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Impairment of patient-reported outcomes among patients with non-alcoholic fatty liver disease: a registry-based study

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Summary

Background: Patients with non-alcoholic fatty liver disease (NAFLD) and more advanced fibrosis tend to have more impairment in their health-related quality of life and other patient-reported outcomes (PROs).

Aim: To assess the association of PROs with select non-invasive tests (NITs) for fibrosis including FAST, Agile 3+ and Agile 4 scores

Methods: We enrolled patients with an established diagnosis of NAFLD who were seen in a tertiary care clinic into the NAFLD/NASH Registry. The FAST, Agile 3+ and Agile 4 scores were calculated using liver stiffness measurements by transient elastography and laboratory parameters. PROs were assessed using FACIT-F, CLDQ-NASH and WPAI instruments (total of 17 domain and summary scores).

Results: There were 1509 patients with NAFLD (mean age: 49 ± 11 years, 50% men, 41% employed, 30% advanced fibrosis and 20% cirrhosis). The mean FAST, Agile 3+ and Agile 4 scores were 0.39 ± 0.26, 0.35 ± 0.31 and 0.12 ± 0.23, respectively. Subjects with lower FAST, Agile 3+ and Agile 4 scores had the highest scores in select domains of FACIT-F, CLDQ-NASH and WPAI ($p < 0.05$ in comparison to subjects with elevated or high-risk NIT scores). Correlations with continuous NITs were significantly negative for Emotional and Functional well-being (FACIT-F), Activity/energy, Systemic symptoms, Worry and total scores (CLDQ-NASH), and Activity of WPAI ($p < 0.05$); the strongest was for Worry (CLDQ-NASH) with FAST ($R = -0.17$, $p < 0.0001$). The PRO scores of patients with NAFLD were lower than those of matched patients with chronic hepatitis B ($p < 0.05$ for 9/17 domain and summary scores).

Conclusion: Patients with NAFLD and high FAST, Agile 3+ or Agile 4 scores experience impairment of health-related quality of life.

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1 | INTRODUCTION

As the proportion of patients with obesity increases, the worldwide burden of non-alcoholic fatty liver disease (NAFLD) is progressively growing.[1–3] This condition can progress to hepatic fibrosis which, unchecked, can eventually lead to cirrhosis resulting in increased morbidity and mortality.[4,5] Although recent data suggest elevated prevalence of fatigue and other non-specific symptoms, NAFLD has historically been considered a "silent disease", especially in early stages.[4–10] Several phase 3 clinical trials are currently ongoing but, at present, there are no approved specific treatments for NAFLD.[11–13] In light of the current therapeutic vacuum concerning disease-modifying treatments, recent years have witnessed an increased focus on measures of how patients with NAFLD feel, function and survive.[14–16] In this context, patient-reported outcomes (PROs) represent an umbrella definition describing patients' subjective perception of the impact of their disease without interpretation from a clinician or anyone else.[17,18] The PROs range from health-related quality of life (HRQL; defined as the impact of NAFLD on different dimensions of patients' daily life) to fatigue and impairment in work productivity.[19] Most recent studies of patients with NAFLD suggest that these patients may have significant impairment of their PROs, and that worsening of liver disease in the form of progression to higher stages of fibrosis and, eventually, hepatic decompensation results in even greater PRO impairment.[20–24] In contrast, improvement of fibrosis not only can potentially lead to improvement of clinical prognosis but also to improvement of PROs.[25–28]

Although NAFLD is a multifaceted disease with at least several mechanistic and pathological substrates contributing to its progression,[5,29,30] liver fibrosis remains the key prognostic determinant.[31–33] Confirmatory diagnosis and staging of fibrosis require liver biopsy which is not invariably performed in the absence of approved therapies.[11–13,34] Thus, a major aim of recent biomarker research has been to develop biochemical and/or imaging-based tools that would enable an accurate non-invasive assessment of fibrosis.[35–37] While there is no single non-invasive test (NIT) that would be clearly superior to all others, one of the most widely used NITs for fibrosis, the fibrosis-4 (FIB-4) index, can be calculated based on four easily available parameters, namely, age, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and platelet count.[38,39] Furthermore, in recent years, liver stiffness measurement (LSM) by transient elastography (TE) is considered as one of the most relevant lines of investigation with respect to the non-invasive screening of hepatic fibrosis.[40–42] As a result, several scoring systems based on the combination of TE with other clinical and/or laboratory parameters have been proposed to improve diagnostic accuracy for fibrosis staging. Among them, FibroScan-AST (FAST) was devised to identify patients with non-alcoholic steatohepatitis showing elevated NAFLD activity score (NAS; ≥4) and fibrosis stage ≥2 (significant fibrosis),[43] whereas Agile 3+ and Agile 4 were developed to detect fibrosis stages 3–4 (advanced fibrosis) and fibrosis stage 4 (cirrhosis), respectively.[44,45] In this context, there is increasing evidence suggesting that NITs for fibrosis could be used as important predictors of long-term clinical outcomes.[39,41,42,46,47]

The question as to whether laboratory- and/or imaging-based NIT scores reflecting severity of hepatic fibrosis could be associated with the burden of NAFLD from the patient's perspective is not fully investigated. By taking advantage of the Global NAFLD/NASH Registry and focusing on the NIT and PRO data collected from patients with NAFLD in Turkey, this registry-based, cross-sectional study assessed the association of PROs with select NITs for fibrosis including FAST, Agile 3+ and Agile 4 scores.

2 | METHODS

2.1 | Study population

Patients with an established diagnosis of NAFLD seen in a tertiary care clinic in Istanbul, Turkey were invited to participate in the NAFLD/NASH Registry. A control group of patients with an established diagnosis of chronic hepatitis B (CHB) enrolled to the Global Liver Registry in the same centre were used as a comparator group. Patients who agreed to be enrolled in both NAFLD and CHB comparator groups signed an informed consent. Excluded from both groups were patients younger than 18 years and those with other causes of chronic liver disease (i.e. hepatitis C, excessive alcohol use defined as more than 14 drinks per week, autoimmune liver disease, decompensated cirrhosis, hepatocellular carcinoma and other hepatic malignancies, post-liver transplant), as were pregnant women or patients unwilling or unable to provide written informed consent. Collected variables included subjects' demographics, most recent height and weight, as well as relevant elements of past medical history and personal habits. All included participants completed PRO questionnaires about their current health-related quality of life and other aspects of daily functioning. The NAFLD/NASH Registry and Global Liver Registry data collection forms were approved by the Marmara University Institutional Review Board.

2.2 | Study variables and definition of TE-based fibrosis scores

All included subjects with NAFLD underwent TE (EchoSens) to measure their LSM and controlled attenuation parameter (CAP). The ALT, AST and platelet count were measured for all participants. The FIB-4 index,[48] FAST score,[43] Agile 3+[44] and Agile 4[45] scores were calculated using published formulae based on age, sex, CAP, LSM, AST, ALT, platelet count and presence of diabetes, as appropriate. Published cutoffs for TE-based scoring systems were applied to rule-out and rule-in fibrosis, as follows: 0.35 and 0.67, respectively, for FAST (fibrosis stage ≥2); 0.45 and 0.68, for Agile 3+ (fibrosis stage 3–4); 0.25 and 0.57, respectively, for Agile 4 (fibrosis stage 4, or cirrhosis).[49–51] Advanced fibrosis was defined as a biopsy-based diagnosis or LSM ≥9.5 kPa, or FIB-4 ≥ 3.25.[52,53]

Cirrhosis was defined as a biopsy-based diagnosis or as LSM ≥12 kPa.[54,55]

2.3 | Patient-reported outcomes

Three extensively validated PRO instruments – that is, the Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH), the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Work Productivity and Activity Index: Specific Health Problem (WPAI:SHP) – were used to assess the burden of disease were selected for the NAFLD/NASH Registry. All instruments were self-administered by subjects in their native language using a validated translation. The CLDQ-NASH is a disease-specific instrument which includes 36 items and six domains used to measure HRQL; the answers to each question are scored from 1 to 7 on a Likert scale (higher scores represent better health) to be averaged to yield the respective domain scores.[56] The FACIT-F is used as a fatigue-specific instrument with four generic core domains and a Fatigue Scale; all domains add up to the total FACIT-F score (range 0–160, higher score represents better health).[57] The WPAI:SHP questionnaire assesses impairment in work productivity due to both absenteeism (missed hours of work due to health problem) and presenteeism (self-reported impaired productivity while working) in employed subjects, and in activities other than work in all subjects. Unlike other PRO instruments, higher WPAI scores that range from 0 to 1 correspond to greater impairment in work productivity and activity.[58]

For the CHB comparator group enrolled in the Global Liver Registry, FACIT-F and WPAI were similarly used along with the

TABLE 1 Clinical and demographic parameters of patients with NAFLD triaged according to Agile 4 scores

	Low Agile 4 (≤0.25)	Moderate Agile 4 (>0.25 to <0.57)	High Agile 4 (≥0.57)	*p*	All
N	1285	108	116		1509
Age (years)	48.2 ± 11.1	53.0 ± 10.4	56.1 ± 10.5	<0.0001	49.1 ± 11.2
Male sex	658 (51.2%)	45 (41.7%)	44 (37.9%)	0.0056	747 (49.5%)
Employed	563 (43.8%)	27 (25.0%)	35 (30.2%)	<0.0001	625 (41.4%)
BMI (kg/m^2)	33.8 ± 6.3	34.5 ± 6.9	34.4 ± 5.8	0.21	33.9 ± 6.3
Advanced fibrosis	265 (20.6%)	83 (76.9%)	110 (94.8%)	<0.0001	458 (30.4%)
Cirrhosis	121 (9.4%)	68 (63.0%)	105 (90.5%)	<0.0001	294 (19.5%)
Medical history					
Type 2 diabetes	596 (46.4%)	80 (74.1%)	87 (75.0%)	<0.0001	763 (50.6%)
Anxiety	543 (42.3%)	45 (41.7%)	52 (44.8%)	0.85	640 (42.4%)
Depression	216 (16.8%)	28 (25.9%)	15 (12.9%)	0.0248	259 (17.2%)
Fatigue	657 (51.2%)	67 (62.0%)	71 (61.2%)	0.0153	795 (52.7%)
Abdominal pain	287 (22.3%)	35 (32.4%)	35 (30.2%)	0.0139	357 (23.7%)
Cancer	64 (5.0%)	9 (8.3%)	5 (4.3%)	0.29	78 (5.2%)
Hypertension	501 (39.0%)	54 (50.0%)	59 (50.9%)	0.0055	614 (40.7%)
Hyperlipidaemia	487 (38.0%)	55 (50.9%)	46 (39.7%)	0.0293	588 (39.0%)
Skin disease	157 (12.5%)	11 (10.7%)	12 (10.5%)	0.73	180 (12.2%)
Sleep apnea	187 (14.9%)	20 (19.4%)	22 (19.6%)	0.23	229 (15.6%)
Alcohol use (moderate or less)	112 (8.7%)	4 (3.7%)	1 (0.9%)	0.0027	117 (7.8%)
Regular exercise (≥30 min ≥3/week)	549 (42.8%)	47 (43.9%)	44 (37.9%)	0.57	640 (42.5%)
Current smoker	246 (19.1%)	11 (10.2%)	17 (14.7%)	0.0404	274 (18.2%)
ALT (U/L)	56.6 ± 43.1	56.0 ± 38.9	49.0 ± 31.0	0.73	56.0 ± 42.1
AST (U/L)	36.5 ± 23.1	45.2 ± 26.1	53.1 ± 31.3	<0.0001	38.4 ± 24.5
Platelet count, 10^9/L	260.2 ± 68.8	189.2 ± 50.3	131.5 ± 49.1	<0.0001	247.4 ± 75.3
FIB-4 score	0.99 ± 0.49	1.92 ± 0.68	3.94 ± 2.59	<0.0001	1.24 ± 1.11
Liver stiffness by Fibroscan (kPa)	7.60 ± 3.55	14.9 ± 6.4	30.9 ± 16.9	<0.0001	9.91 ± 8.70
Agile 3+ score	0.26 ± 0.22	0.83 ± 0.12	0.97 ± 0.05		0.35 ± 0.31
Agile 4 score	0.04 ± 0.05	0.39 ± 0.10	0.82 ± 0.11		0.12 ± 0.23
FAST score	0.35 ± 0.23	0.55 ± 0.26	0.75 ± 0.17	<0.0001	0.39 ± 0.26

Note: Results are given as counts (frequencies) or means ± standard deviations, as appropriate.

original CLDQ.[59] Since CLDQ-NASH includes all items of the original CLDQ, we additionally calculated CLDQ scores for patients with NAFLD in order to compare them to CHB.

2.4 | Statistical analysis

All collected demographic and clinical parameters as well as PRO scores were summarised as mean ± standard deviation or frequency (percentage) separately in patients with low, moderate and high (based on the rule-out and rule-in cutoffs) FAST, Agile 3+ or Agile 4 scores. The parameters were statistically compared among the three groups, for each TE-based fibrosis score separately, using Wilcoxon rank sum non-parametric test (continuous parameters) or Pearson's chi-square test (categorical parameters). Similar tests were used for comparison of the parameters and PRO scores between NAFLD and CHB subjects. In addition, non-parametric correlation coefficients (Spearman's) were calculated for the three continuous TE-based fibrosis scores and PRO scores. For assessment of the independent associations of NAFLD (versus CHB) with PRO scores, a generalised linear regression was used with adjustment for potential confounders (age, sex, advanced fibrosis, BMI, type 2 diabetes, hypertension, hyperlipidaemia, anxiety, depression, fatigue and sleep apnea). All analyses were run in SAS 9.4 (SAS Institute), with all tests two-sided at a 5% level of significance.

3 | RESULTS

3.1 | Study cohort

The study cohort consisted of 1509 patients with NAFLD (mean age: 49 ± 11 years, 50% men) enrolled in the Global NAFLD/NASH Registry who had their FAST, Agile 3+ and Agile 4 scores available. Of them, 41% were employed, 30% had advanced fibrosis and 20% had cirrhosis. The mean FAST, Agile 3+ and Agile 4, scores were 0.39 ± 0.26, 0.35 ± 0.31 and 0.12 ± 0.23, respectively.

3.2 | NAFLD patient characteristics according to TE-based fibrosis scores

Of the study patients, 85%, 7% and 8% had low, moderate and high Agile 4 scores, respectively (Table 1). These distributions were 67%, 14% and 19%, respectively, for Agile 3+ and 48%, 34% and 18%, respectively, for FAST (Tables S1 and S2). On analysing subjects based

TABLE 2 Patient-reported outcome scores of NAFLD subjects triaged according to Agile 4

PRO score (range)	Low Agile 4 (≤0.25)	Moderate Agile 4 (>0.25 to <0.57)	High Agile 4 (≥0.57)	*p*	All
FACIT-F:					
Physical well-being (0–28)	21.7 ± 5.6	20.6 ± 6.1	20.7 ± 6.5	0.13	21.5 ± 5.7
Emotional well-being (0–24)	16.0 ± 5.0	15.1 ± 5.7	14.5 ± 5.9	0.0208	15.8 ± 5.2
Social well-being (0–28)	20.2 ± 6.1	19.6 ± 5.6	20.8 ± 6.0	0.18	20.2 ± 6.1
Functional well-being (0–28)	19.7 ± 5.5	19.1 ± 5.7	18.6 ± 6.3	0.15	19.6 ± 5.6
Fatigue Scale (0–52)	34.9 ± 12.2	33.6 ± 12.8	33.6 ± 12.7	0.37	34.7 ± 12.3
Total (0–160)	112.5 ± 26.6	108.0 ± 29.4	108.1 ± 30.5	0.21	111.9 ± 27.2
CLDQ-NASH (all 1–7):					
Abdominal symptoms	5.00 ± 1.55	4.77 ± 1.71	4.73 ± 1.72	0.17	4.96 ± 1.58
Activity/energy	5.12 ± 1.36	4.75 ± 1.41	4.88 ± 1.48	0.0090	5.08 ± 1.38
Emotional	4.76 ± 1.36	4.58 ± 1.39	4.47 ± 1.43	0.06	4.73 ± 1.37
Fatigue	4.27 ± 1.47	4.07 ± 1.56	4.10 ± 1.53	0.28	4.24 ± 1.48
Systemic symptoms	4.70 ± 1.35	4.41 ± 1.45	4.37 ± 1.57	0.0231	4.66 ± 1.38
Worry	5.25 ± 1.44	4.88 ± 1.61	4.71 ± 1.59	0.0004	5.18 ± 1.47
Total	4.85 ± 1.14	4.58 ± 1.24	4.55 ± 1.29	0.0062	4.81 ± 1.17
WPAI (all 1–0):					
Work productivity impairment	0.191 ± 0.285	0.122 ± 0.202	0.285 ± 0.333	0.20	0.193 ± 0.285
Absenteeism	0.032 ± 0.128	0.009 ± 0.034	0.040 ± 0.100	0.25	0.032 ± 0.124
Presenteeism	0.160 ± 0.255	0.113 ± 0.194	0.244 ± 0.308	0.17	0.163 ± 0.256
Activity impairment	0.206 ± 0.283	0.242 ± 0.276	0.266 ± 0.317	0.0331	0.213 ± 0.286

Note: Results are given as means ± standard deviations.

on their Agile 4 scores, we found that those with high scores were, on average, older, less commonly male and reported a lower rate of moderate (or less) alcohol use than subjects with lower Agile 4 scores ($p < 0.05$; Table 1). In contrast, subjects with low Agile 4 scores were the youngest, more commonly male, employed and had substantially lower rates of some comorbidities (type 2 diabetes, hypertension, clinically overt fatigue, abdominal pain) compared with patients with higher Agile 4 scores ($p < 0.05$; Table 1). Similar findings were noted regarding subjects with lower vs. higher Agile 3+ scores: higher scores were associated with older age, female sex, lower employment, less alcohol use and higher rates of comorbidities (type 2 diabetes, fatigue, hypertension and hyperlipidaemia; $p < 0.05$; Table S1). Subjects with higher FAST scores were also older with more type 2 diabetes and hypertension ($p < 0.05$) but were otherwise similar to the rest of the sample (Table S2).

3.3 | Analysis of PROs in NAFLD according to TE-based fibrosis scores

On analysing PRO scores, subjects with low Agile 4 scores had the highest scores in the domains of Emotional Well-Being (FACIT-F), Activity/energy (CLDQ-NASH), Systemic symptoms (CLDQ-NASH), Worry (CLDQ-NASH) and total score (CLDQ-NASH), and also the lowest Activity Impairment (WPAI; $p < 0.05$; Table 2). In addition, high Agile 3+ scores were associated with lower scores in the domains of Functional Well-Being (FACIT-F) and Activity/energy (CLDQ-NASH), Systemic symptoms (CLDQ-NASH) and Worry (CLDQ-NASH; $p < 0.05$; Table S1). The trends in PRO scores of those with high FAST scores were similar to those reported for subjects with higher Agile 4 scores and included impairments in the domains of Emotional Well-Being (FACIT-F), Worry (CLDQ-NASH) and total score (CLDQ-NASH; $p < 0.05$; Table S2).

3.4 | Correlations between PROs and TE-based fibrosis scores

Correlations between PROs and TE-based fibrosis scores were as follows (Table 3). Emotional Well-Being (FACIT-F) was significantly and inversely correlated with all three fibrosis scores; Functional Well-Being and total score (FACIT-F) were inversely correlated with Agile 3+ only; Activity/energy (CLDQ-NASH) was negatively correlated with Agile 3+ and Agile 4; Systemic symptoms (CLDQ-NASH) with Agile 3+ only; Worry and total score (CLDQ-NASH) were negatively correlated with all three fibrosis scores. Finally, activity impairment (WPAI) was correlated only with FAST ($p < 0.05$). The negative correlation of the strongest magnitude was observed for Worry (CLDQ-NASH) with FAST ($R = -0.17$, $p < 0.0001$). No correlation of work productivity with the three fibrosis scores was observed (all $p > 0.10$; Table 3).

TABLE 3 Correlations of Agile 3+, Agile 4 and FAST with patient-reported outcome scores (Spearman's coefficient, *p*-value)

	FAST		Agile 3+		Agile 4	
PRO score	***R***	***p***	***R***	***p***	***R***	***p***
FACIT-F						
Physical well-being	−0.02	0.51	−0.04	0.12	−0.02	0.41
Emotional well-being	−0.07	0.0074	−0.06	0.0243	−0.05	0.0432
Social well-being	0.03	0.25	−0.05	0.06	−0.03	0.22
Functional Well-Being	0.00	0.94	−0.08	0.0034	−0.05	0.06
Fatigue Scale	−0.03	0.24	−0.04	0.11	−0.03	0.27
Total	−0.02	0.43	−0.06	0.0321	−0.04	0.17
CLDQ-NASH						
Abdominal symptoms	−0.05	0.06	0.01	0.70	0.00	0.93
Activity/energy	−0.02	0.35	−0.09	0.0003	−0.06	0.0198
Emotional	−0.01	0.69	−0.04	0.11	−0.02	0.41
Fatigue	−0.05	0.07	−0.04	0.15	−0.03	0.24
Systemic symptoms	−0.01	0.56	−0.09	0.0004	−0.05	0.06
Worry	−0.17	<0.0001	−0.07	0.0092	−0.07	0.0038
Total	−0.06	0.0192	−0.07	0.0081	−0.05	0.0508
WPAI						
Work productivity impairment	0.04	0.27	−0.05	0.20	−0.06	0.15
Absenteeism	0.01	0.81	−0.04	0.36	−0.03	0.40
Presenteeism	0.06	0.11	−0.05	0.24	−0.05	0.21
Activity impairment	0.07	0.0043	0.03	0.31	0.02	0.55

3.5 | Comparison of PRO scores between NAFLD and chronic hepatitis B controls

There were 665 CHB patients enrolled in the Global Liver Registry in the same centre with PRO data (Table S3). The PRO scores of patients with NAFLD were significantly lower than those of CHB patients in all domains of FACIT-F, all but one domain of CLDQ, and presenteeism and activity impairment domains of WPAI ($p < 0.05$; Table 4). In multivariate analysis, significantly lower scores in NAFLD in comparison to CHB were observed in select domains even after adjustment for demographic parameters, the presence of fibrosis, BMI and comorbidities ($p < 0.05$; Table 4).

4 | DISCUSSION

In this study, we assessed the distribution of different PROs reflecting patients' HRQL, fatigue and impairment in work productivity in a real-world sample of patients with NAFLD enrolled in the Global NAFLD/NASH Registry. Additionally, we estimated the associations of these PROs with three commonly used non-invasive TE-based fibrosis scores (FAST, Agile 3+ and Agile 4). There are three principal findings from our study. First, patients with NAFLD have more impairment of PROs as compared to patients with CHB enrolled from the same site. Furthermore, as shown by multivariate analysis in which NAFLD was found to be independently associated with lower PRO scores even after adjustment for potential confounders, that impairment was not fully explained by patients' clinicodemographic profile. The potential reasons may include the presence of unaccounted confounders, as well as differences in the pathophysiology of the diseases with a greater impact of metabolic abnormalities in NAFLD. Second, patients with NAFLD and higher FAST, Agile 3+ or Agile 4 scores consistently reported significant impairments in HRQL as documented by lower scores in specific domains of CLDQ-NASH. Third, we found no overall association between fatigue and elevated FAST, Agile 3+ or Agile 4 scores, although some FACIT-F domains did indicate deteriorations in patients at high risk of significant fibrosis, advanced fibrosis or cirrhosis (defined according to the FAST, Agile 3+ and Agile 4 rule-in cutoffs, respectively). Finally, non-invasive fibrosis scores did not show major associations with work productivity metrics.

Our study addresses an evidence gap regarding the association between PROs and TE-based NIT scores which have been developed

TABLE 4 Comparison of PRO scores between subjects with NAFLD and CHB (their demographic and clinical parameters are summarised in Table S3).

PRO score	NAFLD	Chronic hepatitis B	*p*	Beta[a] ± SE	*p*
N	1509	665			
FACIT-F					
Physical well-being	21.5 ± 5.7	23.7 ± 4.6	<0.0001	−0.63 ± 0.25	0.0128
Emotional well-being	15.8 ± 5.2	16.6 ± 4.8	0.0010	−0.09 ± 0.25	0.72
Social well-being	20.2 ± 6.1	21.9 ± 5.8	<0.0001	−1.44 ± 0.33	<0.0001
Functional well-being	19.6 ± 5.6	21.4 ± 5.4	<0.0001	−0.78 ± 0.29	0.0067
Fatigue Scale	34.7 ± 12.3	38.7 ± 11.1	<0.0001	−1.15 ± 0.52	0.0274
Total	111.9 ± 27.2	122.3 ± 23.8	<0.0001	−4.09 ± 1.19	0.0006
CLDQ-NASH					
Abdominal symptoms	4.96 ± 1.58	5.64 ± 1.36	<0.0001	−0.54 ± 0.08	<0.0001
Activity/energy	5.37 ± 1.29	5.83 ± 1.14	<0.0001	−0.14 ± 0.06	0.0273
Emotional	4.69 ± 1.38	4.96 ± 1.28	0.0001	−0.05 ± 0.06	0.39
Fatigue	4.22 ± 1.52	4.68 ± 1.47	<0.0001	−0.13 ± 0.07	0.05
Systemic symptoms	4.75 ± 1.35	5.44 ± 1.17	<0.0001	−0.24 ± 0.06	<0.0001
Worry	5.19 ± 1.47	5.29 ± 1.43	0.19	0.07 ± 0.07	0.33
Total	4.86 ± 1.14	5.30 ± 1.02	<0.0001	−0.17 ± 0.05	0.0006
WPAI					
Work productivity impairment	0.193 ± 0.285	0.141 ± 0.227	0.11	0.038 ± 0.02	0.06
Absenteeism	0.032 ± 0.124	0.030 ± 0.101	0.05	0.007 ± 0.009	0.44
Presenteeism	0.163 ± 0.256	0.111 ± 0.202	0.0197	0.032 ± 0.018	0.08
Activity impairment	0.213 ± 0.286	0.154 ± 0.245	<0.0001	0.013 ± 0.014	0.36

[a]Beta value reflects the mean least-square difference in a PRO score between the NAFLD and CHB groups (reference: CHB) returned by a generalised linear regression model adjusted for age, sex, advanced fibrosis, BMI, type 2 diabetes, hypertension, hyperlipidaemia, anxiety, depression, fatigue and sleep apnea.

to optimise positive predictive value and narrow the intermediate risk group ("grey zone") during non-invasive screening for different fibrosis stages. In this study, we observed significant declines in CLDQ-NASH total score as well as in the Worry domain score for patients with NAFLD triaged in the rule-in groups by all of the three fibrosis scores. These results suggest that HRQL in NAFLD may be negatively affected by hepatic fibrosis, consistent with prior reports.[21–26] The association with the Worry domain score likely indicates that worsening fibrosis can impair HRQL by posing a "fear for the future" burden on patients, that is, a worry that their condition would get worse over time and/or they would not be able to get help. Furthermore, fatigue has been previously described as one of the main drivers of PRO impairment in NAFLD being also associated with lower work productivity.[60] In this study, fatigue- and activity-related domains of CLDQ-NASH and FACIT-F also showed trends for association with select TE-based NITs but some of those trends did not reach statistical significance in our sample. Further research is needed to understand the pathophysiologic mechanisms of fatigue in NAFLD and how they may manifest in non-invasive liver function tests.

There are several limitations to this study. First, because of the retrospective observational cross-sectional design, the observed associations between TE-based NIT scores and PROs should not be interpreted as causal effects. Future studies can use longitudinal methods to determine whether being triaged in the high-risk groups by the NIT scores at baseline would independently predict long-term trends in PRO scores. Second, its single-centre nature may have limited the external validity of the results and, for that reason, large-scale prospective multicentre studies are needed. Limited availability of clinical data may also result in residual confounding which may have affected the observed associations. Finally, patients included in this study did not routinely undergo liver biopsy; historic biopsies were available for roughly 25% of the sample and were not chosen to be a reference.

In summary, our data suggest that patients with NAFLD and high FAST, Agile 3+ or Agile 4 scores may experience HRQL impairment; these PRO deficits should be considered during the clinical decision-making process. Our findings concerning PRO data have clinical implications in NAFLD as they can enrich our understanding of the patients' experience with unique information that could not be gained from clinical outcomes alone; accordingly, certain domains are difficult to observe and outcomes such as the degree of symptom bother are subjective and best collected through patient report. Future research is needed to evaluate the impact of TE-based fibrosis scores on temporal decline in PROs as well as to identify effective, patient-centred interventions for patients triaged in the high-risk groups by non-invasive scores.

AUTHOR CONTRIBUTIONS

Yusuf Yilmaz: Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); writing – original draft (equal); writing – review and editing (equal). **Ahmet Eren Toraman:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Ceyda Alp:** Data curation (equal); investigation (equal); writing – original draft (equal). **Zehra Doğan:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Caglayan Keklikkiran:** Data curation (equal); investigation (equal); writing – review and editing (equal). **Maria Stepanova:** Conceptualization (equal); formal analysis (equal); methodology (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal). **ZOBAIR M. YOUNOSSI:** Conceptualization (equal); data curation (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); visualization (equal); writing – original draft (equal); writing – review and editing (equal).

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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