Fatigue and Pruritus in Patients with Advanced Fibrosis Due to Nonalcoholic Steatohepatitis: The Impact on Patient-Reported Outcomes

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Fatigue and pruritus are common in patients with chronic liver diseases of all etiologies, but clinical awareness is mostly restricted to those with cholestatic liver diseases. We assessed the impact of fatigue and pruritus on patient-reported outcomes (PROs) of patients with advanced nonalcoholic steatohepatitis (NASH). Specifically, PROs (Short Form–36, Chronic Liver Disease Questionnaire–NASH, Euro-Qol 5 Dimension, and Work Productivity and Activity Impairment instruments) were assessed at baseline in patients with histologically confirmed bridging fibrosis (F3) or compensated cirrhosis (F4) due to NASH enrolled in STELLAR 3 and 4. Presence of fatigue and pruritus were indicated by a score of 4 or less on the respective items of the Chronic Liver Disease Questionnaire–NASH (scale range, 1-7). Among the included 1,669 patients with advanced NASH (mean age = 58 ± 9 years, 48% F3, 42% with psychiatric comorbidities), 33% and 27% had fatigue and pruritus, respectively. Patients with NASH with fatigue were younger, more likely to be female, cirrhotic, and diabetic, and had higher body mass index and more comorbidities (all $P < 0.05$). All PRO scores of patients with fatigue were significantly impaired (mean up to −31% of a PRO range size in comparison to patients without fatigue). In multivariate analysis, predictors of fatigue included diabetes, history of depression or nervous system comorbidities, and lower serum albumin ($P < 0.05$). Patients with pruritus had demographic characteristics similar to those with fatigue, but a higher prevalence of dermatologic comorbidities. All PROs were impaired (by up to −19% of a range size, all $P < 0.01$) in patients with NASH with pruritus. Female gender, lower serum albumin, and a history of depression, nervous system, and dermatologic comorbidities were associated with increased risk of pruritus ($P < 0.05$). *Conclusion:* Clinically significant fatigue and pruritus are common in patients with advanced NASH, and these symptoms negatively affect PROs. (*Hepatology Communications* 2020;4:1637-1650).

The global prevalence of nonalcoholic fatty liver disease (NAFLD) is estimated at approximately 25%, and the prevalence of nonalcoholic steatohepatitis (NASH) ranges from 1.5% to 6.5%.[1-4] In addition, as shown in a meta-analysis, the latter could be as high as 37% among individuals with type

Abbreviations: ALP, alkaline phosphatase; APRI, AST-to-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; CLDQ-NASH, Chronic Liver Disease Questionnaire–NASH; CRP, C-reactive protein; ELF, enhanced liver fibrosis; EQ-5D, Euro-Qol 5 Dimension; FIB-4, Fibrosis-4; GGT, gamma-glutamyl transferase; HbA1C, hemoglobin A1c; HCC, hepatocellular carcinoma; HOMA-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; medDRA, Medical Dictionary for Regulatory Activities; MELD, Model of End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; NFS, NAFLD fibrosis score; NIT, noninvasive test; OR, odds ratio; PRO, patient-reported outcome; SF-36, Short Form–36; TIMP-1, tissue inhibitor of metalloproteinase 1; VCTE, vibration-controlled transient elastography; WPAI:SHP, Work Productivity and Activity Impairment: Specific Health Problem; α-SMA, alpha smooth muscle actin.

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2 diabetes.[2] Other reports have suggested that those prevalence rates could be even higher, both in the general population and in subpopulations with metabolic syndrome components such as obesity and diabetes.[5,6] The prevalence of NASH also varies across demographic groups. In fact, in the United States, a substantially higher prevalence among Hispanic Americans in comparison to African Americans and Caucasians has been reported in multiple studies.[5,6] Worldwide, the highest prevalence of NAFLD and NASH is believed to be in the Middle East and South America.[1]

This high prevalence of NASH has already led to significant clinical burden, as documented by increased rates of cirrhosis, hepatocellular carcinoma (HCC), and mortality. In fact, in one study that analyzed U.S. mortality data from 2007-2016, investigators reported that 82% of liver-related deaths were from cirrhosis, while 17% were from HCC, and that NAFLD/NASH was responsible for 35% of HCC deaths and for almost 50% of cirrhosis deaths.[7,8] Using an age-specific death rate (ASDR) metric, researchers reported that the ASDR for NAFLD in the United

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States increased by 15% over the decade.[7] Consistent with these observations, other reports confirmed that NASH is currently the second leading indication for liver transplantation and is the most common indication in some demographic groups such as women in the United States.[9-11]

Despite the significant clinical burden, NASH has generally been considered to be asymptomatic and is often diagnosed inadvertently after a finding of elevated liver enzymes or evidence of fatty liver on ultrasound performed for other reasons. This paradigm is currently shifting with more providers becoming aware of NAFLD, NASH, and their associated risks. However, there remain substantial gaps in knowledge about these liver diseases, which is especially alarming for medical specialties who likely see most patients with NAFLD such as primary care specialists, endocrinologists, and cardiologists.[12]

Although early stages of NASH may not be associated with severe symptoms, it is increasingly appreciated that NASH is not an asymptomatic disease. In fact, systematic assessments of patients with NASH using validated health-related quality-of-life instruments suggest significant impairment of patient-reported outcomes (PROs).[13-16] Physical health–related domains of PROs and those that reflect fatigue appear to be the most negatively affected, particularly in patients with NASH and advanced fibrosis.[17,18] In addition to fatigue, other previously underappreciated symptoms of liver disease are being increasingly reported in patients with NASH. In fact, among patients with NASH enrolled in recent clinical trials, between 32% and 35% and 21% and 27% have reported clinically significant fatigue and pruritus at baseline, respectively.[19-21] Therefore, the aim of this study was to assess fatigue and pruritus and their impact on PROs of patients with advanced fibrosis due to NASH.

Patients and Methods

STUDY POPULATION

The data for this study were collected in the STELLAR phase 3 clinical trials of selonsertib (#NCT03053050 and #NCT03053063). The trials were conducted in 27 countries (North America, South America, Europe, Asia, Australia, and New Zealand) in 2017-2019, and were terminated due to the lack of efficacy of the study drug.[22] As previously described, enrolled subjects were required to have a liver biopsy consistent with NASH and bridging fibrosis or cirrhosis. Subjects with a prior history of decompensated liver disease, Child-Pugh score greater than 6, Model for End-Stage Liver Disease (MELD) score greater than 12, other causes of liver disease, liver transplant, HCC, human immunodeficiency virus infection, recent excessive alcohol or illicit drug use, any major or unstable comorbidities other than NASH and metabolic syndrome as determined by the investigators, concomitant use of certain medications, or those participating in other clinical trials were excluded.[22]

ASSESSMENTS

Medical history was coded using the Medical Dictionary for Regulatory Activities (medDRA).[23] Laboratory parameters were collected at baseline and during treatment, and were used to calculate commonly used noninvasive tests of fibrosis (NITs) at baseline and treatment week 48, including the Enhanced Liver Fibrosis score (ELF), aspartate aminotransferase (AST)–to-platelet ratio index (APRI), Fibrosis-4 index (FIB-4), FibroTest, and the NAFLD fibrosis score (NFS).[24-28] In addition, most enrolled patients underwent liver stiffness measurement by vibration-controlled transient elastography (VCTE; FibroScan; Echosens, Paris, France) using a prespecified protocol.[29] Liver biopsies, which were obtained at screening and week 48, were evaluated by a single central pathologist (Z.G.) using the NASH Clinical Research Network classification for hepatic fibrosis[30-32] and the NAFLD activity score (NAS) for steatosis, hepatocellular ballooning, and lobular inflammation.[32] The proportionate areas of hepatic collagen, alpha-smooth muscle actin (α-SMA) expression, and fat in biopsy specimens were assessed using computer-assisted morphometry, as previously described.[33]

PRO MEASURES INCLUDING PRURITUS AND FATIGUE SCORES

In both studies, patients self-administered four validated PRO instruments: Short Form–36 (SF-36), the Euro-Qol 5 Dimension (EQ-5D), the Chronic Liver

Disease Questionnaire–NASH (CLDQ-NASH), and the Work Productivity and Activity Impairment: Specific Health Problem (WPAI:SHP)[34-40] in their native languages. For the purpose of this study, pruritus and fatigue were quantified using the respective scores of the disease-specific CLDQ-NASH instrument. Scores of 4 or less on this semi-quantitative scale, which ranges from 1 to 7, were considered indicative of clinically significant pruritus or fatigue.

STATISTICAL ANALYSIS

Clinico-demographic parameters as well as PRO scores were compared between NASH patients with and without clinically significant pruritus or fatigue using Pearson's chi-square test or Wilcoxon rank sum test, as appropriate. Independent predictors of clinically significant pruritus and fatigue at baseline were evaluated using logistic regression models with stepwise selection of predictors out of the complete list of clinical, demographic, laboratory, and histologic parameters. Comparison of postbaseline scores to patients' own baseline levels was performed using the sign-rank test for matched pairs in patients treated with placebo during the trials. In those patients, independent predictors of changes in pruritus and fatigue from baseline to week 48 (observed cases only) were studied using generalized linear regression models with stepwise selection of parameters and changes in these parameters from baseline.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC). The trials were approved by each site's institutional review board, and all participants provided informed consent.

Results

PREVALENCE OF PRURITUS AND FATIGUE AT BASELINE

A total of 1,669 patients with advanced fibrosis due to NASH were included in this study. The mean age was 58 ± 9 years, 40% were male, 42% had psychiatric comorbidities, and 52% had cirrhosis (F4). Based on the respective scores of the CLDQ-NASH, clinically significant pruritus and fatigue were present in 27% and 33% of patients, respectively. The median pruritus score was 6 (interquartile range [IQR] 4-7) and did not differ between patients with bridging fibrosis and compensated cirrhosis (P = 0.55). The median fatigue score was 4.8 (IQR 3.7-5.7). Although patients with bridging fibrosis had higher median fatigue scores (indicative of *less* fatigue) than those with cirrhosis (5.0 [IQR 4.0-5.8] vs. 4.7 [3.5-5.7]; P = 0.0028), the difference does not meet the threshold of a minimal clinically important difference for domain scores of the CLDQ-NASH (approximately 0.5 points).

PREDICTORS OF CLINICALLY SIGNIFICANT PRURITUS

Clinico-demographic, laboratory, and histologic parameters of patients with clinically significant pruritus at baseline are given in Table 1. Compared to patients without pruritus, those with pruritus were more likely to be female and white, less likely to be Asian, had a lower employment rate, and a higher body mass index (BMI). Clinically significant fatigue, as well as dermatologic and nondermatologic comorbidities (e.g., psychiatric, gastrointestinal, fatigue, immune, infections, musculoskeletal, nervous, respiratory, vascular, vision) were more common in patients with pruritus, but an association with diabetes was not observed. Patients with pruritus had lower hemoglobin and serum albumin, and higher serum alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bile acids, fasting glucose, homeostasis model assessment of insulin resistance (HOMA-IR), hemoglobin A1c (HbA1c), and C-reactive protein (CRP). Although patients with pruritus had greater liver stiffness by VCTE and higher ELF and NFS (all $P < 0.05$), there was no association between pruritus and the presence of cirrhosis or other histologic parameters (all $P > 0.05$) (Table 1).

In multivariate analysis, female gender, a history of depression, nervous system disorders, skin-related comorbidities, and lower serum albumin were associated with an increased risk of pruritus in patients with advanced fibrosis due to NASH (all $P < 0.05$) (Table 2).

PREDICTORS OF CLINICALLY SIGNIFICANT FATIGUE

Parameters of patients with clinically significant fatigue are provided in Table 3. Compared to patients without fatigue, those with fatigue were younger (mean

TABLE 1. BASELINE CLINICO-DEMOGRAPHIC PARAMETERS OF PATIENTS WITH NASH WITH ADVANCED FIBROSIS BY THE PRESENCE OF CLINICALLY SIGNIFICANT ITCH

	Clinically Significant Itch (Score ≤ 4)	No Clinically Significant Itch	*P*
N	447	1,222	
Age, years	58.0 ± 8.3	57.8 ± 9.0	0.87
Male gender	144 (32.2%)	529 (43.3%)	<0.0001
White race	353 (79.0%)	873 (71.4%)	0.0020
Black race	10 (2.2%)	15 (1.2%)	0.13
Asian race	71 (15.9%)	306 (25.0%)	0.0001
Current smoker	50 (11.2%)	116 (9.5%)	0.30
Employed	179 (40.0%)	634 (52.1%)	<0.0001
Enrolled in the United States	268 (60.0%)	659 (53.9%)	0.0282
Cirrhosis	233 (52.1%)	635 (52.0%)	0.95
BMI, kg/m^2	34.5 ± 6.4	33.1 ± 6.7	<0.0001
Comorbidities from medical history (by MedDRA):			
Diabetes mellitus	341 (76.3%)	890 (72.8%)	0.16
Anxiety	122 (27.3%)	213 (17.4%)	<0.0001
Depression	159 (35.6%)	272 (22.3%)	<0.0001
Clinically overt fatigue	66 (14.8%)	107 (8.8%)	0.0004
Gastrointestinal disorders	342 (76.5%)	846 (69.2%)	0.0036
Immune system disorders	207 (46.3%)	478 (39.1%)	0.0082
Infections or infestations	190 (42.5%)	435 (35.6%)	0.0098
Sleep disorders	94 (21.0%)	177 (14.5%)	0.0013
Musculo-skeletal disorders	299 (66.9%)	688 (56.3%)	0.0001
Nervous system disorders	227 (50.8%)	449 (36.7%)	<0.0001
Respiratory disorders	206 (46.1%)	447 (36.6%)	0.0004
Skin disorders	176 (39.4%)	321 (26.3%)	<0.0001
Vascular disorders	336 (75.2%)	849 (69.5%)	0.0233
Eye disorders	126 (28.2%)	282 (23.1%)	0.0314
Laboratory parameters and derived scores			
ALT, U/L	55.7 ± 37.6	57.2 ± 35.4	0.13
AST, U/L	54.0 ± 30.1	52.1 ± 30.1	0.22
Platelets, $x10^9/L$	188.7 ± 65.9	188.2 ± 67.2	0.63
Hemoglobin, g/dL	13.7 ± 1.5	14.0 ± 1.5	0.0007
Albumin, g/dL	4.39 ± 0.35	4.48 ± 0.33	0.0001
ALP, U/L	95.5 ± 32.7	92.0 ± 35.7	0.0055
Bilirubin, mg/dL	0.641 ± 0.350	0.690 ± 0.373	0.0025
Direct bilirubin, mg/dL	0.187 ± 0.105	0.189 ± 0.092	0.14
Bile acids, umol/L	13.5 ± 15.2	12.1 ± 13.5	0.0160
Fasting glucose, mg/dL	134.8 ± 49.9	127.5 ± 40.8	0.0195
Fasting HOMA-IR score	11.7 ± 20.9	9.22 ± 15.74	<0.0001
HbA1c, %	6.74 ± 1.18	6.57 ± 1.19	0.0034
CRP, mg/dL	0.580 ± 0.655	0.504 ± 0.741	<0.0001
GGT, U/L	112.8 ± 127.4	109.1 ± 137.6	0.0250
Alpha-2 macroglobulin, mg/dL	271.9 ± 77.8	275.6 ± 81.5	0.43
Apolipoprotein A1, mg/dL	142.2 ± 25.6	142.4 ± 26.0	0.67
Apolipoprotein B, mg/dL	91.2 ± 27.0	89.0 ± 24.6	0.20
Haptoglobin, mg/dL	125.6 ± 61.3	118.4 ± 66.2	0.0133
Hyaluronic acid, ng/mL	177.8 ± 217.8	160.0 ± 211.4	0.0123
PIIINP, ng/mL	14.2 ± 6.7	13.2 ± 6.5	0.0009
TIMP-1, ng/mL	317.9 ± 99.6	300.3 ± 94.2	0.0002

TABLE 1. *Continued*

	Clinically Significant Itch (Score ≤ 4)	No Clinically Significant Itch	*P*
APRI score	0.926 ± 0.640	0.914 ± 0.719	0.23
FIB-4 score	2.60 ± 1.63	2.50 ± 1.60	0.15
FibroTest score	0.489 ± 0.225	0.518 ± 0.237	0.0156
ELF score	10.5 ± 1.0	10.3 ± 1.0	0.0007
MELD score	7.03 ± 1.57	7.13 ± 1.66	0.28
NFS	0.443 ± 1.381	0.168 ± 1.381	0.0024
Liver imaging:			
Liver stiffness by transient elastography, kPa	20.7 ± 13.2	19.2 ± 12.3	0.0180
Controlled attenuation parameter, dB/m	325.8 ± 51.9	319.2 ± 55.4	0.17
Liver histology:			
NAFLD activity: steatosis grade 1	424 (94.9%)	1,152 (94.3%)	0.65
NAFLD activity: steatosis grade 2	23 (5.1%)	68 (5.6%)	0.74
NAFLD activity: lobular inflammation grade 1	37 (8.3%)	112 (9.2%)	0.57
NAFLD activity: lobular inflammation grade 2	159 (35.6%)	476 (39.0%)	0.21
NAFLD activity: lobular inflammation grade 3	251 (56.2%)	634 (51.9%)	0.12
NAFLD activity: hepatocyte ballooning grade 1	72 (16.1%)	247 (20.2%)	0.06
NAFLD activity: hepatocyte ballooning grade 2	375 (83.9%)	973 (79.6%)	0.05
Total NAS	5.37 ± 0.89	5.28 ± 0.92	0.06
Hepatic collagen content, %	8.32 ± 6.45	8.27 ± 6.10	0.91
α-SMA, %	11.1 ± 8.3	10.5 ± 8.0	0.22
Morphometric fat content, %	11.2 ± 6.4	11.3 ± 6.6	0.89

Abbreviations: ALT, alanine aminotransferase; PIIINP, procollagen III amino terminal propeptide; TIMP-1, tissue inhibitor of metalloproteinase 1.

age: 56 vs. 59 years old), more likely to be female (70% vs. 55%) and white, and less likely to be employed. Patients with fatigue also had a higher BMI and more comorbidities including diabetes (78% vs. 72%) and smoking, and a higher prevalence of clinically significant pruritus (45% vs. 18%) (all $P < 0.05$). Patients with fatigue also had lower serum albumin and higher serum ALP, GGT, bile acids, fasting glucose, HbA1c, and CRP compared to patients without fatigue. In addition to a higher prevalence of cirrhosis (58% vs. 49%), patients with fatigue also had higher serum ELF scores, FibroTest and NFS, greater liver stiffness by VCTE, and higher hepatic collagen content and α-SMA expression by morphometry (Table 3).

To eliminate the potential impact of biopsy sampling error on classification of fibrosis, the association between fatigue at baseline with cirrhosis was also assessed in a subgroup of patients in whom the fibrosis stage was unchanged between baseline and week 48 (n = 1,161, including n = 638 with stable bridging fibrosis and n = 523 with stable cirrhosis). In this sensitivity analysis, clinically significant fatigue remained more common in patients with cirrhotic NASH versus bridging fibrosis (60% vs. 52%; $P = 0.02$).

In multivariate analysis, independent predictors of clinically significant fatigue included clinically significant pruritus (odds ratio [OR] 3.30; 95% confidence interval 2.57-4.24; $P < 0.0001$), female gender, younger age, non-Asian race, history of depression, diabetes and other comorbidities, and some laboratory tests including lower serum albumin and platelets (all $P < 0.05$; Table 2). After adjustment for laboratory tests including platelet count, serum albumin, and several serum NITs, the association between fatigue and cirrhosis was not statistically significant ($P = 0.21$).

COMORBID FATIGUE AND PRURITUS IN PATIENTS WITH NASH

Due to the strong association between clinically significant pruritus and fatigue shown previously, we aimed to specifically study patients who have both pruritus and fatigue. In this context, 15% of enrolled patients with NASH had both fatigue and pruritus, 18% had fatigue without pruritus, 12% had pruritus without fatigue, and 55% had neither. Patients who had both fatigue and pruritus were predominantly

TABLE 2. MULTIVARIATE ANALYSIS OF CLINICO-DEMOGRAPHIC FACTORS INDEPENDENTLY ASSOCIATED WITH BASELINE PRURITUS AND FATIGUE IN PATIENTS WITH ADVANCED NASH (LOGISTIC REGRESSION, $P < 0.05$ AFTER STEPWISE SELECTION OF CLINICO-DEMOGRAPHIC AND LABORATORY PREDICTORS FROM TABLE 1)

Predictor of Pruritus	Odds Ratio (95% CI)	*P*
Male gender (ref: female)	0.75 (0.59-0.95)	0.0194
Depression	1.53 (1.19-1.96)	0.0009
Nervous system disorder	1.40 (1.11-1.77)	0.0042
Skin disorder	1.59 (1.25-2.01)	0.0001
Albumin, per g/dL	0.56 (0.40-0.78)	0.0006
Predictor of fatigue		
Age, per year	0.96 (0.95-0.98)	<.0001
Male gender (ref: female)	0.66 (0.51-0.86)	0.002
Asian race (ref: white)	0.55 (0.39-0.77)	0.0006
Type 2 diabetes	1.51 (1.14-1.99)	0.0037
Depression	2.18 (1.67-2.83)	<.0001
Clinically overt fatigue	1.85 (1.28-2.67)	0.0011
Gastrointestinal disorder	1.33 (1.00-1.78)	0.0497
Nervous system disorder	1.29 (1.01-1.66)	0.0454
Platelet, per 10^9/L	0.998 (0.996-1.000)	0.0225
Albumin, per g/dL	0.45 (0.31-0.66)	<.0001
Alpha-2 macroglobulin, per mg/dL	0.998 (0.996-0.999)	0.0094
Apolipoprotein A1, per mg/dL	0.994 (0.989-0.999)	0.0126
Apolipoprotein B, per mg/dL	1.006 (1.002-1.011)	0.0096
TIMP-1, per ng/mL	1.002 (1.000-1.003)	0.0179
Clinically significant pruritus	3.30 (2.57-4.24)	<.0001

Abbreviation: CI, confidence interval.

female and white, had more cirrhosis (59.4% vs. 50.7%), higher BMI (35.8 ± 6.6 vs. 33.1 ± 6.6), and significantly more comorbidities of all types (with the exception of only diabetes) (all $P < 0.05$) (Supporting Table S1). Consistent with the higher rate of cirrhosis, those patients also had higher NIT fibrosis scores, greater liver stiffness by imaging, lower serum albumin, and higher α-SMA percentage ($P < 0.05$) (Supporting Table S1).

In multivariate analysis, independent predictors of having both pruritus and fatigue included female gender (OR = 1.58 [1.15-2.16], $P = 0.0043$), higher BMI (OR = 1.034 [1.012-1.057] per kg/m^2, $P = 0.0021$), history of depression (OR = 2.04 [1.52-2.75], $P < 0.0001$), clinically overt fatigue (1.92 [1.30-2.83], $P = 0.0011$), nervous system disorders (1.47 [1.10-1.97], $P = 0.0104$), and lower serum albumin (0.52 [0.33-0.81] per g/dL, $P = 0.0037$). It is important to note that these predictors are similar to those of having either of these conditions.

IMPACT OF PRURITUS AND FATIGUE ON OTHER PROS

Patients with NASH with advanced fibrosis who reported clinically significant pruritus also had significant impairment in all concurrently measured PROs (Table 4). The greatest impairments were observed in Role Physical of the SF-36 as well as Abdominal Symptoms and Fatigue of the CLDQ-NASH (mean up to −19.5% of a PRO range size; all $P < 0.01$). Furthermore, correlations of the CLDQ-NASH pruritus score with other PRO scores were all statistically significant with Spearman correlation (all $P < 0.001$). The strongest correlation with pruritus among the scales of the SF-36 was with Vitality ($r_s = 0.34$) and the Systemic domain among the domains of the CLDQ-NASH ($r_s = 0.61$).

Similarly, patients with clinically significant fatigue had significant impairment in all the measured PROs. The greatest impairments were observed in Vitality of the SF-36 and Systemic and Fatigue among the CLDQ-NASH (mean impairment up to −31.4% of a PRO range size) (Table 4). The correlations among those with fatigue and the measured PROs were noticeably stronger than for pruritus, especially for the Vitality scale of the SF-36 ($r_s = 0.75$) and the Emotional domain score ($r_s = 0.74$) and total score of the CLDQ-NASH ($r_s = 0.86$).

Finally, in patients who had both fatigue and pruritus, PRO scores were the most profoundly impaired; the mean impairment in comparison to patients who had neither fatigue nor pruritus was between −5% and −37.5% of a PRO range size (Fig. 1).

CHANGES IN PRURITUS AND FATIGUE DURING FOLLOW-UP

Postbaseline data were available in 331 placebo-treated patients, including 86 patients (26%) with clinically significant pruritus and 103 patients (31%) with fatigue at baseline. In patients with baseline pruritus, mean pruritus scores increased (indicative of improvement) such that, by week 48 of placebo treatment, only 38 (44%) still had clinically significant pruritus (Fig. 2A). However, only 32 patients (13%) without clinically significant pruritus at baseline developed it by week 48. Multivariate analysis showed that greater spontaneous improvement in pruritus in patients with clinically significant

TABLE 3. BASELINE CLINICO-DEMOGRAPHIC PARAMETERS OF PATIENTS WITH NASH WITH ADVANCED FIBROSIS BY THE PRESENCE OF CLINICALLY SIGNIFICANT FATIGUE

	Clinically Significant Fatigue (Score ≤ 4)	No Clinically Significant Fatigue	*P*
N	549	1,121	
Age, years	56.2 ± 8.9	58.7 ± 8.6	<0.0001
Male gender	167 (30.4%)	507 (45.2%)	<0.0001
White race	459 (83.6%)	768 (68.5%)	<0.0001
Black race	12 (2.2%)	13 (1.2%)	0.10
Asian race	63 (11.5%)	314 (28.0%)	<0.0001
Current smoker	69 (12.6%)	97 (8.7%)	0.0122
Employed	232 (42.3%)	582 (52.1%)	0.0002
Enrolled in the United States	357 (65.0%)	571 (50.9%)	<0.0001
Cirrhosis	319 (58.1%)	550 (49.1%)	0.0005
BMI, kg/m^2	35.3 ± 6.8	32.6 ± 6.3	<0.0001
Comorbidities from medical history (MedDRA):			
Diabetes mellitus	428 (78.0%)	803 (71.6%)	0.0058
Anxiety	171 (31.1%)	165 (14.7%)	<0.0001
Blood and lymphatic system disorders	143 (26.0%)	219 (19.5%)	0.0024
Depression	233 (42.4%)	199 (17.8%)	<0.0001
Clinically overt fatigue	93 (16.9%)	80 (7.1%)	<0.0001
Gastrointestinal disorders	442 (80.5%)	747 (66.6%)	<0.0001
Immune system disorders	272 (49.5%)	413 (36.8%)	<0.0001
Infections or infestations	227 (41.3%)	399 (35.6%)	0.0225
Sleep disorders	128 (23.3%)	143 (12.8%)	<0.0001
Musculo-skeletal disorders	369 (67.2%)	618 (55.1%)	<0.0001
Nervous system disorders	292 (53.2%)	384 (34.3%)	<0.0001
Respiratory disorders	262 (47.7%)	392 (35.0%)	<0.0001
Skin disorders	175 (31.9%)	322 (28.7%)	0.19
Vascular disorders	397 (72.3%)	789 (70.4%)	0.41
Eye disorders	129 (23.5%)	280 (25.0%)	0.51
Clinically significant itch (score ≤ 4)	249 (45.4%)	198 (17.7%)	<0.0001
Laboratory parameters and derived scores:			
ALT, U/L	55.9 ± 37.7	57.2 ± 35.2	0.06
AST, U/L	54.2 ± 35.3	51.9 ± 27.2	0.73
Platelets, $\times 10^9$/L	188.9 ± 70.2	188.0 ± 65.1	0.84
Hemoglobin, g/dL	13.7 ± 1.5	14.1 ± 1.5	<0.0001
Albumin, g/dL	4.36 ± 0.35	4.50 ± 0.32	<0.0001
ALP, U/L	98.5 ± 36.5	90.2 ± 33.9	<0.0001
Bilirubin, mg/dL	0.635 ± 0.361	0.697 ± 0.369	<0.0001
Direct bilirubin, mg/dL	0.185 ± 0.105	0.190 ± 0.090	0.0196
Bile acids, umol/L	14.5 ± 15.8	11.5 ± 12.9	0.0001
Fasting glucose, mg/dL	136.4 ± 51.2	126.0 ± 38.9	0.0003
Fasting HOMA-IR score	12.8 ± 21.9	8.45 ± 14.34	<0.0001
HbA1c, %	6.82 ± 1.25	6.51 ± 1.15	<0.0001
CRP, mg/dL	0.675 ± 0.812	0.450 ± 0.658	<0.0001
GGT, U/L	112.8 ± 131.2	108.7 ± 136.7	0.0149
Alpha-2 macroglobulin, mg/dL	264.4 ± 76.0	279.6 ± 82.2	0.0002
Apolipoprotein A1, mg/dL	139.3 ± 25.3	143.9 ± 26.1	0.0003
Apolipoprotein B, mg/dL	92.7 ± 28.4	88.0 ± 23.4	0.0098
Haptoglobin, mg/dL	129.0 ± 67.0	116.1 ± 63.6	0.0001
Hyaluronic acid, ng/mL	181.5 ± 217.9	156.4 ± 210.4	0.0449

TABLE 3. *Continued*

	Clinically Significant Fatigue (Score ≤ 4)	No Clinically Significant Fatigue	*P*
PIIINP, ng/mL	14.5 ± 7.3	13.0 ± 6.1	<0.0001
TIMP-1, ng/mL	327.1 ± 111.5	294.1 ± 85.3	<0.0001
APRI score	0.961 ± 0.801	0.896 ± 0.643	0.25
FIB-4 score	2.60 ± 1.83	2.49 ± 1.48	0.96
FibroTest score	0.474 ± 0.234	0.528 ± 0.232	<0.0001
ELF score	10.5 ± 1.1	10.3 ± 1.0	0.0007
MELD score	7.10 ± 1.72	7.10 ± 1.59	0.38
NFS	0.464 ± 1.488	0.132 ± 1.319	<0.0001
Liver imaging:			
Liver stiffness by transient elastography, kPa	21.7 ± 14.6	18.5 ± 11.2	0.0008
Controlled attenuation parameter, dB/m	326.9 ± 57.0	317.8 ± 52.9	0.0029
Liver histology:			
NAFLD activity: steatosis grade 1	521 (94.9%)	1056 (94.2%)	0.56
NAFLD activity: steatosis grade 2	27 (4.9%)	64 (5.7%)	0.50
NAFLD activity: lobular inflammation grade 1	46 (8.4%)	103 (9.2%)	0.59
NAFLD activity: lobular inflammation grade 2	208 (37.9%)	428 (38.2%)	0.91
NAFLD activity: lobular inflammation grade 3	295 (53.7%)	590 (52.6%)	0.67
NAFLD activity: hepatocyte ballooning grade 1	93 (16.9%)	226 (20.2%)	0.12
NAFLD activity: hepatocyte ballooning grade 2	455 (82.9%)	894 (79.8%)	0.13
Total NAS	5.33 ± 0.90	5.29 ± 0.92	0.32
Hepatic collagen content, %	9.03 ± 7.03	7.94 ± 5.72	0.0373
α-SMA, %	11.8 ± 9.1	10.2 ± 7.6	0.0081
Morphometric fat content, %	11.6 ± 6.6	11.1 ± 6.5	0.19

Abbreviations: ALT, alanine aminotransferase; PIIINP, procollagen III amino terminal propeptide.

pruritus at baseline, after adjustment for the baseline value, was independently associated with white race (β = +1.09 ± 0.41; P = 0.0094), lower baseline serum ALP (–0.017 ± 0.005 per U/L; P = 0.0017), and lack of immune system disorders (–1.34 ± 0.35; P = 0.0002).

Similar trends were observed regarding temporal changes in fatigue scores. Specifically, by week 48 of treatment with placebo, only 57 patients (55%) with fatigue at baseline still had clinically significant fatigue, whereas 31 patients (14%) without clinically significant fatigue at baseline developed it later (Fig. 2B). In multivariate analysis, the only independent predictor of spontaneous improvement in fatigue among patients with clinically significant fatigue at baseline was the absence of current smoking (β = –0.61 ± 0.30; P = 0.047).

Discussion

In this study, we assessed the prevalence, predictors, and impact of clinically significant fatigue and pruritus among patients with advanced fibrosis due to NASH who participated in two large phase 3 clinical trials. Because these symptoms are sometimes not recognized as common or considered as important in NASH compared with cholestatic liver disorders, the aim was to relate their presence to health-related quality of life and other PROs in patients with NASH.

Our data suggest that about one-third of patients with advanced fibrosis due to NASH enrolled in these studies may have clinically significant fatigue, as indicated by a CLDQ-NASH fatigue score at or below the middle of the range of this PRO. Patients with fatigue were more frequently younger, female, Caucasian, unemployed, and obese. As expected, fatigue was also associated with a number of comorbidities including diabetes mellitus, smoking, as well as gastrointestinal, sleep, and psychiatric disorders. In addition, fatigue was more common among patients with cirrhosis, and those with fatigue had significantly higher NITs of fibrosis including the ELF score, NFS, and liver stiffness by VCTE. Furthermore, the PROs of patients

TABLE 4. BASELINE PRO SCORES OF PATIENTS WITH NASH WITH ADVANCED FIBROSIS BY THE PRESENCE OF CLINICALLY SIGNIFICANT ITCH AND FATIGUE (ALL $P < 0.001$ BETWEEN THE GROUPS)

PRO Score	Clinically Significant Itch (Score ≤ 4)	No Clinically Significant Itch	Clinically Significant Fatigue (Score ≤ 4)	No Clinically Significant Fatigue
SF-36 (range 0-100)				
Physical Functioning	61.0 ± 26.7	75.9 ± 24.1	55.6 ± 26.5	79.9 ± 21.1
Role physical	59.9 ± 29.8	78.3 ± 26.1	52.3 ± 28.9	83.7 ± 21.4
Bodily pain	54.1 ± 25.4	71.3 ± 24.7	48.9 ± 24.4	75.4 ± 22.0
General health	44.4 ± 20.5	55.9 ± 21.0	38.8 ± 18.2	59.7 ± 19.5
Vitality	44.7 ± 22.2	59.8 ± 22.7	34.7 ± 18.3	66.1 ± 18.4
Social functioning	68.9 ± 27.1	83.9 ± 22.7	62.0 ± 26.9	88.6 ± 18.3
Role emotional	70.9 ± 29.1	85.0 ± 22.9	64.3 ± 29.9	89.4 ± 17.9
Mental health	66.0 ± 20.5	76.7 ± 18.6	61.5 ± 20.0	79.8 ± 16.4
Physical summary	42.1 ± 9.5	48.0 ± 8.9	40.0 ± 9.6	49.5 ± 7.6
Mental summary	45.4 ± 11.4	51.0 ± 9.6	42.3 ± 11.1	53.1 ± 7.9
Health utility scores (range 0-1)				
SF-6D	0.613 ± 0.120	0.706 ± 0.135	0.576 ± 0.099	0.732 ± 0.124
EQ-5D	0.759 ± 0.156	0.853 ± 0.130	0.725 ± 0.155	0.877 ± 0.106
CLDQ-NASH (range 1-7)				
Abdominal	4.52 ± 1.56	5.69 ± 1.34	4.24 ± 1.50	5.94 ± 1.13
Activity	4.66 ± 1.38	5.71 ± 1.20	4.31 ± 1.29	5.97 ± 0.95
Emotional	4.58 ± 1.26	5.59 ± 1.07	4.29 ± 1.11	5.82 ± 0.89
Fatigue	3.85 ± 1.32	4.96 ± 1.31	3.02 ± 0.79	5.47 ± 0.81
Systemic	3.89 ± 1.12	5.45 ± 1.03	3.96 ± 1.13	5.56 ± 0.95
Worry	4.43 ± 1.62	5.37 ± 1.39	4.23 ± 1.58	5.56 ± 1.27
Total CLDQ-NASH score	4.32 ± 1.13	5.46 ± 0.98	4.01 ± 0.91	5.72 ± 0.75
WPAI:SHP (range 1-0)				
Work productivity impairment	0.188 ± 0.248	0.102 ± 0.200	0.271 ± 0.280	0.059 ± 0.140
Absenteeism	0.036 ± 0.127	0.020 ± 0.104	0.062 ± 0.176	0.007 ± 0.058
Presenteeism	0.154 ± 0.201	0.082 ± 0.163	0.212 ± 0.220	0.051 ± ± 0.125
Activity impairment	0.298 ± 0.293	0.130 ± 0.219	0.341 ± 0.292	0.093 ± 0.181

with NASH with fatigue were significantly lower across all domains when compared to those without fatigue, supporting the profound impact of this symptom on health-related quality of life. Domains related to general health, vitality, and the ability to go to and perform work, as well as activities of daily living, were the domains that were most substantially affected. Multivariate analysis determined that type 2 diabetes mellitus, depression, and having a nervous system disorder were independently associated with the presence of fatigue among patients with NASH with advanced fibrosis. In contrast, younger age, male sex, Asian ethnicity, having higher platelets and serum albumin levels, and lower NITs were associated with a reduced likelihood of fatigue. Collinearity between the latter biochemical parameters and cirrhosis likely explain the lack of association between fatigue and histologic cirrhosis in this analysis.

In addition to fatigue, clinically significant pruritus was commonly observed in these patients with NASH with advanced fibrosis, affecting approximately 27% of individuals. Although fewer clinicodemographic factors were found to be associated with pruritus than observed for fatigue, the PRO scores across all measured domains were significantly lower among patients with versus without pruritus. As noted regarding fatigue, patients with depression and/or a nervous system disorder were more likely to report clinically significant pruritus. Not surprisingly, the presence of comorbid dermatologic disorders was also independently associated with pruritus. In contrast, being male and having a higher serum albumin level were associated with a lower likelihood of pruritus. An interesting observation is the lack of difference in the prevalence of pruritus between patients with bridging fibrosis and those with cirrhosis. These

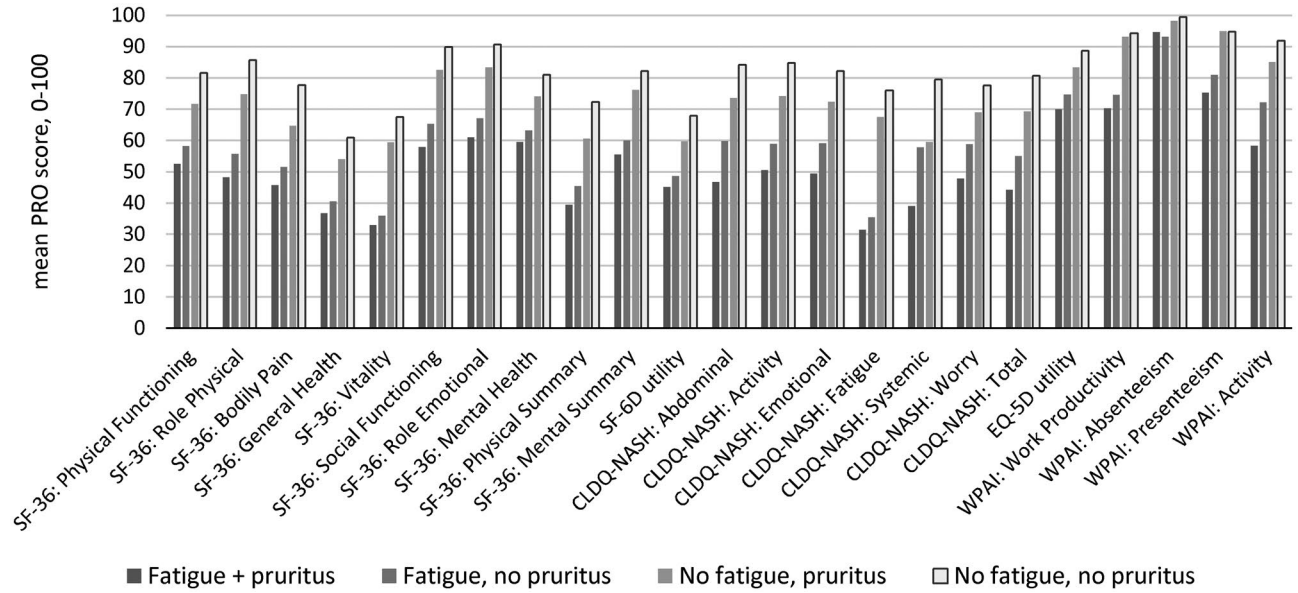

FIG. 1. Mean PRO scores (normalized to 0-100 score) in patients with NASH by the presence of clinically significant fatigue and pruritus.

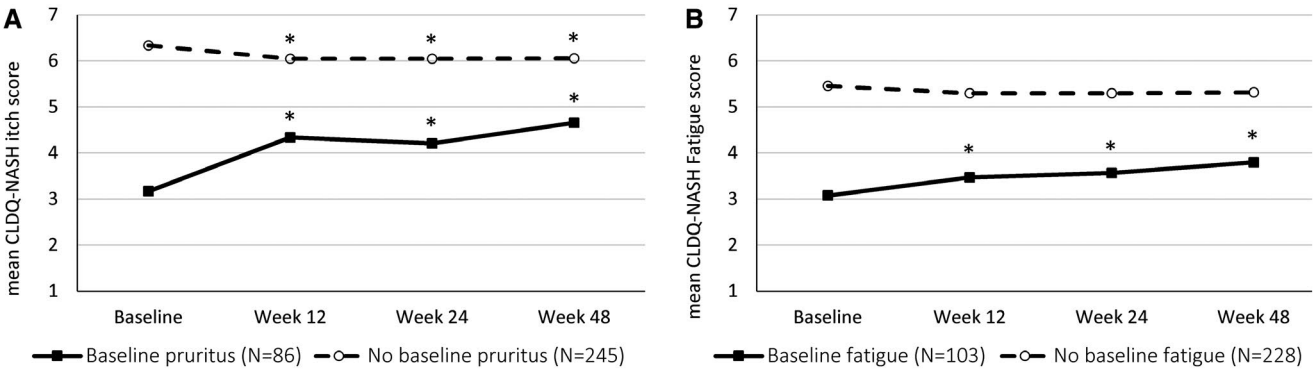

FIG. 2. Changes in pruritus (A) and fatigue (B) scores in patients with NASH treated with placebo. *$P < 0.01$ when compared with patients' own baseline score levels.

findings support the relative homogeneity of these patient populations, at least from a pruritus perspective. However, sampling error of liver biopsy may have affected these findings, because patients with pruritus had higher NITs (e.g., liver stiffness by VCTE, ELF score, NFS) than those without pruritus.

Interestingly, we also found a strong association between the presence of fatigue and pruritus in this patient population with NASH, in both univariate and multivariate analyses. Although the exact reasons are unclear, it is plausible that nocturnal pruritus can cause sleep disturbance, which contributes to fatigue. Indeed, sleep disorders were more common in patients with fatigue and pruritus versus those without these symptoms. It is also possible that both symptoms are driven, at least in part, by a common cause in patients with advanced NASH. Indeed, the pathophysiology behind these symptoms may be linked to hepatic injury and hepatic and/or chronic systemic inflammation as well as disturbed bile acid metabolism or cholestasis associated with chronic liver disease.[41,42] In fact, the analysis of bile acid composition in patients with NASH who experience pruritus will be of great interest not only for development of

potential treatment options to manage pruritus, but also to understand drug-induced pruritus that is seen among side effects of some of the drugs tested for treatment of NASH. Considering fatigue in NASH, it is possible that it is not only associated with metabolic abnormalities such as diabetes or insulin resistance, but can also be exacerbated by reduced muscle mass or performance in patients with advanced liver disease.[43] In this context, a systematic assessment for sarcopenia in NASH and its management with a targeted nutrition regimen may be required. However, fatigue in NASH may also be associated with sleep disturbances or neuropsychiatric disorders.[42-44] In light of this, a targeted treatment approach that would address the underlying fatigue drivers in patients with NASH should be considered.[44]

These findings suggest that patients with advanced NASH are not asymptomatic. Indeed, clinically significant fatigue and/or pruritus are quite common and negatively affect almost all aspects of patients' daily functioning, perception of their health, and overall wellbeing. In this context, we found that both fatigue and pruritus appear to adversely affect patients' ability to work, as only approximately 40% of patients with either of these conditions reported being employed, despite most being in the employment age range. As such, the economic burden of NASH may be greater than previously reported, especially now that the impact of NASH-related fatigue and pruritus has been quantified.[45] However, further work is necessary to better appreciate the true economic burden of NASH, especially as NAFLD and NASH are forecasted to substantially increase in the coming years due to the unmitigated increase in the rates of obesity and type 2 diabetes mellitus.[46,47]

Given these findings, the development of therapies with potential histologic and clinical benefits is paramount, as improvement in patients' PRO burden may ensue. At the same time, these trials must also account for the effect of interventions on pruritus and fatigue. In particular, because some currently investigated therapies (e.g., farnesoid X receptor agonists) may exacerbate pruritus,[48] it is critical to optimize management of treatment-emergent pruritus in these trials. In this context, our data demonstrate that a notable proportion of patients experience spontaneous improvement in both fatigue and pruritus after placebo treatment. This is not unexpected, given both regression to the mean and the placebo effect, which has been reported to be as high as 72% in some studies.[49] Owing to the limited sample size in the current study, we were unable to quantify the contribution of spontaneous improvement in laboratory or histologic parameters to the improvements in pruritus or fatigue that we observed.

This study has several limitations. First, the patients included in this study were enrolled in clinical trials with highly specific enrollment criteria; hence, the generalizability of our findings to patients enrolled in real-world settings and across a wider spectrum of NAFLD severity are unclear. In fact, data from a registry suggest that the prevalence of fatigue may be even higher in the real-world setting.[50] Second, the results may have been affected by the subjectivity of PROs and recall bias, as subjects were asked to think back over a certain time period in completing the PRO assessments. Third, the severity of pruritus was not assessed with an instrument that has been validated for this purpose. Therefore, the absence of an association between pruritus and histologic parameters should be interpreted with caution. Similarly, the definitions of clinically significant fatigue and pruritus used in this study, based on the midrange of the respective scales, were somewhat arbitrary. Nevertheless, the correlations of both continuous scores with other PROs were highly significant across the range evaluated, suggesting the presence of monotonous trends. Moreover, all PRO tools used in this study are valid and reliable and have been used extensively in PRO research, so that any bias introduced should be consistent over time.

In summary, the STELLAR trials demonstrate that among patients with advanced fibrosis due to NASH, up to 30% experience significant pruritus or fatigue. These symptoms are associated with extraordinarily low PRO scores across all measured domains. This still largely underappreciated symptom burden suggests that NASH is not an asymptomatic disease; indeed, symptoms such as fatigue and pruritus worsen patients' experience with their disease. These data emphasize the need for continued evaluation of novel therapies for NASH that may lead to improved patient-relevant outcomes including PROs.

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