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Fibrosis Risk Factors and Serum Noninvasive Fibrosis Markers in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

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Abstract

Introduction: The prevalence of Metabolic dysfunction-associated steatotic liver disease (MASLD) is increasing globally, ranging from simple steatosis to cirrhosis. This study evaluates the correlation between serum noninvasive fibrosis markers and histopathological and FibroScan fibrosis data, identifying potential risk factors for fibrosis progression in MASLD and Metabolic dysfunction-associated steatohepatitis (MASH)patients.

Methods: We included 40 biopsy-confirmed MASLD and MASH patients. Serum levels of collagen type IV, fibroblast growth factor 21 (FGF21), hyaluronic acid, and YKL-40 were measured using ELISA. Patients were stratified into mild and advanced fibrosis groups based on biopsy and FibroScan results.

Results: Advanced fibrosis patients had significantly higher Homeostatic Model Assessment of Insulin Resistance(HOMA-IR), fasting insulin, and Body Mass Index(BMI) . Hyaluronic acid, FGF21, collagen type IV, and YKL-40 were significantly elevated in the advanced fibrosis group. Linear regression showed BMI influenced HOMA-IR (β=0.036), but not triglycerides or HDL. ROC analysis identified hyaluronic acid as a significant fibrosis marker (AUROC=0.73). Multivariate regression revealed hyaluronic acid and FGF21 as independent risk factors for fibrosis progression (OR=1.001, 95% CI: 0.99–1.003; OR=1.004, 95% CI: 0.99–1.01). Fibrosis severity was higher in patients with elevated GGT and AST, but not ALT .

Conclusion: Insulin resistance, obesity, elevated serum levels of AST (aspartate aminotransferase) and gamma-glutamyl transferase (GGT) key risk factors for advanced fibrosis in MASLD. Elevated FGF21 and hyaluronic acid levels may serve as noninvasive fibrosis markers.

Key words: Liver Diseases; fibrosis; fibroblast growth factor-21

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a condition characterized by excessive hepatic fat accumulation in individuals with minimal or no alcohol consumption (1). Previously termed Nonalcoholic fatty liver disease (NAFLD), its nomenclature and diagnostic criteria were revised in July 2023 by an international consensus of liver societies to reduce ambiguity and emphasize its metabolic origin under the broader term "steatotic liver disease" (SLD) (2). MASLD is now recognized as chronic liver disease, affecting 40% of the adult population (3), with an estimated prevalence of 45–60% in Turkey (4). Its incidence increases in the presence of metabolic conditions such as insulin resistance (IR), diabetes mellitus (DM), obesity, metabolic syndrome, and dyslipidemia (5, 6). MASLD manifests as either simple steatosis or metabolic dysfunction-associated steatohepatitis (MASH). While simple steatosis is typically nonprogressive, MASH-characterized by hepatocellular injury and inflammation (7). IR and hyperinsulinemia play a central role in MASLD / MASH pathogenesis, promoting lipolysis, increasing free fatty acids, and leading to hepatic triglyceride accumulation (8). The most critical prognostic factors in MASH are hepatic inflammation and fibrosis severity(9), necessitating reliable diagnostic and monitoring tools (6). Currently, MASLD/MASH diagnosis relies on invasive (liver biopsy), noninvasive (serum biomarkers), and imaging-based (ultrasound, MRI) modalities. While liver biopsy remains the gold standard for fibrosis staging, its operator dependency and risk of complications necessitate alternative noninvasive methods(6, 10). FibroScan, an ultrasound-based elastography technique, quantifies fibrosis severity in kilopascals (kPa), aiding disease assessment and treatment monitoring (11). Among serum biomarkers, hyaluronic acid, an extracellular matrix component, correlates with fibrosis progression (12). Similarly, collagen type IV, an inflammation-associated extracellular matrix protein, has been validated as a fibrosis marker (13-15). FGF-21, primarily synthesized by the liver and adipose

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tissue, is upregulated in hepatic steatosis (16). YKL-40 (chitinase 3 – like - 1), secreted by chondrocytes and synovial fluid, is involved in tissue repair and has been implicated in MASLD fibrosis progression (14).Our study aims to assess the concordance between serum noninvasive fibrosis markers and histopathological/FibroScan findings in biopsy-confirmed MASLD and MASH patients while identifying potential risk factors for fibrosis progression.

Materials and Methods

Study included 40 patients diagnosed with MASLD or MASH through liver biopsy and followed in the gastroenterology outpatient clinic. Patients with alcohol consumption (≥20 g/day for female, ≥30 g/day for male), portal hypertension and patients with vascular pathology, HBsAg, anti-HCV positivity, Wilson, autoimmune hepatitis, or hemochromatosis were excluded.

Data collection: The following parameters were recorded for all participants: age, sex, waist circumference, liver enzymes (AST, ALT, ALP, GGT), fasting glucose, lipid profile (LDL, HDL, triglycerides), insulin levels, IR, TSH, HbA1c, albumin, prothrombin time, platelet count, mean platelet volume, FibroScan findings, and liver biopsy results. IR was assessed using the HOMA-IR formula, with a threshold of ≥2.5 indicating IR.

Fibrosis and histopathological assessment: FibroScan was used to determine liver fibrosis and steatosis severity, with fibrosis ≥F2 classified as advanced fibrosis. Histopathological evaluation of liver biopsies was performed according to the Brunt classification (17). MASH diagnosis was based on the presence of hepatocellular steatosis, cytologic ballooning, portal or acinar inflammation, Mallory bodies, and/or fibrosis. Hepatic steatosis and inflammation (grades 1–3), and fibrosis (stages 0-4) were assessed. Patients with fibrosis stage ≥2 were categorized as the advanced fibrosis group.

Body mass index (BMI) and biomarker analysis: Patients with BMI ≥30 kg/m² were classified as the obese group according to the classification of the World Health Organization (WHO). DM was diagnosed according to the American Diabetes Association (ADA) criteria, which include one or more of the following; Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L),2-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test (OGTT),Hemoglobin A1c (HbA1c) ≥6.5%,Random plasma glucose ≥200 mg/dL in patients with classic symptoms of hyperglycemia. Serum FGF21, hyaluronic acid, YKL-40, and collagen type IV levels were measured using ELISA kits.

Ethical considerations: The study was approval was obtained from the Ethics Committee of our faculty of Medicine hospital.(No:2020-219). Written informed consent was obtained from all participants.

Statistical analysis: Descriptive statistics were presented as Mean and Standard deviation for the continuous variables, while count and percentages for the categorical variables. Pearson correlation, Spearman correlation, and ANOVA were used to assess relationships between variables. The student's t test is used to compare between two groups. Multiple logistic regression analysis was performed to determine whether hyaluronic acid and FGF21 as independent risk factors for

Table 1: General characteristics of all patients

Parameter(n:40 Patients)	Mean ± St. Dev	Parameter(n:40 Patients)	Mean ± St. Dev
Age	55 ±10.7	Platelet count	214.9±89.7
BMI	32.2 ±4.5	Mean platelet volume	9.4±1.9
Waist Circumference	105.6 ±9.6	Prothrombin time	12.7±0.83
AST	35.02 ±16.2	Ferritin	89.3 ±70.3
ALT	48.7 ±44.3	Ultrasonography(Fatty grade)	1.87±0.88
GGT	81.2 ±75.6	Fibroscan steatosis	1.46 ±0.9
LDL	112.4 ±39.4	Fibroscan kpa	9.7±7.3
HDL	55.4 ±16.3	Fibroscan fibrosis	1.77±1.56
Triglyceride	151 ±74.7	Biopsy steatosis	1.83 ±0.89
Fasting glucose	119.7 ±42.3	Biopsy inflammation	1.34 ±0.47
Insulin	19.1±13.7	Biopsy fibrosis	0.87 ±1
Insulin resistance (HOMA)	5.8±4.9	Hyaluronic acid	405.06±174.9
HbA1c	6.4±1,2	Fibroblastgrowth factor 21	1465.76±438.65
Albumin	4.2±0.37	Collagen type 4	39.85±9.64
		YKL40	272.45±103.46

BMI : Body mass index, **HOMA:** Homeostatic Model Assessment, **AST:** Aspartate aminotransferase, **ALT:** Alanine Aminotransferase, **GGT :** Gamma-Glutamyl Transferase, **LDL :** Low-Density Lipoprotein Cholesterol, **HDL:** High-Density Lipoprotein Cholesterol

fibrosis progression in FibroScan. In addition ROC analysis also was performed to determine whether hyaluronic acid as a significant marker for biopsy- confirmed fibrosis. Statistical significance level was considered as 5% and SPSS (ver: 21) statistical program was used for all statistical computations.

Results

Fourty patients (22 females, 18 males) were included in the study, with a mean age of 55 ± 10.7 years (Table 1). Based on liver biopsy findings, 18 patients had MASLD (simple steatosis), while 22 had MASH. T2 DM was present in 18 patients, while 28 had increased waist circumference (>90 cm in females, >100 cm in males), and 22 were classified as obese. Among MASLD patients, 8 (44.4%) had diabetes, and 9 (50%) were obese, while in the MASH group, 10 (45.5%) had diabetes, and 13 (59.1%) were obese.

FibroScan and fibrosis assessment: FibroScan was performed in 31 patients, who were stratified into mild fibrosis (n=18) and advanced fibrosis (n=13). Advanced fibrosis patients had significantly higher BMI, fasting insulin, and HOMA-IR compared to the mild fibrosis group (p=0.027, p=0.041, p=0.025, respectively). When comparing obese (n=22) and non-obese (n=18) patients, those with obesity had significantly higher waist circumference and FibroScan steatosis scores (waist circumference: 97.1 ± 9.6 cm vs. 107.3 ± 6.9 cm, p=0.004; FibroScan steatosis: 1.0 ± 0.9 vs. 1.9 ± 0.2, p=0.003).

Liver enzymes and fibrosis severity: Patients were categorized based on normal vs. elevated ALT levels, revealing significant differences in AST (25.2 ± 6.8 vs. 79.6 ± 55, p=0.01) and FibroScan steatosis score (1.21 ± 0.975 vs. 1.82 ± 0.405, p=0.05), but no significant difference in FibroScan fibrosis scores (p=0.204). When patients were stratified by normal vs. elevated AST, significant differences were observed in ALT (30.04 ± 12.78 vs. 76.77 ± 60.11, p=0.016), GGT (58.91 ± 62.99 vs. 115.00 ± 80.22, p=0.026), and FibroScan fibrosis (1.05 ± 1.13 vs. 3.22 ± 1.39, p=0.0001). Similarly, patients with high vs. normal GGT had significantly higher AST (26.88 ± 9.49 vs. 40.42 ± 20.07, p=0.014) and FibroScan fibrosis scores (0.92 ± 0.95 vs. 2.47 ± 1.69, p=0.006).

Serum biomarkers and waist circumference: Among 32 patients with waist circumference measurements, 27 had increased waist circumference, while 5 had normal values. Serum hyaluronic acid, FGF21, collagen type IV, and YKL-40 levels were significantly higher in those with increased waist circumference (p=0.0001 for all) (Table 2).

Regression and ROC analysis: Linear regression analysis indicated that HOMA-IR was significantly influenced by BMI (β = 0.036, p=0.008) but was not affected by triglycerides or HDL cholesterol. ROC analysis identified hyaluronic acid as a significant marker for biopsy-confirmed fibrosis (AUROC=0.73) (Figure 1). The AUROC with 95%CI was 0.73 (0.61,0.86) for biopsy confirmed fibrosis (P<0.05). ROC curve analysis identified 461 ng/ml level hyaluronic acid of as the optimal fibrosis cut-off, yielding 73% sensitivity and 85% specificity.

Advanced fibrosis and serum markers: Patients were classified based on biopsy findings into mild fibrosis (n=30) and advanced fibrosis (n=10). Serum hyaluronic acid, FGF21, collagen type IV,

Table 2: Comparison of patients with normal and high waist circumference

Number of patients (n:32)	Waist circumference Normal (n:5) Mean ± St. Dev	Waist circumference High (n:27) Mean ± St. Dev	p value
Age	51.3±22.7	55±9.7	0.703
BMI	24.2±4.27	31.9±3.7	0.001
Waist Circumference	88±8.04	106.2±6.5	0.001
Hyaluronic acid	355.9±165.9	650±12	0.001
Fibroblast growth factor 21	1375.9±448.3	1920±320	0.001
Collagen type4	34.4±9.2	48±7.8	0.001
YKL40	246.5±99	400±15	0.001

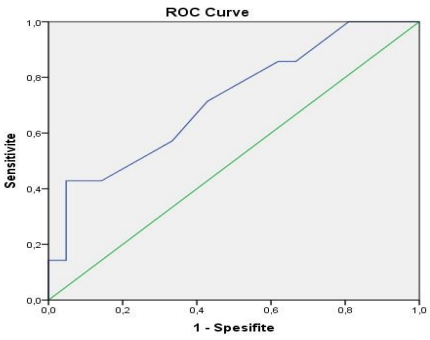

Figure 1: ROC CURVE analysis of hyaluronic acid in determining liver biopsy fibrosis (AUROC=0.73)

Table 3: Comparison of patients with mild and advanced fibrosis in liver biopsy

Number of patients (n:40)	F 0-1 (n:30) Mean ± St. Dev	F 2-4(n:10) Mean ± St. Dev	p value
Age	57.5±12.4	54.6±12.3	0.533
Hyaluronic acid	264.4±39.9	433.8±190	0.001
Fibroblast growth factor 21	960.3±350.1	1579.3±375.3	0.001
Collagen type 4	30±3.6	38.3±9.8	0.002
YKL 40	188.7±48.5	287.4±105.5	0.003

and YKL-40 levels were significantly elevated in the advanced fibrosis group (p=0.0001, p=0.001, p=0.002, and p=0.003, respectively) (Table 3).

Multiple logistic regression analysis: Multiple logistic regression identified hyaluronic acid and FGF21 as independent risk factors for fibrosis progression in FibroScan (OR=1.004, 95% CI: 0.99–1.01; OR=1.001, 95% CI: 0.99–1.003). The model's overall accuracy was 58.5%. Collagen type IV and YKL-40 were not significant fibrosis risk factors (OR=0.97, 95% CI: 0.79–1.19; OR=0.99, 95% CI: 0.97–1.01).

Discussion

This study investigated fibrosis progression in MASLD and MASH patients using FibroScan, liver biopsy, and noninvasive serum fibrosis markers. Our findings demonstrate a significant correlation between FibroScan-measured fibrosis severity and HOMA-IR, with fasting insulin levels significantly elevated in advanced fibrosis patients. Additionally, obesity was more prevalent in the MASH group, and BMI was associated with FibroScan fibrosis and steatosis severity. Among serum fibrosis markers, FGF21, hyaluronic acid, collagen type IV, and YKL-40 were significantly elevated in biopsy-confirmed advanced fibrosis patients. However, only hyaluronic acid and FGF21 emerged as independent risk factors for fibrosis progression, whereas elevated AST and GGT were associated with higher fibrosis severity. While MASLD is generally considered a benign condition, MASH is a known risk factor for fibrosis, cirrhosis. In a metaanalysis by Younossi et al., 59% of MASLD patients with clinical indications for biopsy had MASH, while in patients without clinical indications, the prevalence was 6.6% (18). In our study, 55% of patients had MASH, aligning with these findings. Additionally, Younossi et al. reported T2DM in 23% of MASLD and 47% of MASH patients, while Ooi et al. found that obese MASLD patients with advanced fibrosis had significantly higher T2DM prevalence and fasting glucose levels (19). In our cohort, 44% of MASLD and 45% of MASH patients had diabetes, with no statistically significant difference between groups.HOMA-IR was significantly elevated in FibroScan-confirmed advanced fibrosis patients (7.15±4.72 vs. 3.54±2.69, p=0.025), consistent with Dvorak et al., who reported markedly higher fasting insulin levels in advanced fibrosis patients (20). Similarly, our findings showed higher fasting insulin levels in the advanced fibrosis group (p=0.041). Obesity is a major contributor to MASLD pathogenesis due to its role in increasing free fatty acid flux to the liver. Younossi et al. reported obesity in 51% of MASLD and 81% of MASH patients, while our study found 50% obesity in MASLD and 60% in MASH, reinforcing obesity's role in disease progression (18). Additionally, previous studies have shown higher BMI and waist circumference in patients with advanced fibrosis, which was also confirmed in our study(21). Our linear regression analysis further demonstrated that BMI influenced HOMA-IR, FibroScan fibrosis scores, and hepatic steatosis severity. FGF21, a metabolic regulator primarily synthesized in the adipose tissue and liver, has been implicated in MASH fibrosis progression, although its primary role is in hepatic lipid accumulation (16). Wu et al. found elevated FGF21 levels in hepatic steatosis but not in fibrosis severity (22), whereas Yang et al. reported that FGF21 was increased in MASH and correlated with disease progression (23). Our study supports the latter, as FGF21 levels were significantly higher in advanced fibrosis patients (1579.3±375.3 vs. 960.3±350.1, p=0.001) and were an independent risk factor for FibroScan-confirmed fibrosis progression (OR=1.001, 95% CI: 0.99–1.003). YKL-40, produced by hepatic stellate cells, fibroblasts, and activated macrophages, has been linked to extracellular matrix remodeling and fibrosis progression (15, 24, 25). While studies have shown a correlation

between YKL-40 and fibrosis severity (15, 26), others, such as Lebensztejn et al., found no association between YKL-40 and fibrosis in MASLD children (27). Our results showed significantly higher YKL-40 levels in advanced fibrosis patients (287.4±105.5 vs. 188.7±48.5, p=0.003). However, multiple logistic regression analysis did not confirm it as an independent fibrosis risk factor (OR=0.99, 95% CI: 0.97–1.01). Hyaluronic acid, has been linked to fibrosis progression due to increased collagen synthesis and endothelial dysfunction (12, 13, 27). In Kaneda et al.'s study of 148 MASLD patients, hyaluronic acid was a significant marker of advanced fibrosis, a finding echoed in our study, where hyaluronic acid levels were significantly higher in advanced fibrosis patients (433.8±190 vs. 264.4±39.9, p=0.003). ROC analysis showed that hyaluronic acid was a significant predictor of FibroScan-confirmed fibrosis (AUROC=0.73), and multiple logistic regression identified it as an independent risk factor (OR=1.004, 95% CI: 0.99–1.01). Collagen type IV, a basement membrane component, has been suggested as a potential fibrosis marker, with Aida et al. showing significantly higher levels in advanced fibrosis (14). Other studies also found elevated collagen type IV levels in MASH-associated fibrosis (13, 15). Our findings confirmed that collagen type IV was significantly elevated in advanced fibrosis patients (38.3±9.8 vs. 30±3.6, p=0.002). However, multiple logistic regression did not identify it as an independent risk factor (OR=0.97, 95% CI: 0.79–1.19). The role of ALT elevation as a fibrosis marker remains debated. While some studies found no association between ALT and fibrosis severity (28), others, such as Fracanzani et al., reported a higher prevalence of MASH in ALT-elevated patients (74% vs. 59%) (29). Our study found no significant difference in histopathological fibrosis severity between normal and elevated ALT groups, though steatosis severity was significantly higher in the ALT-elevated group. This suggests ALT alone may not be a reliable fibrosis predictor. Conversely, GGT elevation has been associated with fibrosis progression, though findings remain inconsistent. In a study evaluating 50 MASLD patients, fibrosis severity and apoptotic markers were significantly higher in GGT-elevated patients (30). Similarly, our study found that patients with elevated GGT had significantly higher FibroScan fibrosis scores (p=0.006), supporting its potential role as a fibrosis progression marker. A primary limitation and weaknesses of this study is the small sample size, which may affect statistical power.

Study limitations: Limitation of our study is the relatively small sample size, necessitating larger studies for more comprehensive analysis.

Conclusion

Although MASLD is generally considered benign, our findings suggest that patients with obesity, IR, and elevated GGT are at increased risk for MASH and advanced fibrosis. Among noninvasive fibrosis markers, FGF21 and hyaluronic acid were identified as independent predictors of fibrosis progression, highlighting their potential clinical utility in MASLD monitoring.

Conflict of interest: There is no conflict of interest.
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