

# Evaluation of Fatigue in U.S. Patients with Primary Biliary Cirrhosis

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- OBJECTIVES:** Fatigue, which may have a significant impact on quality of life, is the most common reported symptom in primary biliary cirrhosis (PBC). Multiple instruments to quantify fatigue and quality of life in liver disease have been validated, but have not been broadly applied to U.S. PBC patients. This study examines the extent of fatigue and its effect on quality of life in U.S. PBC patients.
- METHODS:** Seventy patients with PBC were administered two validated questionnaires about quality of life (the Mayo version of the NIDDK-QA) and fatigue (the Fisk Fatigue Impact Score) and a proposed physical measure of fatigue in PBC (the grip strength test) on the day of routine physician visit. Nonparametric methods were employed.
- RESULTS:** The fatigue and quality of life domain scores (physical functioning, liver symptoms, health satisfaction, Karnofsky index) discriminated between patients with and without self-reported fatigue ( $p < 0.05$ ), as opposed to the grip strength results. Fatigue and quality of life domains correlated strongly with each other ( $r$  between 0.33 and 0.74,  $p \leq 0.006$ ) and not with the grip strength results. Neither quality of life nor fatigue scores correlated with age.
- CONCLUSIONS:** The correlation between fatigue and quality of life scores suggests fatigue has an impact on quality of life in U.S. primary biliary cirrhosis patients. However, our fatigue scores suggest U.S. PBC patients have less fatigue than non-U.S. PBC patients. The grip strength is an insensitive measure of fatigue in U.S. PBC patients.

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## INTRODUCTION

Primary biliary cirrhosis (PBC) is a slowly progressive liver disease characterized by immune mediated, nonsuppurative destruction of intrahepatic bile duct epithelial cells and high titers of autoantibodies (1, 2). Following the introduction of ursodeoxycholic acid (3, 4), disease progression has become even slower (2, 5–8). Consequently, increasing attention is being given to symptom reduction and quality of life improvement in PBC patients. The most prevalent symptom is fatigue, which reportedly affects between 60% and 80% of PBC patients (9–11); it is not related to exercise, nor is it improved by rest (12). While fatigue in PBC is believed to have a central origin (13–18), a recent report has suggested that measurement of grip strength may be an accurate measure of fatigue in PBC (19). Studies conducted in Toronto, Canada (20), and Newcastle-upon-Tyne, England (21) have clearly shown that fatigue has a significant impact on quality of life. Researchers at the Mayo Clinic, Rochester (22) have similarly shown that quality of life is impaired, using an instrument that incorporates elements related to fatigue. However, comparing the results of fatigue studies in PBC is complicated by the use of different instruments developed to objectively assess quality of life and fatigue in patients with PBC. One of the fatigue instruments has been widely used in clinical studies,

but not in PBC patients from the United States. Our goal was to determine how closely the results of different instruments correlate with one another when administered to a U.S. PBC population.

## PATIENTS AND METHODS

### *Patients*

A serial group of patients with PBC were recruited within the Division of Liver Diseases at the Mount Sinai School of Medicine, New York, and informed consent was given by each patient. Five PBC patients with decompensated liver disease were excluded, as well as three patients whose associated diseases may have influenced their responses, independent of the presence of their liver disease.

The median Child-Pugh score was 5 (range 0–10). All patients were Caucasian and prescribed ursodeoxycholic acid (12–15 mg/kg/d), vitamins A and D, and calcium.

The diagnosis of PBC required the presence of an anti-mitochondrial antibody titer of  $\geq 1:40$  and the presence of a cholestatic pattern of serum liver enzyme values, and/or a compatible liver histology.

Nonliver disease controls were recruited from consecutive women coming to a gynecology practice for routine visits.

**Table 1.** Patient Clinical and Laboratory Characteristics

Sex (F/M)	64/6
Age (yr)	60.5 (35.9–88.0)
MRS	4.66 (2.13–8.54)
Time since diagnosis (yr)	11 (0–27)
Albumin (g/dl)	4.2 (3.0–5.1)
Alkaline phosphatase (IU/l)	139 (37–1409)
Bilirubin (mg/dl)	0.65 (0.20–4.60)

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the Mount Sinai Institutional Review Board.

### Instruments and Scoring

The Mayo version of the NIDDK-QA questionnaire (QOL) (22), previously validated in ambulatory patients with cholestatic liver disease, quantitatively assesses the impact of liver disease on the quality of life over the previous month, from the patients' perspective. This questionnaire contains 47 questions divided into 4 domains: liver disease symptoms, physical functioning, health satisfaction, and overall well-being. The liver disease symptom domain includes questions regarding symptoms, including fatigue, depression, and pruritus. The responses are scored on a 5-point Likert scale, from 0 (not at all) to 4 (extreme). We defined the responses to these questions as "self-assessed" fatigue, depression, and pruritus. For statistical analyses, patients with scores of 1–4 were classified as positive for self-assessment of the condition, and compared with patients whose score was 0. Summary scores were calculated for each domain; higher scores indicate better quality of life. (For details regarding the questionnaire, see Kim *et al.* (22).)

The Fisk Fatigue Impact Score (FIS) (21, 23) is a questionnaire requiring patients to rate the impact of fatigue on aspects of daily life over the previous month. The 40 questions from three domains (psycho-social function, cognitive function, and physical activity) are mixed within the questionnaire. The answers are graded into five levels of severity (0–4), with higher scores representing greater fatigue. The total score was calculated for each patient.

A dynamometer (JAMAR 5030J1 Hydraulic Hand Dynamometer; Sammons Preston, Chicago, IL) was used to measure peripheral muscle fatigue, the Grip Strength Test (GST), as in a small study by Goldblatt *et al.* (19). The dynamometer measures grip force in pounds and kilograms. Nondominant hand grip strength was assessed by repeatedly squeezing a JAMAR dynamometer every 5 s for 5 min or until the values reached 50% of the starting value, as previously described (19).  $GS_{\text{initial}}$  (average of the first three measurements of grip strength) and  $GS_{\text{decrease}}$  (median percentage of decrease per repeated measurement) were determined.

### Data Collection

During routine visits, the physician performed a review of systems, which included the presence of fatigue, depression, and pruritus for each patient. Each subject was administered the instruments on the same day of the visit. Patients first

performed the GST, and then were asked to privately complete the QOL and FIS questionnaires. The research coordinator was available to answer any questions. The Mayo Risk Score (24, 25) (MRS) was calculated for each patient using lab values and physical exam findings from the same visit. A random subgroup of patients were asked to complete the questionnaires again 6 months after their original visit.

### Statistical Analysis

The data were analyzed using the statistical software package SPSS for Windows (SPSS Inc., version 12.0, Chicago, IL). Results are reported as median values and range, unless otherwise stated. The data were not normally distributed, and therefore nonparametric tests were employed. Continuous variables were compared using the Mann-Whitney test. Categorical variables were analyzed using either  $\chi^2$  or Fisher's exact test. The frequency of positive responses regarding fatigue during the review of systems (verbally reported fatigue) was calculated and compared to the frequency of positive responses (1–4 on the Likert scale) to the specific question regarding fatigue in the liver symptom domain of the QOL (self-assessed fatigue). The results obtained for each instrument were evaluated for their ability to discriminate between patients with and without self-assessed fatigue, depression, or pruritus. Excluding the specific question about fatigue in the QOL did not affect the results of the statistical analysis. The relationship between each instrument's score and other continuous variables (*e.g.*, patient's age, MRS) was analyzed using Spearman rank correlation coefficients. For all analyses, *p* values of less than 0.05 were considered statistically significant.

## RESULTS

### Subject Characteristics

Seventy patients with antimitochondrial antibody positive PBC were included in the study. The patients had well compensated liver disease without any history of ascites, spontaneous bacterial peritonitis, variceal bleeding, or encephalopathy. Their clinical and biochemical characteristics are presented in Table 1. The 21 nonliver disease controls enrolled in this study were women between 27 and 77 yr of age who were seen for routine visits at a gynecology practice. The ages of the controls were not significantly different from the ages of the PBC patients (*p* = 0.07).

### Only the FIS and QOL Scores Discriminate between Patients with and without Self-reported Fatigue or Depression

From the 70 patients, only 11 (16%) verbally reported fatigue as a subjective complaint during the physicians' review of systems; one reported depression and four (6%) pruritus. However, when asked to grade these same symptoms on a 5-point scale, fatigue was reported by 50 (71%) patients, depression by 34 (49%), and pruritus by 31 (44%) (Table 2).

Few assessed their fatigue as severe. As expected, there was greater overlap between patients reporting fatigue and

**Table 2.** Severity of Major Symptoms in PBC

Symptom	Severity of Symptom				
	Not At All	A Little Bit	Moderately	Quite a Bit	Extremely
Fatigue	20 (28.6%)	27 (38.6%)	13 (18.6%)	7 (10.0%)	3 (4.3%)
Depression	36 (51.4%)	24 (34.3%)	7 (10.0%)	1 (1.4%)	2 (2.9%)
Pruritus	39 (55.7%)	23 (32.9%)	2 (2.9%)	4 (5.7%)	2 (2.9%)

Symptoms were reported by patients as part of the Mayo version of the NIDDK-QA questionnaire (subjects were asked to evaluate how much they were distressed by each of fatigue, depression and pruritus during the prior month on a 5-point scale ranging from “not at all” to “extremely”; we defined this as “self-assessed” fatigue, depression, and pruritus). Data shown are number of patients (percentage).

depression than those reporting fatigue and pruritus (data not shown). There was no significant difference in age, MRS, time since diagnosis of PBC, or serum chemistries between those reporting fatigue and those without fatigue.

We observed a significant difference in FIS and QOL scores between patients with and without self-assessed fatigue (Table 3). Additionally, changing the definition of the “fatigue” group to include only those with 2–4 points, a significant difference in the FIS ( $p < 0.001$ ) and QOL ( $p \leq 0.020$ ) scores remained, without a significant difference in the MRS ( $p = 0.561$ ). Elimination of men with PBC ( $N = 6$ ) did not significantly change the median FIS and QOL scores of the PBC patients (data not shown). Not surprisingly, FIS and QOL scores in those with and without depression were significantly different, but not in those with and without pruritus (data not shown). Nor was there significant difference in age, MRS, time since diagnosis, or serum chemistries between those reporting some or no pruritus (data not shown).

The GST score did not discriminate between the presence and absence of self-assessed fatigue in PBC. Using either the  $GS_{\text{initial}}$  or  $GS_{\text{decrease}}$  values, there was no significant difference (Table 3). Unlike the prior study (19), most patients completed the test without a significant decrease in grip strength.

#### **The FIS and QOL Scores Correlate Strongly with Each Other**

It is unknown how well FIS and QOL results in PBC patients correlate with one another, though fatigue is thought to be

the major determinant of quality of life in PBC. In order to examine this question, the scores of the FIS and QOL were compared. Indeed, each component of QOL correlated significantly with the total FIS (Table 4); the strongest correlation was between FIS and the liver symptoms domain of the QOL (Spearman's  $r = -0.74$ ;  $p < 0.001$ ) (Fig. 1).

Though each domain of QOL is not equally weighted, the total QOL score similarly correlates with FIS. However, the validity of a total QOL score has not been formally evaluated.

#### **The GST Does not Correlate with FIS and Disease Severity**

Neither FIS nor the QOL domain scores correlated significantly with GST values ( $GS_{\text{initial}}$  and  $GS_{\text{decrease}}$ ) ( $r$  between 0.09 and 0.26,  $p > 0.05$ ). GST values did not correlate with the MRS, nor with total bilirubin or INR.  $GS_{\text{initial}}$  strictly correlated with age, which is a component of the MRS, and with albumin ( $r = 0.42$ ;  $p = 0.001$ ).

#### **Neither FIS nor QOL Scores Correlate with Age, while only the QOL Physical Functioning Domain Correlates with the MRS**

Importantly, neither the QOL scores nor FIS results correlated significantly with patient age ( $r$  between 0.02 and 0.21,  $p > 0.05$ ). The MRS is used as a surrogate marker of disease progression, though it was originally designed as a prognostic marker. We noted a statistically significant, though modest

**Table 3.** Clinical and Laboratory Data of Patients with or without Self-assessed Fatigue

Variable	Fatigue Present (n = 50)	Fatigue Absent (n = 20)	<i>p</i>
Age (yr)	60.1	63.2	0.217
MRS	4.91	4.52	0.198
Time since diagnosis (yr)	10.0	12.0	0.497
Bilirubin (mg/dl)	0.7	0.6	0.545
Albumin (g/dl)	4.15	4.25	0.096
Alkaline phosphatase (IU/l)	150	126	0.339
FIS score	14.50	0.5	0.001*
QOL physical functioning	92	100	0.011*
QOL well-being	11.6	12.3	0.125
QOL liver symptoms	3.4	3.7	<0.001*
QOL health perception	5	6	0.016*
QOL Karnofsky index	90	100	0.041*
$GS_{\text{initial}}$ (kg force)	18.8	20.5	0.435
$GS_{\text{decrease}}$ (kg force)	0.0	0.0	0.258

Median values are shown; *p* shows significance level for the Mann-Whitney test. \* indicates a statistically significant difference. Abbreviations used: Mayo version of the NIDDK-QA instrument (QOL); Fisk Fatigue Impact Score (FIS); average of the first three measurements of grip strength ( $GS_{\text{initial}}$ ); median percentage of decrease per repeated measurement of grip strength ( $GS_{\text{decrease}}$ ).

**Table 4.** Correlation Between FIS and Components of QOL

QOL Components	Correlation with FIS Score	
	r	p
QOL physical functioning	−0.51	<0.001*
QOL well-being	−0.33	0.006*
QOL liver symptoms	−0.74	<0.001*
QOL health perception	−0.39	0.001*
Karnofsky index	−0.57	<0.001*

r = Spearman's rank correlation coefficient; p = significance level; \* indicates a statistically significant correlation. Abbreviations used: Mayo version of the NIDDK-QA instrument (QOL); Fisk Fatigue Impact Score (FIS).

correlation between the QOL physical functioning domain and the patients' MRS (Spearman's  $r = -0.32$ ,  $p = 0.003$ ). There was no significant correlation between MRS and FIS (Spearman's  $r = 0.19$ ,  $p = 0.055$ ).

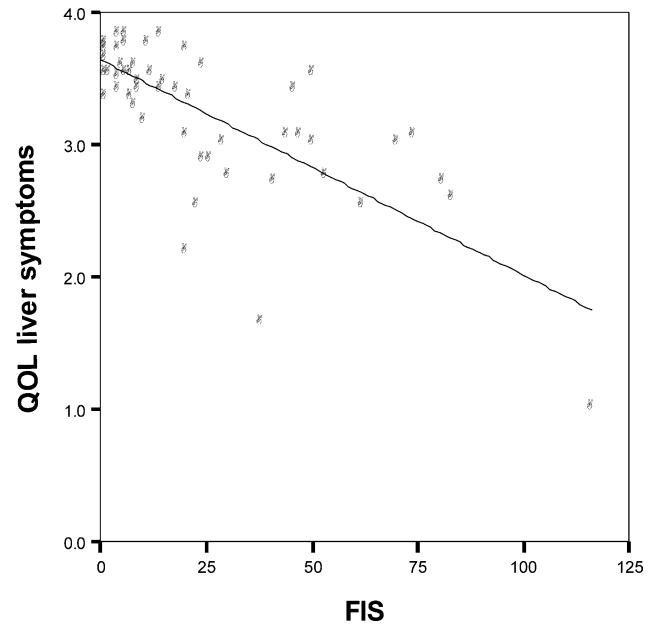
#### **Fatigue Levels Are Similar between PBC Patients and Controls**

Despite using an instrument previously validated to assess fatigue (FIS) in PBC patients, we were surprised by the low scores in our PBC patient population. Our FIS scores were significantly lower than scores reported in two non-U.S. studies of PBC patients (11, 21), who had clinical characteristics similar to our patients. In a U.S. study of patients with cirrhosis, the FIS scores were significantly higher than for our patient population as expected (26). To test the reliability of the questionnaire in our U.S. PBC patient population, the FIS questionnaire was applied twice, at 6-month intervals, to a random sample of 24 PBC patients. No significant changes in FIS results were noted ( $p$  value = n.s.). We also administered both the FIS and QOL to a control group without liver disease, and no significant difference was found between the PBC patient scores (median 8; range 0–116; 209: 95–224, respectively) and the scores of the control group (11: 0–75; 213: 93–224, respectively) ( $p$  values = n.s.).

## **DISCUSSION**

This is the first study to administer FIS and QOL to the same group of patients, and it is the first extensive study of fatigue in a U.S. PBC population. Scores obtained using these questionnaires correlated closely with each other, which confirms the perception that fatigue is a major determinant of quality of life in PBC patients. We show that FIS and QOL domain scores are sensitive measures of fatigue, given their ability to discriminate between patients with no fatigue versus mild fatigue. Additionally, this is the first study to show that neither QOL nor FIS results correlate with age. Thus, no adjustments for changes in age during longitudinal studies of fatigue are needed when using either the QOL or FIS.

The GST results, surprisingly, did not discriminate between patients with and without fatigue nor did they correlate with FIS results. This differs from the previous report by Goldblatt *et al.* (19). Our study population was much larger



**Figure 1.** Correlation between the Fisk Fatigue Impact Score (FIS) and the liver symptoms domain of the Mayo version of the NIDDK-QA questionnaire (QOL liver symptoms). The Spearman's rank correlation coefficient was  $-0.74$  indicating a strong inverse relationship, with  $p < 0.001$ .

(70 vs 18 PBC patients), but had lower mean FIS values. It is possible that the GST is useful for measuring fatigue in PBC populations with greater levels of fatigue; however, subgroup analysis of the 10 patients in our study with the highest FIS values did not support this hypothesis. The lack of correlation of either FIS or QOL scores with grip strength does not support the hypothesis that fatigue in PBC has a peripheral origin.

The discrepancy between verbally reported fatigue and self-assessed grading of fatigue likely reflected the generally mild nature of the symptoms (*i.e.*, few reported severe symptoms). Mild fatigue is apparently underreported to physicians by patients.

MRS has been used to monitor disease progression in some studies. The lack of correlation between FIS and the MRS, in agreement with prior studies (21, 23), suggests that fatigue in PBC patients, as explored by the FIS, is not associated with, nor can it be explained by the laboratory and clinical findings used to calculate the MRS. There was one domain of the QOL (physical functioning) that correlated with MRS. In a prior study, a different domain of QOL correlated with MRS (22). That suggests that the QOL may more closely reflect disease progression than the FIS. Longitudinal studies would be needed to confirm this. Liver biopsies are also used to stage disease and follow disease progression; however, recent liver biopsies were not available for most patients for comparison to FIS and QOL domain scores.

Our QOL scores were similar to those previously published for a U.S. PBC population that was comparable in terms of gender and MRS components (22). This suggests quality of

life for PBC patients is similar across the United States. The FIS has not been used in a U.S. PBC population before now. Compared to studies conducted in Newcastle-upon-Tyne (21) and Toronto (11), our PBC patient FIS results were significantly lower (meaning less fatigue). The clinical characteristics and management of the patients in each study were similar. Our PBC patients were recruited from a tertiary care center (the same manner as in the Toronto study), whereas the Newcastle-upon-Tyne study is a population-based study. Due to differences in the health-care systems between the United States versus Canada and the United Kingdom, our study population may have excluded those with the lowest socio-economic background. However, no correlation between fatigue and socio-economic background has been reported.

In our study, the FIS results of the PBC patients were not significantly different from those of the controls we enrolled. A similar control group (patients seen at a primary care practice) was used in the Newcastle-upon-Tyne study (21). In a patient population well-known to have increased levels of fatigue (27, 28), cirrhotic individuals visiting a pretransplant clinic, a U.S. patient study obtained FIS results surprisingly similar to those reported for PBC patients in the non-U.S. studies (26). It is unlikely that PBC patients have as severe fatigue as cirrhotic individuals. The FIS results for our controls were also lower than those of similar control groups in the non-U.S. PBC patient studies. Thus, FIS results may tend to be lower in the U.S. populations than in the clinically similar non-U.S. populations. However, our PBC patient FIS results were similar to our control group, patients visiting a gynecologic practice for routine care, unlike in the non-U.S. studies. Despite these differences, the percentage of PBC patients self-reporting fatigue was not significantly different in our study compared to previous reports (9–11). Thus, in the U.S. PBC patients without decompensated liver disease fatigue may be less severe than in the similar non-U.S. PBC patient populations. Additional U.S. studies will be needed to confirm this finding.

Objective assessment of symptoms in patients with PBC has become increasingly important as treatment focuses more on improvement in quality of life. It is not clear at all that FIS and QOL measure fatigue *per se*. The evaluation of fatigue, depression, pruritus, and quality of life in patients with PBC is a formidable challenge for the clinician due to their subjective and overlapping nature. However, FIS and QOL, unlike GST, are useful instruments to assess symptoms in PBC clinical studies, despite their somewhat subjective nature compared to the GST. The results of our study confirm previous non-U.S. studies suggesting that fatigue is the major symptom affecting quality of life in PBC and likely is of central, not peripheral, origin.

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