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Assessment and Comparison of Cognitive Function and Depression level among patients with Chronic Liver Disease and Healthy Controls

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Abstract
Background & Aims: *Chronic liver disease (CLD) is a progressive disorder which causes deterioration and regeneration of parenchymal cells in liver and has become an increasingly important public health issue worldwide. Cognitive impairment together with depression may substantially diminish the functional capacity of life in patients with CLD. Many a time's both cognitive impairment and depression are not observed by health workers and not assessed in clinical area routinely. Therefore, studies in this area are vital to fulfil the gap of practice and this can facilitate the nursing personnel to support clinician in this challenging area. The aim of the present study was to assess the cognitive function and depression level of patients with CLD and compare withhealthy controls.**Methods**: A case control study was conducted in hepatology department of selected hospital on patients with CLD and healthy controls. Convenience sampling technique was used to select 220 subjects (110patients with CLD and 110 healthy controls). Matching was done in patients with CLD and healthy controls in terms of age and gender. Both the groups were examined with Modified Mini Mental State Examination and Beck Depression Inventory to assess the cognitive function and depression level respectively. Data was analysed using appropriatedescriptive (mean, standard deviation, frequency and percentage) and inferential statistics (independent sample t test, ANOVA and chi-square test).**Results:** Patients with CLD and healthy controls were comparable in terms of age, gender, marital status, employment status and monthly income. Significant difference was found between patients with CLD and healthy controls in terms of cognitive function ($t=12.1$, $p<0.001$) and depression level ($\chi^2=56.7$, $p<0.001$). Cognitive function score of patients with CLD was significantly associated with educational status ($t=3.8$, $p<0.001$), monthly income ($F=7.8$, $p=0.001$), presence of cirrhosis ($t=2.3$, $p=0.025$) and presence of Minimal Hepatic Encephalopathy ($t=4.8$, $p<0.001$). Depression level of patients with CLD was significantly associated only with gender ($\chi^2=10.2$, $p=0.006$). There was significant negative correlation between cognitive function and depression level ($r= -0.298$, $p= 0.002$) among patients with CLD and significant negative correlation between age and cognitive function score ($r= -0.401$, $p<0.001$) among healthy controls. **Conclusions:** Based on the findings, the study concluded that patients with CLD had poor cognitive function and severe depression compared to healthy controls.Cognitive function among patients with CLD was associated with educational status, monthly income, presence of cirrhosis and MHE. Depression level was associated with gender among patients with CLD.*

Keyword: *Cognitive Function, Depression level, Patients with CLD, Healthy controls*

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I. Introduction

Chronic Liver Disease (CLD) is a common public health care problemworldwide where rates of liver disease are increasing tremendously over years (Sarin &Maiwall, n.d).Total number of patients with CLD ranges from 844 - 1130 million globally. The prevalence of CLD worldwide is 18.5 percentage and the mortality per year is 2 million(Hirschfield, 2017). CLD is defined as a progressive disorder which causes deterioration and regeneration of parenchymal cells in liver and continuously leads to fibrosis and cirrhosis: and it is the 14thleading cause of deaths in the world(Wikipedia; Liver diseases 10th common cause of death among Indians,2018).Moreover, chronic liver disease is associated with more comorbidities than mortality. Portal hypertension, esophageal varices, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy (constipation, GI bleed, infection, and renal failure), hepatocellular carcinoma, coagulopathy, hepato-renal syndrome and liver failure are the complications of chronic liver disease. Chronic liver disease also leads to psychological complications such as cognitive impairment, anxiety and depression.

Abnormalities in cognitive function are common complication of chronic liver disease(Collie, 2005). The prevalence of cognitive impairment is growing nationally and internationally and is forecasting to be excessive in developing nations(Mavrodaris, Powell & Thorogood, 2013). It is also a growing medical issue in

India (Kedare&Vispute, 2016). The prevalence of cirrhosis in general population is 4.5% to 9.5% worldwide. In this 20 to 60 % of patients are affected by cognitive impairment ranging from mild to severe (American Gastroenterological Association, 2011). Irrespective of various causes for CLD, the central nervous system is usually involved and affected in patients with CLD. This influence can cause altered mental function, deviations in psychomotility, and/or hepatic coma connected with irreversible brain damage depending on its degree of severity (Brodersen et al., 2014). Mood alterations could also be affected with the neurotransmitter action variations(Stewart, Enders, Mitchell, Devine & Smith, 2011).

It is suggested that emotional disturbance can occur due to progressive cognitive dysfunction which may lead to depressive disorders among CLD patients (Brodersen et al., 2014). CLD patients with different causes have depression, out of which 30% are cirrhotic patients (Faris, 2012). Major depression (15 - 49.5%) has been noted among patients with chronic hepatitis C infection. (Schaefer et al., 2012; Golden, O'Dwyer&Conroy, 2005). Less than 5% of the population with chronic HBV infection and one-quarter of patients with NAFLD (Lee, Otgonsuren, Younoszai&Younossi, 2013; Weinstein et al., 2011)has depression. Pathogenesis of depression in chronic liver disease is not well defined and neuropsychological deficits may additionally remain the certain contributing element in these patients. This disorder occurs as a consequence of accumulation of neuropathogenic molecules and toxins in blood due to the inadequate clearance in a damaged liver (Popovic et al., 2015).

Besides, it has been mentioned that the mental dysfunction is one of the mostcommon clinical manifestations in a broad range of different diseases (Hauser, Holtmann&Grandt, 2004). Outcomes from numerous studies have showed that among those range of disease CLD are regularly connected with psychiatric comorbidity, particularly mood disorders (depression and anxiety), personality changes, sleep disturbance and other behavior and cognitive deficits. (Miotto et al., 2010; Bianchi et al., 2005;Hauser, Holtmann&Grandt, 2004). However, most of the previous studies have focused either on depression (Popovic et al. (2015);Weinstein et al. (2011); Bianchi et al. (2005)) or on cognitive impairment (Abrantes, Torres and Mello (2013); Mohamed, Fath-Elbab, Rabie and Abel-Hamid (2013))in patients with CLD while only few have assessed both together. The few studies conducted on both cognitive dysfunction and depression shows some weaknesses as small sample size.(Miotto et al., 2010). Several studies conducted to assess the relationship between depression and chronic liver disease mainly with HCV infection but rarely they examine the relation of depression with cirrhosis (Stewart et al., 2011). For this reason, the present studymonitored the cognitive function and depression in patient with and without cirrhosis among large sample size.

Nurses working in gastroenterology department commonly provides care to patients with chronic liver disease. While taking care of the physical manifestations of these patients the mental health is not noticed and treated. Cognitive impairment and depression are the two major psychological disturbances in chronic liver disease. These should be early identified and treated. Assessment and screening are the vital components of nursing responsibilities. Therefore, nurse should take initiatives to assess depression and cognitive function along with the assessment of physical symptoms among these patients.

Overall, in CLD patients the cognitive impairment is always discussed along with hepatic encephalopathy and the presence of depression is not clearly defined. It further leads to complication and affects quality of life. Most of the time both of these dysfunctions are misdiagnosed as hepatic encephalopathy which leads to improper treatment and poor outcome. However, in this complicated area still misperceptions are present(Mullish et al., 2014). Therefore, there is a vital need to assess and monitor the cognitive function and depression in chronic liver disease patients for the early identification and for proper treatment as both these illnesses are curable and treatable.

II. Materials and Methods

It was a case control study conducted in hepatology department of ILBS among patients with CLD. Convenient sampling technique was used to select one hundred and ten subjects from each group (patients with CLD and healthy controls).Matching was done between patients with CLD and healthy controls in terms of age and gender. Patients with hepatic encephalopathy other than minimal hepatic encephalopathy (MHE) and having severe hypothyroidism were excluded with the help of psychometric hepatic encephalopathy score and laboratory values respectively. Moreover, self-reported information was used to exclude the patients with pre-diagnosed psychiatric disorders.

Pilot study was conducted on ten percentage of subjects in similar settings of main study in December 2017 and ensured that those subjects were not repeated in the main study. During the pilot study, methodology and tools were found to be feasible.

The final data collection was conducted from January to February 2017. Permission to conduct the study was approved by the Institute Ethics Committee. Purpose of the study was explained to subjects before enrolling. Patient information sheet (Appendix J) was provided and informed consent (Appendix K) was obtained from patients with CLD and from healthy controls in the presence of their relatives.

Total 220 subjects i.e.110 patients with CLD and 110 healthy controls who fulfilled the inclusion criteria were enrolled into the study. Initially the socio demographic (age, gender, marital status, educational status, employment status and monthly income) and clinical data (cause of liver disease, duration of CLD, presence of cirrhosis, intake of any vitamin supplement and presence of MHE) were collected followed by a structured interview conducted to assess cognitive impairment with the help of Modified Mini Mental State Examination. Beck Depression Inventory (self-administered questionnaire) was self-administered to assess the depression level.

Data analysis

Data obtained during time period were entered into Microsoft Office Excel sheet and SPSS (Statistical Package for the Social Sciences) Version 22.0 for analysis(Appendix L). The data analysis was performed using both descriptive and inferential statistics. Frequency and percentage was used to the distribution of socio demographic and clinical variables. Chi-square was used to calculate homogeneity of distribution of socio demographic characteristics between patients with CLD and healthy controls.An independent sample 't' test and One-way ANOVAwas used to compare the mean cognitive function score of patients with CLD and healthy controls and to assess the association of cognitive function with socio demographic and clinical variables.
Chi-square test was used to test equality of proportion of depression level between patients with CLD and healthy controls and to assess the association between depression level and socio demographic variables.

III. Results

Total 41.8 percentage of the patients with CLD aged between 41-50 years and 33.6 percentage of the healthy controls aged between 31-40 years. Matching wasdone between patients with CLD and healthy controls in terms of age.The proportion of males (83.6%) and females (16.4%) in both patients with CLD and the healthy controls were same as matching was done beforehand in terms of gender.Most of patients with CLD (93.6%) and healthy controls (89.1%) were married and 6.4 percentage of patients with CLD and 10.9 percentage of healthy controls were single.

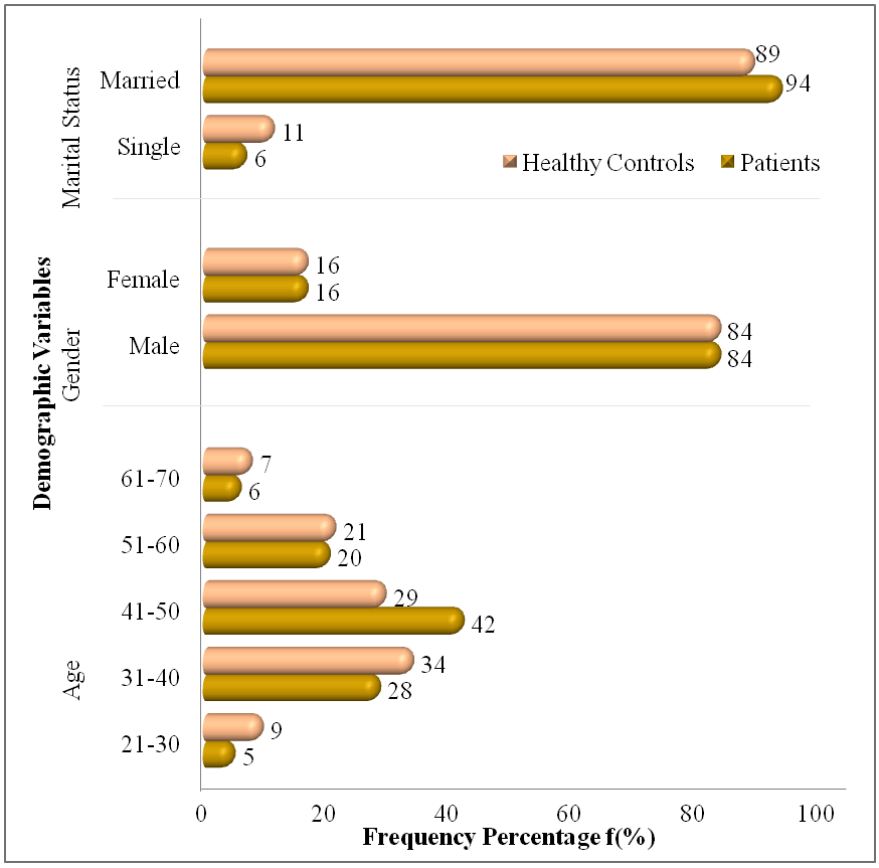

Figure 1.Clusteredbar graph showing the frequency percentage of patients and healthy controls according to their Age, Gender and Marital status.

Total43.6 percentage of the patients with CLD and 22.7 percentage of the healthy controls had high school or higher secondary education. The percentage of post graduates and above were 20.9 and 22.7 among patients with CLD and healthy controls respectively.In terms of total29.1 percentage of patients with CLD and 25.5 percentage of healthy controls were not working. Similar number (21.8%) of both patients with CLD and healthy controls were self-employed or running business. One fifth of the patients with CLD (20%) and 24.5 percentage of the healthy controls were private employees.The highest percentage of patients with CLD (48.2%) and healthy controls (31.8%) had monthly income less than Rs. 10,000/- and 16.4 percentage of the patients with CLD and 23.6 percentage of the healthy controls had monthly income more than Rs. 40,000/-.

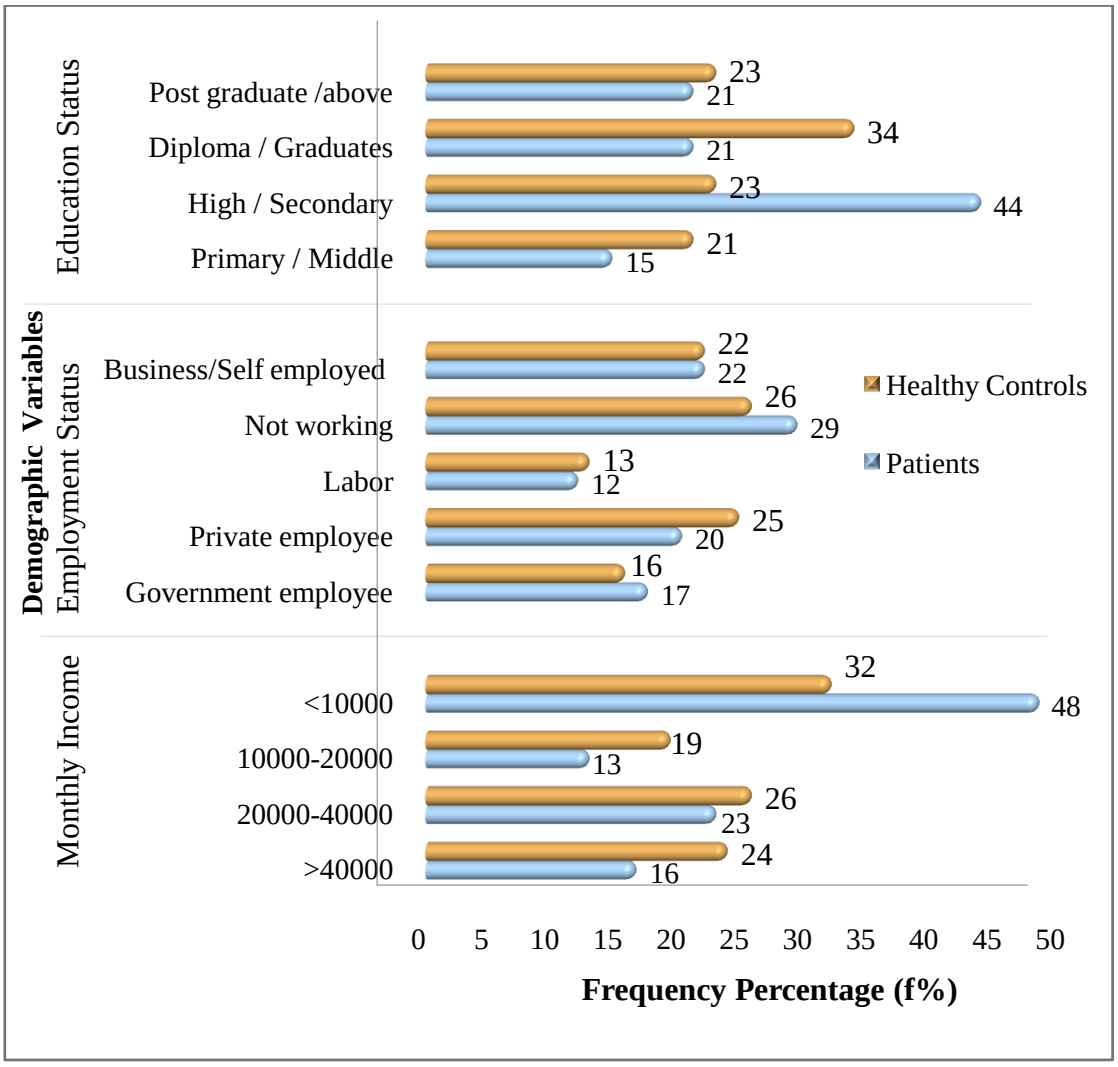

Figure 2.Clusteredbar graph showing the frequency percentage of patients and healthy controls according to their Education, Employment and Monthly Income

Total47.3 percentage of the patients with CLD were found to have alcohol consumption as a cause of liver disease whereas 17.3 percentage of the patients with CLD were diagnosed with non-alcoholic steato hepatitis and 13.6 percentage had Hepatitis-C as a cause of liver disease.Duration of CLD was 6 to12 months for 32.7 percentage and 12 to 24 months for another 32.7 percentage of patients with CLD.Most (80%) of the patients with CLD did not have cirrhosis of liver whereas 20 percentage were identified with cirrhosis.More than half (51.8%) of the patients with CLD were not receiving vitamin supplements and 48.2 percentage of patients with CLD were taking vitamin supplements regularly.Total 62.7 percentage of patients with CLD were found with MHE and 37.3 percentage of patients with CLD were found without MHE.

Table 1

Frequency and Percentage distribution of Clinical Variables of patients

n=110

Clinical Variables	Frequency (%)
Cause of liver disease	
Alcohol	52(47.3)
Hepatitis C	15(13.6)
Cryptogenic	08(07.3)
Hepatitis B	07(06.4)
Non-alcoholic steato hepatitis(NASH)	19(17.3)
Hepatomas	01(00.9)
Others*	08(07.3)
Duration of CLD(in months)	
6–12	36(32.7)
12–24	36(32.7)
24–36	17(15.5)
>36	21(19.1)
Presence of cirrhosis	
Yes	22(20.0)
No	88(80.0)
Intake of any vitamin supplement	
Yes	53(48.2)
No	57(51.8)
Presence of Minimal Hepatic Encephalopathy	
Yes	69(62.7)
No	41(37.3)

*Autoimmune hepatitis, Primary Sclerosing Cholangitis and Wilson's disease

The percentage of the patients with CLD having normal cognitive function were 33.6 whereas 64.5 percentage of the patients with CLD had mild to moderate and 1.8 percentage had severe cognitive impairment. Out of 110 healthy controls, only two (1.8%) had mild to moderate cognitive impairment and the remaining (98.2%) had normal cognitive function.The mean difference between cognitive function score of patients with CLD and healthy control was 11.6 and the calculated 't' value was 12.1 which was statistically significant ($p<0.001$). Therefore, it can be inferred that patients with CLD had impaired cognitive function as compared to healthy controls.

Table 2

Comparison of the Mean Cognitive Function score between patients and healthy controls **$n_1+n_2=110+110$**

Group	Mean±SD	MD	MD at 95%CI	t-Value	p Value
Patients	75.2±8.5	11.6	9.7-13.5	12.1	<0.001**
Healthy Controls	86.8±5.5				

** Highly significant ($p<0.01$)

Majority of the patients with CLD (74.5%) had some or the other levels of depression whereas majority of the healthy controls (72.7%) had no depression.Calculated chi-square test in term of depression level between patients with CLD and healthy controls was 56.7 which was statistically significant ($p<0.001$). Hence significantly higher proportions of patients with CLD had depression than that of healthy controls.

Table 3

Comparison of Frequencyand percentage of Depressionlevelbetween patients and healthycontrols **$n_1+n_2=110+110$**

Levels of Depression	Group		χ^2	df	p Value
	Patients f (%)	Healthy Controls f (%)			
No Depression	28(25.5)	80(72.7)			
Mild to Borderline	33(30.0)	22(20.0)	56.7	2	<0.001**
Moderate to Severe	49(44.5)	08(07.3)			

** Highly significant ($p<0.01$)

There was a significant association between cognitive function score and educational status of patients with CLD (t=3.8, p<0.001). It can be inferred that patients with CLD who were educated up to graduation or above had significantly higher cognitive function score than that of primary or secondary school educated.Cognitive function score was also significantly associated with monthly income of patients with CLD (F=7.8, p=0.001). Patients with CLD having income less than Rs. 10,000/- per month had significantly lower cognitive function score than patients with CLD of higher income as assessed by post-hoc analysis (Turkey).There was a significant association between cognitive function score and cirrhosis of liver (t=2.3, p=0.025). Patients with CLD having no cirrhosis of liver had significantly higher cognitive function score than that of patients with CLD having cirrhosis of liver.Cognitive function score was significantly associated with Minimal Hepatic Encephalopathy (t=4.8, p<0.001). Patients with CLD having no Minimal Hepatic Encephalopathy had significantly higher cognitive function score than that of patients with CLD having Minimal Hepatic Encephalopathy.Depression level was significantly associated with gender. Majority of females (77.8%) had moderate to severe depression whereas only 38 percentage of males were in the same category. The calculated chi square value was 10.2 which was statistically significant (p=0.006).

IV. Discussion

In the present study majority of the patients with CLD (90.2%) and healthy controls (83.6%) were aged between 31-60 years and most of the subjects were male (83.6%) in both groups. Most of the patients with CLD and healthy controls had high school or above education. These findings of sociodemographic variables are in accordance with other studies by Stewart et al. (2011) and Sorrell et al. (2006).

In the current study, most of the patients with CLD (93.6%) and healthy controls (89.1%) were married and in employment status, the higher proportion of patients with CLD (29.1%) and healthy controls (25.5%) were not working. This data was in compliance with the findings of study conducted by Popovic et al. (2015).Present study showedalcohol (47.3%) as the major cause of CLD. This was opposite to the study conducted by Sorrel et al (2006) who stated that predominant cause of CLD was hepatitis C. The study conducted in 11 hospital of India by Mukherjee et al (2017) showed that the major reason of CLD in India was hepatitis B and followed by hepatitis C and alcoholism. The proportions of patients detected with Minimal Hepatic Encephalopathy were 62.7 percentage in the study which was similar in the study conducted by Nwabuaku, Onyekwere and Ogun (2016).

Findings of current study showed that patients with CLD had more cognitive impairment (75.2$\pm$8.5) than the healthy controls (86.8$\pm$5.5) as assessed by Modified Mini Mental State Examination. This finding was consistent with the studies done by Metwally and Eid (2011) on assessment of cognitive function in patients with liver cirrhosis who reported that cirrhotic patients (25.35± 1.63) had poor cognitive function than that of healthy controls (27.60±1.93). Also, the study conducted by Forton et al. (2002) revealed that HCV-infected patients (mean=2.15, SD=1.56) had poor cognitive impairment (p= 0.02) than the HCV-cleared group (mean=1.06, SD=0.24). However, the study conducted by Abrantes, Torres and Mello(2013)concluded that there was no significant association between hepatitis C and cognitive dysfunction. Difference in both studies with regard to cognitive function may be because the study excluded the patients having cirrhosis, fibrosis and depression who were having significant cognitive dysfunction unlike present study.

With regard to depression, 74.5 percentage of patients with CLD had different level of depression and out of which 30 percentage had mild to borderline depression and 44.5percentage had moderate to severe depression as assessed byBeck Depression Inventory. Consistent data obtained from Popovic et al. (2015) showed that among patients with CLD 34 percentage had mild. 16.5 percentage had moderate and 12.4 percentage had severe stage of depression. Mullish et al. (2014) also stated in systematic review of managing depression among patients with Chronic Liver Disease (CLD) that level of depression was high in chronic liver disease irrespective of causes.Similar findings were reported by Bianchiet al. (2005) who conducted a study on Psychological Status and Depression in patients with liver cirrhosis and revealed that 56.7percentage of patients had scores suggestive of depression of which 40.7percentage had mild to moderate depression, 10percentagehad moderate to severe depression and 6percentagehad severe to extremely severe depression. Another study conducted by Stewart et al. (2011) showed thatCLD patients with cirrhosis had lesser percentage (31%) of depression. It is unclear that depression leads to cirrhosis or vice versa in patients with CLD.

Soriano et al.(2012) presented in their study that people with increasing age had cognitive dysfunction which was favored with present study which showed poor cognitive function of age group of 51-70 years (74.1±08.9) than 21-50 years (75.6±08.3). Female (73.9±07.8) had poor cognitive function than male (75.5±08.6) in the current study which was also similar to the study conducted by Soriano et al. (2002).Highly significant association between cognitive function score and educational statuswas seen in present study (t=3.8, p<0.001) and patients educated up to graduates or above had significantly higher cognitive function score than that of primary or secondary school educated. These results were consistent with other studies conducted by

Miotto et al. (2010) and Amodio et al. (1999) which showed that hepatic patients with higher education had high cognitive reserve. In this study, patients with CLD having alcoholism as a cause had poor cognitive function (74.4±07.5) than other causes of CLD which was similar to the study conducted by Sorrell et al. (2006) which showed that alcoholic liver disease patients (82.04±13.49) had poor cognitive function than CLD patients with hepatitis C (85.89±11.67) and cholestatic liver disease (93.38±13.69). Consistent results were also shown in the study conducted by Brodersen et al. (2014). Stewart et al. (2011) indicated in a study that patients with cirrhosis had a cognitive impairment which was supporting the findings of present study. The result of the present study showed that patients with no cirrhosis of liver had significantly higher cognitive function score ($p = 0.025$) than that of patients with cirrhosis of liver.Present study found that patients with noMHE(79.8±07.0) had significantly higher cognitive function score than that of patients with MHE (72.5±08.1). This was in favour to the finding of other study conducted by Miotto et al. (2010) which showed cognitive deficit with minimal hepatic encephalopathy.

The result from present study showed that there was no influence between age and depression which was consistent with many studies by Rocca et al. (2003) and Martins, Sankarankutty, Silva and Gorayeb(2006). However, this finding was inconsistent with the studies conducted by Kraus, Schafer, Scheurlen, Csef and Faller (2000) and Theofilou (2011) showing that patients >50 years had significantly higher level of depression indicating that elder patients had higher level of depression than younger ones. Inconsistancy in findings of these studies may be due to the cultural differencein the areas where the studies were conducted. In the present study, old aged parents were supported and taken care by their family members during their illness whereas in other studies the elderly patients faced loneliness and isolation in the society. This may be the reason to have less depression in old aged patients with CLD in the present study.Present study showed that females were having significantly more ($p=0.006$) depression than that of males. It was similar with the study conducted by Stewart et al. (2011) which showed that women had more depression than men. This finding was opposite to the study conducted by Popovic et al. (2015) which showed that women and men did not differ in depression level. It is commonly found that women have more depression than men due to biological and social factor but in chronic liver disease substance abuse and alcoholism are some contributing factors of depression in men (though could not be generalized). That may be the reason there was no difference in depression level between men and women. Present study excluded the subjects who were consuming alcohol and required at least three months of interruption in the use of alcohol for inclusion. This criterion was demanded for the purpose of psychological improvement and clinical stabilization in subjects who had the habits of alcoholism. This may be the reason that the study showed reduced depression in males.The current study also showed that depression level was not different in terms of employment status and cause of chronic liver disease which was in favour to the findings of the study conducted by Popovic et al. (2015).

The current study stated that there was a negative correlation ($r=-0.298$) between cognitive function score and depression score of patients which was highly significant ($p=0.002$). This finding was similar with the study conducted by Stewart et al. (2011) that showed statistically significant association ($p=0.026$) between decreasing cognitive function (working memory) and increasing depression score. The finding was opposed by another study conducted by Soriano et al. (2002) that stated cognitive dysfunction was not associated ($p=0.07$) with psychiatric symptom like depression. Small sample size (10 - 11 patients per group) was demanded as the reason behind this conclusion in the study whereas the present study has large sample size (110 in each group).

V. Conclusion

The current study concluded that the cognitive impairment and depression were apparently present in patients with Chronic Liver Disease as compared to healthy controls. Cognitive function among patients with CLD was associated with educational status, monthly income and presence of cirrhosis and MHE. Depression level was associated with gender among patients with CLD. Early identification of these variables is necessary to make the patient adherent to the treatment and follow up which further helps in identification and prevention of complication.

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