Research Article

Predicting fibrosis progression in NAFLD

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Predicting fibrosis progression in non-alcoholic fatty liver disease patients using the FAST Score: A paired biopsy study

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Abstract

Background and Aim: This study aimed to investigate the predictive value of various non-invasive scores for identifying the progression of hepatic fibrosis over time in patients with Non-Alcoholic Fatty Liver Disease (NAFLD).

Materials and Methods: We examined 69 patients with NAFLD who had undergone two liver biopsies at an average interval of 21.3±9.7 months. Progression and regression of fibrosis were defined as an increase or decrease of at least one stage in fibrosis between the initial and follow-up biopsies, respectively. The Fibrosis-4 Index (FIB-4), NAFLD Fibrosis Score (NFS), Agile 3+, Agile 4, and FibroScan-AST (FAST) scores were calculated at the initial biopsy.

Results: Comparison of paired biopsies revealed that 45% of participants (n=31) exhibited no change in fibrosis stages, 26% (n=18) experienced progression, and 29% (n=20) demonstrated regression. Multivariable logistic regression analysis identified the FAST score as the only independent predictor of progressive fibrosis, with the odds increasing by 19% (95% CI: 8–38%, p<0.05) for each unit increase in the FAST score at the initial biopsy. No independent predictors for fibrosis regression were identified.

Conclusion: Higher baseline FAST scores were associated with an increased likelihood of fibrosis progression, independent of other variables. Thus, the FAST score could serve as both a diagnostic and prognostic tool for fibrosis in patients with NAFLD.

Keywords: FibroScan-AST scor; hepatic fibrosis; non-alcoholic fatty liver disease; non-invasive scores, prognosis.

Introduction

Liver fibrosis is currently considered the key determinant of long-term clinical outcomes in patients with non-alcoholic fatty liver disease (NAFLD).[1,2] As fibrosis progresses, the risk of liver-related complications, including cirrhosis, hepatocellular carcinoma, hepatic failure, and ultimately, the necessity for liver transplantation, increases.[3] Additionally, fibrosis is associated with an increased probability of non-hepatic adverse outcomes, such as cardiovascular disease,[4] chronic kidney disease,[5] and osteoporosis,[6] independent of established risk factors.

Traditionally, longitudinal studies evaluating the natural history of liver fibrosis in NAFLD have employed paired liver biopsies taken at different time points from the same patient.[7,8] An increasing body of evidence has revealed diverse patterns in the evolution of fibrosis in NAFLD, including stability, progression, or regression, with considerable variation among individual patients.[7,9] Unfortunately, the factors influencing the temporal evolution of hepatic fibrosis in this context remain incompletely understood.[9]

Although paired liver biopsies are the reference standard for investigating the natural history of fibrosis in NAFLD, they have several limitations, including high costs, invasiveness, risk of complications, and sampling variability.[10] Consequently, there is growing interest in the development and validation of non-invasive markers that can accurately predict the evolution of fibrosis over time, thereby reducing the need for repeated liver biopsies.[11] In this study, utilizing paired liver biopsies, we examined five distinct non-invasive indices in relation to the natural history of fibrosis in NAFLD. We grouped patients into three categories based on the temporal evolution of hepatic fibrosis: stability, regression, and progression. We then investigated the predictive value of the Fibrosis-4 index (FIB-4),[12] NAFLD Fibrosis Score (NFS),[13] Agile 3+ score,[14] Agile 4 score,[15] and FibroScan-AST (FAST) score,[16] as measured at the time of the initial biopsy, for identifying these outcomes.

Materials and Methods

Study Population

This retrospective analysis was based on prospectively gathered data. We identified the patient cohort at the Department of Gastroenterology Marmara University Hospital, a prominent tertiary care facility in Istanbul, Turkiye. Eligible adult patients, over 18 years of age, diagnosed with NAFLD and who had undergone two paired liver biopsies were considered for inclusion. At the time of their initial biopsy, patients were required to have all necessary imaging and laboratory parameters available for calculating FIB-4, NFS, Agile 3+ score, Agile 4 score, and FAST score. Patients enrolled in therapeutic clinical trials were excluded. Individuals with fatty liver disease caused by other factors such as alcoholic liver disease, chronic viral hepatitis, autoimmune liver disease, drug-induced steatosis, Wilson's disease, and hemochromatosis were also excluded. The study adhered to the principles of the Declaration of Helsinki and was

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Table 1. Patient characteristics, non-invasive indices, and fibrosis changes at follow-up

Parameter	Stable fibrosis	Fibrosis progression	Fibrosis regression	p
Number of patients	31	18	20	–
Age, years	48.7±11.6	45.0±9.8	47.9±11.2	0.51
Men/women, n	16/15	11/7	15/5	0.24
Interval between biopsies, months	18.7±6.4	24.1±11.0	22.9±10.0	0.12
Body mass index, kg/m^2	32±5	33±4	33±5	0.33
Waist circumference, cm	104±11	110±9	111±10	0.08
AST	57±43	78±40	50±24	0.07
ALT	92±80	123±61	86±52	0.26
Platelets, 1000/mm^3	233±60	225±50	239±51	0.74
Albumin	4.55±0.33	4.53±0.42	4.52±0.30	0.98
Creatinine	0.75±0.16	0.75±0.14	0.82±0.15	0.22
Biliribin	0.78±0.42	0.74±0.43	0.76±0.43	0.82
Diabetes mellitus (yes/no), n	14/17	8/10	8/12	0.93
Non-invasive indices				
FIB-4	1.27±0.41	1.50±0.76	1.16±0.55	0.17
NFS	1.32±1.02	1.23±0.80	1.07±1.01	0.74
Agile 3+	0.51±0.29	0.44±0.26	0.37±0.27	0.27
Agile 4	0.11±0.10	0.10±0.09	0.08±0.06	0.24
FAST	**0.56±0.20**	**0.69±0.16**	**0.53±0.21**	**0.03**

The mean interval between paired biopsies in the entire study sample (n=69) was 21.3±9.7 months. The FAST score, emphasized in bold, emerged as the sole variable exhibiting notable variability across the three patient categories (one-way ANOVA; p=0.03). This was particularly evident when comparing the groups that underwent progression and regression (Tukey's post *hoc test*; p=0.009) as well as progression and stability (Tukey's *post hoc* test; p=0.02). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

approved by the local ethics committee (reference: 09.2022.1252). Due to the study's retrospective nature and the use of de-identified data, obtaining informed consent from participants was waived by the ethics committee.

Histology and Temporal Evolution of Fibrosis

Both paired liver biopsy specimens underwent staining with hematoxylin-eosin and Masson's trichrome. Subsequently, an experienced hepatopathologist, blinded to the results of the non-invasive indices, assessed and graded the specimens using Kleiner's[17] classification system. Each specimen was at least 1.5 cm in length or encompassed six to eight portal tracts.[18] The degree of fibrosis was classified into five stages: stage 0 represented no fibrosis, stage 1 indicated perisinusoidal or periportal fibrosis, stage 2 represented perisinusoidal and portal/periportal fibrosis, stage 3 indicated bridging fibrosis, and stage 4 represented cirrhosis. Fibrosis progression was defined as an increase of at least one stage in fibrosis between the initial and second biopsy, while fibrosis regression was a decrease of at least one stage between the two biopsies.[19]

Data Collection and Calculation of Non-Invasive Scores

We retrospectively obtained the clinical, laboratory, and imaging parameters of the patients at the time of their initial liver biopsy from their medical records. These variables were used to calculate the five non-invasive indices, which were then employed to evaluate their potential for predicting the temporal course of fibrosis. FIB-4 scores were computed using the established methodology,[12] incorporating age, platelet count, aspartate aminotransferase (AST), and alanine aminotransferase (ALT). NFS scores were determined according to a published formula that considers six parameters: age, body mass index, impaired glucose tolerance or diabetes, platelet count, albumin levels, and the AST to ALT ratio.[13] The Agile 3+ score, Agile 4 score, and FAST score, based on Fibroscan, were calculated using previously described equations.[14–16]

Statistical Analysis

To compare continuous variables among groups with fibrosis progression, regression, and stable disease, we used analysis of variance. Non-normally distributed variables were log-transformed prior to analysis. Pearson's χ^2 test was used to investigate differences in categorical data between groups. A multivariable logistic regression analysis identified independent associations between baseline characteristics, non-invasive indices, and fibrosis progression (or regression), with stable disease as the reference category. Statistical calculations were performed using SPSS version 20 (IBM, Armonk, NY, USA), and significance was defined as $p<0.05$ (two-tailed).

Results

The study included 69 NAFLD patients (mean age: 47.6±11.0 years; 42 men and 27 women) who underwent two paired liver biopsies (mean interval: 21.3±9.7 months). Analysis of paired biopsy results showed that 45% of participants (n=31) had stable fibrosis, while 26% (n=18) experienced fibrosis progression, and 29% (n=20) showed evidence of fibrosis regression according to predefined criteria. Age, sex, duration between biopsies, body mass index, waist circumference, liver aminotransferases, platelets, albumin, creatinine, bilirubin, and diabetes mellitus showed no significant differences among the regression, stable, and progression groups (Table 1). Examination of the five non-invasive scor-

ing systems revealed significant variability in the FAST score among the three patient categories (Table 1), particularly between the groups with progression and regression (p=0.009) and progression and stability (p=0.02). However, no differences were found between any groups in FIB-4, NFS, Agile 3+ score, and Agile 4 score. In multivariable logistic regression analysis, the only independent predictive factor for progressive disease was the FAST score. The odds ratio for progressive fibrosis increased by 19% (95% confidence interval: 8–38%, p<0.05) with every unit increase in the FAST score at the time of the initial liver biopsy. No independent predictors for fibrosis regression were identified.

Discussion

Prior paired biopsy studies have indicated the feasibility of both fibrosis progression and regression in individuals with NAFLD. In a systematic review and meta-analysis by Singh[7] and colleagues, 411 patients with NAFLD were examined across 11 paired biopsy studies. The analysis revealed that, during a follow-up period of 2145.5 person-years, 33.6% of patients experienced fibrosis progression, 43.1% had stable fibrosis, and 22.3% showed improvement in fibrosis stage.[7] The distribution pattern observed in our study was notably similar, with 26%, 45%, and 29% of our patients with NAFLD classified under the fibrosis progression, stable disease, and fibrosis regression groups, respectively. In addition to this confirming observation, this is the first paired biopsy study to compare the potential usefulness of five different non-invasive scores computed during the initial liver biopsy to forecast the histological evolution of fibrosis at follow-up. Our findings revealed that higher baseline FAST scores were independently predictive of fibrosis progression after a mean interval of 21.3±9.7 months. Thus, patients newly diagnosed with NAFLD and having increased FAST values at the time of their first biopsy may be recognized as having a greater risk of progressive fibrosis over time.

The FAST score incorporates liver stiffness measurements obtained by vibration-controlled transient elastography, the controlled attenuation parameter (which measures hepatic steatosis), and the serum level of AST. Originally developed by Newsome et al.,[16] it serves as a non-invasive diagnostic tool to identify patients at risk of developing significant fibrosis, an elevated NAFLD activity score, and steatohepatitis. The application of the FAST score is expected to lessen the need for liver biopsies in patients not at risk of having significant disease,[20] and a recent study on a Japanese cohort of 2254 participants reported successful classification of fatty liver severity using FAST.[21] Our paired biopsy analysis expands on these findings, indicating that higher baseline FAST scores are linked to an increased risk of fibrosis progression over a follow-up of almost two years.

The precise mechanisms underlying the reversibility of liver fibrosis in NAFLD are not fully understood, but the cessation of chronic damage resulting from positive lifestyle modifications and the reversal of underlying risk factors could be contributing factors.[19] This may lead to the deactivation of myofibroblasts and, eventually, to the degradation of collagen. It is evident that certain factors that may bolster resilience and impede the advancement of fibrosis in NAFLD remain unknown. Regrettably, our study did not identify any baseline indices that could specifically pinpoint patients exhibiting fibrosis regression over time. These findings emphasize the future significance of identifying protective factors to understand the varying trajectories of fibrosis.[22] Detecting such factors could aid in identifying patients with a higher probability of achieving regression, which might subsequently enhance prognostic classification and improve existing approaches for clinical management.

The current study is subject to certain limitations, including the length of observation in a chronic process, generalizability of the findings, and lack of mechanistic insights. To demonstrate the dynamic nature of hepatic fibrosis in NAFLD, we used only two paired biopsies, and further sampling of the time evolution curve of fibrosis is desirable in future studies. Additionally, the study participants were exclusively Turkish patients referred to a tertiary care facility, thereby constraining the applicability of the findings to other populations. Finally, we acknowledge the need for additional mechanistic investigations to enhance comprehension of the mechanisms responsible for fibrosis regression.

Conclusion

Despite these limitations, our results suggest that patients with higher baseline FAST scores are more likely to experience fibrosis progression independent of potential confounders. Consequently, FAST could serve not only as a diagnostic tool for screening fibrosis in NAFLD but also as a prognostic indicator. Further confirmation of our findings in larger and more diverse populations is warranted.

Ethics Committee Approval: The Marmara University School of Medicine Clinical Research Ethics Committee granted approval for this study (date: 07.10.2022, number: 09.2022.1252).

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Conflict of Interest: YY has received consultancy fees, speaker honoraria, and/or participated in clinical trials sponsored by Zydus, Cymabay, Novo Nordisk, and Echosens. HTK has received honoraria as a speaker on behalf of AbbVie. The other contributing authors have no competing interests to declare.

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