Health Related Quality of Life Comparison Among Patients With Autoimmune Liver Diseases and Non-Alcoholic Fatty Liver Disease.

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Accessibility
Scholarly Report submitted in partial fulfillment of the MD Degree at Harvard Medical School

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Scholarly Report Title: The impact of autoimmune hepatitis on health-related quality of life

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Collaborators: Karen Campoverde, MD, Daniela Goyes, MD, Jennifer Lee, MD
Project Question: Does fibrosis lead to impairment in health-related quality of life in patients with autoimmune hepatitis? Do patients with autoimmune hepatitis worry more than patients with non-alcoholic fatty liver disease? What differences and what accounts for those differences in health-related quality of life amongst patients with autoimmune liver disease versus patients with NAFLD?

Within this project, my role was to update the data repository on patients with autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. We acquired this data through the online medical record at BIDMC and inputted this data into REDCaps, an online repository, for each patient visit and the initial diagnosis data. We did a thorough chart review for each patient in our database, collecting data on several variables, including liver function tests, platelet count, serologies, biopsy and imaging findings. With the mentorship of Dr. Patwardhan, we discussed which variables we wanted to analyze in relation to the questionnaire. I was involved in the literature review, reading and analyzing the papers which already looked at patient reported outcomes and health related quality of life in patients with autoimmune hepatitis. We decided to do a cross sectional prospective study since for each clinical visit we had lab data with chronic liver disease questionnaire surveys filled out. We wanted to capture a moment in time, particularly the first visit, though we considered doing this for each visit to track changes in quality of life and which underlying factors correlated with that. The statistical methods were executed by Karen Campoverde, MD, and Daniela Goyes, MD, research fellows at the Liver center at the BIDMC. Jennifer Lee, MD, a third-year internal medicine resident at the BIDMC, helped with the results and discussion section. I wrote the abstract, introduction, and was involved with the discussion as well. We decided to group all patients with autoimmune liver disease together to compare them with patients with NAFLD as well as look for any differences within the autoimmune etiologies. The CLDQ was the preferred tool for HRQoL as every patient enrolled in the prospective registry filled one out during a clinic visit, and had labs drawn including LFTs. This allowed us to track for any changes that might be correlated to the underlying clinical data. Patients enrolled had either a prior biopsy or fibroscan, and patients with cirrhosis were also enrolled to account for changes in disease severity and how that might affect HRQoL. Dr. Patwardhan oversaw this project and provided guidance and feedback, and we met several times over the course of the last months to discuss which variables might make sense to look at and likely to have an impact on the quality of life. We did not compare patients with autoimmune hepatitis to the general population as this has been demonstrated previously with the SF-36, which is a more general questionnaire, showing this
disease alone causes marked impairment in the quality of life compared to the general population.

**Health related quality of life comparison among patients with autoimmune liver diseases and non-alcoholic fatty liver disease.**

**Abstract**

**Purpose:** The purpose of this study was to characterize health related quality of life in a cohort of patients with autoimmune liver disease compared to patients with non-alcoholic fatty liver disease. Furthermore, we aimed to understand which demographic, clinical, or biochemical markers correlated with marked impairment in quality of life, and which domains were differentially affected by these separate disease entities.

**Methods:** This was a prospective cross-sectional study enrolling patients with autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. Data was extracted from a separate well-established database for non-alcoholic fatty liver disease from the same hospital site. Patients were administered the well validated and reliable chronic liver disease questionnaire form at each of their patient visits and had labs collected on the same day. This questionnaire consists of 29 items classified in 6 domains including abdominal, fatigue, systemic, activity, emotional and worry related symptoms. Diagnosis data was established from chart review. All patients had a prior fibro scan or biopsy documented in the online medical record. Data entry for each visit was acquired from chart review and included demographic data, liver function tests, autoimmune serologies, medication, presence of cirrhosis and complications and other factors pertinent to quality of life.

**Results:** Using the CLDQ, the unadjusted results show patients with autoimmune liver disease have significantly more fatigue compared to patients with non-alcoholic fatty liver disease, while patients with NAFLD have significantly worse impairment in the worry domain. When adjusted for other variables, this loses significance.

**Conclusions:** Our results indicate patients with autoimmune hepatitis, when compared to patients with NAFLD, experience significantly more fatigue, driving their impairment in quality of life. In particular, the difference in fatigue remained significant after adjusting for age, platelet count, BMI and fibrosis stage.
Introduction:

Health-related quality of life (HRQoL) is an emerging component of patient reported outcomes research, especially in patients with chronic diseases characterized by a relapsing and remitting course or on lifelong therapies. Clinicians are beginning to understand the factors associated with detrimental outcomes and functional impairment. Several disease specific and general questionnaires have been validated in clinical studies for their ability to identify which domains are affected by a disease compared to the general population as well as to track changes over time. Patients with autoimmune hepatitis (AIH), a form of autoimmune liver disease and cause of acute and chronic liver disease, live with significant impairment as a result of their disease [1-5]. These patients are often on immunosuppressive therapy for life given most patients will inevitably relapse if taken off [6, 7]. Not only is HRQoL significantly impaired in patients with AIH, but it is also impaired in patients with various other forms of chronic liver disease [8-16]. Studies are limited and lacking in patients specifically with autoimmune hepatitis [17], though have demonstrated impairment in various domains including physical and mental well-being [4] and overall significant reduction in quality of life with depression identified as one of the strongest drivers of this impairment [2] and prolonged corticosteroid use [5]. Several studies have already begun to look at health related quality of life, specifically in patients with Primary Sclerosing Cholangitis (PSC) [18, 19, 22] and fatigue in patients with Primary Biliary Cholangitis (PBC) [20, 21].

In our well characterized cohort of patients with AIH, PBC, and PSC, we hypothesize patients with autoimmune liver disease have significantly impaired quality of life as measured by a survey questionnaire and demonstrated in prior work. Additionally, we hypothesize patients with higher grade fibrosis and a clinical diagnosis of cirrhosis will have worse health-related quality of life. Our aim is to characterize which demographic, clinical and biochemical factors are associated with significantly impaired health-related quality of life. Additionally, in order to understand how the disease process or etiology affects patient reported outcomes, we will compare this group of patients to a second well characterized group of patients at our center with non-alcoholic fatty liver disease, another form of chronic liver disease. We hypothesize there will be differences, as detected by the survey questionnaire used in this study, in degree and the domains of health-related quality of life impairment.

Patients with NAFLD also have reduced patient-reported outcomes, which has been shown to associate with the level of fibrosis [23] as well as female gender and obesity [26]. As
compared to patients with chronic hepatitis C, patients with NASH also exhibited severe impairment of health-related quality of life, particularly lower HRQoL scores related to physical health, even after adjusting for several factors including demographic parameters, cirrhosis and a history of psychiatric disorders [24]. Interestingly, in a study performed at our center, these patients experienced improvement in their quality of life after experiencing weight loss and found patients who were non-diabetics with active NASH and F0-F2 fibrosis were most likely to experience this benefit [25]. Therefore, we aim to study differences between these two patient groups using the Chronic Liver Disease Questionnaire (CLDQ) to compare which symptoms drive the impairment in quality of life and what factors common to both diseases are associated with this impairment. We hypothesize patients with autoimmune liver disease have marked impairment in the worry and fatigue sub-domains of the CLDQ compared to patients with NAFLD.

Population and Methods:

Patient Population

Cross-sectional data from two registries: an autoimmune diseases registry of 225 patients and a NAFLD registry of 234 patients were prospectively collected at Beth Israel Deaconess Medical Center (BIDMC, Boston, MA).

Patients with diagnosis of AIH, PBC, and PSC were referred to the Liver Clinic that specializes in Autoimmune Diseases from April 2018 to September 2019. Criteria for enrollment into this registry included confirmed diagnosis of AIH, PBC, PSC based on liver biopsy histology, laboratories and radiographic and/or endoscopic studies. Data collection included blood work, medical treatments performed, and results of liver histology or liver elastography (Fibroscan®). Patients were excluded if they did not give consent.

Patients with diagnosis of NAFLD were also referred to our Liver Clinic specialized in NAFLD for evaluation of elevated liver enzymes or incidental hepatic steatosis on imaging from December 2009 to December 2016. Criteria for enrollment into this registry included histological diagnosis of NAFLD within 3 months preceding the enrollment visit. Patients with other chronic liver diseases or daily consumption of greater than 20 g of alcohol were excluded. Patients were evaluated with serological testing for viral hepatitis, hemochromatosis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, and Wilson’s disease on an individual basis when appropriate.
Patients of all genders, ethnicities, and ages over 18 years were included in these registries. Questionnaires related to quality of life (QOL) that inquire patient experiences within the two weeks before their standard-of-care visit were collected in both of these populations by a trained research fellow. Our primary outcome was a comparison in QOL as measured by the CLDQ. The CLDQ is a tool used to measure health-related QOL and has been validated in multiple chronic liver diseases (CLDs). It includes 29 items and is divided into six domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function, and worry. Each question receives a score that ranges from 1 as “all of the time” to 7 as “none of the time.” An overall CLDQ score is calculated and reported between 1 and 7. Higher scores indicate better QOL [4, 14, 26, 27].

**Statistical methods**

We used JMP V.13.0 for analyses and report data are as means ± SD for normal distributions or median interquartile range (IQR) for not normal distributions. The Shapiro-Wilk test for normality was performed for continuous variables. Baseline characteristics were compared using student t-test and Mann–Whitney–Wilcoxon test based on their distributions. Categorical variables, such as race/ethnicity, gender, and biopsy stage were summarized using percentages and compared using Pearson's chi-squared test (χ²).

Our primary endpoints were the cross-sectional comparison of the 6 CDLQ domains between subjects with the diagnosis of autoimmune disease (AIH, PBC, PSC) and NAFLD. Patients with incomplete questionnaires were excluded from the analyses. Each domain score was calculated based on the 29 items. Items 1,5 and 17 belong to abdominal symptoms, items 2,4,8,11, and 13 correspond to fatigue, items 3,6,21,23,27 to systemic symptoms, items 7,9, and 14 to activity domain. Likewise, items 10, 12,15,16,19, and 20 belonged to emotional function and items 18,22,25,28, and 29 to worry [27]. These were analyzed as continuous variables. They were not normally distributed; therefore Mann–Whitney–Wilcoxon test was used for unadjusted analyses.

We report the findings of unadjusted analyses, as well as analyses adjusted for age, race, gender, platelets, LFTs, Alkaline phosphatase, INR, PT, albumin, biopsy stage, BMI, weight, age/LFTs/biopsy stage/sex/race/height, age/BMI, LFTs/biopsy stage using multivariate analysis (ANCOVA).

A subset analysis for comparisons among AIH, PBC and PSC groups, if variables were normally distributed, we conducted an overall ANOVA, whereas for those not normally distributed, we used
the Kruskal Wallis test. We report the findings of unadjusted analyses, as well as analyses adjusted for age, Alkaline phosphatase, INR, PT, gender, and race.

Results:

Patient characteristics
Overall, 185 autoimmune liver disease patients were included in this study, composed of 93 AIH, 56 PBC and 36 PSC patients. A total of 218 NAFLD patients were studied. In terms of patient demographics, there was a greater proportion of females in the autoimmune liver group as compared to the NAFLD group (74% vs 39.9%, p<0.001). Within autoimmune liver diseases, AIH and PBC were more female predominant than PSC. Autoimmune liver patients were significantly older than NAFLD patients (55.8 vs 49.7 years, p<0.0001). NAFLD patients were significantly heavier than autoimmune liver patients (220.8 vs 170.8 lbs, p<0.0001). Patients overall were primarily non-Hispanic and majority white Caucasian, but significant differences existed in the racial composition of autoimmune liver patients as compared to NAFLD patients.

Disease characteristics
There was no significant difference in Fibroscan scores between autoimmune liver and NAFLD patients. The distribution of fibrosis stage on liver biopsy between autoimmune liver and NAFLD patients also did not reach significance (p=0.073). When comparing the autoimmune liver subgroups of AIH, PBC and PSC to each other, however, there was a significant difference (p=0.0013) in fibrosis stage on biopsy. It is worth noting that 28% of AIH patients had fibrosis stage of 0 on biopsy, whereas no PBC or PSC patients were stage 0. It is possible that this may be related to the utility of liver biopsy in establishing a diagnosis of AIH. NAFLD patients had higher AST (49.5 vs 41.6, p<0.0001) and ALT (73.2 vs 43.8, p<0.0001) values than autoimmune liver disease patients. However, alkaline phosphatase was higher in autoimmune liver disease patients than NAFLD patients (157.3 vs 77, p<0.0001), and within the autoimmune liver group the cholestatic diseases PBC and PSC had the highest alkaline phosphatase. There was no significant difference in Fibroscan scores between AIH, PBC and PSC autoimmune liver disease subgroups.

CLDQ results
There was no significant difference in the overall CLDQ scores between autoimmune liver patients and NAFLD patients. Each of the 6 domains of the CLDQ, which are scored on a Likert scale from
1 (most impairment) to 7 (least impairment), was then individually reviewed. In unadjusted analysis, autoimmune liver patients reported significantly more fatigue than NAFLD patients (4.75 vs 5.04 respectively, \( p=0.045 \)), but NAFLD patients reported significantly more worry than autoimmune liver patients (5.29 vs 5.6 respectively, \( p=0.0074 \)). Subsequently in adjusted analysis controlling for the variables of age, AST and ALT, fibrosis stage, sex and race, autoimmune liver patients continued to be significantly more fatigued than NAFLD patients (\( p=0.0182 \)). After adjusting for the same variables, the difference in worry between the two groups was no longer significant (\( p=0.19 \)). There were no other notable differences in the remaining abdominal symptoms, systemic symptoms, activity, and emotional domains of the CLDQ between autoimmune liver and NAFLD patients. There was no difference in CLDQ scores when comparing within the autoimmune liver disease group between AIH, PBC and PSC. In a subsequent analysis, patients with F2-F4 fibrosis reported significantly more impairment in activity (5.60 vs 5.92, \( p=0.02 \)) and worry (5.24 vs 5.64, \( p=0.035 \)) when compared to patients with F0-F1 fibrosis.

Discussion:

Patient reported outcomes and health related quality of life remain important functional measures in the clinical setting and with well validated questionnaires are being incorporated into patient care. Autoimmune hepatitis is a rare disease and as such studies on health-related quality of life are limited [1-5], but all have demonstrated impaired quality of life in this group of patients. In one study, when comparing patients with autoimmune hepatitis using the SF-36 against controls, they found these patients had significant impairment in the quality of life, particularly female patients as it pertains to the physical domain and fatigue, but this was not affected by the presence of cirrhosis, age at the diagnosis, duration of the disease, and there was no significant correlation between elastography measured liver stiffness and HRQoL [1]. In a different study, patients with autoimmune hepatitis were found to have higher rates of depression and anxiety symptoms linked to concerns about the progression of their liver disease [3]. Patients with autoimmune hepatitis had previously been compared to patients with chronic hepatitis C using the CLDQ with no significant differences in their CLDQ scores, but compared to the general population, had worse scores on the SF-36, which was associated with cirrhosis, comorbid disease and treatment for autoimmune hepatitis with prednisolone also associated with a lower score on the worry domain [4]. A different study did reveal all CLDQ domain scores and the overall CLDQ score in patients with cholestatic liver disease declined from early to advanced cirrhosis and the severity of disease [13]. In particular, CLDQ systemic function, activity and overall CLDQ domain scores were significantly lower in more advanced stages in terms of histological staging [13]. These studies
demonstrate autoimmune hepatitis and other types of autoimmune liver disease exert a profound detrimental impact on the quality of life of these patients. In this present study, we demonstrated differences in health-related quality of life as measured by the CLDQ between patients with autoimmune liver disease and patients with NAFLD, which is rising in the United States. HRQoL in patients with NAFLD has previously been compared to patients with Chronic Hepatitis C [24,26] and both Chronic Hepatitis B & C [26].

In this study, our data shows there are differences in health-related quality of life amongst patients with autoimmune liver disease compared to patients with NAFLD as measured by the CLDQ. Autoimmune liver patients reported significantly more fatigue than NAFLD patients, while patients with NAFLD reported significantly more worry than autoimmune liver patients, though when adjusted for other factors, this was no longer a significant finding. Even after adjusting for several different variables such as age, AST and ALT, fibrosis stage, sex and race, patients with autoimmune liver disease continued to have significantly more fatigue than patients with NAFLD.

In a subsequent analysis, we also demonstrated patients with F2-F4 fibrosis reported significant impairment in the activity and worry domains of the CLDQ. We suspect this is likely due to increasing functional impairment, worsening liver function, complications associated with this, and likely driven by fear of transplant, liver failure, and end stage disease progression. Fatigue is a frequent and debilitating symptom that commonly affects patients with chronic liver disease. It has been studied particularly in patients with PBC who often report dramatic impairments in their quality of life due to fatigue. However, within patients with autoimmune liver disease, there were no differences detected by CLDQ.

Limitations: Some of the limitations within this study include generalizability (patients are seen at a liver center in a tertiary referral center), homogeneity of patients (largely Caucasian), and not having uniform biopsy or Fibroscan data for all patients. It is difficult to compare treatments across these etiologies as management for patients with autoimmune liver disease is largely immunosuppressive while therapy for patients with NAFLD may include weight loss, exercise, and management of other comorbidities including diabetes and hypertension. Furthermore, there are several immunosuppressive therapies available for patients with autoimmune liver disease, while some patients may be in remission and not on any active therapy. Thus, it is unlikely we are able to compare how therapy affects HRQoL across this disease spectrum, but we suspect, as has already been established in the literature, that corticosteroid use affects HRQoL.
Conclusion:
Outside the prevention of liver disease progression and related complications, factors such as mental and physical functioning should drive patient-centered care. Several studies have shown that HRQoL is impaired in patients with chronic liver disease. According to our study patients with autoimmune liver conditions report significantly more fatigue symptoms than NAFLD patients. Further studies examining the cause of different patient reported concerns by disease are warranted along with solutions to address them.
References:


