



## Assessment of Medication Adherence and Health-Related Quality of Life in Chronic Liver Disease Patients

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### ABSTRACT

Cirrhosis is a growing cause of morbidity and mortality in developed countries. It is associated with multiple life-threatening complications. Improving medication adherence could have a greater impact on the health of the population. Health-Related Quality of Life (HRQoL) has become a common outcome indicator in clinical and epidemiological studies. It is a multidimensional concept that includes self-reported measures of one's physical and mental health as well as their social well-being. This study aimed to assess the HRQoL and medication adherence in Chronic Liver Disease (CLD) patients. Medication adherence was determined using the Adherence to Refills and Medication Scale (ARMS) and RAND's SF-36 was used to assess HRQoL. A total of 102 Chronic Liver Disease patients were enrolled in the study, the majority of whom belonged to Child-Turcotte-Pugh class C (45.1%). The majority of the patients had a history of alcohol consumption (77.5%). The total average of four dimensions under PCS and MCS of SF-36 was 45.49 and 72.89 respectively and the overall average of all domains was 59.19. Concerning the Child-Turcotte-Pugh score of the patients, a significant correlation was obtained between physical functioning and RLPH domains. ARMS score had a significant impact on 3 of the PCS and all MCS domains of SF-36, indicating that the patient's medication adherence has an important role in HRQoL.

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### INTRODUCTION

Chronic Liver Disease and its end-stage cirrhosis can result in a wide array of healthcare problems. The disease consists of a wide spectrum of pathophysiological events characterized by an increase in total liver collagen and other matrix proteins,

which disrupt the framework of the liver and impair its function (Iredale, 2003). Cirrhosis is the 14<sup>th</sup> most common cause of death worldwide, but in Central Europe, it is the fourth leading cause of death and is a growing cause of morbidity and mortality in developed countries (Tsochatzis *et al.*, 2014). The most common etiologies of CLD include Alcoholic Liver Disease (ALD), Non-alcoholic Fatty Liver Disease (NAFLD/NASH), Chronic Viral Hepatitis including chronic hepatitis B, C and D, genetic causes such as alpha-1 antitrypsin deficiency and hereditary hemochromatosis followed by autoimmune causes (Moon *et al.*, 2020). CLD is associated with multiple life-threatening complications such as hepatic encephalopathy (HE) or hepatic coma (HC), portal hypertension, oesophageal varices, intraabdominal infections, and hepatocellular carcinoma (HCC) (Sempokuya *et al.*, 2019). Patients with CLD who develop new diagnoses are put on new medica-

tions that require alteration/ adjustment in dosages of existing medications (Volk *et al.*, 2012). Subsequently, medication mismanagement and non-adherence are fairly common in patients with decompensated cirrhosis (Hayward *et al.*, 2017). Inadequate medication adherence contributes to increased morbidity, mortality and healthcare costs as well as patient and provider frustration (Conn and Ruppert, 2017).

According to WHO, medication adherence may be defined as the "extent to which a person's behaviour- taking medication, following a diet, and/or executing lifestyle changes- corresponds with agreed recommendations from a health care provider". Regardless of innovations, unless we instate new methods of improving medication adherence, the potential improvements in overall healthcare outcomes cannot be achieved. Despite the availability of effective medicines for a wide range of conditions, patients are non-adherent to their medication more or less half of the time (Brown *et al.*, 2016). Complex regimens are extremely challenging to maintain since they may include various formulations, numerous daily dosages and in certain situations, particular administration instructions (e.g. take 1 h before food). Adherence can be hampered by cognitive and psychological changes that occur with increasing age (e.g. swallowing difficulties). Non-adherence can be either intentional (i.e. including a deliberate decision-making process) or inadvertent, in which the patient intends to follow the treatment plan but runs into practical issues (e.g. forgetfulness). However, both types of non-compliance might be observed in certain patients. In older adults, non-adherence rates range from 25 to 75 percent and are attributed to poor clinical results, higher hospital admissions and medical expenses (Patton *et al.*, 2017).

Assessing or measuring adherence is the first step in understanding adherence. There is a need in outpatient clinical settings for a valid, cost-effective and reliable tool for measuring medication adherence accepted by both patients and health care providers. Comprehensive use of this tool to gather information on factors that influence Adherence in diverse patient populations will lead to a better understanding of non-compliance and aid in adopting measures to increase adherence to treatments (Morisky *et al.*, 2008). Patient self-report continues to be a popular method of assessing medication adherence. It is simple and inexpensive, especially when compared with medication event monitoring systems, the measurement of drug levels in the body or the calculation of refill compliance from claims data (Kripalani

*et al.*, 2009).

In clinical and epidemiological studies, health-related quality of life (HRQoL) has become a common outcome indicator (Häuser *et al.*, 2004). According to CDC, "Health-related quality (HRQoL) is an individual's or a group's perceived physical and mental health over time. On an individual level, HRQoL includes perceptions of physical and mental health, as well as their correlates such as health risks and conditions, functional status, social support, and socioeconomic status" (Younossi and Henry, 2015). Generic measurement scales provide an overview of HRQoL, typically taking physical, mental, and social aspects of health into account. One advantage of generic scales is that they allow us to study the relative impact of various diseases, which can be useful for health policymakers. The main drawback is a lack of sensitivity to clinically significant changes such as lab parameters which may have particularly large implications of disease outcomes. As a result, generic scales are frequently combined with disease-specific scales, which measure clinical and social factors directly related to the condition under investigation. Disease-specific scales should demonstrate how disease severity, clinical outcomes and treatment affect HRQoL ((Orr *et al.*, 2014).

## MATERIALS AND METHODS

The study was carried out in the inpatient ward of the department of General Medicine of a tertiary care teaching hospital. This was an observational study that was conducted over 6 months. Patients who were of age 18 years and above, those with a confirmed diagnosis of chronic liver disease with or without co-morbidities and who were willing to participate in the study with signed written informed consent forms were included. Patients on palliative care, severely ill to respond to the questionnaire, on Psychiatry treatment or hemodynamically unstable were excluded.

A structured questionnaire was used to collect data from the selected subjects. The collected data were entered into Microsoft Excel and appropriate statistical analysis was performed to evaluate the study's results.

### Study tools

Data was collected using a self-designed data collection form which contained details like demography, chief complaints, medical history, laboratory and radiological investigations, and present medications. RAND's SF-36 was used to assess HRQoL. This scale consists of 8 multi-item sections/domains

(Physical functioning, role limitation due to physical health, bodily pain, general health, vitality, role limitations due to emotional problems, social functioning, and mental health). The domains were categorized as Physical component summary (PCS), which includes physical functioning, role limitation due to physical health, bodily pain, and general health and Mental Component Summary (MCS) consisting of vitality, role limitations due to emotional problem, social functioning, and mental health. The lower the score, the greater the disability. Adherence to medication and refills scale (ARMS) was used to assess medication adherence. It consists of 14 questions administered verbally by healthcare professionals to assess patients' medication-taking behaviour. Each item is structured for a response on a Likert scale with responses of "none", "some", "most" or "all" the time, which are given values from 1 to 4. Item scores are summed to produce an overall adherence score which ranges from 12 to 48, with lower scores indicating better adherence.

#### Ethical clearance

This study was approved by the Institutional Ethics Committee of Father Muller Medical College Hospital, Mangalore (Ref. no. FMM-CIEC/CCM/285/2019).

#### Statistical Analysis

Chi-Square Test was performed to find the association between the demographic profile of the patient and the Child-Turcotte-Pugh Score. Karl Pearson's coefficient of correlation method was used to find the associations between quality of life and medication adherence. The results were expressed in terms of a 95% confidence interval. The results were also presented in the form of frequency format with appropriate tabular forms.

## RESULTS

**Table 1: Distribution on the basis of Child-Turcotte-Pugh score**

Child-Turcotte-Pugh Score	Frequency (%) (n=102)
A	18(17.6%)
B	38(37.3%)
C	46(45.1%)

The majority of the 102 patients with CLD enrolled in the study were in the age group of 41-60 years(59.8%). Out of the 102 patients, 83 (81.4%) were male and 19 (18.6%) were female.

11(10.8%) out of the 102 patients were illiterate;

**Table 2: Frequency distribution of Complications**

Complications	Frequency (%)
Nil	9(8.8%)
Portal hypertension	80(78.4%)
Ascites	74(72.5%)
Esophageal varices	27(26.4%)
Anemia	18(17.6%)
Portal gastropathy	14(13.7%)
Encephalopathy	12(11.7%)
Hepatorenal syndrome	7(6.8%)
Portal vein thrombi	3(2.9%)

meanwhile, a majority was high school educated (45.1%). 55 (53.9%) were from rural settings and the remaining 47 (46.1%) were from urban areas. History of alcohol consumption was observed in 79 (77.5%) patients and a majority of them had a history of duration of alcohol consumption between 11 to 20 years (70.9%). The most commonly seen comorbidities were type 2 diabetes mellitus (36.2%) and hypertension (20.5%).

Of the 102 enrolled, the majority of the patients were categorized under Child-Turcotte-Pugh C (45.1%), followed by Child-Turcotte-Pugh B (37.3%) and Child-Turcotte-Pugh A (17.6%), as shown in Table 1.

In the study population, 93 (91.2%) patients had one or more complications associated with Chronic Liver Disease. The most commonly seen complication was portal hypertension (78.4%) followed by ascites (72.5%) (Table 2).

The mean value of ARMS scores was  $15.62 \pm 5.34$ , with a majority of the patients showing the highest adherence score (46.07%). It was found that age, gender, education, alcohol consumption and the number of prescriptions had no statistically significant impact on medication adherence ( $p=0.68$ ,  $p=0.71$ ,  $p=0.72$  and  $p=0.19$ , respectively).

Assessment of QoL in the study population using SF-36 revealed that the average score of physical functioning, role limitation due to physical health (RLPH), bodily pain, and general health was  $49.55 \pm 29.13$ ,  $44.85 \pm 45.77$ ,  $47.20 \pm 34.44$ , and  $40.43 \pm 15.24$ , respectively. Analysis of mental components of SF-36 revealed the average of vitality, social functioning, role limitation due to emotional problems (RLEP) and mental health to be  $52.69 \pm 21.89$ ,  $80.53 \pm 21.3$ ,  $77.12 \pm 39.79$ , and  $81.21 \pm 16.17$ , respectively. The total average of four dimensions under PCS and MCS was 45.49 and

**Table 3: Gender and SF-36 domains**

Gender		Physical Component Summary		
	Physical Functioning	RLPH	Bodily pain	General Health
Male	54.09±28.99	48.2±46.16	51.14±34.43	41.61±15.82
Female	29.73±20.58	30.3±42.14	30±29.55	34.86±10.68
Gender		Mental Component Summary		
	Vitality	Social Functioning	RLEP	Mental Health
Male	54.7±21.56	80.75±21.77	75.5±40.35	81.44±16.30
Female	43.94±21.76	79.60±20	84.2±37.00	80.21±16.00

RLEP- Role Limitations Due to Emotional Problem, RLPH- Role Limitation Due to Physical Health

**Table 4: Age and SF-36 domains**

Age		Physical Component Summary		
	Physical Functioning	RLPH	Bodily pain	General Health
<40	63.33±30.19	59.72±49.36	61.52±37.13	41.66±16.54
41-60	46.23±28.35	42.62±44.10	44.42±32.88	40.09±14.59
>60	49.55±29.13	39.13±46.96	43.36±35.06	40.35±15.18
Age		Mental Component Summary		
	Vitality	Social Functioning	RLEP	Mental Health
<40	61.66±24.37	82.08±25.12	77.77±37.91	81.55±15.94
41-60	51.55±21.30	79.50±20.92	76.50±40.98	81.50±16.76
>60	52.69±21.89	82.53±21.30	77.12±39.79	80.17±15.37

**Table 5: Child-Turcotte-Pugh Score and SF-36 domains**

Domains	Mean±SD	Karl Pearson correlation Coefficient	p value	Significance
Physical Functioning	49.55±29.13	-0.209	0.040	Significant
RLPH	44.85±45.77	-0.204	0.039	Significant
Bodily Pain	47.20±34.44	-0.000	0.996	Not Significant
General Health	40.43±15.24	-0.138	0.173	Not Significant
Vitality	52.69±21.89	-0.064	0.524	Not Significant
Social Functioning	80.53±21.3	-0.065	0.576	Not Significant
RLEP	77.12±39.79	-0.056	0.596	Not Significant
Mental Health	81.21±16.17	-0.053	0.706	Not Significant

**Table 6: Correlation between ARMS and SF-36 domains**

Domains	Mean±SD	Karl pearson correlation Coefficient	p value	Significance
Physical Functioning	49.55±29.13	-0.198	0.046	Significant
RLPH	44.85±45.77	-0.345	0.000	Significant
Bodily Pain	47.20±34.44	-0.259	0.009	Significant
General Health	40.43±15.24	-0.190	0.060	Not Significant
Vitality	52.69±21.89	-0.203	0.040	Significant
Social Functioning	80.53±21.3	-0.390	0.000	Significant
RLEP	77.12±39.79	-0.343	0.000	Significant
Mental Health	81.21±16.17	-0.248	0.012	Significant

72.89, respectively and the overall average of all domains was 59.19.

A comparison of the QOL scores in both male and female patients revealed that females had slightly lower PCS scores and vitality scores than males. However, the mean RLEP score was more in females as compared to males. The scores for mental health and social functioning showed the lowest disparity between males and females (Table 3).

Based on the study, a clear difference in the mean scores of Physical Functioning, RLPH, Bodily pain, and Vitality between the age group of <40 and >40 years was observed, with the younger population faring Better in terms of scores (Table 4).

Using the Karl Pearson coefficient of correlation method, it was found that age, gender, education, and alcohol consumption had no significant effect on any of the domains of SF-36 ( $p=0.24$ ,  $p=0.1$ ,  $p=0.15$ , and  $p=0.31$ , respectively). A significant correlation was obtained between physical functioning and RLPH scores of SF-36 with the Child-Turcotte-Pugh score of the patients. The Child-Turcotte-Pugh scores had no statistically significant effect on bodily pain, general health and MCS domains, indicating that the severity of the disease did not cause a marked decrease in the emotional and social well-being of the patients (Table 5).

Karl Pearson coefficient of correlation method was used to determine the influence of medication adherence on SF-36 domains. ARMS score had a significant effect on all domains of SF-36 (except General health), indicating that the patient's medication adherence had marked improvement on HRQoL (Table 6).

The most commonly prescribed medications in the current study were Thiamine (81.34%), Ondansetron (39.2%), Ursodeoxycholic acid (30.38%), Propranolol (48.02%), Multi vitamin (78.2%), Pantoprazole (76.44%), Vitamin K (57.85%), Lactulose (68.58%), Sucralfate (29.4%) and protein powder (32.34%). The most often administered antibiotics were Rifaximin (48.02%), Ceftriaxone (42.14%), Cefixime (15.68%) and Piperacillin+ Tazobactam (13.72%).

## DISCUSSION

In the current study, it was found that the prevalence of Chronic Liver Disease was higher in males as compared to females. This is supported by the study conducted by Benegal V et al., and this increased prevalence in males may be attributed to the fact that alcohol use among women (5.8%) in southern India is much lower than among men (33.2%), a result

which was obtained from previous studies (Benegal et al., 2003).

The highest prevalence of CLD was found in the age group of 41-60 years of age. This is consistent with the study conducted by Fedeli U et al., which indicated that the prevalence of CLD among males increased with age until 50-54 years (Fedeli et al., 2019).

Of the 102 patients enrolled in the study, the majority of the patients were alcoholics and a greater number of them were consuming alcohol for 10-20 years. A study conducted by Mann R E et al. found that patients with cirrhosis had a history of alcohol consumption for more than 17.1 years on average, whereas those with normal liver function had an average of around 8 years of alcohol consumption, thus underpinning the effect of duration of alcohol consumption and CLD development (Mann et al., 2003).

The most common comorbid conditions were found to be Diabetes mellitus and hypertension. This is consistent with the findings of the study conducted by Vaz J et al., which found that the most common comorbidities at diagnosis were arterial hypertension (33%) and type 2 diabetes (29%) (Vaz et al., 2020).

The study results indicated that medication adherence of the patient was not associated with age, gender, and the number of prescribed medications. However, a systemic review conducted by Clepton A J et al. observed that the prescribed number of doses per day is inversely related to compliance (Claxton et al., 2001). A study conducted by Park H Y et al. to determine medication adherence and beliefs about medication in elderly patients living alone with the chronic disease showed that gender, age group, and the number of prescribed medication were not associated with medication adherence (Park et al., 2018). The study conducted by Hayward K et al. also showed no association between age, gender, and the number of medications prescribed with medication adherence among patients with liver cirrhosis (Hayward et al., 2017).

According to the ARMS scores obtained from the study, overall high medication adherence was seen among the patients. High medication adherence can be because the drugs prescribed for CLD are less expensive than those prescribed for other diseases. Fewer side effects and easier administration of prescribed medications may also contribute to better medication adherence. However, Hayward et al. conducted a study that showed up to 70% of cirrhotic patients are classified as having "low" or "Medium" levels of medication adherence (Hayward

*et al.*, 2016).

A significant difference was observed in the mean scores of Physical Functioning, RLPH, Bodily pain and Vitality between <40 and >40 years of age. It was also observed that alcohol consumption did not significantly influence the HRQoL. Contrasting our result, a study conducted by Hauser W et al. found no significant effect of age and gender on HRQoL (Häuser *et al.*, 2004). However, a study conducted by Kim et al., and Sobhonslidsuk A et al., revealed that age and gender were significantly associated with HRQoL and the duration of alcohol abuse was insignificant (Kim *et al.*, 2018; Sobhonslidsuk, 2006). The disparity observed among different studies regarding the effect of age and gender on QoL may be attributed to the sociocultural differences that occur with the varying geography of these studies.

Patients with progressive cirrhosis have greatly impaired physical aspects of HRQoL (Marchesini *et al.*, 2001; Afendy *et al.*, 2009). The severity of the disease, measured using the Child-Turcotte-Pugh score have a strong impact on the HRQoL of the patients in the domains of Physical Functioning and RLPH. There was no significant association between disease severity and other domains of PCS and MCS of SF-36. Several studies have shown a similar pattern of association between Child-Turcotte-Pugh score and HRQoL. Few studies indicated significant differences only in some domains of the PCS but not the MCS, although these were smaller studies (Younossi *et al.*, 2001; Arguedas *et al.*, 2003; Orr *et al.*, 2014). However, a study conducted by Sobhonslidsuk A et al. found an association between severity of the disease and RLEP along with PCS domains. However, a conclusion could not be reached based on this due to other confounding factors (Sobhonslidsuk, 2006). Given that the Child-Turcotte-Pugh score is predominantly calculated by complications that influence physical health, this observation may suggest that the Child-Turcotte-Pugh score can be considered a surrogate marker to assess the impaired physical functioning.

It was found that 3 out of 4 domains of PCS and all 4 domains of MCS were significantly influenced by medication adherence. Previous studies have shown an association between health-related quality of life, well-being and adherence behaviour. A study conducted by Polis S et al. indicated that quality of life domains- 'less fatigue', 'less abdominal symptoms', and 'emotional function' were significantly correlated with medication adherence. Past studies had observed a weak correlation between 'never missed medication' and

quality of life domains (Burge *et al.*, 2005; Polis *et al.*, 2016; Hayward *et al.*, 2017). Conversely, decreased HRQoL may negatively impact the medication adherence of the patient. We observed that the 'General Health' domain was not significantly associated with medication adherence. This may be due to highly subjective questions of the domain, which can force the patient's reply to skew towards a positive response.

There are some potential limitations to this study. The study's effect estimates are based on a cross-sectional study. As a result, they are susceptible to inherent biases and confounding factors due to the subjective nature of the patient's responses that may have influenced our findings. Because the sample size was limited to 102 patients from a relatively narrow geographical region in India, the findings of this study may not be completely generalizable.

## CONCLUSIONS

In conclusion, the physical aspects of HRQoL is significantly reduced as the disease progresses in Chronic Liver Disease. Patients with alcohol intake of more than 10 years are more susceptible to suffer from liver cirrhosis. However, the severity of the disease does not depend on the duration of alcohol consumption. Patients had high medication adherence, which can be explicated by the fact that medications prescribed for CLD are cheaper, have lesser side effects and are easily available and administered as opposed to medications prescribed for other chronic diseases. Males had better QoL than females with respect to physical functioning and bodily pain and similar QoL in terms of social and mental health. The HRQoL significantly reduced after 40 years in physical functioning, RLPH, bodily pain and vitality domains. The severity of the disease caused a decrease in the physical aspects of HRQoL and had no significant impact on the mental and social well-being of the patient.

Given that the Child-Turcotte-Pugh score is primarily calculated by parameters that affect physical health, this observation may imply that severity based on the Child-Turcotte-Pugh score can only be used as a marker of the patient's impaired physical health. The study indicated that medication adherence was significantly associated to 7 out of 8 domains of SF-36. Therefore, we conclude that medication adherence can play a significant role in the HRQoL and vice versa.

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## Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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