21S105 Health-related Quality of Life in Non-alcoholic Fatty Liver Disease Associates with Hepatic Inflammation

Marie Boyle[1], Yvonne Huber[2], Dina Tiniakos[1], Quentin M Anstee[1], Jörn M Schattenberg[2], EPoS Consortium Investigators.

[1] Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom.
[2]Department of Medicine, University Medical Centre of the Johannes Gutenberg-University Mainz, Mainz, Germany

INTRODUCTION & AIMS

Non-alcoholic fatty liver disease (NAFLD) is the fastest growing and most common cause of liver disease globally. Patients with chronic liver disease exhibit nonspecific symptoms that add to the disease burden and lead to a significant impairment in the quality of life. There is a conflicting body of literature in NAFLD regarding the influence of histological disease severity on total symptom burden. With the emergence of medical therapy for NASH, it will be of importance to identify patients with the highest unmet need for treatment. Patient reported outcomes (PROs) are an important tool to assess the individual burden of a disease.

The aim of this prospective study was to determine factors that affect HRQL in a population with histologically defined NAFLD.

METHODS

Study Participants Patients with NAFLD were recruited at the Freeman Hospital Liver Unit, Newcastle Upon Tyne Hospitals NHS Trust, United Kingdom (UK) as part of the prospectively enrolling European NAFLD Registry and completed the Chronic Liver Disease Questionnaire (CLDQ), the Beck's Inventory Version 2 (BIV2) and the Fatigue Impact Scale (FIS). All PROs were completed within 6 months of diagnostic liver biopsy. NAFLD Patients were also recruited from the University Medical Centre of the Johannes Gutenberg-University, Mainz, Germany and the University Hospital of the University of Seville, Spain, to complete the CLDQ.

Histological Assessment Liver histology was assessed by central scoring from expert histopathologists that belong to the EPoS Pathology consortium, a group that undertook extensive harmonisation procedures for NAFLD pathological assessment and demonstrated high kappa-value reproducibility. NASH was diagnosed and scored according to the NASH CRN criteria.

Statistical Analysis; Analysis of covariance (ANCOVA) to test the main and interaction effects of histological disease stage on PRO scales. Associations between two variables were assessed using univariate regression analysis. The Mann-Whitney-U-Rank test or Chi-square test was used to calculate differences between two groups while the Kruskal-Wallis rank test was used to compare multiple different groups. All statistical analyses were performed using SPSS software version 24.0 (SPSS Inc, Chicago, USA).

RESULTS

UK COHORT

147 patients were included in the UK arm of the study. Clinical details are summarised in **table 1**

Table 1: Variable	Study Cohort (n=147)
Patient demographics and metabolic profile	
Gender (Male)	85 (58%)
Age	53 +/- 13
BMI	35 +/- 5
Obesity	134 (91%)
T2DM	90 (61%)
Hypertension	87 (57%)
Hyperlipidaemia	88 (57%)
ALT	93 +/- 62
AST	60 +/-33
Histology	
Steatosis (0/1/2/3)	1/33/79/34
Ballooning (0/1/2)	44/72/31
Lobular inflammation (0/1/2/3)	27/69/49/2
Fibrosis (0/1/2/3/4)	29/29/28/40/21
Patient Reported Outcomes	
CLDQ	4.72 +/- 1.31
FIS	79.45 +/- 33.89
BIV2	13.75+/- 10.95

Preliminary Exploration of the influence of NAFLD histology on CLDQ, FIS and BIV2 Scores

A one-way ANCOVA controlling for significant biological co-variates showed that

- Grade of lobular inflammation influenced CLDQ scores (F=3.802, p=0.012) and FIS scores (F=4.908, p=0.012).
- Liver histology did not influence BIV2 scores.

Significant trends in CLDQ data are reported in **table 2**

Table 2 CLDQ Trends	
NAFLD Versus Other CLD (HCV,PBC and HBV) **CLDQ scores in the UK NAFLD cohort were 4.73+/-1.3**	Significantly better CLDQ scores were reported in the control population (6.0+/-1) and the HBV population (6.0+/-0.9). Inferior CLDQ scores were observed in the PBC (4.4+/-1.3) and HCV populations (4.4+/-1.6)
Correlation of total CLDQ score with clinical and demographic patient details	There was a significant negative linear correlation between total CLDQ scores and male gender (Rs -0.298), BMI (Rs -0.307 and NASH (Rs -0.172)
Gender, metabolic profile and CLDQ Scores	CLDQ scores were lower for females versus males (4.27 versus 5.1, p=<0.0001), obesity versus overweight/normal (4.66 versus 5.44, p=0.036) and for NASH versus NAFL (4.49 versus 4.9, p=0.038).

NAFLD HISTOLOGY AND CLDQ SCORES

Patients with more severe hepatic steatosis, ballooning and fibrosis had a trend towards lower scores however these trends did not reach statistical significance. Degree of lobular inflammation correlated significantly with total CLDQ scores (Rs = -0.200, p=0.015), extending to the subdomains of fatigue, systemic symptoms, activity and worry. More severe lobular inflammation (grade 3 vs grade 1: 3.03 vs 5.00; p = 0.046) and grade 2 vs grade 1:4.38 vs 5.00; p=0.017) were associated with lower CLDQ scores **Table 3. Figure 1**

Table 3 Lobular Inflammation	Mean CLDQ Score	N (%)
0	4.79	27(18.4%)
1	5.00	69 (46.9%)
2	4.38	49 (33.3%)
3	3.03	2(1.4%)

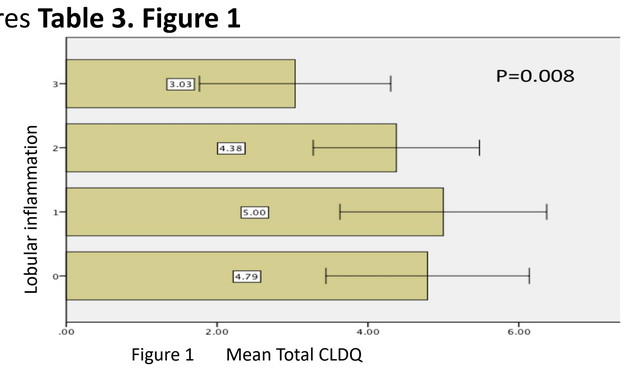

Figure 1 Mean Total CLDQ

DIFFERENCES IN HEALTH-RELATED QOL IN EUROPE

The CLDQ scores for each European country are shown in **table 4.** Significant differences in CLDQ scores exist between the 3 European countries

Table 4: Parameter	Total (n=304)	UK cohort (n=154)	German cohort (n=133)	Spanish cohort (n=17)	P-Value
CLDQ overall score	4.99 (±1.2)	4.73 +/- 1.3	5.27 (±1.1)	5.14 (±1.1)	<0.01
Abdominal symptoms	5.33 (±1.6)	5.24 +/- 1.6	5.51 (±1.5)	4.76 (±1.6)	0.12
Fatigue	4.31 (±1.6)	4.12 +/- 1.6	4.48 (±1.5)	4..64 (±1.7)	0.09
Systemic symptoms	5.09 (±1.3)	3.94 +/-1.1	5.37 (±1.2)	5.35 (±1.2)	<0.01
Activity	5.43 (±1.4)	5.2 +/- 1.5	5.73 (±1.2)	5.12 (±1.4)	<0.01
Emotional functioning	4.93 (±1.5)	4.6 +/- 1.6	5.30 (±1.3)	5.32 (±1.4)	<0.001
Worry	5.18 (±1.5)	4.91 +/- 1.6	5.46 (±1.3)	5.38 (±1.1)	<0.01

NAFLD patients scored lowest in the subdomains of fatigue (4.12), systemic symptoms (3.94) and emotional functioning (4.6), therefore additional analyses into the themes fatigue and depression were conducted.

UK NAFLD COHORT: DEPRESSION AND FATIGUE DATA

There are strong negative linear correlations between CLDQ scores, fatigue (Rs=-0.801) and depression (BIV2) scores (Rs=-0.470) underlining the fact that these factors lead to a significantly impaired QoL.

Fatigue scores were higher in NASH population (87 versus 74, p=0.010) and significantly correlated with degree of lobular inflammation (Rs 0.228, p=0.006) and BMI (Rs=0.225, p=0.006).

BIV2 scores did not significantly correlate with steatosis, ballooning, lobular inflammation or fibrosis (p>0.05). Uncontrolled, depressive symptoms were not significantly different between the NASH and NAFLD group (14 versus 13, p=0.084).

POTENTIAL CONFOUNDING EFFECT OF DEPRESSION ON CLDQ AND FATIGUE

In order to consider the potential confounding of depression on CLDQ and FIS scores, patients with moderate or severe depression were excluded. This generated a cohort of subjects (n=113) For fatigue, BMI and Lobular inflammation correlated with FIS scores in a positive, linear and significant manner. For CLDQ, male gender and BMI correlation with CLDQ scores in a negative, linear and significant manner. The reported trends were the same as those observed in the complete cohort including patients with severe depression

CONCLUSIONS

This study highlights the link of impaired HRQL with liver parenchymal inflammation. In contrast to the published data reporting fibrosis as they key determinant of NAFLD mortality, lobular inflammation appears to correlate independently with HRQL. The apparent divergence of fibrosis on mortality and HRQL potentially reflects differences in the underlying mechanisms that contribute to progression of the respective histologic lesion and HRQL impairment.

Our findings underline the need for an appropriate tool to assess the symptoms that contribute to the high disease burden in NASH. Delineation of the factors which drive impaired QoL in NAFLD will permit the development of therapeutic targets and increased awareness of QoL in NAFLD will allow clinicians to consider both clinical and patient factors in treatment selection