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# Association of severity of esophageal varix with Minimal Hepatic Encephalopathy in patients with Cirrhosis of Liver

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## ABSTRACT

**Background:** Cirrhotic patient develops esophageal varix due to portal hypertension also increase the risk of developing encephalopathy. Hepatic encephalopathy is a neuropsychiatric syndrome caused by liver disease that occurs in 30-40% of patients with cirrhosis. Minimal hepatic encephalopathy (MHE) is a state in which patients with cirrhosis of liver regardless of its cause show a number of quantifiable abnormal psychometric tests. This study aimed to see the association of severity of esophageal varix with Minimal Hepatic Encephalopathy in patients with Cirrhosis of Liver. **Methods:** This hospital based observational analytical study included 40 patients with Cirrhosis of liver admitted to the Department of Medicine, Rajshahi Medical College Hospital from July-December 2012. Complete history was taken either from patients or accompanying attendants. Thorough clinical examination was done. Relevant investigations report was collected. All the information's were recorded on the fixed protocol. Collected data was classified, edited, coded and entered into the computer for statistical analysis by using SPSS. **Results:** Severity of liver disease according to Child-Pugh Grading, Grade-A was 02(5%), Grade-B was 30(75%) and Grade-C was 08(20%). Prevalence of number connection tests positive was 15(37.5%), line tracing test positive were 15(37.5%), serial dotting test positive were 16(40.0%) and two test positives were 15(37.5%). Association between line tracing test with Child-Pugh Grading, out of 15 positive line tracing test, 09 had Grade-B and 06 had Grade-C, p value was ($p<0.05$) that was statistically significant. Association between serial dotting tests with Child-Pugh Grading, out of 16 positive serial dotting tests, 09 had Grade- B and 07 had Grade- C, p value was ($p<0.05$) that was statistically significant. Association between psychometric tests with esophageal varix by Paquet's grading, out of 40 patients 15 patients were grade-III, who were psychometric test positive groups and 16 patients were grade-III and 09 patients were grade-II who were psychometric test negative groups, p value was ($p<0.05$) statistically significant. In psychometric test positive groups mean duration of disease were 7.25(1.12) months and psychometric test negative groups were 5.09(1.99) months, p value were (<0.001) that was statistically significant. **Conclusion:** Minimal hepatic encephalopathy (MHE) is common in patients with stable cirrhosis of liver. There is a good relationship between MHE with advanced liver disease by Child-Pugh Grading. Esophageal varix with high grade severity is common in cirrhotic patients who have MHE and longer duration of disease.

**Keywords:** MHE, Cirrhosis of Liver, Esophageal Varix.

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## INTRODUCTION

Liver cirrhosis (LC) often causes portal hypertension by changing the structure of hepatic tissue and blood flow in the liver [1]. There are numerous collateral vessels between the portal vein and the vena cava. When there is high pressure in the portal vein to

allow blood to flow back from the congested portal vein system, these collateral vessels open up in large numbers to establish collateral circulation. One of the main collateral circulations is the variances between the lower part of the esophagus and the gastric fundus veins. Thus, portal hypertension is strongly associated with esophageal varices (EV) [1]. The incidence of progression to EV is approximately 7% per year [2]. It is estimated that 20% to 40% of patients with EV will have at least one episode of hemorrhaging as a result of a ruptured varix [3, 4]. A major cause of death in patients with cirrhosis is esophageal variceal bleeding (EVB). The EVB-related mortality rate at six weeks has been reported to be as high as 15% to 20% [5]. The gold standard for the screening and diagnosis of EV and EVB is endoscopy [6]. Hepatic encephalopathy (HE) is a neuropsychiatric disorder that may accompany either acute or chronic liver disease. It is defined as a disturbance of central nervous system function due to hepatic insufficiency and includes a large spectrum of clinical manifestations such as decreased intellectual function, personality disorders, alterations in level of consciousness and neuromuscular dysfunctions [7]. Minimal hepatic encephalopathy (MHE) is defined as the condition in which patients with liver cirrhosis show several quantifiable neuropsychological defects together with a normal neurological Examination [8]. MHE is present in 25%-80% of cirrhotic patients without overt hepatic encephalopathy (HE) [9-12]. Due to lack of gold standard for the diagnosis of MHE various studies have found varying prevalence of MHE. Cirrhotic patients without evidence of overt HE, 25%-80% are found to have MHE on specialized psychometric tests [9-12]. In western countries, the rate of MHE in several research series has been reported to be 60%-80%, again using a combination of psychometric and neuro-physiological techniques [10-12]. In Asian countries especially India reconfirmed the high prevalence of MHE [10, 12]. In cirrhotic patients with good liver function (Child-Pugh-A) the prevalence is low (15%), while in those with advanced cirrhosis (Child-Pugh- B/C) half of them may be suffering from MHE [16, 17]. In one study, three of nine patients with cirrhosis with MHE developed overt HE during a one-year follows up [18].

There are many methods to assess neurological function that have been applied for the diagnosis of MHE. Psychometric and neurophysiologic methods have been the most trusted and widely used tests. Cirrhotic patients with MHE more frequently develop episodes of overt HE than those without MHE and the actuarial probability of overt HE at 3 years was 56% for those with MHE and 8% for those without MHE [19]. It is probable that MHE is a marker of advanced liver failure, because it is associated with shorter survival time [20]. Some authors have proposed testing all cirrhotic patients for MHE [21]. A standardized test includes the NCT-A and NCT-B, the line-tracing test, the serial-dotting test and the Digit symbol test is recommended.

**West Haven Criteria for Semiquantative Grading of Mental State**

| | |
|---|---|
| Grade 1 | Trivial lack of awareness |
| | Euphoria or anxiety |
| | Shortened attention spa |
| | Impaired performance of addition |
| Grade 2 | Lethargy or apathy |
| | Minimal disorientation for time or place |
| | Subtle personality change |
| | Inappropriate behaviour |
| | Impaired performance of subtraction |
| Grade 3 | Somnolence to semi stupor, but responsive to verbal stimuli |
| | Confusion |
| | Gross disorientation |
| Grade 4 | Coma (unresponsive to verbal or noxious stimuli) |

**Child-Pugh grading chart of severity of liver cirrhosis**

| Parameter | Numerical score | | |
|---|---|---|---|
| | 1 | 2 | 3 |
| Ascites | None | Mild | Marked |
| Encephalopathy | None | Mild | Marked |
| Bilirubin (mg/dl) | < 2.0 mg/dl | 2-3 mg/dl | > 3.0 mg/dl |
| Albumin (gm/dl) | > 3.5 gm/dl | 2.8-3.5 gm/dl | < 2.8 gm/dl |
| Prothrombin time (seconds prolonged) | 1-3 | 4-6 | >6 |
| Total score < 7 (grade A), score 7-9 (grade B), score > 9 (grade C) | | | |

**Paquet's Grading of esophageal varix**

| | |
|---|---|
| Grade I | Small varices without luminal prolapse |
| Grade II | Moderate sized varices showing luminal prolapse with minimal obscuring of GE (gastro-esophageal) junction. |
| Grade III | Large varices showing luminal prolapse with substantial obscuring of GE junction. |
| Grade IV | Very large varices completely obscuring of GE junction |

## METHODS

This hospital based observational analytical study included 40 patients with Cirrhosis of liver admitted to the Department of Medicine, Rajshahi Medical College Hospital from July 2012-December 2012 who fulfill the inclusion and exclusion criteria was enrolled in this study. Complete history and physical examination were done and recorded in a case record form by investigator himself. Diagnosis of cases was based on clinical suspicion, by ultrasonography and endoscopic findings of esophageal varix. After taking informed consent all patients were undergo psychometric test in the Department of Gastroenterology and Hepatology, RMCH. If two tests were abnormal then considered the patients having MHE. This procedure was performed with Number connection test, Line tracing test, Serial dotting test. Before performing the actual test, the procedure was explained and demonstrated. Normal values for psychometric test results were obtained from normal control subjects. The data was analyzed with the help of SPSS software program version-12.0

## RESULTS

140 patients of which 40 patients with cirrhosis and remaining 100 patients as controls for the psychometric tests were included in the study. None of the patients had evidence of neurological and/or psychiatric abnormalities on global clinical examination.

**Table 1: Age group distribution of the study population**

| Age group | Study group | | | P value |
|---|---|---|---|---|
| | Case | Control | Total | |
| 30-40 years | 17(42.5) | 44(44.0) | 61 | 0.24 |
| 41-50 years | 12(30.0) | 18(18.0) | 30 | |
| 51-60 years | 11(27.5) | 38(38.0) | 49 | |
| Total | 40(100) | 100(100) | 140 | |
| Mean ±SD | 44.12(±9.14) | 45.41(±10.12) | 30-60 years | 0.48 |

The mean age was in case 44.12 (±9.14) years comprised of 40 patients with minimum age of 30 year and maximum of 60 year. In the control group of 100 patients the mean age was 45.41(±10.12) years, minimum age of 30 year and maximum of 60 year. In the case group majority were in the age group of 30 – 40 (n= 17) years and in controls 30- 40 (n= 44) years.

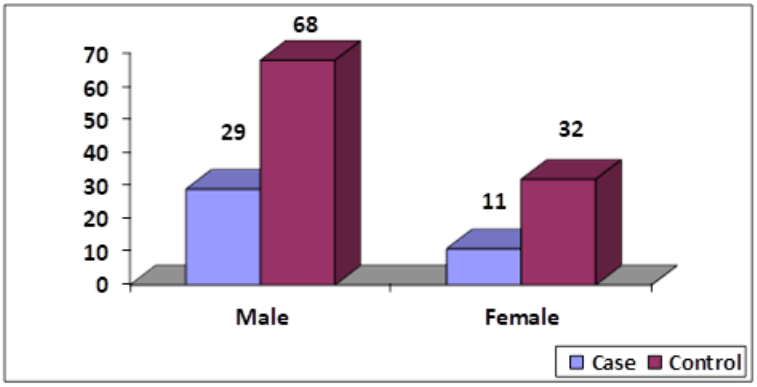


**Figure 1: Distribution of sex according to study group**

In the study group 72.5% (n=29) were males and 27.5% (n=11) were females. A male preponderance was observed. In the controls 68.0 %(n=68) were males and 32 % (n=32) were females

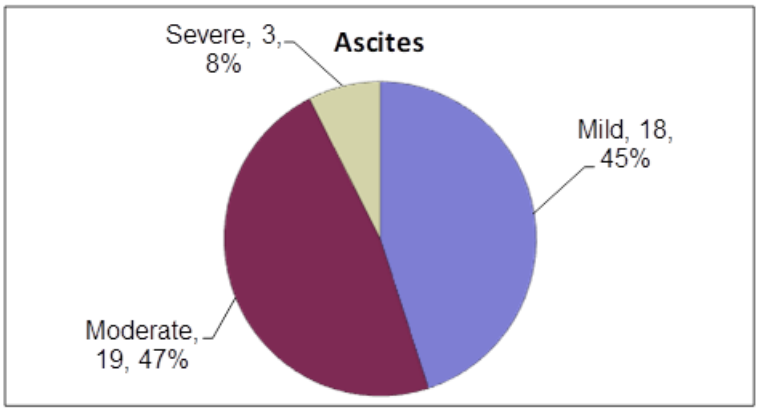


**Figure 2: Ascites pattern in cases**

In the cases 18 (45%) had mild, 19(47%) had moderate ascites and 3 (8%) had severe ascites.

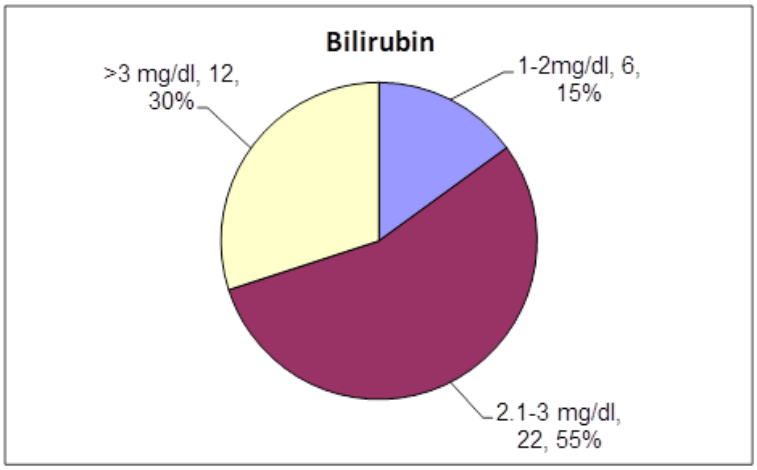


**Figure 3: Serum bilirubin level**

Out of 40 cases 22 (55%) had serum bilirubin level in the range of 2.1-3 mg/ dl. 12(30%) had >3 mg/dl and remaining 6(15%) between 1 to 2 mg/dl.

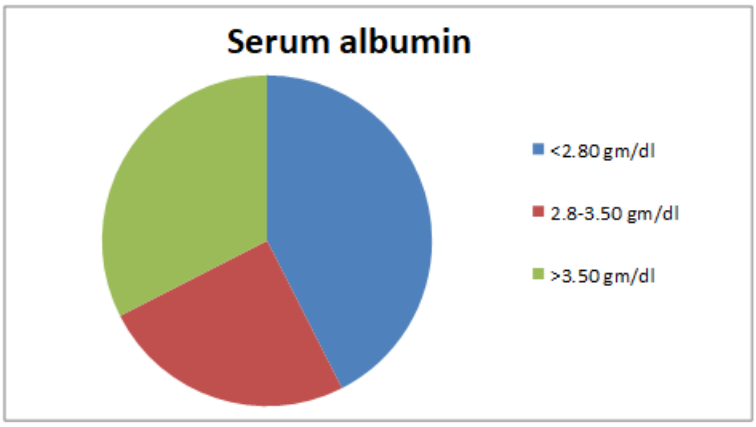


**Figure 4: Serum Albumin level in cases**

Serum albumin was <2.8 gm/dl (42.5%) in 17 cases, 25.0% (n=10) had serum albumin in the range of 2.8 to 3.5 gm/dl and 13 (32.5%) cases had> 3.5 gm/dl.

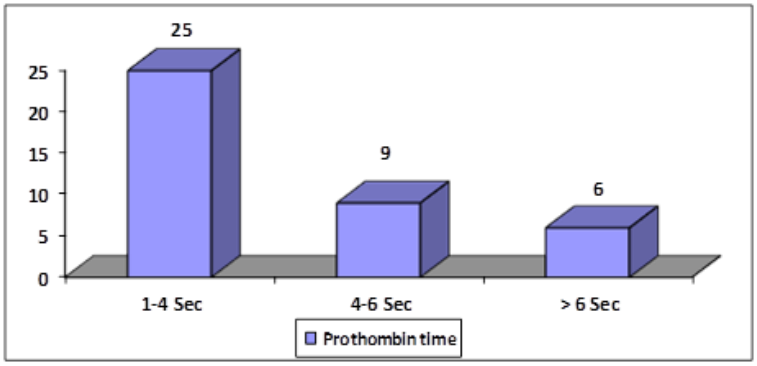


**Figure 5: Prothrombin time**

Prothrombin time was prolonged in 1-4 sec in 25 cases, between 4 and 6 sec in 9 cases and more than 6 sec in 6 cases.

**Table 2: Psychometric test in 100 healthy subjects and cut-off based on these**

| Name of psychometric test | Time taken for test completion (in seconds) | Upper cut-off values (in seconds) |
|---|---|---|
| Number connection test | 23.20-56.5 | 57 |
| Line tracing test | 36.80-62.82 | 63 |
| Serial dotting test | 8.35-14.29 | 15 |

Table shows upper cut-off values of psychometric test (in seconds) in control group, Number connection test was 57sec, line tracing test was 63 sec and serial dotting test was 15 sec.

**Table 3: Psychometric test findings in case and control group**

| Psychometric test (in seconds) | Case (Mean ±SD) | Range (Min-max) | Control (Mean ±SD) | Range (Min-max) | P value |
|---|---|---|---|---|---|
| Number connection test | 59.01 ±12.98 | 37.50-79.81 | 41.95±5.63 | 23.20-56.5 | <0.001 |
| Line tracing test | 59.27±13.48 | 48.5-91.40 | 51.77±4.09 | 36.80-62.82 | <0.001 |
| Serial dotting test | 15.57±7.36 | 10.56-34.56 | 11.65±1.25 | 8.35-14.29 | < 0.001 |

Table shows that Psychometric test findings of case and control group, the mean time was taken by number connection test 59.01 (±12.98) seconds were in case group and 41.95(±5.63) seconds were in control group, ($p<0.05$) that was statistically significant, the mean time was taken by line tracing test 59.27(±13.48) seconds were in case group and 51.77(±4.09) seconds were in control group, ($p<0.05$) that was statistically significant. The mean time was taken by serial dotting test 15.57(±7.36) seconds were in case group, and 11.65(±1.25) seconds were in control group, ($p<0.05$) that was statistically significant.

**Table 4: Prevalence of Psychometric test in case group**

| Criteria | Positive | Negative | Total |
|---|---|---|---|
| Number connection test | 15(37.5%) | 25(62.5%) | 40(100) |
| Line tracing test | 15(37.5%) | 25(62.5%) | 40(100) |
| Serial dotting test | 16(40.0%) | 24(60.0%) | 40(100) |
| Two test positive | 15(37.5%) | 25(62.5%) | 40(100) |

Table shows prevalence of number connection test were 15(37.5%), line tracing test positive were 15(37.5%), serial dotting test were 16(40.0%) and two tests positive were 15(37.5%)

**Table 5: Severity of liver disease by Child-Pugh Grading**

| Categories | Frequency | Percent |
|---|---|---|
| Grade A | 02 | 05 |
| Grade B | 30 | 75 |
| Grade C | 08 | 20 |
| Total | 40 | 100 |

Table shows severity of liver disease Child-Pugh Grade, Grade-A was 02(5%), Grade-B was 30(75%) and Grade-C 08(20%).

**Table 6: Association between Number connection tests with child-Pugh Grading**

| Number connection test | Child-Pugh Grading | | | Total | P value |
|---|---|---|---|---|---|
| | Grade A | Grade B | Grade C | | |
| Negative | 2 | 21 | 02 | 25 | 0.03 |
| Positive | 0 | 09 | 06 | 15 | |
| Total | 2 | 30 | 8 | 40 | |

Pearson Chi-Square test

Table shows association between number connection test with child-Pugh Grading, out of 15 positive Number connection test, 09 had Grade-B and 06 had Grade- C, ($p<0.05$) that was statistically significant.

**Table 7: Association between lines tracing test with child-Pugh Grading**

| Line tracing test | Child-Pugh Grading | | | Total | P value |
|---|---|---|---|---|---|
| | Grade A | Grade B | Grade C | | |
| Negative | 2 | 21 | 02 | 25 | 0.03 |
| Positive | 0 | 09 | 06 | 15 | |
| Total | 2 | 30 | 8 | 40 | |

Pearson Chi-Square test

Table shows association between line tracing test with child-Pugh Class, out of 15 positive Line tracing test, 09 had Grade-B and 06 had Grade-C. ($p<0.05$) that was statistically significant.

**Table 8: Association between serial dotting tests with Child-Pugh Grading**

| Serial dotting test | Child-Pugh Grading | | | Total | P value |
|---|---|---|---|---|---|
| | Grade A | Grade B | Grade C | | |
| Negative | 2 | 20 | 3 | 24 | 0.03 |
| Positive | 0 | 09 | 7 | 16 | |
| Total | 2 | 30 | 8 | 40 | |

Pearson Chi-Square test

Table shows association between serial dotting test with child-Pugh Class, out of 15 positive Serial dotting tests, 09 had Grade B and 07 had Grade-C. ($p<0.05$) that was statistically significant.

**Table 9: Relation of duration of disease with psychometric test**

| | Psychometric test | | P value |
|---|---|---|---|
| | Positive | Negative | |
| **Duration of disease (in months)** | 7.25 (±1.12) | 5.09(±1.99) | <0.001 |

Unpaired "t" test

Table shows mean duration in months different between psychometric tests. In psychometric test positive group mean duration of disease was 7.25(1.12) months and psychometric test negative were 5.09(1.99) months, p value (<0.001) that was statistically significant.

**Table 10: Association between psychometric tests with esophageal varix (**Paquet's grading**)**

| Esophageal varix | Psychometric test | | | P value |
|---|---|---|---|---|
| | Negative | Positive | Total | |
| Grade II | 09(36.0) | 00 | 09 | 0.01 |
| Grade III | 16(64.0) | 15 (100) | 31 | |
| Total | 25(100.0) | 15(100) | 40 | |

**Pearson Chi-Square test**

Table shows association between psychometric tests with esophageal varix, 15 psychometric tests positive patients out of 40 patients have Paquet's grade-III esophageal varix, ($p<0.05$) that was statistically significant.

## DISCUSSION

Cirrhosis of liver is an abnormal liver condition characterized by diffuse hepatic fibrosis and nodule formation, clinically diagnosed usually by the presence of jaundice, hepatomegally, ascites, circulatory & endocrine change, haemorrhagic tendency, features of portal hypertention, hepatic encephalopathy [1-5]. Minimal hepatic encephalopathy (MHE) is a condition in which

patients with cirrhosis of liver that has normal mental and neurological status on standard clinical examination exhibit a number of neuropsychiatric and neurophysiological defects.

This study was carried out inpatient Departments of Medicine Rajshahi Medical College Hospital, Rajshahi. The case group comprised of 40 patients with mean age of 44.12 years, minimum age of 30 years and maximum of 60 years. In the control group of 100 patients the mean age was 45.41 years, minimum age of 30 years and maximum of 60 years. In the case group majority were in the age group of 30 - 40 (n= 17) years and in controls 30 - 40 (n= 44) years. In case group 72.5% (n=29) were males and 27.5% (n=11) were females. A male preponderance was observed. In the control group 68.0% (n=68) were males and 32 % (n=32) were females. Aravinda[22] study reported, the mean age in his study was 50.33 years for case group and 51.34 year for control group. The majority of patients were males; they constituted for about 76.7% and 76% in cases and control groups respectively. That result is similar to our study. MHE is present in 25%-80% of cirrhotic patients without overt hepatic encephalopathy (HE) [9-12]. Incidence of MHE is estimated to vary from 30% to 84% in apparently healthy, non-encephalopathy cirrhotic patients reported by Cordoba-Cardona [23]. In present study prevalence of Minimal hepatic encephalopathy by psychometric test was 37.5%. Positive number connection test was 15(37.5%), line tracing test were 15(37.5%), serial dotting test were 16(40.0%) and two tests positive were 15(37.5%). In our study the prevalence of MHE is within the prevalence of previous study.

Regarding severity of liver disease Child-Pugh Grading, Grade-A was 02(5%), Grade-B 30(75%) and Grade-C 08(20%). Out of 40 patients 18(45%) had mild,19(47%) had moderate and 03(8%) had severe ascites. Serum bilirubin level of 22 (55%) were in the range of 2.1-3 mg/dl,12(30%) was >3mg/dl and remaining 06(15%) were between 1 to 2 mg/dl. Serum albumin level was <2.8 gm/dl in 17(42.5%) patients, 10 (25.0%) had in the range of 2.8 to 3.5 gm/dl and 13 (32.5%) had > 3.5 gm/dl. Prothrombin time was prolonged in 1-4 seconds in 25 cases, between 4 and 6 seconds in 9 cases and >6 seconds in 6 cases. Association between number connection test with Child-Pugh grading, out of 15 positive number connection tests, 09 had grade-B and 06 had Grade-C, ($p<0.05$) that was statistically significant. Association between line tracing test with Child-Pugh Grading, out of 15 positive line tracing test, 09 had Grade-B and 06 had Grade-C, ($p<0.05$) that was statistically significant. Association between serial dotting test with Child-Pugh Grading, out of 16 positive serial dotting tests, 09 had Grade-B and 07 had Grade-C, ($p<0.05$) that was statistically significant. Sharma and Sharma study, a total of 200 cirrhotic patients (Child A, 74 [37%]; Child B, 72 [36%]; Child C, 54 [27%]) were evaluated by psychometry, MHE was diagnosed by abnormal psychometry (>2 S.D.) [24]. Univariate and multivariate logistic regression analyses were performed to determine the predictors of MHE. Eighty-two (41%) patients were diagnosed to have MHE 26/74 (35%) in Child A, 26/72 (36%) in Child B and 30/54 (56%) in Child C. Ninety-seven (48.5%) patients had abnormal psychometric tests. This result is approximately similar to in this study. This study shows, mean time was taken by number connection test in case group 59.01 (±12.98) seconds and control group 41.95(±5.63) seconds, ($p<0.05$) that was statistically significant, Mean time was taken by line tracing test case group 59.27(±13.48)seconds and control group 51.77(±4.09) seconds, ($p<0.05$) that was statistically significant, Mean time was taken by serial dotting test case group 15.57(±7.36) seconds and control group 11.65(±1.25) seconds, ($p<0.05$) that was statistically significant.

Bajaj *et al.* study showed psychometric tests result in cirrhosis patients out of 49 patients, 11 had normal testing on all 3 standard tests, 12 had abnormalities in one test only, 8 had abnormalities in two tests, and 14 had abnormalities on all three tests [25]. In this study out of 40 patients number connection test positive were 15(37.5%), line tracing test positive were 15(37.5%), serial dotting test positive were 16(40.0%) and two test positives were 15(37.5%). In this study psychometric test positive group, the mean duration of disease was 7.25(1.12) months, and psychometric test negative were 5.09(1.99) months, ($p<0.001$) which was statistically significant. That means in psychometric test positive group patient had longer duration of disease from test negative patients. In this study out of 40 patients 09(22.5%) psychometric tests negative patients have Paquet's grade-II esophageal varix and 16(40%) psychometric tests negative patients have Paquet's grade-III esophageal varix ($p<0.01$). 15(37.5%) psychometric tests positive patients have Paquet's grade-III esophageal varix, ($p<0.01$) that was statistically significant.

## CONCLUSION

Minimal hepatic encephalopathy (MHE) is common in patients with stable cirrhosis of liver. There is a good relationship between MHE with advanced liver disease by Child-Pugh Grading. Esophageal varix with high grade severity is common in cirrhotic patients who have MHE and longer duration of disease.

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