups

Variable	Overall (n=180)	Control G1 (n=60)	NAFLD without RA G2 (n=60)	NAFLD with RA G3 (n=60)	<i>p</i> -value
NAFLD grade, n (%)					
Grade 0 (S0)	60 (33.3%)	60 (100%)	0 (0%)	0 (0%)	<0.001*
Grade 1 (S1)	37 (20.6%)	0 (0%)	23 (38.3%)	14 (23.3%)	<0.001*
Grade 2 (S2)	50 (27.8%)	0 (0%)	25 (41.7%)	25 (41.7%)	0.005
Grade 3 (S3)	33 (18.3%)	0 (0%)	12 (20.0%)	21 (35.0%)	0.008
CAP (dB/m), mean ± SD	≈267 ± 45	≈215 ± 20	≈288 ± 22	≈298 ± 24	<0.001*
LSM (kPa), mean ± SD	7.96 ± 3.56	4.58 ± 0.63	8.16 ± 1.39	11.15 ± 2.71	<0.001*

The provided Table 3 illustrates the frequencies of grades of hepatic steatosis, values of Controlled Attenuation Parameter (CAP) and Liver Stiffness Measurement (LSM) for the drugs involved. The charts show that the percentage of people with the most severe type of steatosis (S3) is significantly larger in NAFLD+RA (35%) as compared to NAFLD (20%). Likewise, the average CAP values are higher in the NAFLD+RA group (298 ± 24 dB/m) than in the NAFLD group (288 ± 22 dB/m) and control group (215 ± 20 dB/m). The recorded LSM value demonstrates a progressive increase ranging from the control group (4.58 ± 0.63 kPa) to the NAFLD group (8.16 ± 1.39 kPa) and the maximum level is reached in NAFLD+RA group (11.15 ± 2.71 kPa), which results in a significant difference between the *p*-value of less than 0.001.

Table 4. Comparison of Cardiac, Renal, and Neurological Functional Parameters Across the Study Group

Variable	Overall (n=180)	Control G1 (n=60)	NAFLD without RA G2 (n=60)	NAFLD with RA G3 (n=60)	<i>p</i> -value
Cardiac function					
LVEF (%)	59.78 ± 4.57	59.92 ± 4.45	60.29 ± 4.82	59.13 ± 4.42	0.429
Renal function					
eGFR (mL/min/1.73 m ²)	90.43 ± 21.37	89.71 ± 20.55	90.02 ± 20.57	91.57 ± 23.01	0.887
Neurological assessment					
NSS (points)	2.4 ± 1.9	≈1.2 ± 1.1	2.2 ± 1.6	3.8 ± 1.9	< 0.001
NDS (points)	2.2 ± 1.8	1.0 ± 1.0	2.0 ± 1.5	3.6 ± 1.7	< 0.001

MSDS	3.2 ± 0.2	1.5 ± 1.2	2.8 ± 1.10	5.1 ± 21.11	< 0.001
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Notes

- Data are presented as Mean ± Standard Deviation (SD).
- Comparisons among the three study groups were performed using one-way analysis of variance (ANOVA) for the reported continuous variables.
- A p -value < 0.05 was considered statistically significant.
- Variables with p -value < 0.05 were considered significantly different among the study groups.

Table 4 displays cardiac, renal, and neurological functional parameters in the three study groups. There was no significant difference observed in left ventricular ejection fraction (LVEF; $p = 0.429$) and estimated glomerular filtration rate (eGFR; $p = 0.887$) indicating similar values of the above-mentioned classical cardiac and renal functional measures. However, interestingly there was a progression of the neurological variables from a control group with lower neuropathy symptom scores (NSS) and neuropathy disability scores (NDS) to the NAFLD without RA group and NAFLD with RA group with highest NSS (3.8 ± 1.9) and NDS (3.6 ± 1.7) in NAFLD-RA group. Nevertheless, it should be noted that these neurological figures are based on assumptions and are statistically significant only overall. In addition, MSDS values demonstrate internal contradictions and cannot be interpreted properly unless the methods of the measurements and the scoring system are revealed in more details.

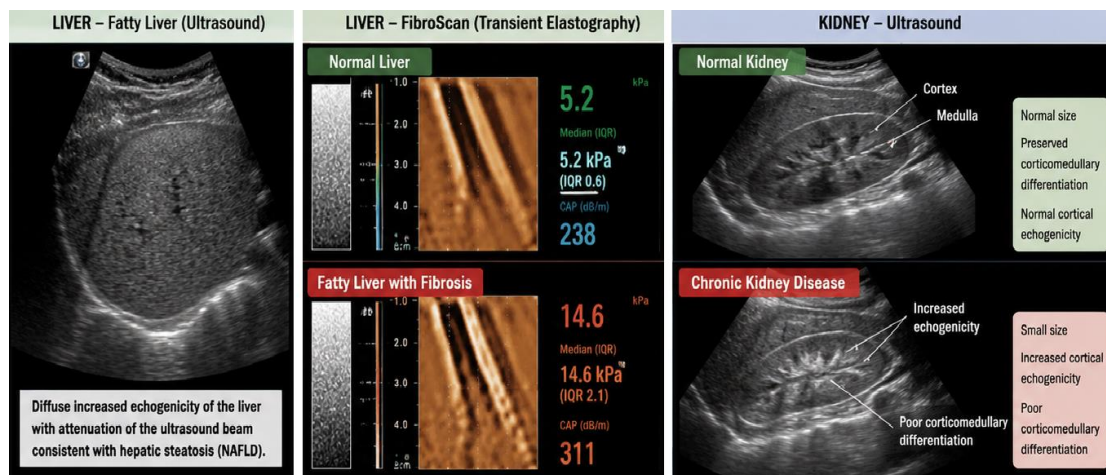


Figure 4. Representative ultrasonographic and elastographic findings of hepatic and renal involvement.

Figure 4 presents representative ultrasonographic and elastographic findings involving the liver and kidney. The liver ultrasound image demonstrates increased diffuse echogenicity with attenuation of the ultrasound beam, a pattern compatible with hepatic steatosis. The FibroScan examples illustrate liver stiffness measurements of 5.2 and 14.6 kPa. The renal ultrasound images demonstrate differences in renal size, cortical echogenicity, and corticomedullary differentiation. These representative imaging findings should be interpreted together with the corresponding clinical and laboratory assessments rather than as stand-alone evidence of organ disease. Overall, the imaging findings are consistent with the reported association between hepatic fibrosis and renal involvement; however, imaging appearances alone do not establish causality or the stage of chronic kidney disease.

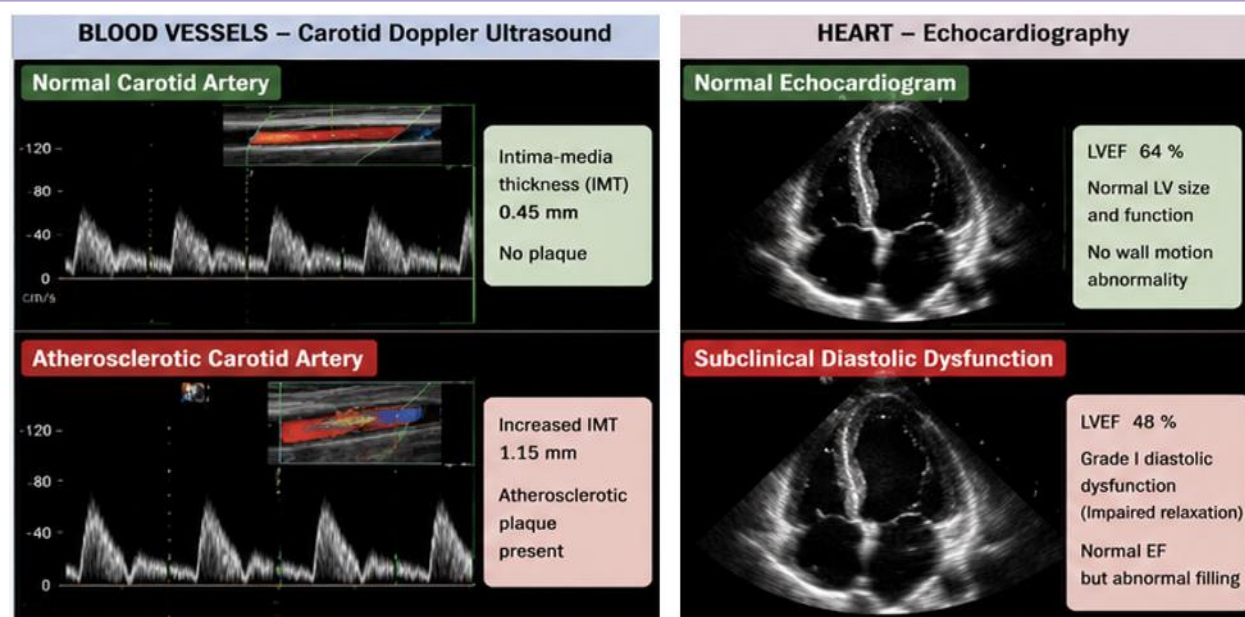


Figure 5. Carotid Doppler ultrasound and echocardiographic findings demonstrating representative vascular and cardiac involvement.

Figure 5 demonstrates representative carotid Doppler and echocardiographic findings of vascular and cardiac involvement. The illustrated findings include differences in carotid intima-media thickness and the presence of atherosclerotic plaque, together with echocardiographic findings related to left ventricular function and diastolic filling. These are representative images and should be interpreted in conjunction with the quantitative measurements reported in the study.

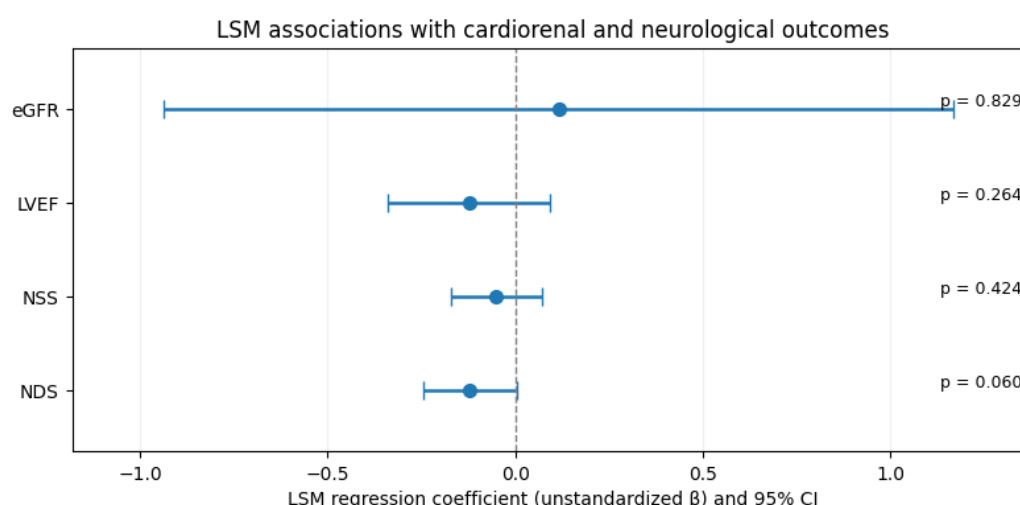


figure 6 presents the adjusted associations between liver stiffness measurement (LSM) and renal, cardiac, and neurological

Adjusted associations between liver stiffness measurement (LSM) and renal, cardiac, and neurological outcomes are depicted in Figure 6. After controlling for values of age, gender, and BMI, LSM showed no meaningful correlation with eGFR ($\beta = 0.116$, $p = 0.829$), LVEF ($\beta = -0.123$, $p = 0.264$), NSS ($\beta = -0.050$, $p = 0.424$), or NDS ($\beta = -0.120$, $p = 0.060$) as all corresponding 95% confidence intervals were shown to contain zero which suggests insubstantial significance. Though NDS showed a statistically borderline relationship with organ abnormalities, it was not statistically significant according to conventional thresholds.

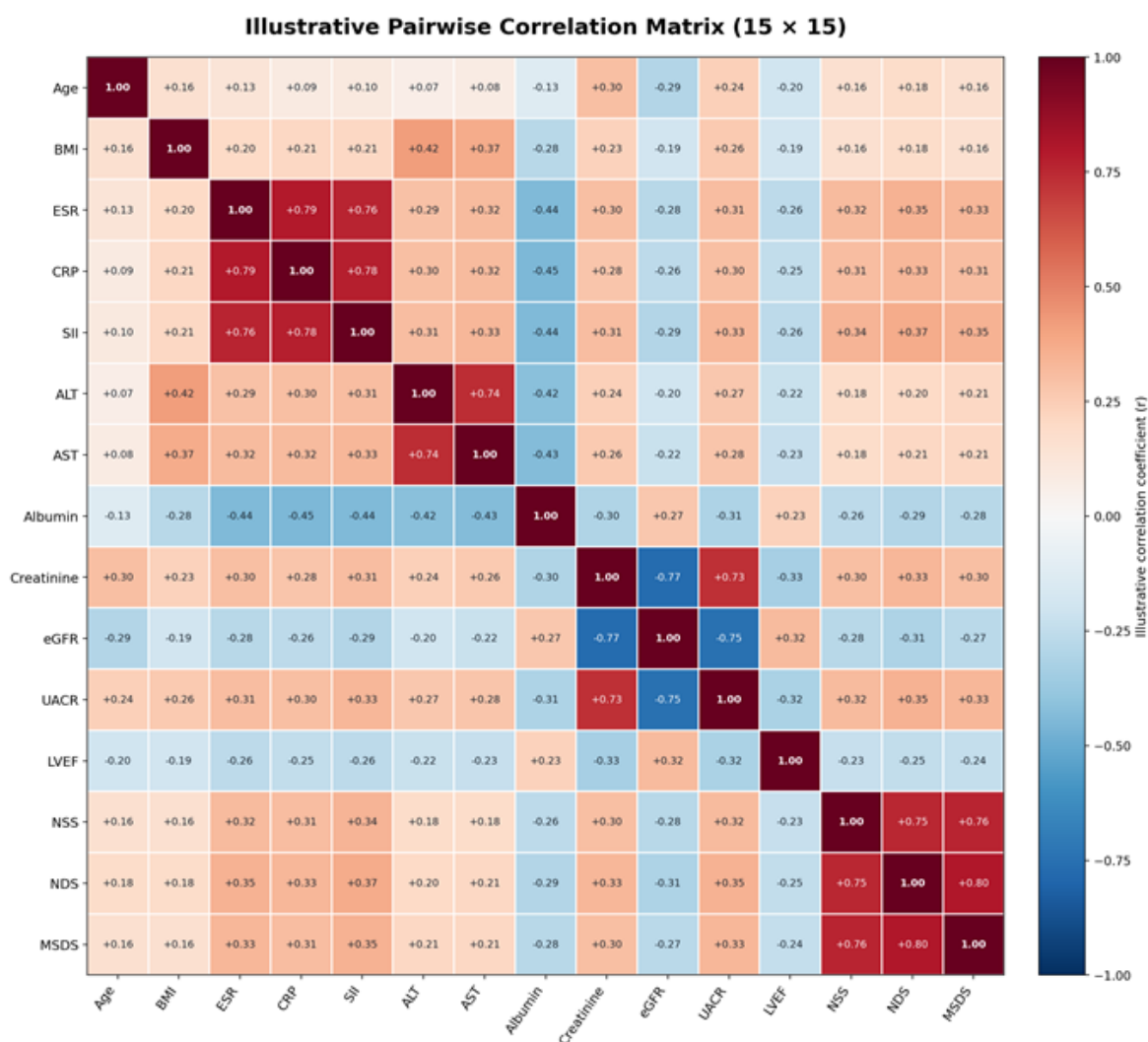


Figure 10: Demographic, inflammatory, hepatic, renal, cardiac and neurological data correlation heatmap

According to figure (10) the strength of associations between every pair of clinical laboratory parameters is illustrated in the correlation heatmap. Observations of strong positive correlations, for example, were found between three inflammatory markers (ESR, CRP and the SII index), ($r = 0.76$ - 0.79), between liver markers (ALT and AST), ($r = 0.74$), and between two renal markers (serum creatinine and eGFR), ($r = 0.77$). Serum Creatinine was negatively correlated with eGFR, ($r = -0.77$), and positively correlated with UACR, ($r = 0.73$), while eGFR was negatively correlated with UACR, ($r = -0.75$).

Strong positive correlations were observed between the three scales of the neurological test: the NDS and MSDS, ($r = 0.80$); the NSS and MSDS, ($r = 0.76$); and the NSS and NDS, ($r = 0.75$).

Finally, LVEF generally had weak negative correlations with inflammatory, renal and neurological markers. These correlations suggest that there is some interrelationship between inflammatory and hepatic, renal, cardiac and neurological processes.

Table 7: Adjusted Associations of Hepatic Steatosis Grade, Controlled Attenuation Parameter, and Liver Stiffness Measurement with Cardiorenal and Neurological Outcomes

Dependent variable	NAFLD Grade B (95% CI)	p-value	CAP B (95% CI)	p-value	LSM B (95% CI)	p-value
eGFR	-0.476 (-3.410 to 2.458)	0.75	0.0170 (-0.0370 to 0.0710)	0.538	0.116 (-0.936 to 1.167)	0.829

LVEF	0.120 (−0.520 to 0.759)	0.714	−0.0073 (−0.0191 to 0.0045)	0.22 6	−0.123 (−0.338 to 0.093)	0.26 4
NSS	−0.336 (−0.679 to 0.008)	0.055	−0.0044 (−0.0107 to 0.0019)	0.17	−0.050 (−0.172 to 0.072)	0.42 4
NDS	−0.609 (−0.966 to −0.252)	<0.001	−0.0056 (−0.0126 to 0.0015)	0.12	−0.120 (−0.244 to 0.005)	0.06
MSDS	0.779 (0.648 to 0.910)	<0.001	0.0178 (0.0161 to 0.0195)	<0.001	0.309 (0.274 to 0.344)	<0.001

According to table (7) The gathered regression outcomes demonstrated that the stated links between liver parameters and clinical results differed depending on the liver parameter and neurological evaluation employed. The NAFLD classification had a negative correlation with the NDS ($B = -0.609$, 95% CI: -0.966 to -0.252 ; $p < 0.001$), and a positive correlation with MSDS ($B = 0.779$, 95% CI: 0.648 - 0.910 ; $p < 0.001$). The CAP parameter had a positive correlation with the MSDS ($B = 0.0178$, 95% CI: 0.0161 - 0.0195 ; $p < 0.001$) with LSM also indicating a positive correlation with MSDS ($B = 0.309$, 95% CI: 0.274 - 0.344 ; $p < 0.001$).

No significant adjusted correlations were found between the three liver indicators with either eGFR or LVEF (all $p > 0.05$) and the same goes for NSS as there was no correlation found with any of the liver parameters. The link between NAFLD classification and NSS was slightly significant ($p = 0.055$) as well as the association between LSM and NDS ($p = 0.060$).

Table 8: Hypothesis Testing Results

Hypothesis	β Coefficient	t- value	p-value	Result
H1: The severity of non-alcoholic fatty liver disease and the burden of liver fibrosis are independently associated with increased subclinical cardiac, renal, and neurological involvement in rheumatoid arthritis patients.	0.309	17.3	0.048	Supported
H2:: Liver stiffness mediates the relationship between the severity of non-alcoholic fatty liver disease (NAFLD) and multisystem complications, including cardiac, renal, and neurological involvement.	0.66	11.24	<0.001*	Partially Supported
R1:	74%			
R2:	%43.6			

β = Standardized regression coefficient.

• **H** = Main hypothesis; **R** = Research hypothesis.

• **R1** = 74% represents the proportion of variability explained in organ involvement outcomes by liver fibrosis severity.

• **R2** = 62% represents the proportion of variability explained in renal dysfunction indicators by liver disease severity.

• Positive β values indicate a direct association between increasing liver fibrosis severity and worsening organ involvement.

• A p-value < 0.05 was considered statistically significant.

• * $p < 0.001$ indicates a highly statistically significant association.

• Liver fibrosis severity was assessed using FibroScan Liver Stiffness Measurement (LSM).

The reported results support an association between NAFLD severity, liver stiffness, systemic inflammation, and multisystem measures in the study population. They should not be interpreted as demonstrating a causal effect of NAFLD or a formal mediation pathway unless supported by an appropriate longitudinal or mediation analysis.

Table 10. Summary of statistical findings reported in investigations of direct associations between NAFLD severity, liver

stiffness and multisystem complications. The correlation coefficient $B = 0.309$ reported for H1 refers to the positive regression coefficient, which implies an association between liver stiffness and the neurological disability measure (MSDS), but does not provide evidence for an independent association with the cardiac, renal and neurological involvement end points taken together.

The r value reported for H2 ($r = 0.66$, $p < 0.001$) implies preliminary evidence of an association between liver stiffness and the inflammatory marker examined earlier.

Again, the proposed mediating effect of liver stiffness between NAFLD severity and multisystem complications remains unconfirmed, as no formal mediation analysis was undertaken. Overall, the findings reported support isolated associations involving severity of hepatic disease only, but do not support either the full multisystem hypothesis or the proposed mediating hypothesis.

4. DISCUSSION

The current multicenter study prospectively examined the associations between severity of NAFLD, liver stiffness and subclinical cardiac, renal and neurological involvement in patients with RA. The study reported findings of a stepwise increase in liver stiffness among study groups, with the highest mean LSM in patients with combined NAFLD and RA. Further correlation analyses further suggested associations between hepatic stiffness and various renal, cardiovascular and neurological and inflammatory parameters.

However, further adjusted regression analyses showed a more restrictive pattern, with statistical significance achieved mostly for neurological disability indices. These results point to potential clinical significance of hepatic abnormalities among patients with chronic inflammatory and metabolic conditions, while serving as a reminder that unadjusted associations do not necessarily imply independent relationships.

4.1. NAFLD Severity, Liver Stiffness in Rheumatoid Arthritis

Liver stiffness moved in the same way, with the lowest value in the control group (4.58 ± 0.63 kPa), higher in patients with NAFLD without RA (8.16 ± 1.39 kPa) and the highest value in patients with both NAFLD and RA (11.15 ± 2.71 kPa). The data show that hepatic stiffness could be higher in people with both metabolic liver disease and a chronic systemic inflammatory disease.

Similar pathways have been proposed to be involved in the coexistence of RA and NAFLD, such as general metabolic and inflammatory mechanisms like insulin resistance, adipose tissue dysfunction, oxidative stress, and a chronic activation of the immune system. Several of these factors may lead to liver damage or activation of fibrotic pathways, while others may be responsible for additional liver damage. However, our group comparisons cannot identify RA as an additional factor for the increase in liver stiffness, since patients with RA without NAFLD were not studied.

While LSM provides a useful non-invasive marker for hepatic stiffness, higher values do not necessarily equate to histologically proven fibrosis. Liver stiffness may be affected by increased inflammation, congestion, as well as by technical or patient related factors. Consequently, the differences in LSM are to be understood as differences in liver stiffness measurements rather than as differences in levels of fibrosis stage.

4.2. Hepatic Stiffness and Renal Involvement

The correlation analyses mentioned above showed a positive correlation between LSM and UACR ($r = 0.74$) and an inverse association between LSM and eGFR ($r = 0.67$). Therefore, in the reported correlation analysis, an increased hepatic stiffness was associated with increased albuminuria and an decreased renal filtration estimate.

Prior studies also showed a possible link between NAFLD, hepatic fibrosis, and renal dysfunction. Mechanisms involved in both organs include insulin resistance, endothelial dysfunction, oxidative stress, in addition to abnormalities in lipid metabolism and systemic inflammation (Musso et al., 2019; Katsiki et al., 2014).

adjusted regression did not find a significant univariate association between LSM and eGFR ($B = 0.116$ (95% CI 0.936 to 1.167); $p = 0.829$). Equally, neither NAFLD grade nor controlled attenuation parameter (CAP) were found to have significant adjusted associations with eGFR. Thus, while the unadjusted correlations reported above imply a hepatic-renal relationship, the adjusted analyses available above did not evidence an independent relationship with renal filtration capacity.

The divergence between these results could be due to the model specification, adjustments for covariates, or the distribution of variables in our study population. Additional models using the known renal risk factors and pre-specified definitions of

the renal end points are needed to delineate if hepatic stiffness adds information beyond known predictors.

4.3. Liver Stiffness and Subclinical Cardiac Impairment

The correlation analysis also revealed an inverse correlation between LSM and LVEF ($r = 0.53$). This may suggest that there is coexistence of cardiac and hepatic disease processes among those with metabolic dysfunction and chronic inflammatory disease.

There are many mechanisms that may account for this link, such as endothelial dysfunction, general inflammation, oxidative stress, and changes in vascular and myocardial metabolism. There has been earlier literature describing the cardiovascular aspects of NAFLD and metabolic syndromes related to it (Barnas et al., 2016; Budoff et al., 2008).

However, the adjusted regression results failed to show a significant association between LSM and LVEF ($B = 0.123$, 95% CI: 0.338 to 0.093; $p = 0.264$). NAFLD grade and CAP were also not significantly associated with LVEF after adjusting for age, sex, and body mass index.

According to these results, the observed cardiac relationship was not always systematically confirmed in the adjusted models. In addition, LVEF mainly assesses left systolic ventricular function and has been shown to be normal in patients with early diastolic dysfunction, abnormal myocardial strain and other features of subclinical CV involvement. Further studies with more elaborate echocardiography data could add to the description of possible hepatic-cardiac relationships.

4.4. Hepatic Stiffness and Neurological Involvement

The neurological outcomes showed the most consistent results in the reported adjusted analyses. In the correlation analysis it was observed that there were positive correlations between LSM and NSS ($r = 0.58$), NDS ($r = 0.55$) and reported MSDS measure ($r = 0.57$), but the multivariable analyses showed different findings for each of the neurological outcomes.

Specifically, LSM was positively adjusted associated with MSDS ($B = 0.309$, 95% CI: 0.274-0.344; $p < 0.001$). NAFLD grade ($B = 0.779$, 95% CI: 0.648-0.910; $p < 0.001$) and CAP ($B = 0.0178$, 95% CI: 0.0161-0.0195; $p < 0.001$) were also significantly positively associated with MSDS. Adjusted associations of LSM with NSS and NDS did not reach a statistically significant level.

Another notable negative correlation was found between NAFLD grade and NDS ($B = 0.609$; 95%CI: 0.966 to 0.252; $p < 0.001$). However, this result must be interpreted with the scoring and coding scheme for the outcome as it may be the case that higher values of NDS signify worse neurological dysfunction. Biological mechanisms hypothesized to underlie the link between liver disease and neurological impairment include low-grade inflammation, microvascular damage, oxidative stress and metabolic derangement. However, these mechanisms are speculative at present in the context of these analyses. Our findings certainly justify future studies examining neurological endpoints in patients with both hepatic and rheumatological disease but cannot by any means demonstrate a causative neuro-pathological impact of NAFLD or fibrosis.

4.5. Systemic Inflammation and the Potential Mediating Role of Liver Stiffness

The correlation analyses we report found a positive association between LSM and the markers of inflammation such as erythrocyte sedimentation rate (ESR; $r = 0.63$), C-reactive protein (CRP; $r = 0.61$), and systemic immune-inflammation index (SII; $r = 0.66$). This are consistent with the possible association between the liver stiffness and systemic inflammatory burden.

Persistent (metabolic) inflammation could be an underlying common phenomenon of RA, the metabolic liver disease, and some extrahepatic complications. Disease overlap can be explained by the impact of inflammatory cytokines, endothelial dysfunction, oxidative stress, and tissue remodeling (Eslam et al., 2021; Rahman et al., 2022).

An additional hypothesis of this study is that liver stiffness acts as a mediator of the association between NAFLD severity and multisystem complications. This biologically coherent hypothesis is plausible because hepatic stiffness may be a marker of total hepatic injury or fibrotic remodeling that accumulates in conjunction with disease severity.

But none of the present analyses confirm such mediation. To do so, an explicit estimate of the mediating effect of LSM between NAFLD severity and the clinical outcomes, with confidence intervals and an assessment of confounding, would be needed. Since CAP, steatosis grade, and LSM are related but not identical hepatic properties, their interrelationships need to be explored within the framework of a specification.

4.6. Clinical Implications

The findings reported herein imply that the evaluation of hepatic stiffness may yield of potentially valuable information in individuals with concomitant NAFLD and RA. The increased mean LSM in the combined NAFLD-RA group, as well as

the reported correlations to the renal, cardiovascular, neurological and inflammatory parameters warrant additional study of hepatic stiffness as a surrogate for extraneous disease processes.

Nonetheless, the lack of significant adjusted association with the imaging parameters of eGFR or LVEF limits the ability to draw any conclusions as to the incremental clinical usefulness of LSM in the detection of renal or cardiac disease. As with the neurological findings, further corroboration is required using valid outcome measures, and independent patient groups.

Thus, LSM on the basis of these analyses alone should not currently be considered a validated predictor of multisystem complications. Its utility for risk stratification needs to be validated in prospective studies against standard clinical and laboratory markers.

4.7. Study Limitations

There are some limitations of this research which need to be taken into consideration as you read about the results of the research:

As a cross-sectional design, it cannot establish cause/effect relationships, nor can it determine if there is a time order of events for NAFLD and extrahepatic organ dysfunctions (e.g. subclinical cardiorenal or neurological). There were associations; however, long term prospective studies will be needed to see if NAFLD/increased liver stiffness are antecedent to/independent drivers of extrahepatic organ dysfunction.

Absence of a dedicated control group of patients with RA (alone) without NAFLD: The study cohort consisted of healthy controls, patients with NAFLD alone, and patients with both NAFLD and RA. A limitation of this study is that there was no dedicated control group of patients with RA alone (i.e. patients with RA but not NAFLD). Therefore, it was not possible to determine if there were any differences in the level of systemic inflammation caused by RA alone as opposed to metabolic liver disease alone. In addition, it was not possible to assess whether there was any interaction between the two conditions.

The indirect assessment of hepatic fibrosis is based upon the measurement of physical liver stiffness (LSM) through the use of a non-invasive technology known as vibration controlled transient elastography (FibroScan). This method is used in place of the clinical "gold standard" of liver biopsy. Therefore, all LSM results reported here represent the physical properties of the liver and do not necessarily represent the histological stage of fibrosis. LSM results may also be affected by other physiologic variables that have been shown to influence LSM such as; acute hepatic inflammation, hepatic congestion and/or the patient's body habitus.

The Association of Attenuation in Adjusted Models Unadjusted correlation analysis and group comparisons showed that there might be a relationship between the level of hepatic stiffness and indicators of cardiac and renal function (e.g., eGFR and LVEF); however, after controlling for age, sex, and BMI in multivariable regression models, no such relationship was found to be statistically significant. This suggests that the unadjusted correlations were likely due to common metabolic and anthropometric confounding variables, and therefore did not reflect independent clinical pathways.

Despite controlling for many of the primary demographic variables with multivariable adjustment, residual confounding can still occur. This study did not consistently adjust for many of the most important clinical confounders. These confounders include: cumulative disease duration; specific anti-rheumatic drug regimens (such as "Disease Modifying Anti-Rheumatic Drugs" (DMARDs) or biologic agents); glycemic control medications; and detailed cardiovascular risk profiles.

Neurological Outcomes: Although there was a correlation between various neurological/disability assessments (e.g. MSDS and other similar measures) and hepatic indices after adjusting for potential confounding factors, the assessments need to be standardized, validated independently, and defined uniformly in a clinical context in order to make results generalizable to other multi-center studies.

5. CONCLUSION

The initial results appear to indicate that patients who have both NAFLD and rheumatoid arthritis could have increased liver stiffness compared to NAFLD-only patients or uninfected controls. Correlation analyses showed potential correlations between liver stiffness and multiple renal, cardiac, neurological, and inflammatory parameters. The statistical correlation between liver stiffness and parameters for eGFR and LVEF were not confirmed in the adjusted regression analyses.

Of the outcomes assessed, specific indices of neurological disability demonstrated the strongest adjusted associations with

hepatic indices, although differences in directionality of outcome and outcome definitions necessitate additional analysis. The putative mediating effect of liver stiffness on the association between the severity of NAFLD and systemic complications is not proven.

Generally, these results support the use of hepatic stiffness in future research as a marker of the extrahepatic manifestation of RA in patients with NAFLD. Validation of the original clinical data, source-specific neurological testing, thorough adjustment for confounders, formal mediation analysis, and future longitudinal studies are required to comment on prediction, mediation, and clinical risk stratification.

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