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Baseline Hepatic Steatosis Influences Longitudinal FIB-4 Trajectories During TNF Inhibitor Therapy in Axial Spondyloarthritis

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Abstract

Objectives: Whether baseline hepatic steatosis influences longitudinal Fibrosis-4 (FIB-4) trajectories during TNF inhibitor therapy in axial spondyloarthritis (axSpA) remains unknown. This study addressed this question.

Methods: This retrospective longitudinal cohort study included 154 patients with axSpA treated with TNF inhibitors for at least 6 months. Patients were classified according to baseline ultrasonographic hepatic steatosis, and FIB-4 scores were compared between baseline and the final follow-up visit.

Results: Baseline FIB-4 values were higher in patients with hepatic steatosis (p=0.035). During follow-up, patients without steatosis showed a significant increase in FIB-4, whereas those with steatosis demonstrated a non-significant decrease. Delta FIB-4 differed significantly between groups (p=0.008), while FIB-4 values remained within the low-risk range throughout follow-up. Findings were similar across sex, TNF inhibitor type, and steatosis grade. Longer cumulative biologic exposure was associated with smaller changes in FIB-4.

Conclusion: Baseline hepatic steatosis was associated with distinct longitudinal FIB-4 trajectories during TNF inhibitor therapy. Rather than indicating progressive liver fibrosis, these findings suggest that baseline hepatic status substantially influences the interpretation of serial FIB-4 measurements in patients with axSpA. If confirmed prospectively, baseline hepatic steatosis should be considered when using FIB-4 for longitudinal liver monitoring during biologic therapy.

Introduction

Axial spondyloarthritis (axSpA) is a chronic immune-mediated inflammatory disease characterized by persistent inflammation, progressive structural damage, and substantial functional impairment [1]. Beyond its musculoskeletal manifestations, increasing attention has been directed toward extra-articular comorbidities, including hepatic steatosis, which is increasingly recognized in patients with chronic inflammatory diseases. Chronic systemic inflammation, metabolic dysfunction, and prolonged exposure to immunomodulatory therapies may all contribute to hepatic injury, highlighting the importance of practical approaches for longitudinal liver assessment in patients receiving biologic treatment.

Among the available non-invasive tools, the Fibrosis-4 (FIB-4) index has emerged as a simple, inexpensive, and readily available surrogate marker for estimating hepatic fibrosis risk [2]. Initially validated in chronic liver diseases, particularly metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic viral hepatitis, FIB-4 has recently attracted growing interest as a practical marker of hepatic involvement in systemic inflammatory disorders [3, 4]. Its widespread availability and ease of calculation make it an attractive option for longitudinal hepatic monitoring in routine rheumatology practice [5].

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) has transformed the management of axSpA [6]. Among these agents, tumor necrosis factor (TNF) inhibitors remain the cornerstone biologic therapy owing to their well-established efficacy and long-term safety profile [7, 8]. Although clinically significant hepatotoxicity is uncommon, mild aminotransferase elevations and rare immune-mediated hepatic adverse events have been reported, supporting the need for continued hepatic surveillance during long-term treatment [9, 10].

Despite increasing interest in non-invasive assessment of liver fibrosis, evidence regarding longitudinal FIB-4 dynamics in patients with axSpA receiving TNF inhibitor therapy remains limited [11, 12]. More importantly, whether baseline hepatic steatosis influences longitudinal FIB-4 trajectories during TNF inhibitor treatment has not been systematically investigated. Addressing this question may facilitate interpretation of serial FIB-4 measurements during biologic therapy in routine clinical practice. Therefore, the present study aimed to evaluate longitudinal changes in FIB-4 scores in patients with axSpA receiving TNF inhibitor therapy and to determine whether baseline hepatic steatosis status modifies these trajectories.

Materials & Methods

Study Design

This investigation was conducted as a retrospective longitudinal cohort study based on a review of digital medical records of patients followed in the rheumatology and internal medicine outpatient clinics, with a predefined data cutoff of August 2025. Because all eligible patients identified within the study period were systematically included, no a priori sample size calculation was performed.

Participants

The study population comprised patients aged 18–65 years who had been diagnosed with axSpA by a rheumatology specialist and had received TNF inhibitor therapy (infliximab, adalimumab, etanercept, golimumab, or certolizumab pegol) for at least 6 months, with platelet counts ≥ 100 × 10^3/μL. Patients with known malignancy, diabetes mellitus and/or hypertension (excluded due to their independent contribution to hepatic fibrosis and FIB-4 variability), Behçet's disease, or Familial Mediterranean Fever were excluded (Fig. 1).

Although the study employed a retrospective design, patients were routinely evaluated in internal medicine outpatient visits throughout the duration of their biological therapy—a practice mandated by national pharmacovigilance regulations for biologic drug monitoring in Turkey—allowing systematic verification of concomitant medication use. Consequently, individuals with exposure to drugs known to cause thrombocytopenia—such as heparin, rifampin (for anti-tuberculosis prophylaxis), valproate, linezolid, oxcarbazepine, non-heparin oral anticoagulants, ranitidine, colchicine, amiodarone,

indomethacin, and diclofenac—were also excluded from the analysis (Fig. 1). Patients prescribed systemic corticosteroids during the study period were likewise excluded.

Data Sources:

Demographic data and all laboratory test results were extracted from the digital hospital information system. Demographic and clinical variables included age, sex, body mass index (BMI), smoking and alcohol use, disease duration, and comorbid conditions. Treatment-related variables comprised the type of biological agent, any changes in biological therapy and cumulative duration of use for each agent.

Liver-related parameters included serum transaminases, lipid profiles, viral hepatitis markers, FIB-4 scores, and hepatic echogenicity. The FIB-4 index was calculated using the formula: FIB-4 = (Age × AST) / (Platelet count × √ALT). A FIB-4 score of < 1.30 was interpreted as low fibrosis risk, 1.30–2.67 as indeterminate, and > 2.67 as high fibrosis risk [13, 14].

For hepatic imaging, all abdominal ultrasonography (USG) examinations available in the hospital system—performed within the surveillance intervals recommended by the Turkish Medicines and Medical Devices Agency (TITCK) guidelines for biological agents, or based on the anticipated hepatotoxicity profile of the drug class (generally annually)—were reviewed [15].

Hepatosteatosis was defined based on explicit terminology in the USG report or descriptive findings consistent with hepatic steatosis, including diffuse increased hepatic parenchymal echogenicity and accentuation of the hepatorenal echogenicity contrast [16, 17]. Hepatic steatosis was graded on a four-point scale: grade 0 (absent), grade 1 (mild), grade 2 (moderate), and grade 3 (severe), based on ultrasonographic findings documented in the radiology reports.

Formation of Study Groups:

Patients were stratified into two groups based on hepatic ultrasonography findings. Those without steatosis constituted Group 1 (control group), while those with ultrasonographically confirmed hepatosteatosis were assigned to Group 2.

Data Collection and Approvals:

All data were recorded into an Excel-based database by the investigators. Ethical approval for the study was obtained from the Selçuk University Faculty of Medicine Local Ethics Committee (approval date: 23.09.2025; decision number: 2025/16).

Statistical Analyses:

Statistical analyses were performed using SPSS version 27.0.1 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 10.3. The distribution of continuous variables was assessed prior to analysis. Normally distributed variables are presented as mean ± standard deviation, while non-normally distributed variables are reported as median (interquartile range [IQR]). Associations between continuous variables were evaluated using Pearson correlation for normally distributed data and Spearman's rank correlation for non-normally distributed data.

Between-group comparisons were performed using the independent samples Student's t-test or the Mann–Whitney U test for continuous variables, as appropriate to their distributional properties. Categorical variables were compared using the chi-square test or Fisher's exact test. Longitudinal changes in FIB-4 scores within each group were assessed using the Wilcoxon signed-rank test for paired observations.

To account for the potential confounding effect of body mass index—which demonstrated a statistically significant between-group difference and is an established determinant of hepatic steatosis—analysis of covariance (ANCOVA) was applied to evaluate its influence on FIB-4 score changes.

To minimize the age-related discriminatory effect on platelet counts, which constitutes a critical component of the FIB-4 formula, an upper age limit of 65 years was applied as an inclusion criterion [18]. This threshold is consistent with widely adopted cutoffs in epidemiological research for defining older age and was selected to reduce systematic bias in FIB-4 estimation attributable to age-associated thrombocytopenia [19, 20].

As a sensitivity analysis, all primary comparisons were repeated in the subgroup of patients with a minimum biologic therapy duration of 12 months (n = 96) to assess the robustness of findings across varying follow-up durations.

A two-tailed p-value of < 0.05 was considered statistically significant for all analyses.

Results

Our final analytical cohort comprised 154 patients who met the inclusion criteria. The mean age of the cohort was 41.10 ± 9.59 years, with a maximum age of 63 years. The mean BMI for the entire cohort was 25.91 ± 4.13 kg/m². The mean follow-up duration within the study period was 15.61 ± 7.29 months (minimum: 6 months). The median cumulative duration of biologic agent use prior to or during the study period was 2 years (IQR: 1–4 years). All patients carried a confirmed diagnosis of axial spondyloarthritis, with a median disease duration of 7 years (IQR: 2–15 years).

Upon evaluation of viral serologies, one patient (0.6%) tested positive for HBsAg. Fifteen patients (9.7%) were positive for Anti-HBc IgG, indicating past or resolved hepatitis B infection. Anti-HBs positivity, consistent with vaccine-induced immunity, was present in 71 patients (46.1%). One patient (0.6%) was

positive for Anti-HCV. No cases of Anti-HBc IgM or Anti-HIV positivity were detected. Among the TNF inhibitors prescribed, etanercept was the most commonly used agent (Table 1).

Table 1
Baseline demographic, clinical, and laboratory characteristics of the study cohort, stratified by hepatic steatosis status: Group 1 (no steatosis) and Group 2 (hepatosteatosis)).

Age, year ± SD[a]	**Group 1**	**Group 2**	***p* value**
	(n = 88)	**(n = 66)**	
	40.01 ± 10.52	**42.56 ± 8.03**	**0.103**
Sex, Female / Male, n (%)	35 (40) / 53 (60)	21 (32) / 45 (68)	0.310
Body Mass Index	23.04 (22.01–24.40)	29.35 (27.23–31.78)	0.001*
Disease duration, year	5 (2–11)	9 (3–16)	0.093
Follow-up duration, month	15.35 ± 7.39	15.96 ± 7.19	0.607
Biologic agent, n (%)			
Adalimumab	25 / 28	15 /23	0.691
Certolizumab	7 / 8	5 / 8	0.327
Etanercept	36 / 41	35 / 53	0.145
Golimumab	12 / 14	8 / 12	0.810
Infliximab	8 / 9	3 / 4	0.353
Erythrocyte sedimentation rate, mm/h	6 (3–16)	10 (6–19)	0,043*
C-reactive protein, mg/L	4 (2–7)	7 (4–11)	0.170
WBC[b], 10^3/μL	7.90 (6.40–9.13)	8.53 (7.21–9.49)	0.055
ANC[c], 10^3/μL	4.27 (3.50–5.98)	4.80 (4.19–5.77)	0.024*
ALC[d], 10^3/μL	2.50 (1.83–3.01)	2.60 (2.08–3.30)	0.151
Hemoglobin, g/dL	14.27 ± 1.75	14.39 ± 1.95	0.689
Platelet, 10^3/μL	316 (254–373)	278 (224–320)	0.003*
Glucose, mg/dL	87 (82–99)	93 (86–103)	0.020*
AST[e], U/L	16 (14–21)	19 (14–23)	0.161
ALT[f], U/L	16 (12–23)	19 (15–29)	0.023*
Creatinine, mg/dL	0.77 ± 0.16	0.81 ± 0.16	0.097

a, Standart deviation; **b**, White blood cell; **c**, Absolute neutrophyl count; **d**, Absolute leucocyte count; **e**, Aspartate transaminase; **f**, Alanine transaminase; **g**, Low-density lipoprotein; **h**, High-density lipoprotein; **i**, Fibrosis-4; **j**, Delta (Last FIB-4 – initial FIB-4).

Age, year ± SD[a]	**Group 1 (n = 88)**	**Group 2 (n = 66)**	***p* value**
	40.01 ± 10.52	**42.56 ± 8.03**	**0.103**
Total cholestrol, mg/dL	184 (151–245)	192 (165–210)	0.994
Triglyseride, mg/dL	84 (67–144)	113 (82–223)	0.257
LDL[g], mg/dL	128.5 ± 49.68	114.33 ± 21.17	0.914
HDL[h], mg/dL	45 (35–53)	42 (29–55)	0.762
Baseline FIB-4[i]	0.51 (0.38–0.72)	0.63 (0.42–0.86)	0.035*
Final FIB-4	0.56 (0.43–0.82)	0.59 (0.39–0.87)	0.712
Δ[j] FIB-4	0.53 (-0.07-0.18)	-0.02 (-0.12-0.08)	0.007*

a, Standart deviation; **b**, White blood cell; **c**, Absolute neutrophyl count; **d**, Absolute leucocyte count; **e**, Aspartate transaminase; **f**, Alanine transaminase; **g**, Low-density lipoprotein; **h**, High-density lipoprotein; **i**, Fibrosis-4; **j**, Delta (Last FIB-4 – initial FIB-4).

The calculated FIB-4 scores across all patients were consistently within the very low-risk range. The overall median FIB-4 score was 0.58 (IQR: 0.42–0.79). At the first visit, the median score was 0.58 (IQR: 0.40–0.79), which demonstrated no appreciable change in the median value [0.58 (IQR: 0.41–0.86)] at the last follow-up visit; both values remained well within the clinically low-risk threshold. Of note, the delta FIB-4 value—calculated as the last visit score minus the first visit score—showed a small positive shift of 0.016 (IQR: −0.89 to 0.14).

At baseline, the distribution of hepatic steatosis grades was as follows: 88 patients (57.1%) had no steatosis (grade 0), 42 patients (27.3%) had mild steatosis (grade 1), 17 patients (11.0%) had moderate steatosis (grade 2), and 7 patients (4.5%) had severe steatosis (grade 3). When comparing baseline and final ultrasonographic findings, 74 patients remained steatosis-free at the end of follow-up, although 14 of these had developed steatosis of varying grades by the final assessment. Among patients with steatosis at baseline, 54 maintained their initial steatosis grade throughout the follow-up period. In the remaining 26 patients, a change in steatosis grade was observed: six showed progression to a higher grade, while 20 demonstrated regression to a lower grade.

The demographic and clinical characteristics of the cohort, stratified by abdominal ultrasound findings into Group 1 (no steatosis) and Group 2 (hepatosteatosis), are presented in Table 1.

Comparison of FIB-4 scores between groups revealed that baseline FIB-4 values were significantly higher in Group 2 compared to Group 1 ($p = 0.035$, $\eta^2 = 0.029$). At the final follow-up visit, FIB-4 scores were numerically higher in Group 1 compared to Group 2, although this difference did not reach statistical significance ($p = 0.712$). Delta FIB-4 values were significantly different between the two groups ($p =$

0.008, $\eta^2 = 0.047$; Fig. 2), with Group 1 demonstrating a positive shift and Group 2 a negative shift, indicating divergent trajectories in hepatic fibrosis risk over the follow-up period.

Because BMI differed significantly between groups at baseline, an exploratory ANCOVA was performed to assess its potential confounding effect on delta FIB-4. BMI was not independently associated with delta FIB-4 ($p = 0.709$), suggesting that baseline differences in body habitus are unlikely to account for the observed divergence in FIB-4 trajectories..

In subgroup analyses, no statistically significant association was found between the degree of hepatic steatosis and FIB-4 change among patients in Group 2 ($p > 0.05$). Similarly, no significant difference in FIB-4 scores was observed between male and female patients within either group ($p > 0.05$). Furthermore, Kruskal-Wallis analysis revealed no statistically significant difference in either baseline or final FIB-4 values in subgroups according to the specific TNF inhibitor used ($p > 0.05$).

A further analysis examined longitudinal changes in FIB-4 scores between study entry and the final follow-up visit. Overall, a non-significant increase in FIB-4 scores was observed across the entire cohort ($p = 0.248$). When analyzed by group, Group 1 demonstrated a statistically significant increase in FIB-4 scores over the follow-up period ($p = 0.019$, $r = 0.585$), whereas Group 2 showed a non-significant decrease ($p > 0.05$) (Fig. 3). These findings were consistent with the delta FIB-4 results observed between the two groups.

In the sensitivity analysis restricted to patients with a minimum of 12 months of biologic therapy exposure ($n = 96$; Group 1: $n = 53$, Group 2: $n = 43$), baseline and final FIB-4 values did not differ significantly between groups ($p > 0.05$). However, delta FIB-4 values remained significantly different between the two groups ($p = 0.045$). Wilcoxon signed-rank analysis within each group yielded consistent results with the primary analysis: Group 1 demonstrated a borderline statistically significant increase in FIB-4 scores ($p = 0.05$), whereas Group 2 showed a non-significant decrease ($p > 0.05$), confirming the robustness of the observed divergent trajectories.

Spearman correlation analysis revealed several clinically relevant associations between FIB-4 scores and key study variables, as summarized in Table 2.

Table 2
Spearman correlation coefficients between FIB-4a parameters and selected clinical variables.

Variable	Baseline FIB-4	Final FIB-4	Delta FIB-4
Age	r^b **= 0.592**, p < 0.001	**r = 0.558**, p < 0.001	r = -0.015, p = 0.858
Body Mass Index	r = 0.118, p = 0.145	r = 0.003, p = 0.975	**r = -0.193**, p = 0.016
Hepatosteatosis	**r = 0.171**, p = 0.034	r = 0.043, p = 0.594	**r = -0.216**, p = 0.007
Disease duration	**r = 0.216**, p = 0.034	r = 0.152, p = 0.137	r = -0.021, p = 0.835
Biologic use duration	r = 0.096, p = 0.361	r = -0.096, p = 0.360	**r = -0.241**, p = 0.020

a, Fibrosis-4; **b**, correlation coefficient; Bold values indicate statistical significance (p < 0.05).

Discussion

The principal finding of the present study is that baseline hepatic steatosis was associated with distinct longitudinal FIB-4 trajectories in patients with axSpA receiving TNF inhibitor therapy. Although FIB-4 values remained within the low-risk range throughout follow-up in the overall cohort, patients without baseline steatosis demonstrated a modest but statistically significant increase in FIB-4, whereas those with hepatosteatosis showed a non-significant decrease. Delta FIB-4 values also differed significantly between the groups, while no agent-specific differences were observed among individual TNF inhibitors. Collectively, these findings suggest that baseline hepatic status may influence the longitudinal behavior and interpretation of FIB-4 during biologic therapy. To our knowledge, this is among the first studies specifically evaluating longitudinal FIB-4 trajectories according to baseline hepatic steatosis status in TNF inhibitor-treated patients with axSpA.

The observation that baseline FIB-4 scores were significantly higher in Group 2 (hepatosteatosis) is consistent with the established role of metabolic liver disease in promoting hepatic fibrosis, and aligns with the extensive validation of FIB-4 as a surrogate fibrosis marker in MASLD [3, 21-23]. This between-group difference at baseline is therefore not unexpected and lends construct validity to the study design. On a pathophysiological level, steatosis (frequently associated with increased BMI and metabolic dysregulation) is thought to create a susceptible hepatic environment that may facilitate fibrosis progression [24, 25]. Accordingly, at study outset, patients in Group 2 might have been expected to demonstrate more rapid FIB-4 progression during follow-up.

The longitudinal trajectories observed in the two groups, however, were not entirely consistent with this expectation. Group 1 (no steatosis) demonstrated a statistically significant increase in FIB-4 scores over the follow-up period, whereas Group 2 showed a non-significant decrease; a pattern that warrants careful interpretation. One plausible, albeit speculative, explanation is that TNF inhibitor therapy may exert a stabilizing hepatic effect that is more pronounced in patients with pre-existing steatosis, possibly through attenuation of TNF-α-mediated hepatic inflammation. An alternative explanation that must be

acknowledged is regression to the mean: patients in Group 2 had higher baseline FIB-4 values, and a subsequent decline may partly reflect statistical regression rather than a true biological effect. Nevertheless, the inverse correlation between baseline FIB-4 and delta FIB-4 observed across the entire cohort, combined with the significant between-group difference in delta FIB-4 values, suggests that regression to the mean alone is an insufficient explanation for the observed divergence. Any definitive conclusion, however, requires prospective validation with histological endpoints.

Previous studies evaluating FIB-4 in inflammatory rheumatic diseases have primarily focused on its cross-sectional associations with insulin resistance, cardiovascular risk, and mortality rather than longitudinal changes during biologic therapy [5, 11, 12]. Likewise, studies investigating serial FIB-4 behavior following biologic treatment remain limited [11]. Our findings extend this literature by demonstrating that baseline hepatic steatosis may influence longitudinal FIB-4 trajectories during TNF inhibitor therapy. Although the clinical implications of these divergent trajectories remain uncertain, they suggest that serial FIB-4 measurements should be interpreted in the context of baseline hepatic status rather than in isolation.

The finding that cumulative duration of biologic agent use was inversely correlated with delta FIB-4 provides additional context. This association raises the possibility that longer exposure to TNF inhibitors may be associated with a more favorable hepatic fibrosis trajectory, at least as assessed by FIB-4. This observation is hypothesis-generating rather than conclusive, and prospective studies with longer follow-up durations are needed to evaluate whether this relationship reflects a true pharmacological effect or confounding by indication.

Because BMI differed significantly between groups at baseline and represents an established determinant of hepatic steatosis, an exploratory ANCOVA was performed to assess its potential confounding effect. BMI was not independently associated with delta FIB-4, suggesting that differences in body habitus alone are unlikely to account for the divergent longitudinal trajectories observed between the groups, thereby strengthening the internal validity of the primary analysis. Nevertheless, given the limited explanatory power of the model, these findings should not be regarded as evidence of an independent effect of hepatosteatosis.

Furthermore, as the study objective was to evaluate the influence of hepatosteatosis on FIB-4 dynamics within a TNF inhibitor-treated cohort rather than to compare treated and untreated patients, the absence of a biologic-naïve control group does not compromise the within-cohort comparisons performed.

Subgroup analyses did not reveal significant differences in FIB-4 scores according to sex, specific TNF inhibitor used, or degree of hepatic steatosis within Group 2. The absence of a drug-specific effect is noteworthy, as it suggests that the observed FIB-4 trajectories may reflect a class effect of TNF inhibition rather than agent-specific pharmacological properties. Similarly, the lack of a sex-based difference is consistent with prior reports indicating comparable hepatic outcomes in male and female patients with inflammatory arthritis receiving biologic therapy [26].

The present study has several limitations that should be considered when interpreting these findings. First, the lack of serial liver elastography or biopsy precludes confirmation of the observed FIB-4 dynamics with direct histopathological or stiffness data; the absence of standardized serial ultrasonographic intervals further restricts the ability to track steatosis dynamics in a granular manner. Second, its single-center, retrospective design may limit the generalizability of findings to broader axSpA populations, and unmeasured confounders cannot be fully excluded. Third, and most notably, the interpretation of the divergent FIB-4 trajectories between groups requires caution. The statistically significant increase in Group 1, despite very low absolute values, may be influenced by regression to the mean, natural fluctuation within the low-risk range, or subtle variations in extra-hepatic formula components, rather than representing true hepatic fibrogenesis. This underscores that FIB-4, while useful, is an indirect surrogate marker. Conversely, the stabilization observed in Group 2, though encouraging, should be interpreted as a signal for a potential hepatoprotective effect rather than definitive proof, necessitating validation in studies with direct liver-specific endpoints. Fourth, the study may have been underpowered for specific subgroup analyses, particularly those involving smaller patient subgroups, and the lack of statistical significance in some comparisons may reflect a type II error due to limited sample size rather than a true absence of association. Finally, although strict exclusion criteria were applied regarding concomitant drug use at study entry, intermittent NSAID use after baseline cannot be fully excluded, which may have influenced platelet counts at follow-up visits and, consequently, FIB-4 score calculations.

In conclusion, this study demonstrated distinct longitudinal FIB-4 trajectories according to baseline hepatic steatosis status in patients with axSpA receiving TNF inhibitor therapy. Although FIB-4 values remained within the low-risk range throughout follow-up, patients without steatosis exhibited a modest increase, whereas those with hepatosteatosis showed stable or slightly declining values. These findings, while preliminary, do not establish progression or regression of hepatic fibrosis nor a direct hepatoprotective effect of TNF inhibition. Rather, they suggest that baseline hepatic status should be considered when interpreting serial FIB-4 measurements during biologic therapy. Prospective studies incorporating elastography or histological assessment are warranted to determine whether these divergent trajectories correspond to meaningful differences in hepatic fibrosis over time.

Declarations

Ethics Approval The study was conducted in accordance with the Declaration of Helsinki and was approved by the Selçuk University Non-Interventional Clinical Research Ethics Committee (Approval No: 2025/16). Consent to Participate Given the retrospective nature of the study and the use of anonymized patient data, the requirement for informed consent was waived by the Selçuk University Non-Interventional Clinical Research Ethics Committee.

Authors' contributions: Study Conception and Design: AC, KE. Data Acquisition: AC, MKS, KE. Analysis and interpretation of data: HAC, AC. Manuscript writing – draft: AC. Manuscript writing – approval of final version: AC, KE.

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Data availability: Sharing of the data underlying this article will be considered on reasonable request to the corresponding author.

Ethical approval and consent: Ethical approval was obtained from the Selçuk University Faculty of Medicine Local Ethics Committee (reference: 2025/16).

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Figures

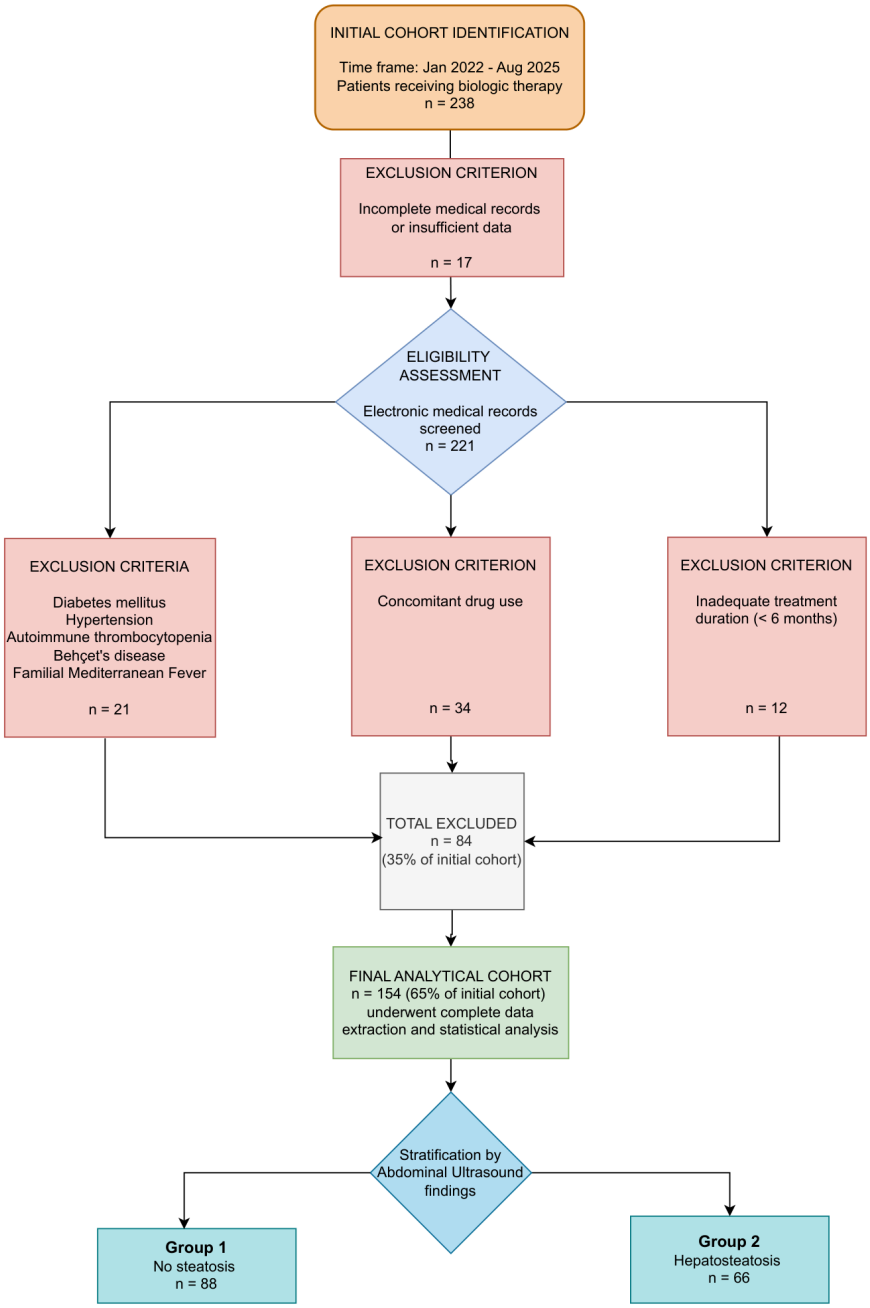


Figure 1

Flowchart illustrating the patient selection process. Of 268 patients receiving biologic therapy identified between January 2022 and August 2025, 154 were included in the final analytical cohort following the sequential application of exclusion criteria. The eligible cohort was subsequently stratified into Group 1

(no hepatosteatosis, n = 88) and Group 2 (hepatosteatosis, n = 66) based on abdominal ultrasonographic findings.

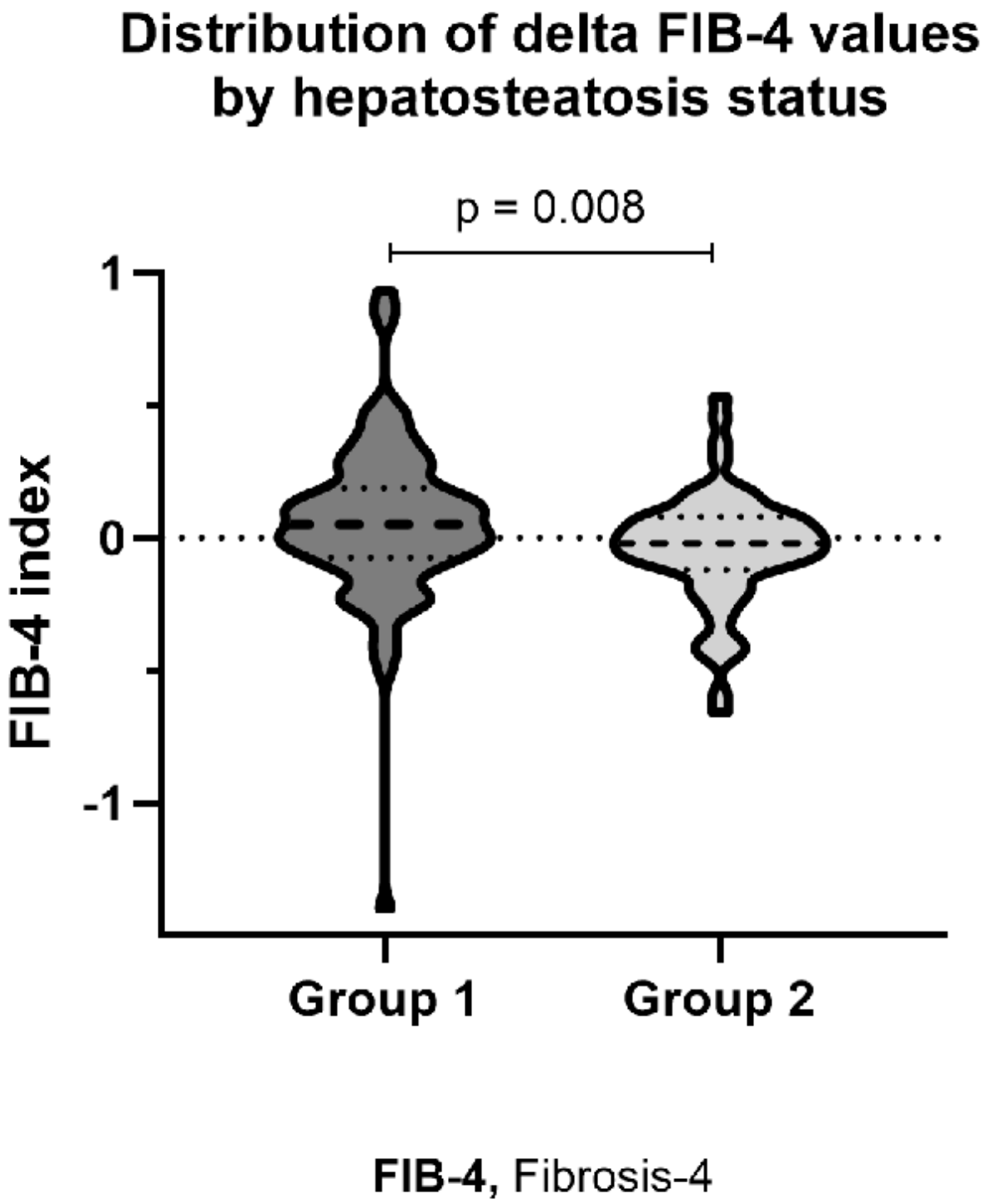


Figure 2

Distribution of delta FIB-4 values (final minus baseline) in Group 1 (no hepatosteatosis) and Group 2 (hepatosteatosis). Data are presented as violin plots with median (dashed line) and interquartile range. A

statistically significant difference in delta FIB-4 values was observed between the two groups (p = 0.008), with Group 1 demonstrating a positive shift and Group 2 a negative shift relative to baseline.

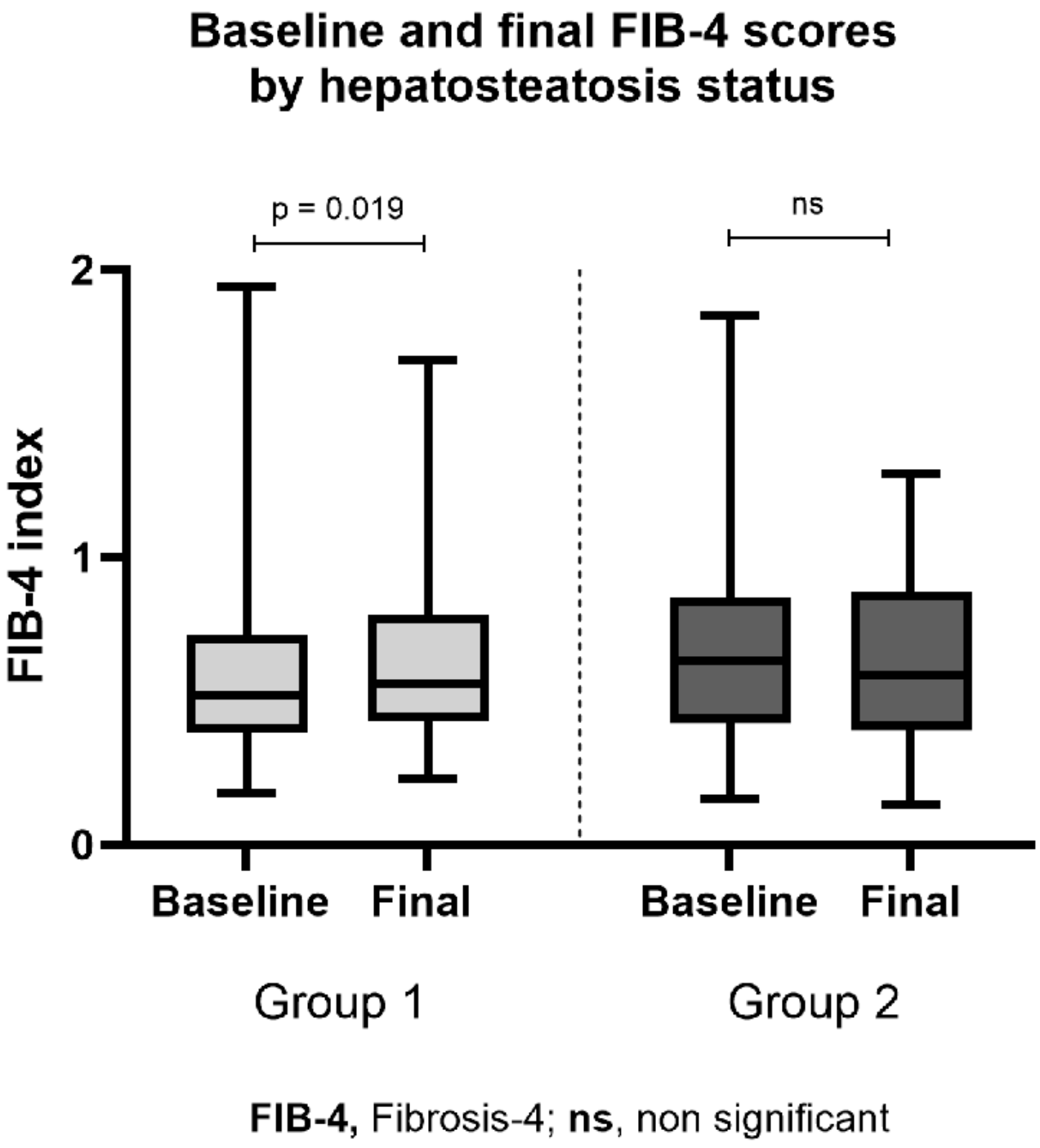


Figure 3

Comparison of baseline and final FIB-4 scores in Group 1 (no hepatosteatosis) and Group 2 (hepatosteatosis). Data are presented as box plots with median, interquartile range, and minimum-

maximum values. A statistically significant increase in FIB-4 scores was observed in Group 1 ($p = 0.019$), whereas no significant change was detected in Group 2 (ns).