Clinical and Patient-Reported Outcomes From Patients With Nonalcoholic Fatty Liver Disease Across the World: Data From the Global Non-Alcoholic Steatohepatitis (NASH)/ Non-Alcoholic Fatty Liver Disease (NAFLD) Registry

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BACKGROUND & AIMS: Globally, nonalcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease. We assessed the clinical presentation and patient-reported outcomes (PROs) among NAFLD patients from different countries. **METHODS**: Clinical, laboratory, and PRO data (Chronic Liver Disease Questionnaire–nonalcoholic steatohepatitis [NASH], Functional Assessment of Chronic Illness Therapy–Fatigue, and the Work Productivity and Activity Index) were collected from NAFLD patients seen in real-world practices and enrolled in the Global NAFLD/NASH Registry encompassing 18 countries in 6 global burden of disease super-regions. **RESULTS**: Across the global burden of disease super-regions, NAFLD patients (n [5691) were oldest in Latin America and Eastern Europe and youngest in South Asia. Most men were enrolled at the Southeast and South Asia sites. Latin America and South Asia had the highest employment rates (>60%). Rates of cirrhosis varied (12%–21%), and were highest in North Africa/Middle East and Eastern Europe. Rates of metabolic syndrome components varied: 20% to 25% in South Asia and 60% to 80% in Eastern Europe. Chronic Liver Disease Questionnaire–NASH and Functional Assessment of Chronic Illness Therapy–Fatigue PRO scores were lower in NAFLD patients than general population norms (all $P < .001$). Across the super-regions, the lowest PRO scores were seen in Eastern Europe and North Africa/Middle East. In multivariate analysis adjusted for enrollment region, independent predictors of lower PRO scores included younger age, women, and nonhepatic comorbidities including fatigue ($P < .01$). Patients whose fatigue scores improved over time experienced a substantial PRO improvement. Nearly 8% of Global NAFLD/ NASH Registry patients had a lean body mass index, with fewer metabolic syndrome components, fewer comorbidities, less cirrhosis, and significantly better PRO scores ($P < .01$). **CONCLUSIONS**: NAFLD patients seen in real-world practices in different countries experience a high comorbidity burden and impaired quality of life. Future research using global data will enable more precise management and treatment strategies for these patients.

Nonalcoholic fatty liver disease (NAFLD) is rapidly becoming the most prevalent liver disease worldwide.1–3 In this context, NAFLD is the second most common indication for liver transplantation in the United States4 and one of the main causes of liver cancer.5–10 Data from the Global Burden of Disease (GBD) study suggest that the burden of NAFLD measured by incidence, associated mortality, and disability-adjusted lifeyears is high and rapidly increasing.11,12 Previous reports have shown that there may be country-specific differences in the diagnosis, interventions and management of NAFLD patients.1–3 This study aims to assess and compare clinical presentation and patient-reported outcomes (PROs) of NAFLD patients enrolled in the Global NAFLD/Nonalcoholic Steatohepatitis (NASH) Registry (GNR).

Methods

Study Population

In 2017, the GNR was created as a collaborative effort among investigators from more than 20 countries who were involved in the Global NASH Council. Each investigator who was willing to

establish a GNR site within their country obtained an approval to enroll and obtain patient consent from their local Institutional Review Board or a similar supervisory institution. Per GNR protocol, patients seen in participating sites with an established diagnosis of NAFLD by a historic liver biopsy or imaging (ultrasound, computed tomography, or magnetic resonance imaging) in the absence of other chronic liver diseases and excessive alcohol use were eligible for enrollment into the GNR. Both non-NASH and NASH patients were eligible. Patients younger than age 18, patients with other causes of chronic liver disease (viral hepatitis, excessive alcohol use defined as >14 drinks/ wk, autoimmune liver disease, decompensated cirrhosis, hepatocellular carcinoma and other liver malignancies, post–liver transplant), pregnancy, and unwilling or unable to provide informed consent were excluded.

Data Collection and Definitions

The data collection form was approved by the Institutional Review Board and included patients' demographics (age, sex, race, site of enrollment), most recent height and weight, relevant elements of past medical history, personal habits, results of diagnostic tests (liver imaging, biopsy), and recent laboratory test results (liver enzyme levels, platelet count). The majority of patients also completed PRO questionnaires about their current health-related quality of life and other aspects of daily functioning. An annual follow-up evaluation was recommended for all enrollees, and PRO scores were to be collected with each follow-up record. The clinical data collection forms were completed in English by trained personnel at each site. For the purpose of this study, obesity was defined as a body mass index (BMI) greater than 30 kg/m2 , or greater than 27.5 kg/m2 for participants of East Asian origin. Similarly, participants with a BMI less than 25 or 23.5 kg/m2 , respectively, were presumed lean. Cirrhosis was defined as a biopsy-based diagnosis or as liver stiffness by a transient elastography of 12 kPa or greater; an alternative cut-off value of 13.6 kPa was applied in a round of sensitivity analysis.13,14 In addition, Fibrosis-4 (FIB-4) noninvasive test scores were calculated using patients' age, alanine aminotransferase level, aspartate aminotransferase level, and platelet count.

Patient-Reported Outcomes

In this study, we used the following widely used and extensively validated PRO instruments or questionnaires: Chronic Liver Disease Questionnaire-NASH (CLDQ-NASH), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and the Work Productivity and Activity Index (WPAI) Specific Health Problem. The instruments were self-administered by patients in their native language using validated translations. The CLDQ-NASH is a validated disease-specific instrument that includes 36 items and 6 domains. 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.16,17 The FACIT-F is used as a fatigue-specific instrument with 4 core domains and a Fatigue scale. All domains add up to the total FACIT-F score (range, 0–160, a higher score represents better health).18 The WPAI Specific Health Problem questionnaire assesses impairment in work productivity resulting from both absenteeism (missed hours of work because of the health problem) and presenteeism (self-reported impaired productivity while working) in employed patients, and in activities other than work in all patients. Unlike other PRO instruments, higher WPAI scores that range from 0 to 1 correspond to greater impairment in work productivity and activity.19

Statistical Analysis

For geography-based comparisons, included sites were grouped using GBD super-regions.20 Of a total of 7 GBD super-regions, only 1 was not represented in GNR (sub-Saharan Africa). The remaining super regions are high income; Central Europe, Eastern Europe, and Central Asia; Latin America and the Caribbean; Middle East and North Africa (MENA); South Asia; and Southeast Asia, East Asia, and Oceania. All collected demographic and clinical parameters as well as PRO scores were summarized as means SD, or frequency (percentage), and were compared between the super-regions and other comparison groups using the Wilcoxon rank-sum nonparametric test (continuous parameters) or the Pearson chisquare test (categoric parameters). In a subgroup of patients who had both baseline and 1-year follow-up PRO scores, the decrements/improvements in the scores from patients' own baseline levels also were calculated. Independent predictors of summary PRO scores were assessed using generalized linear regression; independent predictors of binary outcomes were assessed using logistic regression. All analyses were run in SAS 9.4 (SAS Institute, Cary, NC). The study was approved by the Western Institutional Review Board and by Institutional Review Boards or similar supervisory institutions from each participating site. All patients provided informed consent before being enrolled in the registry.

Results

A total of 5691 NAFLD patients from GNR were included in this analysis. Subjects were enrolled from 23 sites located in 18 countries (Australia, China, Cuba, Egypt, Greece, Hong Kong, India, Italy, Japan, Saudi Arabia, Malaysia, Mexico, Pakistan, Russia, Spain, Taiwan, Turkey, and the United States). According to GBD superregions, 50% were enrolled at sites located in the highincome region, 22% in MENA, 14% in Southeast and East Asia, 7% in Latin America and the Caribbean, 4% from Eastern and Central Europe, and 3% from South Asia.

Clinical Data of Patients With Nonalcoholic Fatty Liver Disease

Patients were, on average, 51 years of age, 46% men, 47% employed, 68% obese and 8% lean, 15% had cirrhosis, 40% had type 2 diabetes, 51% had hypertension, and 50% had hyperlipidemia.

Across the GBD super-regions, NAFLD patients from GNR were the oldest in Latin America and Eastern Europe, and the youngest in South Asia (Table 1). The rates of cirrhosis varied between 12% and 21%, with the highest rates seen in MENA and Eastern Europe. The rates of metabolic syndrome components varied even more substantially: from 20% to 25% in South Asia to 60% to 80% in Eastern Europe (Table 1). The rates of other comorbidities also varied across GBD superregions (Table 1). Fifteen percent of NAFLD patients enrolled in GNR had cirrhosis defined using either liver biopsy or transient elastography with a cut-off of 12 kPa (n ¼ 565). In comparison with noncirrhotic patients, patients with cirrhosis were older (mean age, 56 vs 50 y), equally likely to be man or woman, more commonly from the MENA region, less commonly employed (34% vs 50%), had more obesity (76% vs 68%), diabetes (69% vs 37%), hypertension (60% vs 48%), clinically overt fatigue (45% vs 38%), and abdominal pain (20% vs 16%) (all $P < .05$), and a higher FIB-4 score (mean, 2.48 vs 1.11; $P < .0001$). In an alternative scenario of a cut-off of 13.6 kPa used

for the diagnosis of cirrhosis, the prevalence was 13% (n ¼ 484) while the trends in clinical parameters remained the same (data not shown).

Patient-Reported Outcomes in Patients With Nonalcoholic Fatty Liver Disease

Approximately half of GNR patients had their PRO data collected at the time of enrollment. In comparison with general population norms,16–18 all CLDQ-NASH domain scores were significantly lower in GNR patients along with Emotional Well-Being, Fatigue Scale, and total FACIT-F scores (all P < .001). Consistent with the varying rates of comorbidities across GBD super-regions, the lowest PRO scores across multiple domains were seen in GNR enrollees from Eastern Europe and MENA regions (Table 2). Interestingly, however, the lowest mean total CLDQ-NASH score was seen in Latin America, driven by the lowest Worry domain score, which was not correlated with the rate of any comorbidity including psychiatric or with severity of liver disease (Table 2). Furthermore, the lowest fatigue scores (more severe fatigue) were seen in GNR patients from Eastern Europe, consistent between the Fatigue domain of CLDQ-NASH and the Fatigue Scale of FACIT-F (Table 2). Finally, the greatest impairment in work productivity and daily activities was seen in participants from Latin America and the Caribbean (Table 2). Patients with cirrhosis had more PRO impairment in comparison with patients without cirrhosis (P < .05 for 4 of 6 CLDQNASH domains, and 3 of 5 FACIT-F domains by either definition of cirrhosis) (Figure 1A). In multivariate analysis, being enrolled from the MENA region was found to be predictive of lower scores in both CLDQ-NASH and FACIT-F assessments of healthrelated quality of life as well as higher impairment in work productivity (P < .05) (Table 3). Other predictors of greater PRO impairment included younger age, women, and select comorbidities, with the strongest effect seen for anxiety, depression, clinically overt fatigue, abdominal pain, and sleep apnea (Table 3). In addition, patients who reported regular exercise of more than 30 minutes 3 or more times per week had higher PRO scores by CLDQ-NASH and FACIT-F (P < .05) (Table 3).

Fatigue in Nonalcoholic Fatty Liver Disease

Because fatigue is one of the main drivers of PRO impairment in NAFLD, we sought to compare NAFLD subjects from GNR with and without significant fatigue. Using the definition based on the CLDQ-NASH Fatigue domain (score of < .05) (Table 4). They also were noted to be less active with their weekly exercise (Table 4). Expectedly, all PRO scores were significantly worse in NAFLD patients with fatigue (all P < .001) (Table 4). Because patients with fatigue had more nonhepatic comorbidities, which could have confounded observed trends in PRO scores, we compared patients with and without fatigue in a subgroup of NAFLD patients without a history of cardiovascular comorbidities, cancer, cirrhosis, and current smoking. As shown in Supplementary Table 1, PRO scores of those NAFLD patients with fatigue who did not have listed comorbidities remained significantly lower (all P < .001). Comparison of PRO scores between NAFLD patients with and without fatigue stratified by sex showed that fatigue-associated impairment in PRO scores was similar between males and females (Supplementary Table 2). Finally, multivariate analysis showed that enrollment from the MENA region, women, and a history of depression were associated independently with fatigue among NAFLD (P < .05) (Supplementary Table 3).

Changes of Patient-Reported Outcomes Over Time

A subgroup of patients (n ¼ 777) had their PRO scores collected at baseline and at the 1-year follow-up evaluation. Using these data, we assessed changes in fatigue and other PRO scores over time in GNR participants. A change of 0.5 or more in the CLDQ-NASH Fatigue domain score from patient's own baseline level in either direction was considered clinically significant. As a result, 50% of patients' fatigue improved, 29% did not change, and 21% worsened. Patients with fatigue improvement were younger (mean age, 50 vs 55 y in the unchanged group and 53 y in the worsened group; P < .0001) and predominantly enrolled from the MENA region. No difference in fatigue trends was noted between sexes and patients with and without baseline comorbidities (P > .05) other than the history of clinically overt fatigue (58% in fatigue improved vs 30% in fatigue unchanged vs 36% in fatigue worsened groups; P < .0001) and baseline obesity (68% vs 60% vs 60%, respectively; P ¼ .04). Baseline PRO scores also were initially lower in patients with improved fatigue levels: total CLDQ-NASH, 4.76 1.14 vs 5.39 1.12 vs 5.44 1.09, respectively (P < .0001 for all domains); total FACIT-F, 109.8 26.3 vs 116.7 24.9 vs 119.1 26.5, respectively (P < .0001 for 3 of 5 domains); work productivity impairment, 0.182 0.279 vs 0.116 0.211 vs 0.085 0.215, respectively (P ¼ .007). In multivariate analysis, improvement of fatigue was found to be associated only with lower baseline fatigue scores and being enrolled from Turkey (odds ratio [OR], 2.8; 95% CI, 2.0–3.9; P < .01). However, worsening of fatigue was found to be associated with a higher baseline fatigue score, women (OR, 1.8; 95% CI, 1.1–2.9), history of depression (OR, 2.5; 95% CI, 1.3–5.0), congestive heart failure (OR, 9.4; 95% CI, 2.2–40.5), and an increase in BMI (OR, 1.17; 95% CI, 1.04–1.31) per an increase of 1 kg/m2 from baseline (all P < .05). Patients with improved fatigue scores experienced substantial improvement in all other PRO scores (P < .0001 for all CLDQ-NASH domains and 4 of 5 FACIT-F domains; and P < .05 for work productivity and activity of WPAI) (Figure 2). In particular, improvement of fatigue was found to be associated with a substantial improvement in work productivity: mean change, -0.059 (SE, 0.024; P ¼ .02).

Clinical Presentation and Patient-Reported Outcomes in Lean Nonalcoholic Fatty Liver Disease Patients

A small proportion of enrolled NAFLD patients had a normal BMI (lean NAFLD). That rate was 7.6% in the entire GNR and varied from 0% in Eastern Europe to 34% in South Asia (Table 1, Supplementary Table 4). In multivariate logistic regression analysis, having lean NAFLD (as opposed to overweight/obese) was found to be associated with older age (OR, 1.023; 95% CI: 1.011–1.035 per year), enrollment outside of the MENA region (OR, 0.43; 95% CI: 0.30–0.61), being enrolled from Southeast or East (OR, 1.88; 95% CI: 1.32–2.68) or South (OR, 6.53; 95% CI: 4.30–9.93) Asia sites (reference: high-income countries), absence of type 2 diabetes (OR, 0.65; 95% CI: 0.48–0.86) and hypertension (OR, 0.47; 95% CI: 0.35–0.62), and engaging in regular exercise (OR, 1.62; 95% CI: 1.24–2.12) (all P < .01). Lean NAFLD had higher PRO scores than overweight/obese. This was true for PROs captured by all domains of CLDQ-NASH and FACIT-F (all P < .01) (Figure 2B).

Discussion

This study, using data from a global NAFLD/NASH registry, provides a unique perspective about patients with NAFLD across different regions of the world. First, the data confirm that the majority of patients with NAFLD, regardless of their location, are obese and have multiple components of metabolic syndrome. This is consistent with reports from the GBD study that

suggest that the global epidemic of NAFLD is driven primarily by increasing rates of obesity and type 2 diabetes.10,11 Interestingly, 34% of NAFLD patients had FIB-4 scores greater than 1.3, and another 36% had liver stiffness greater than 8 kPa, putting 2 of every 3 patients at high risk for developing advanced fibrosis. In addition, we found that NAFLD patients in this registry had increased rates of cardiovascular comorbidities as well as sleep apnea and psychiatric disorders such as depression and anxiety. Notably, clinically overt fatigue was very common among NAFLD patients, emphasizing the fact that NAFLD is really not an asymptomatic disease.21 Furthermore, only 15% to 40% of NAFLD patients exercise regularly, confirming the strong association of NAFLD with a sedentary lifestyle.22,23 Our data also suggest that 12% to 20% of NAFLD patients had cirrhosis, which is consistent with prior estimates.2,3 Altogether, our findings confirm a substantial disease burden for NAFLD. In addition to the adverse clinical outcomes, our data clearly show a significant PRO burden of NAFLD, as confirmed by both the disease-specific CLDQ-NASH and the generic FACIT-F. Furthermore, there was also a significant work productivity impairment as seen by presenteeism and absenteeism scores of WPAI. Therefore, in addition to the direct costs of NAFLD related to the risk of developing advanced liver disease, the economic impact resulting from lower work productivity can be substantial to the society.24 Because fatigue is an important driver of PRO impairment in NAFLD, we evaluated the portrait of fatigue among GNR enrollees. As a result, we have shown that NAFLD patients with fatigue have significantly more impairment of health-related quality of life. In addition, NAFLD patients with fatigue experience significantly greater impairment of work productivity. After controlling for confounders, worse fatigue scores were associated independently with psychiatric and some other nonliver comorbidities. Given that, it is important to include specific interventions that would target these potential drivers of fatigue among patients with NAFLD, while treatments that target NASH resolution or fibrosis improvement must be coupled with those that improve clinical and psychiatric comorbidities commonly seen in NAFLD. Our data also provide some insight about changes of PROs over time. Indeed, as shown, approximately half of NAFLD patients had an unchanged or worsened fatigue score from baseline after the 1-year follow-up evaluation. In fact, having a lower baseline fatigue score was found to be the only predictor of future fatigue improvement, suggesting some regression to the mean. Despite this, fatigue worsening was found to be predicted by women, history of depression, and an increase in BMI. Some of these factors also can be targets for future interventions. It also is important to note that patients who had their fatigue improved also experienced a substantial improvement in work productivity, while the opposite was observed in patients with fatigue worsening. This suggests that fatigue in NAFLD has important potential economic implications and deserves a closer look in future studies. Finally, our data provide a unique opportunity to compare lean NAFLD with the rest of NAFLD patients who are commonly overweight or obese. Overall, roughly 8% of subjects with NAFLD enrolled in this registry were considered lean. The majority of lean NAFLD patients were enrolled from South Asia or Southeast or East Asian countries. Interestingly, patients with lean NAFLD reported lower rates of metabolic complications, although large proportions of those lean patients still were diabetic (28%), hypertensive (35%), and/or hyperlipidemic (40%). This indicates that even in lean NAFLD patients metabolic abnormalities are quite common. Indeed, only 25% of lean NAFLD patients did not report any metabolic abnormality. This is consistent with data published from population-based data sets.25,26 However, lean NAFLD patients still had lower rates of cirrhosis and also fewer nonliver comorbidities, which resulted in superior PRO scores. However, it is important to note that BMI may be an imperfect surrogate of body fat percentage. There were limitations to this study. Although this was a multicenter multinational study, some regions had only a few sites with limited diversity of patients and/or selection bias because of principal investigators at most sites being physician–scientists. Liver biopsy data were not universally available and laboratory data were

collected from the local laboratories rather than centrally. Furthermore, potentially relevant sociodemographic and clinical data such as education, income, or more extensive medical history for GNR participants as well as country-specific general population norms for PRO scores were not available. In summary, patients with NAFLD seen in real-world practices in different countries experience high comorbidity burden and impairment of health-related quality of life and other PROs. Clinical presentation and the magnitude of PRO impairment in patients with NAFLD varies between regions of the world and also between clinical subgroups. Despite a strong association with obesity, some patients with NAFLD can be lean. Further research is needed to understand the underlying mechanisms of metabolic abnormalities in patients with hepatic steatosis diagnosed as NAFLD and to develop management and treatment strategies.

References

1. Younossi ZM, Stepanova M, Younossi Y, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. Gut 2020;69:564–568.

2. Younossi ZM, Koenig AB, Abdelatif D, et al. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84.

3. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20.

4. Younossi ZM, Stepanova M, Ong J, et al. Nonalcoholic steatohepatitis is the most rapidly increasing indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2021;19:580–589.e5.

5. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730.

6. Hester D, Golabi P, Paik J, et al. Among Medicare patients with hepatocellular carcinoma, non-alcoholic fatty liver disease is the most common etiology and cause of mortality. J Clin Gastroenterol 2020;54:459–467.

7. Golabi P, Rhea L, Henry L, et al. Hepatocellular carcinoma and non-alcoholic fatty liver disease. Hepatol Int 2019;13:688–694.

8. Paik JM, Golabi P, Biswas R, et al. Nonalcoholic fatty liver disease and alcoholic liver disease are major drivers of liver mortality in the United States. Hepatol Commun 2020;4:890–903.

9. Kim D, Li AA, Perumpail BJ, et al. Changing trends in etiologybased and ethnicity-based annual mortality rates of cirrhosis and hepatocellular carcinoma in the United States. Hepatology 2019;69:1064–1074.

10. Paik JM, Golabi P, Younossi Y, et al. Changes in the global burden of chronic liver diseases from 2012 to 2017: the growing impact of NAFLD. Hepatology 2020;72:1605–1616.

11. Paik JM, Golabi P, Younossi Y, et al. The growing burden of disability related to nonalcoholic fatty liver disease: data from the global burden of disease 2007-2017. Hepatol Commun 2020;4:1769–1780.

12. Arshad T, Paik JM, Biswas R, et al. Nonalcoholic fatty liver disease prevalence trends among adolescents and young adults in the United States, 2007-2016. Hepatology Commun 2021;5:1676–1688.

13. Legros L, Bardou-Jacquet E, Turlin B, et al. Transient elastography accurately screens for compensated advanced chronic liver disease in patients with ongoing or recent alcohol withdrawal. Clin Gastroenterol Hepatol 2021. Epub ahead of print.

14. Eddowes PJ, Sasso M, Allison M, et al. Accuracy of FibroScan controlled attenuation parameter and liver stiffness measurement in assessing steatosis and fibrosis in patients with nonalcoholic fatty liver disease. Gastroenterology 2019;156:1717–1730.

15. Younossi ZM, Loomba R, Anstee QM, et al. Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. Hepatology 2018;68:349–360.

16. Younossi ZM, Stepanova M, Younossi I, et al. Validation of chronic liver disease questionnaire for nonalcoholic steatohepatitis in patients with biopsy-proven nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2019;17:2093–2100.e3.

17. Younossi ZM, Stepanova M, Henry L, et al. A disease-specific quality of life instrument for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: CLDQ-NAFLD. Liver Int 2017; 37:1209–1218.

18. Webster K, Cella D, Yost K. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: properties, applications, and interpretation. Health Qual Life Outcomes 2003;1:79.

19. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4:353–365.

20. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level: results from the Global Burden of Disease Study 2015. JAMA Oncol 2017;3:1683–1691.

21. Gerber LH, Weinstein AA, Mehta R, et al. Importance of fatigue and its measurement in chronic liver disease. World J Gastroenterol 2019;25:3669–3683.

22. Weinstein AA, Escheik C, Oe B, et al. Perception of effort during activity in patients with chronic hepatitis C and nonalcoholic fatty liver disease. PM R 2016;8:28–34.

23. Gerber L, Otgonsuren M, Mishra A, et al. Non-alcoholic fatty liver disease (NAFLD) is associated with low level of physical activity: a population-based study. Aliment Pharmacol Ther 2012;36:772–781.

24. Younossi ZM, Blissett D, Blissett R, et al. The economic and clinical burden of nonalcoholic fatty liver disease in the United States and Europe. Hepatology 2016;64:1577– 1586.

25. Golabi P, Paik J, Fukui N, et al. Patients with lean nonalcoholic fatty liver disease are metabolically abnormal and have a higher risk for mortality. Clin Diabetes 2019; 37:65–72.

26. Ye Q, Zou B, Yeo YH, et al. Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2020;5:739–752.

Table 1. Clinicodemographic Parameters of GNR Participants

	Eastern Europe	High-income countries	Latin America and Caribbean	North Africa and Middle East	Southeast and East Asia	South Asia	All GNR enrollees
N	242	2826	419	1258	776	170	5691
Age, *y*	54.4 ± 11.1	50.9 ± 13.5	54.5 ± 11.5	49.0 ± 11.3	52.5 ± 14.1	44.2 ± 11.5	50.9 ± 13.0
Men	55 (22.7%)	1221 (43.2%)	124 (29.6%)	630 (50.1%)	475 (61.2%)	101 (59.4%)	2606 (45.8%)
White or Caucasian	241 (99.6%)	1975 (70.6%)	25 (6.0%)	1219 (97.4%)	0 (0.0%)	0 (0.0%)	3460 (61.2%)
Black or African ancestry	0 (0.0%)	286 (10.2%)	37 (8.8%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	324 (5.7%)
Hispanic	0 (0.0%)	188 (6.7%)	332 (79.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	520 (9.2%)
Asian	1 (0.4%)	240 (8.6%)	1 (0.2%)	1 (0.1%)	776 (100.0%)	170 (100.0%)	1189 (21.0%)
Other race/ethnicity	0 (0.0%)	109 (3.9%)	24 (5.7%)	30 (2.4%)	0 (0.0%)	0 (0.0%)	163 (2.9%)
Employed	55 (35.3%)	192 (51.2%)	177 (61.2%)	509 (40.6%)	219 (54.2%)	54 (61.4%)	1206 (47.0%)
BMI, kg/m^2	40.8 ± 8.8	37.5 ± 10.3	31.8 ± 6.1	33.6 ± 6.2	28.2 ± 4.8	27.0 ± 4.0	34.8 ± 9.2
Obesity[a]	217 (90.8%)	2016 (75.0%)	238 (57.1%)	862 (69.5%)	371 (51.7%)	32 (19.6%)	3736 (68.3%)
Lean[b]	0 (0.0%)	170 (6.3%)	36 (8.6%)	47 (3.8%)	108 (15.1%)	55 (33.7%)	416 (7.6%)
ALT, *U/L*	31.8 ± 27.4	41.7 ± 31.5	49.5 ± 33.7	57.5 ± 48.6	62.0 ± 45.8	82.3 ± 57.0	49.6 ± 40.6
AST, *U/L*	28.1 ± 22.2	32.7 ± 26.8	41.3 ± 31.3	40.2 ± 33.5	47.1 ± 35.6	58.5 ± 38.4	37.4 ± 30.9
Platelets, $10^9/L$	245.9 ± 60.5	252.3 ± 74.4	212.9 ± 79.4	244.9 ± 94.4	246.7 ± 69.6	204.4 ± 68.3	244.8 ± 79.7
FIB-4 score	1.21 ± 0.78	1.19 ± 0.95	2.34 ± 4.11	1.30 ± 1.29	1.50 ± 2.19	1.67 ± 1.21	1.36 ± 1.71
Liver stiffness, *kPa*	9.28 ± 6.06	8.11 ± 6.91	9.82 ± 7.37	10.0 ± 9.1	8.32 ± 5.05	8.51 ± 9.71	9.06 ± 7.90
FIB-4, >1.3	75 (33.2%)	651 (30.1%)	178 (48.0%)	374 (31.9%)	229 (40.5%)	80 (52.3%)	1587 (34.1%)
Liver stiffness, >8 *kPa*	N/A	268 (27.4%)	46 (46.9%)	502 (41.9%)	149 (38.4%)	17 (28.3%)	984 (36.1%)
FIB-4, >1.3 or liver stiffness, >8 *kPa*	N/A	764 (70.1%)	196 (83.8%)	639 (54.6%)	322 (71.1%)	92 (79.3%)	2090 (66.5%)
Cirrhosis[c]	3 (21.4%)	229 (12.3%)	19 (13.3%)	239 (19.8%)	68 (15.1%)	7 (11.5%)	565 (15.1%)
Type 2 diabetes	150 (62.2%)	916 (33.4%)	207 (49.8%)	633 (50.6%)	271 (36.3%)	37 (22.4%)	2214 (39.8%)
Hypertension	213 (88.4%)	1461 (55.8%)	230 (55.2%)	506 (40.4%)	333 (44.5%)	43 (25.9%)	2786 (51.2%)
Hyperlipidemia	188 (78.0%)	1469 (56.7%)	188 (44.9%)	516 (41.3%)	293 (41.3%)	35 (21.1%)	2689 (50.0%)
Anxiety	158 (65.8%)	291 (10.5%)	193 (46.2%)	500 (39.9%)	15 (5.1%)	28 (16.9%)	1185 (23.0%)
Depression	132 (60.8%)	501 (33.0%)	124 (29.7%)	215 (17.2%)	13 (5.1%)	11 (6.6%)	996 (26.1%)
Clinically overt fatigue	213 (88.4%)	749 (26.9%)	145 (34.6%)	666 (53.3%)	18 (7.1%)	85 (51.2%)	1876 (36.7%)
Abdominal pain	86 (35.8%)	185 (8.2%)	147 (35.3%)	327 (26.1%)	8 (2.2%)	100 (60.2%)	853 (18.1%)
Cancer (any)	20 (8.4%)	146 (24.8%)	16 (3.8%)	66 (5.3%)	20 (3.2%)	1 (0.6%)	269 (8.2%)
Congestive heart failure	32 (13.3%)	31 (2.7%)	10 (2.4%)	33 (2.6%)	7 (1.8%)	1 (0.6%)	114 (3.2%)
Myocardial infarction	16 (6.6%)	83 (7.1%)	11 (2.7%)	55 (4.4%)	32 (5.0%)	0 (0.0%)	197 (5.1%)
Peripheral vascular disease	39 (16.5%)	35 (3.4%)	66 (15.8%)	95 (7.6%)	13 (3.4%)	1 (0.6%)	249 (7.2%)
Skin disease	26 (11.2%)	47 (11.1%)	6 (1.4%)	135 (11.1%)	16 (4.1%)	2 (1.2%)	232 (8.2%)
Sleep apnea	80 (33.9%)	935 (45.6%)	151 (36.2%)	188 (15.3%)	101 (26.0%)	4 (2.4%)	1459 (32.5%)
Stroke	16 (6.6%)	23 (2.1%)	4 (1.0%)	31 (2.5%)	7 (1.1%)	2 (1.2%)	83 (2.2%)

	Eastern Europe	High-income countries	Latin America and Caribbean	North Africa and Middle East	Southeast and East Asia	South Asia	All GNR enrollees
Currently drink any alcohol	56 (23.3%)	936 (58.2%)	40 (9.5%)	81 (6.5%)	107 (14.3%)	15 (9.6%)	1235 (28.0%)
Exercise >30 min, ≥3/wk	46 (19.5%)	426 (43.6%)	77 (18.4%)	525 (42.3%)	150 (39.1%)	22 (14.3%)	1246 (36.5%)
Currently smoke	29 (12.2%)	205 (7.9%)	42 (10.0%)	220 (17.7%)	143 (19.1%)	5 (3.2%)	644 (11.9%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4; GNR, Global Nonalcoholic Fatty Liver Disease/ Nonalcoholic Steatohepatitis Registry; N/A, not available (30 kg/m2 or 27.5 kg/m2 for participants of East Asian origin. b Lean is calculated as a BMI >30 kg/m2 or 27.5 kg/m2 for participants of East Asian origin. b Lean is calculated as a BMI <25 kg/m2 or 23.5 kg/m2 for participants of East Asian origin. c Cirrhosis is diagnosed by biopsy or liver stiffness 12 kPa, or clinical evidence of cirrhosis complications.

Table 2. PROs of GNR Participants

PRO score (general population norm)	Eastern Europe	High-income countries	Latin America and Caribbean	North Africa and Middle East	Southeast and East Asia	South Asia	All GNR enrollees
CLDQ-NASH							
Abdominal symptoms (6.0)	4.9 ± 1.5	5.9 ± 1.3	4.8 ± 1.8	5.0 ± 1.6	6.0 ± 1.2	5.0 ± 0.9	5.3 ± 1.5
Activity/energy (6.0)	4.6 ± 1.3	5.9 ± 1.1	4.8 ± 1.3	5.1 ± 1.4	5.9 ± 1.0	5.7 ± 0.8	5.3 ± 1.3
Emotional (6.0)	4.9 ± 1.2	5.6 ± 1.1	4.6 ± 1.2	4.8 ± 1.4	5.6 ± 1.1	5.8 ± 0.8	5.1 ± 1.3
Fatigue (5.0)	3.9 ± 1.4	4.9 ± 1.2	4.7 ± 1.3	4.2 ± 1.5	5.2 ± 1.1	5.3 ± 0.8	4.6 ± 1.4
Systemic symptoms (6.0)	4.8 ± 1.2	5.5 ± 1.1	4.7 ± 1.3	4.7 ± 1.4	5.6 ± 1.0	5.9 ± 0.8	5.0 ± 1.3
Worry (7.0)	5.6 ± 1.1	5.9 ± 1.2	4.5 ± 1.4	5.2 ± 1.5	6.1 ± 1.0	6.1 ± 0.7	5.5 ± 1.4
Total (6.0)	4.8 ± 1.0	5.6 ± 0.9	4.7 ± 1.1	4.8 ± 1.2	5.7 ± 0.9	5.7 ± 0.6	5.1 ± 1.1
FACIT-F							
Physical well-being (22.7)	19.0 ± 5.2	24.2 ± 4.3	23.0 ± 4.8	21.5 ± 5.8	23.4 ± 4.5	22.3 ± 3.7	22.2 ± 5.4
Emotional well-being (19.9)	15.6 ± 4.8	19.1 ± 4.0	16.4 ± 4.7	16.0 ± 5.1	18.9 ± 3.8	20.1 ± 3.4	17.0 ± 4.9
Social well-being (19.1)	18.8 ± 6.2	19.2 ± 6.9	19.7 ± 5.1	20.2 ± 6.0	17.6 ± 7.7	26.6 ± 2.6	19.8 ± 6.4
Functional well-being (18.5)	16.2 ± 5.1	20.3 ± 5.5	16.8 ± 5.1	19.6 ± 5.7	18.9 ± 6.7	25.3 ± 3.2	19.3 ± 5.9
Fatigue scale (40.1)	32.8 ± 9.9	41.2 ± 10.1	40.5 ± 9.5	34.7 ± 12.2	39.3 ± 9.2	41.3 ± 7.0	37.0 ± 11.4
Total (120.3)	102.4 ± 22.1	124.0 ± 23.4	116.4 ± 22.8	112.0 ± 27.3	118.0 ± 23.4	135.7 ± 16.2	115.2 ± 25.9
WPAI:SHP							
Work productivity impairment	0.53 ± 0.44	0.08 ± 0.19	0.38 ± 0.35	0.21 ± 0.30	0.10 ± 0.21	0.32 ± 0.19	0.22 ± 0.31
Absenteeism	0.46 ± 0.47	0.01 ± 0.08	0.04 ± 0.16	0.04 ± 0.15	0.01 ± 0.08	0.07 ± 0.14	0.05 ± 0.18
Presenteeism	0.13 ± 0.20	0.07 ± 0.17	0.35 ± 0.33	0.16 ± 0.26	0.09 ± 0.20	0.25 ± 0.11	0.17 ± 0.26
Activity impairment	0.24 ± 0.26	0.15 ± 0.33	0.40 ± 0.32	0.22 ± 0.29	0.12 ± 0.20	0.33 ± 0.19	0.22 ± 0.29

CLDQ-NASH, Chronic Liver Disease Questionnaire–Nonalcoholic Steatohepatitis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GNR, Global Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis Registry; PRO, patient-reported outcome; WPAI:SHP, Work Productivity and Activity Index Specific Health Problem.

Table 3. Independent Predictors of Summary PRO Scores in GNR Patients

PRO score (range)	Total CLDQ-NASH (1–7)		Total FACIT-F (0–160)		Work productivity impairment by WPAI (1–0)		Activity impairment by WPAI (1–0)	
Predictor	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*	$\beta \pm$ SE	*P*
Southeast and East Asia (ref: high income)	-0.19 ± 0.10	.06	-10.83 ± 2.48	<.0001	0.07 ± 0.05	.13	0.01 ± 0.03	.79
South Asia (ref: high income)	0.28 ± 0.18	.13	11.98 ± 4.46	.0073	0.10 ± 0.08	.18	0.06 ± 0.06	.35
Eastern Europe (ref: high income)	0.08 ± 0.30	.79	0.92 ± 7.33	.90	0.12 ± 0.16	.46	-0.02 ± 0.10	.86
North Africa and Middle East (ref: high income)	-0.41 ± 0.07	<.0001	-5.41 ± 1.73	.0018	0.09 ± 0.03	.0059	0.01 ± 0.02	.63
Latin America and Caribbean (ref: high income)	-0.24 ± 0.10	.0186	6.21 ± 2.48	.0122	0.20 ± 0.04	<.0001	0.15 ± 0.03	<.0001
Age, per year	0.007 ± 0.002	.0010	0.128 ± 0.051	.0132	-0.001 ± 0.001	.56	-0.001 ± 0.001	.25
Men	0.27 ± 0.05	<.0001	4.56 ± 1.16	<.0001	-0.02 ± 0.03	.54	-0.04 ± 0.02	.0134
Lean	0.16 ± 0.10	.08	2.15 ± 2.31	.35	-0.01 ± 0.04	.78	-0.03 ± 0.03	.25
Obesity	0.01 ± 0.05	.92	-0.45 ± 1.23	.71	-0.03 ± 0.02	.26	-0.01 ± 0.02	.42
Anxiety	-0.33 ± 0.05	<.0001	-8.02 ± 1.26	<.0001	0.04 ± 0.03	.14	0.01 ± 0.02	.67
Depression	-0.29 ± 0.06	<.0001	-11.0 ± 1.51	<.0001	0.03 ± 0.03	.37	0.06 ± 0.02	.0045
Clinically overt fatigue	-0.65 ± 0.05	<.0001	-14.7 ± 1.21	<.0001	0.08 ± 0.02	.0008	0.15 ± 0.02	<.0001
Cirrhosis	-0.06 ± 0.06	.30	-0.65 ± 1.38	.64	0.01 ± 0.03	.84	0.00 ± 0.02	.92
Type 2 diabetes	-0.08 ± 0.05	.10	-2.59 ± 1.17	.0270	0.00 ± 0.02	.85	0.02 ± 0.02	.12
Hyperlipidemia	-0.02 ± 0.05	.63	0.29 ± 1.11	.79	-0.02 ± 0.02	.39	0.00 ± 0.01	.90
Hypertension	-0.11 ± 0.05	.0239	-1.82 ± 1.18	.12	0.00 ± 0.02	.96	0.01 ± 0.02	.74
Myocardial infarction	-0.11 ± 0.11	.34	-2.77 ± 2.72	.31	-0.05 ± 0.07	.51	0.04 ± 0.04	.25
Stroke	-0.27 ± 0.16	.09	-6.26 ± 3.82	.10	-0.17 ± 0.14	.21	-0.02 ± 0.05	.75
Congestive heart failure	-0.22 ± 0.14	.11	-12.9 ± 3.34	.0001	-0.08 ± 0.09	.40	-0.03 ± 0.04	.47
Abdominal pain	-0.65 ± 0.05	<.0001	-9.31 ± 1.31	<.0001	0.14 ± 0.03	<.0001	0.09 ± 0.02	<.0001
Sleep apnea	-0.29 ± 0.06	<.0001	-6.03 ± 1.43	<.0001	0.09 ± 0.03	.0018	0.06 ± 0.02	.0019
Currently drink any alcohol	-0.04 ± 0.08	.61	0.03 ± 1.85	.99	-0.02 ± 0.03	.51	0.00 ± 0.02	.89
Currently smoke	-0.11 ± 0.06	.08	-4.33 ± 1.47	.0033	-0.01 ± 0.03	.66	-0.01 ± 0.02	.75
Exercise >30 min, 3/wk	0.22 ± 0.05	<.0001	4.06 ± 1.10	.0002	-0.01 ± 0.02	.56	-0.02 ± 0.01	.09

CLDQ-NASH, Chronic Liver Disease Questionnaire–Nonalcoholic Steatohepatitis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GNR, Global Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis Registry; PRO, patient-reported outcome; WPAI:SHP, Work Productivity and Activity Index Specific Health Problem.

Table 4. Clinicodemographic Parameters and PRO Scores of GNR Participants According to the Presence of Fatigue (Defined as CLDQ-NASH Fatigue <4 on a Scale of 1–7)

	Fatigue	No Fatigue	*P*
N	842	1979	
Central and Eastern Europe	71 (8.4%)	86 (4.3%)	<.0001
High-income countries	103 (12.2%)	415 (21.0%)	<.0001
Latin America and Caribbean	86 (10.2%)	203 (10.3%)	.97
North Africa and Middle East	520 (61.8%)	733 (37.0%)	<.0001
Southeast and East Asia	60 (7.1%)	452 (22.8%)	<.0001
South Asia	2 (0.2%)	90 (4.5%)	<.0001
Age, *y*	50.8 ± 12.0	52.4 ± 12.8	.0005
Men	294 (34.9%)	1063 (53.7%)	<.0001
White or Caucasian	655 (78.3%)	1058 (53.5%)	<.0001
Black or African ancestry	14 (1.7%)	63 (3.2%)	.0246
Hispanic	67 (8.0%)	168 (8.5%)	.67
Asian	81 (9.7%)	641 (32.4%)	<.0001
Other race/ethnicity	19 (2.3%)	46 (2.3%)	.93
Employed	321 (39.7%)	884 (50.4%)	<.0001
BMI, kg/m^2	34.0 ± 6.7	31.4 ± 6.3	<.0001
Obesity	600 (72.4%)	1131 (58.8%)	<.0001
Lean	37 (4.5%)	186 (9.7%)	<.0001
Cirrhosis	135 (19.7%)	255 (16.7%)	.09
Type 2 diabetes	422 (50.5%)	866 (44.2%)	.0023
Hypertension	423 (50.8%)	941 (48.1%)	.19
Hyperlipidemia	413 (49.6%)	853 (44.0%)	.0068
Anxiety	444 (54.7%)	441 (26.0%)	<.0001
Depression	287 (36.1%)	225 (13.8%)	<.0001
Clinically overt fatigue	607 (75.2%)	527 (31.6%)	<.0001
Abdominal pain	318 (40.2%)	319 (19.7%)	<.0001
Cancer (any)	56 (7.0%)	117 (6.6%)	.70
Congestive heart failure	45 (5.5%)	37 (2.1%)	<.0001
Myocardial infarction	45 (5.5%)	67 (3.6%)	.0257
Peripheral vascular disease	96 (11.9%)	118 (6.9%)	<.0001
Skin disease	67 (8.9%)	134 (8.3%)	.63
Sleep apnea	241 (30.2%)	318 (18.3%)	<.0001
Stroke	27 (3.3%)	29 (1.6%)	.0042
Currently drink any alcohol	85 (10.4%)	278 (14.5%)	.0032
Exercise >30 min, 3/wk	252 (31.2%)	674 (39.0%)	.0001
Currently smoke	145 (17.5%)	251 (12.9%)	.0017
CLDQ-NASH			
Abdominal symptoms	4.19 ± 1.58	5.78 ± 1.26	<.0001
Activity/energy	4.22 ± 1.27	5.82 ± 1.05	<.0001
Emotional	3.97 ± 1.20	5.59 ± 1.04	<.0001
Fatigue	2.86 ± 0.77	5.37 ± 0.86	<.0001
Systemic symptoms	3.90 ± 1.22	5.54 ± 1.04	<.0001
Worry	4.62 ± 1.48	5.86 ± 1.17	<.0001
Total	3.96 ± 0.90	5.66 ± 0.81	<.0001
FACIT-F			
Physical well-being	17.7 ± 5.7	24.3 ± 3.7	<.0001
Emotional well-being	14.2 ± 5.0	18.3 ± 4.3	<.0001
Social well-being	18.9 ± 6.1	20.3 ± 6.5	<.0001
Functional well-being	16.5 ± 5.4	20.6 ± 5.6	<.0001
Fatigue scale	26.6 ± 10.3	41.9 ± 8.0	<.0001
Total	93.8 ± 24.0	125.4 ± 19.9	<.0001
WPAI:SHP			
Work productivity impairment	0.368 ± 0.346	0.162 ± 0.270	<.0001
Absenteeism	0.080 ± 0.218	0.041 ± 0.164	.0002
Presenteeism	0.299 ± 0.310	0.124 ± 0.221	<.0001
Activity impairment	0.351 ± 0.316	0.160 ± 0.257	<.0001

CLDQ-NASH, Chronic Liver Disease Questionnaire–Nonalcoholic Steatohepatitis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; GNR, Global Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis Registry; PRO, patient-reported outcome; WPAI:SHP, Work Productivity and Activity Index Specific Health Problem.

Figures

Figure 1. Patient-reported outcome (PRO) scores in Global Nonalcoholic Fatty Liver Disease Registry enrollees (A) with and without cirrhosis, and (B) lean and overweight/obese. CLDQ-NASH, Chronic Liver Disease Questionnaire–Nonalcoholic Steatohepatitis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI, Work Productivity and Activity Index.

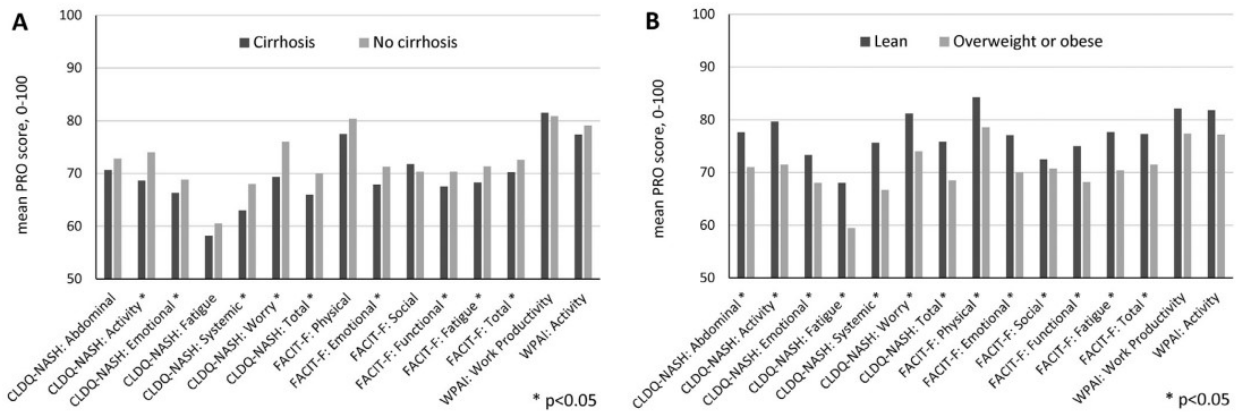

Figure 2. Changes in Patient-reported outcome (PRO) scores by the change in fatigue (greater than or equal to a þ0.5 or a 0.5 points from baseline in the CLDQ-NASH Fatigue domain). CLDQ-NASH, Chronic Liver Disease Questionnaire–Nonalcoholic Steatohepatitis; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; WPAI, Work Productivity and Activity Index.