Assessment of Health Related Quality of Life in Chronic Liver Disease Patients Using the Japanese Versions of CLDQ and SF-36

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Abstract: Liver disease affects health-related quality of life. The CLDQ is a liver disease specific questionnaire. This study attempted to translate the original CLDQ into Japanese and compare it with SF-36 in chronic liver disease patients, mainly chronic hepatitis C. The Japanese versions of CLDQ and SF-36 were administered to 120 CHC; 45 CHB; 29 NAFLD; 21 HCC post treatment and 50 healthy controls, between February and March, 2008. CLDQ scores of CHC patients and controls were unaffected by sex and age. SF-36 scores of female CHC patients were significantly lower (P = 0.0081) compared to male in the domain of physical function. CHC patients over 70 years had significantly lower SF-36 scores in multiple domains compared to CHC patients below 70. CLDQ scores of CHC patients were lower than controls in all 6 domains. CHB & NAFLD patients had significantly low scores in 3 domains, compared to controls. CHC patients scored significantly lower than CHB & NAFLD patients in 2 domains. Significant differences in SF-36 scores between controls, CHC, CHB and NAFLD patients were not observed. CLDQ scores of treatment naïve CHC patients, having ALT levels (≦40 or≧ 40) IU/l; liver cirrhosis patients (child Pugh A) and HCC patients post treatment, revealed that HCC and cirrhosis patients had similar CLDQ scores and significantly lower scores compared to CHC patients with ALT ≦40 IU/l in 5 out of 6 domains. CHC patients with ALT ≧40 IU/l had significantly lower CLDQ scores than CHC patients with ALT ≦40 IU/l in 3 domains. Similar differences was not observed using the SF-36. CLDQ gave a better understanding of HRQL in patients with different forms of chronic liver disease and also disease progression. Age and sex did not affect CLDQ scores. CLDQ appears to be a more convenient tool to study the HRQL in chronic liver disease patients.

INTRODUCTION

The importance of determining the health related quality of life has gained quite a momentum in the past few decades [1-3]. Since 1947, the World Health Organization has redefined health as not only the absence of disease but also a complete state of physical, mental and social well-being. Doctors and health care researchers have put emphasis on the traditional biomedical model as well as the social science model (which includes psychosocial and economical aspects), to assess the patients overall wellbeing [4]. Chronic liver disease resulting from hepatitis B, hepatitis C, alcoholism and non-alcoholic fatty liver disease in particular, is a major cause of morbidity and mortality worldwide. Chronic liver disease patients experience symptoms of fatigue, anxiety, depression, loss of self esteem, etc. as a result of disease progression including side-effects of treatment specific therapy, which have a huge impact on their HRQL. Moreover rising medical costs and declining socio-economic conditions further contribute to the deterioration of the patient's mental health and subsequently, HRQL [5, 6]. Among the various generic instruments developed to measure HRQOL Short Form 36 (SF-36) and the more recent CLDQ, are being widely used. While the SF-36 (27) covers the overall HRQL, the CLDQ responds to specific changes in HRQL, caused by Chronic liver disease [7, 8]. The use of the original CLDQ in western countries [9] and translated versions in other countries [10-14] have all demonstrated that HRQL is reduced in patients with chronic liver disease. Our study aimed to translate and validate the CLDQ in Japanese patients, alongside the SF-36 and observe and compare the subsequent outcomes. The prevalence of hepatitis C, B associated chronic liver disease in Japan and the aging of the Japanese population demands the immediate need for the assessment of HRQL in chronic liver disease patients and better healthcare for the future.

DEVELOPMENT OF THE JAPANESE VERSION OF CLDQ

After acquiring approval of the authors (Younossi *et al.*; Gut; 1999), the original English version of the CLDQ, was translated into Japanese, involving a forward-back ward translation by bilingual medical doctors, nurses and clinical research staff. The original version of the CLDQ measuring 6 domains, namely: abdominal symptoms (AS), fatigue (FA), systemic symptoms (SY), activity (AC), emotional function (EM), worry (WO) and covering 29 items (dealing

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with physical & psychological symptoms associated with liver disease), along with the rating scale of 1-7, (where 7 denotes the best possible), were left unaltered and translated into Japanese, with the intention of maintaining the original meaning as much as possible. The abbreviation "CLDQ" was maintained in the Japanese translation for the purpose of international communication. The final translation was revised in a way understandable by any lay man, with relevance to chronic liver disease.

PATIENTS & METHODS

The study was conducted at the outpatient clinic of Kawasaki Hospital, Okayama, Japan, between February and March, 2008. One hundred and twenty HCV associated Chronic liver disease patients including (70 Chronic hepatitis C patients; 29 Liver cirrhosis patients; and 21 HCC patients), 45 HBV associated patients (35 CHB patients; 5 liver cirrhosis patients and 5 HCC patients), 28 CHC patients who were sustained viral responders (SVR) to IFN therapy and 29 patients with non-alcoholic fatty liver disease (NAFLD), were asked to take part in the survey and answer the Japanese version of the CLDQ and SF-36. A total of 50 healthy controls (hospital staff) were chosen, including 10 people each, in their 20's, 30's, 40's, 50's and 60's, respectively to fill in the same questionnaire. All patients and controls taking part in the study gave their informed consent following a description of the protocol and outcomes.

The first step in data analysis was to derive the average of the total 29 items, which was considered the total CLDQ score for this particular group of patients. Next, the average score of the 6 QOL domains was also taken. Then, the control groups CLDQ score was compared with CLDQ scores of CHC patients, with respect to age and sex. Next, the control groups CLDQ score was compared to CLDQ scores of CHC, CHB and NAFLD patients. To find the effect of disease progression on the HRQL of the present patient population, CLDQ scores of untreated CHC patients with average ALT levels below and above 40 IU/L and liver cirrhosis patients with Child Pugh score A and HCC patients undergoing treatment, were compared. Finally, CLDQ scores of CHC patients who achieved SVR after IFN therapy were compared to IFN untreated CHC patients without IFN therapy and to healthy controls. The same method was applied for the SF-36. In all, patients took about an average of 5 minutes to complete the CLDQ and an average of 10 minutes to complete the SF-36.

STATISTICAL ANALYSIS

All data were analyzed using the SAS statistical software, JMP version 1 for windows. Standard statistical tests performed included students *t* test and the Wilcoxon test.

RESULTS

Table **1** compares the CLDQ and SF-36 scores of patients based on sex. No significant differences were observed among CLDQ scores based on sex. SF-36 scores in females were significantly lower than males in the domain of physical function (PF_N; $P = 0.0081$). Table **2** compares CLDQ and SF-36 scores of patients above and below 70 years of age. There was no significant difference in CLDQ scores with respect to age. SF-36 scores in 4 domains of patients over 70 years, were significantly lower than patients below 70 (PF_N; $P = 0.0029$), (Role physical; RP_N; $P = 0.0033$), (Bodily pain; BP_N; $P = 0.018$) and (General health; GH_N; $P = 0.0033$). Figs. (**1a**) and (**1b**) compare the CLDQ and SF-36 scores of healthy controls with CHC, CHB and NAFLD patients. CLDQ scores of CHC patients were lower than controls in all 6 domains, while CHB & NAFLD patients had significantly low scores in 3 domains (SS; AC and WO), compared to controls. CHC patients scored significantly

Table 1. Comparison of CLDQ & SF-36 Scores of Chronic Hepatitis C Patients Based on Sex

		Female	Male	P-Value
CLDQ Domains	Total CLDQ Score	5.1±1.2	5.3±1.0	NS
	Abdominal Symptoms	5.8±1.3	6.0±1.2	NS
	Fatigue	4.4±1.5	4.6 ±1.4	NS
	Systemic Symptoms	5.3±1.2	5.5±0.9	NS
	Activity	5.4±1.3	5.8±1.1	NS
	Emotional Function	5.0±1.5	5.2±1.3	NS
	Worry	5.1±1.6	5.2±1.4	NS
SF-36 Domains	Physical function	39.7±16.4	49.2±11.7	0.0081
	Role Physical	42.3±15.3	49.4 ±8.3	NS
	Bodily pain	50.2.±11.6	54.5±8.6	NS
	General Health	42.6±9.9	43.5±11.8	NS
	Vitality	49.4±11.8	51.8±10.7	NS
	Social Function	48.7±11.8	48.6±11.6	NS
	Role Emotion	42.8±15.4	48.4±12.8	NS
	Mental Health	50.9±10.1	52.5±9.8	NS

Table 2. Comparison of CLDQ & SF-36 Scores of Chronic Hepatitis C Patients Based on Age

		< 70 yrs	> 70	P-Value
CLDQ Domains	Total CLDQ Score	5.3±1.2	5.0±1.0	NS
	Abdominal Symptoms	5.9±1.4	5.9±1.1	NS
	Fatigue	4.6±1.5	4.3±1.3	NS
	Systemic Symptoms	5.5±1.1	5.3±1.1	NS
	Activity	5.8±1.2	5.2±1.2	NS
	Emotional Function	5.3±1.4	4.9±1.4	NS
	Worry	5.1±1.6	5.2±1.5	NS
SF-36 Domains	Physical function	47.7±13.5	38.2±16.1	0.0029
	Role Physical	48.4±12.3	41.3±14.2	0.0033
	Bodily pain	54.7±9.4	48.8±11.3	0.0185
	General Health	44.3±11.8	41.6±9.2	0.0033
	Vitality	51.8±12.7	48.8±9.9	NS
	Social Function	50.7±9.8	46.8±12.9	NS
	Role Emotion	48.7±13.1	41.1±15.3	0.0123
	Mental Health	52.8 ±11	50.2±8.9	NS

lower than CHB & NAFLD patients in 2 domains (SS and AC) and (SS and WO). In SF-36, CHC patients had lower scores compared to controls and NAFLD in 4 domains; (PF_N; RP_N; BP_N; GH_N; $P < 0.05$) and (PF_N; RP_N; Social functioning: SF_N; Role emotional: RE_N; $P < 0.05$) respectively and lower scores compared to CHB in 6 domains (PF_N; RP_N; BP_N; GH_N; SF_N; RE_N; $P < 0.05$). Differences in SF-36 scores of CHB and controls was significant in only one domain (GH_N; $P < 0.05$) while NALFD scores were significantly lower than controls in 4 domains (PF_N; GH_N; SF_N; RE_N; $P < 0.05$). To assess the effect of disease progression on the HRQL of patients, CLDQ and SF-36 scores of 71 untreated HCV associated chronic liver disease patients divided into 3 groups (CHC, ALT 40 IU/l: n= 37; ALT 40 IU/l, n= 18; cirrhosis Child Pugh A: n= 16) and 21 treated HCC patients, were compared to that of 50 healthy controls (Figs. **2a** and **2b**). The treated HCC group and cirrhosis group had almost similar CLDQ scores. Both HCC and cirrhosis patients had significantly lower scores compared to CHC patients with ALT 40 IU/l in 5 out of 6 domains (FA, SS, AC, EF and WO). CHC patients with ALT 40 IU/l had a significantly lower CLDQ score than CHC patients with ALT 40 IU/l, in 3 domains (SS, AC and WO). In SF-36, though significant differences were observed

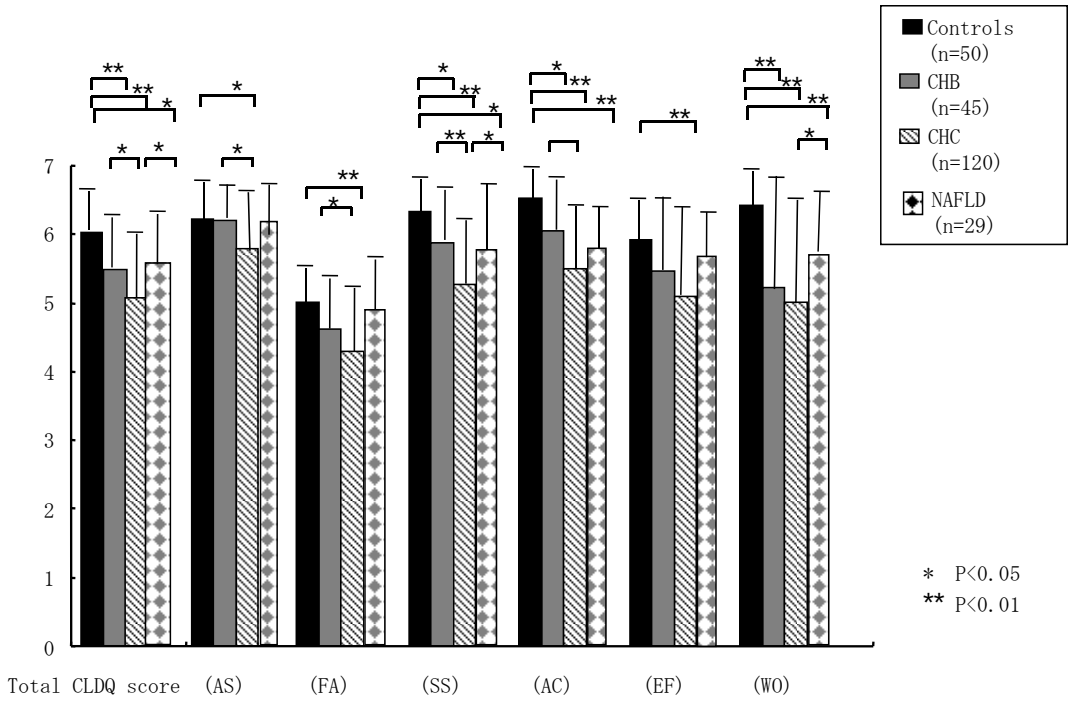

Fig. (1a). Comparison of CLDQ scores of Controls with CHC, CHB & NAFLD patients.

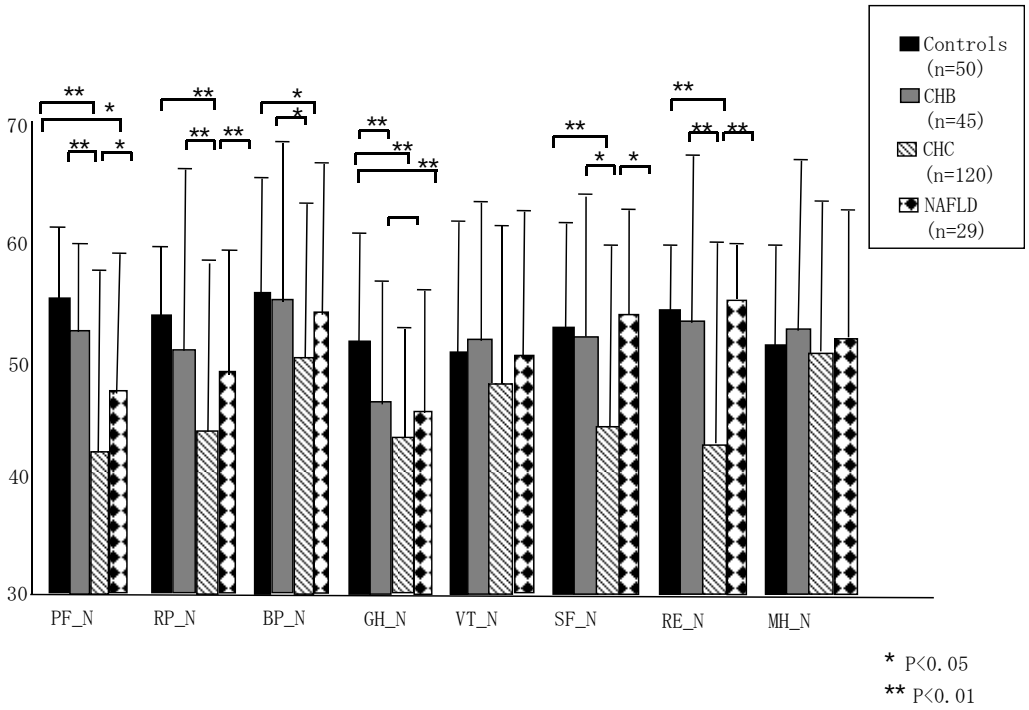

Fig. (1b). Comparison of SF-36 scores of Controls with CHC, CHB & NAFLD patients.

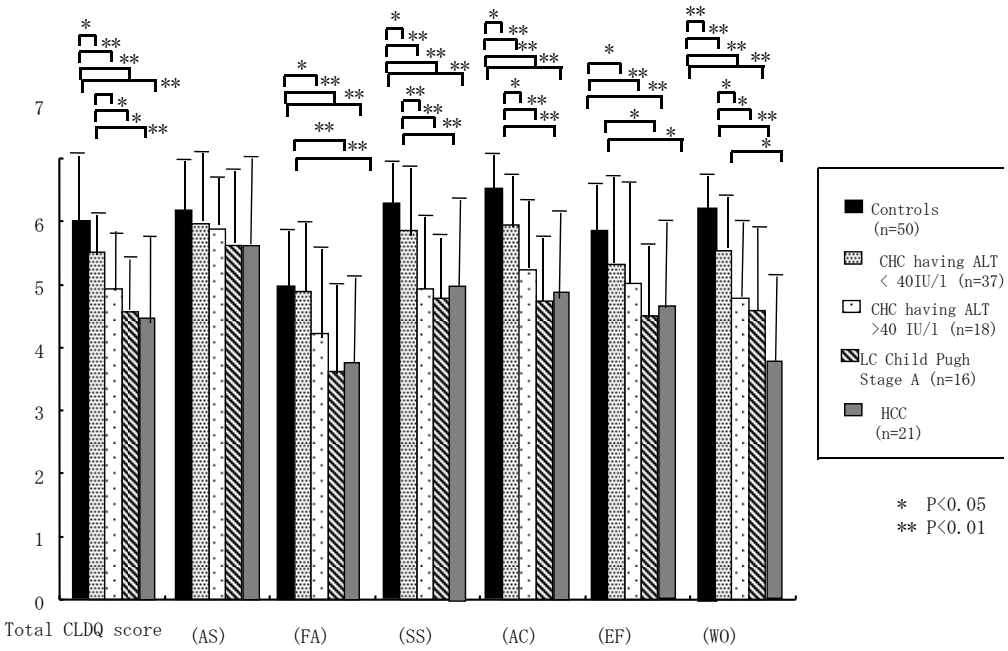

Fig. (2a). Comparison of CLDQ scores of controls with CHC patients having ALT ≦40 IU/l; ≧40 IU/l; LC patients with Child Pugh Stage A and HCC patients.

in all domains with respect to various chronic liver disease, the presence of larger standard deviations in each group, led to confusion and unexplainable data scores. In addition, total CLDQ scores of patients who became SVR to IFN therapy were significantly higher than untreated patients and similar to scores of healthy controls (data not shown). No such observation was made with respect to SF-35 scores of SVR patients.

DISCUSSION

Chronic liver disease due to viral causes is very common worldwide and about 3 million Japanese are persistently infected with HCV and HBV [15]. Primary liver cancer, 95% of which is HCC, has ranked third in men and fifth in women as a cause of death from malignant neoplasm in Japan [16]. Therefore extensive methods are being sought to prevent or treat liver disease. Hepatitis C virus infects

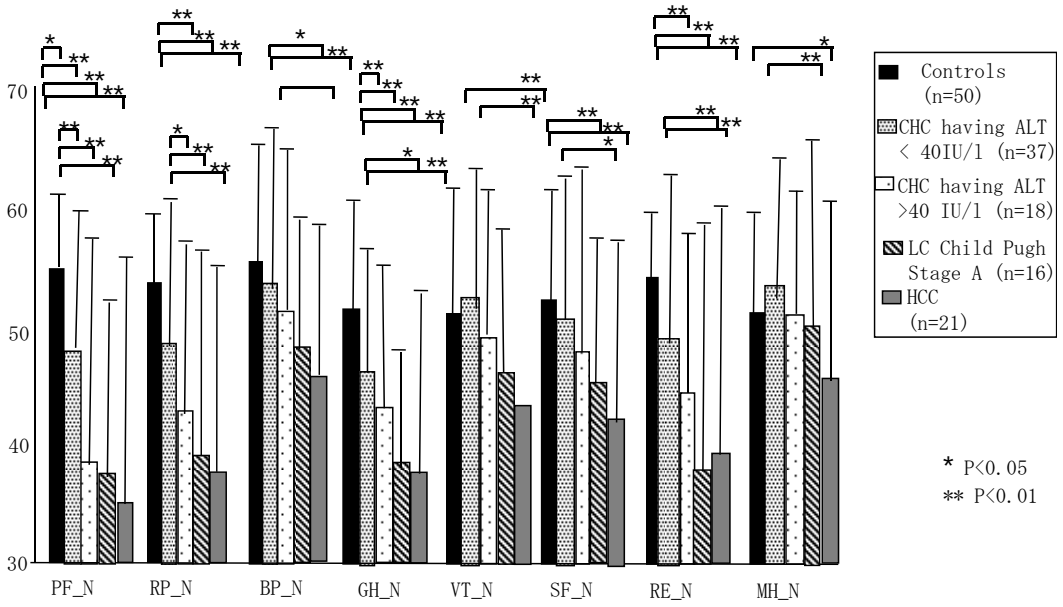

Fig. (2b). Comparison of SF-36 scores of controls with CHC patients having ALT ≦40 IU/l; ≧40 IU/l; LC patients with Child Pugh Stage A and HCC patients.

approximately 170 million people worldwide including 2 million in Japan [17]. About 70-80% of all chronic hepatitis is caused by HCV and about 10-20% is caused by Hepatitis B virus. To prevent the development of liver cirrhosis and liver cancer from chronic HCV and HBV infection, long term treatment regimes are being considered. Particularly in HCC patients, local treatment interventions such as RFA [18], or vascular treatment interventions such as TAE, TACE [19] are being widely used, in conjunction with IFN therapy and chemotherapy [20, 21]. As the silvering of Japan continues to increase, the number of chronic liver disease patients over the age of 60 is also rapidly increasing. At present, a large number of chronic liver disease patients are receiving treatment in the outpatient clinic, while continuing with their everyday lives. Indeed long term IFN therapy in elderly chronic liver disease patients [22-25] achieves satisfactory viral response, lowers levels of tumor markers and reduces tumor size, but also includes side effects of ongoing therapy, which greatly affect the patients HRQL [26]. Until now HRQL questionnaires such as SF-36 has been used effectively to assess HRQL in patients undergoing IFN therapy [27]. The authors have also used SF-36 in CHC patients undergoing Peg-IFN therapy to assess HRQL and found that the increasing age of patients had an overall affect on the patients HRQL [28, 29]. Using the SF-36, age & sex both seemed to play a major role in QOL of patients. However in this study, the authors did not find a significant difference in the CLDQ scores of chronic liver disease patients & healthy controls, with respect to age (below & above 70 years of age) and sex. Younossi *et al.* [9] reported that with increasing age the AC score in the CLDQ drops. The authors had a similar observation in the present group of patients. When the patient's age crosses 70, the AC score reduces. Younossi *et al.* [9] have also mentioned that disease progression seems to be more related to decreasing QOL scores rather than age. The authors also had similar observations. Since the probability of cirrhosis increases after the age of 70, not only age but other important factors too seem to affect the patients QOL. In controls, the CLDQ score of the "FA" was comparatively low compared to the scores of the other 5 domains. This could account for some CLDQ questions being more generalized and not specific for only liver disease patients, such as (tiredness, day long wellbeing, irritability). In CHC patients, compared to patients with other forms of liver disease, symptoms of depression, contribute mainly to the decrease in QOL scores [30]. When compared to HBV and NAFLD patients, CLDQ scores of CHC patients were found to be low in multiple domains and scores of HBV and NAFLD patients appeared similar which is a little different from the data reported by Dan *et al.* [31]. In chronic liver disease patients, unless liver disease progresses rapidly, there are hardly any specific symptoms. For which many chronic liver disease patients continue to lead normal lives without any knowledge of their ongoing disease. By the time they start feeling the symptoms and their HRQL has been greatly affected, the disease has already reached an advanced stage. In the present CHC patient population, similar to the observations of Younossi *et al.* [9], there was a significant decrease in CLDQ scores with the progression of the ongoing disease. In HBV and NALFD patients, due to the small patient population compared to CHC, a solid relationship between disease progression and decrease in QOL could not be clearly observed. Therefore, it is necessary to observe this effect in a bigger population. Moreover, as all patients included in this study were chosen from the out-patient clinic, only the QOL status of cirrhosis patients with Child Pugh score A and HCC patients undergoing treatment, could be observed. Future studies including patients with cirrhosis of Child Pugh stage B and C and their QOL scores according to their disease stage, need observation. Regarding CLDQ scores of CHC patients who have achieved SVR following IFN therapy, compared to the untreated group, the CLDQ scores in all domains was higher and almost similar to those of healthy controls. Particularly, in the domain of WO, the

IFN treated group scored significantly higher compared to untreated patients. The CLDQ initiated in projecting the fact that, achieving SVR relieved the patients of disease worry, thus indicating the importance of IFN therapy in CHC patients. IFN therapy till date is the best antiviral therapy available. Newer, more effective forms of IFN (Peg IFN) alone or in combination with newer anti-viral drugs (Ribavirin), have been able to achieve sustained viral response in about 50% of chronic liver disease patients. However, side effects of such therapy sometimes have a great impact on the patients well-being and sometimes therapy is stopped mid-way, before achieving the targeted viral response. Particularly in the present group of patients, as the average age of patients is very high, the strong side effects of Peg IFN and Ribavirin combination therapy, impacts greatly on the patients HRQL. Therefore with the aid of SF-36 and the CLDQ, if the patients HRQL during therapy can be monitored and attended to, perhaps the cessation of therapy mid way can be lessened to some extent. While administering the SF-36 to chronic liver disease patients it was observed that patients had difficulty in answering questions related to disease progression, as the SF-36 is not disease specific. The use of CLDQ enabled patients to answer liver disease specific questions. However, even while administering the translated version of the CLDQ into Japanese patients, based on the present Japanese social and medical system, questions related to liver transplant (Q 29) or personal questions related to family, were difficult to answer. This being our first attempt at using the CLDQ, we kept the original meaning of the questions intact, though some questions may have been difficult to understand or answer to, from a Japanese perspective. The authors feel, in the future, with the permission of the original authors of the CLDQ, some questions need modification or alternate interpretation to fit the Japanese perspective and easy to understand and answer, by Japanese patients or be omitted as they may not be applicable for the majority of Japanese patients with chronic liver disease.

Thus the original CLDQ was translated into Japanese for the first time and applied different forms of chronic liver disease and compared with the widely used SF-36. Since sex and age over 70 years affected SF-36 scores, it was difficult to conclude from the SF-36 survey alone how much liver disease itself plays a role in lowering HRQL, as aging itself affects HRQL. Clear cut differences among CLDQ scores was observed between patients with CHB, NAFLD and CHC. This is very important in understanding how the CLDQ can differentiate liver diseases of separate origin, such as CHB, NAFLD and CHC. The difference in CLDQ scores among CHC patients in various stages of liver disease enables us to understand how liver disease progression affects the patients HRQL. Further studies using the CLDQ in other liver disease patients need to be carried out to better understand the impact of liver disease on the patients HRQL and improve the patients QOL. Compared to the SF-36, the CLDQ seems to be more disease specified for better understanding HRQL of chronic liver disease patients and should be used in conjunction with SF-36.

ABBREVIATIONS

ALT = Alanine aminotransferase

CHB = Chronic hepatitis B

CHC = Chronic hepatitis C

CLDQ = Chronic liver disease questionnaire

HCC = Hepatocellular carcinoma

NAFLD = Non alcoholic fatty liver disease

HCV = Hepatitis C virus

HRQL = Health related quality of life

IFN = Interferon

Peg-IFN = Pegylated interferon

QOL = Quality of life

SF-36 = Short form 36

SVR = Sustained viral responder

RFA = Radio frequency ablation

TACE = Trans arterial chemoembolization

TAE = Trans arterial embolization

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