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Clinical profile of cirrhosis of liver in a tertiary care hospital of Assam, North East India

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Abstract :
Background*: Epidemiology of liver cirrhosis suggests that although Hepatitis B and C are still common in developing countries, alcohol related cirrhosis is increasing. Rising trends in alcohol consumption in North East India, makes it essential to analyse the influence of these changes in the epidemiology of liver cirrhosis. Therefore, we aimed to study one thousand patients of cirrhosis of liver in North East India with reference to its demography, aetiology, clinical presentation, complications, prognostic features and short term mortality.*
Materials and methods*: One thousand consecutively diagnosed adult cirrhosis patients were prospectively studied at the Department of Gastroenterology, Gauhati Medical College, a tertiary care hospital of North East India from June 2013- May 2014 for their clinical characteristics, prognosis and mortality at one month.*
Results*: Commonest age group was 35-54years, mean age 45.8+ 10.4 years; M: F ratio 7.5:1. Symptoms were ascites (74.3%), gastrointestinal bleeding (43.4%), jaundice (36.3%), low urine output (31%) and altered sensorium in 23%. 37.1% patients had severe malnutrition. Aetiology were alcohol related (72.2%), HBV (8.9%), HCV (3.2%), Autoimmune Hepatitis (0.9%), Cryptogenic cirrhosis (17.2%) and NASH (1%). Complications were ascites (78.6%), variceal bleeding (43.4%), hepatic encephalopathy (21.6%), Spontaneous bacterial peritonitis 4.2%, Hepatorenal syndrome (2.7%) and Hepatocellular carcinoma (1.3%). 50% had Child C disease, 83% had MELD between 10-29 and APRI (AST to Platelet ratio index) >2.5 in 38.5% patients. Mortality was 7.8% and highest among alcoholic cirrhosis (6.8%).*
Conclusion*: Cirrhosis is common in the most productive age and the commonest cause was alcohol cirrhosis which is preventable through proper education and legislation. Proper awareness will lead to prevention of long term morbidity.*
Key words*: Cirrhosis, epidemiology, aetiology, complications, prognosis, mortality*

I. Introduction

In cirrhosis, normal liver is replaced with fibrotic tissue as well as regenerative nodules leading to progressive loss of liver function, [1] representing the final histological pathway for variety of chronic liver disease.It accounts for significant morbidity and mortality worldwide.[2] Cirrhosis can be asymptomatic or present with complications like Ascites, Spontaneous bacterial peritonitis (SBP), Hepatorenal syndrome (HRS), Variceal haemorrhage, Hepatic encephalopathy (HE), Hepatopulmonary syndrome and Hepatocellular carcinoma (HCC). In the West, predominant aetiology is alcohol and NASH. Although in developing countries, viral hepatitis B and C are still common, but alcohol and autoimmune related cirrhosis may be increasing.[3] Other rare causes are Wilson's disease, Haemochromatosis, Alpha-1-antitrypsin deficiency, Primary and secondary biliary cirrhosis and Primary sclerosing cholangitis. Changes in the trend of alcohol consumption in North East India in the last decades makes it important to estimate the influence of these changes on the epidemiology of liver cirrhosis.[4] The profile of cirrhosis may vary with different age and ethnic groups, geographical, social and etiological factor. When patient reaches the stage of cirrhosis, an advanced stage of disease, the patient is more likely to avail the services of a hospital. Therefore, this epidemiological study was conducted in a tertiary care hospital to determine the demography, aetiology, clinical features, complications, prognostic markers and short term mortality of One thousand patients of liver cirrhosis.

II. Material And Methods

A prospective observational study was carried out on 1000 consecutively diagnosed patients of cirrhosis attending the outpatient department of Gastroenterology at Gauhati Medical College and Hospital from June 2013-May 2014. After informed consent, detailed history and clinical examination was done. Relevant

biochemistry including Complete blood count, liver function tests, renal function tests, serum electrolytes, fasting and post prandial blood sugar, serum ammonia etc were done. Abdominal ultrasound for liver and spleen size, parenchymal echogenicity, portal vein diameter, and ascites and other concomitant findings and CT/ MRI abdomen in suspected cases of liver cancer was done. Upper GI endoscopy was carried out in all eligible cases. Prognosis was measured by Child Turcot Pugh scores, MELD and APRI scores. Patients were followed up during their hospitalisation and up to 1 month to determine survival. Variables were recorded in a predesigned proforma, analysed and compared with other studies.

Clinical cirrhosis was defined as a patient having at least one sign of hepatocellular failure,[5] one of portal hypertension[6] along with at least three ultrasound findings suggestive of cirrhosis of liver [7,8] and or liver biopsy evidence of cirrhosis in permissible cases. Socioeconomic status was based on modified Kuppuswamy Socioeconomic scale.[9] Nutritional assessment was done based on anthropometric measurements: body mass index (BMI): weight/height^2 ,[10] Mid arm circumference and Subjective Global assessment (SGA) by Detsky et al.[11] Patients were graded as well nourished; SGA grade A, moderately malnourished; grade B and severely malnourished; grade C.[12] The diagnosis of alcoholic cirrhosis was made on the basis of history of alcohol consumption >80g/dl in men and > 40g/dl in women for 10yrs. [13] Viral hepatitis B and C related cirrhosis was based on serological evidence of HBsAg, HBV DNA estimation, anti-HCV and HCV RNA estimation in patients with cirrhosis. Autoimmune Hepatitis was diagnosed based on the International Diagnostic Criteria for the diagnosis of Autoimmune Hepatitis.[14] NASH related cirrhosis was diagnosed based on presence of cirrhosis in patients with evidence of BMI >28kg/m2, diabetes, negative viral studies, alcohol less than 20gm/day in men and <10gm/day in females and histological features like lobular or portal inflammation , ballooned hepatocytes with Mallory Denk bodes and fibrosis in a pericentral vein or zone 3 distribution. In absence of liver biopsy, even with probable NASH patients were categorised as cryptogenic cirrhosis. Diagnosis of cryptogenic cirrhosis was made on the basis of exclusion of all known causes of cirrhosis.

Hepatic encephalopathy was diagnosed on basis of history, West Haven's criteria and number connection test A and B. [15], Ascites, clinically and ultrasound examination.[16] HRS was diagnosed in cirrhotics with ascites, with serum creatinine >1.5mg/dl, no improvement of ascites after at least 2 days of diuretic withdrawal and plasma expansion, absence of shock and other parenchymal kidney diseases.[17] SBP was diagnosed on the basis of clinical suspicion and presence of PMN>250 cells / mm3 in the ascitic fluid.[18] Gastroesophageal varices were detected and graded by endoscopy. [19] HCC was diagnosed by radiology and or the presence of high alpha foetoprotein (>200 ng/ml) in the setting of a mass in a cirrhotic liver.[20]

Data were managed on Microsoft excel spread sheet. Continuous variables were summarized by means and standard deviations. All statistical analysis was carried out by SPSS 16.0 version. Chi-square test for discrete variables (sex, Childs grade, symptoms etc), Independent t test or non parametric test for continuous variables and ANOVA test have been performed (wherever required) and p value of <0.05 has been considered as significant.\

III. Results

Out of one thousand cirrhosis patients, 883 (88.3%) were males and 117 (11.7%) females with M: F ratio of 7.54:1. Majority (63.6%) belonged to 35-54 years age group. **(Fig. 1)** Mean age at presentation was 45.8± 10.45 years (M: 46.63years and F: 47 years). 13.4% were < 35 years of age. 12.3% were tribals and major aetiology among them was alcohol related (80.48%), 10.56% HBV related cirrhosis and 8.13% patients had HCV related cirrhosis. Majority (70.1%) were from rural background versus 29.9% urban. 72.7% patients were from middle socioeconomic status, 23.4% from lower and only 3.9% were from the higher socioeconomic status. 90.2% were Hindus and Muslims (7.7%)

Most common aetiologies were related to alcohol (72.2%), Hepatitis B infection (8.9%), Hepatitis C infection (3.2%) and Cryptogenic in 17.2%. **(Fig. 2)** Common symptoms at presentation were leg swelling (80.5%), abdominal swelling (74.3%), Gastro intestinal bleed (43.4%), jaundice (36.3%), low urine output (31%) and altered sensorium (23%). Other non specific manifestations were fatigability (49.1%), anorexia (40%), fever (14%), vomiting (13.4%) and pain abdomen in 22.7% patients. (**Fig. 3**) 11% patients had night blindness and all had history of heavy alcohol use. 33.7% had constipation which was a major precipitating factor for complications such as UGI bleeding (30% had constipation) and hepatic encephalopathy (50.5% had constipation). Pallor was seen in 85% and significant number of females (90%) presented with pallor than males (84.2%) (p value: 0.038), Oedema in (82.7%), Icterus in (47.8%), skin changes in (36%) and clubbing in (2.9%) were other findings. Nutritional status showed that 41% patients were moderately malnourished, 37.1% severely malnourished and only 22% were well nourished. The severely malnourished had significantly lower BMI (19.8 + 2.4) p: 0.000 and higher mortality (p: 0.002) compared to patients with Grade A and B nutrition (p value: 0.000).

Biochemistry findings are recorded in **Table 1**.Serum bilirubin >3 mg/dl was seen in 370 (37%). Approximately 50% (511 patients) had coagulation abnormality with prothrombin time >17secs and platelet count < 1 lakh/cub mm of blood was seen in 28% individuals. Total leukocyte count >12000/cub mm of blood was seen in 128(12.8%) patients indicating sepsis. Severe anaemia ie. Haemoglobin < 6 gm/dl was seen in 118 (11.8%) patients. About half the patients (49.3%) had early renal abnormalities in the form of Serum Na levels <135 meq/l. Serum creatinine >1.5mg/dl was seen in 20.7%. Serum Ammonia levels >35mg/dl was seen in 56.6%. Ultrasound examination showed cirrhotic changes in 99.2% patients. Other common findings were splenomegaly in 82.8%, ascites in 76.6% patients. Chronic pancreatic changes were seen in 5.6% patients. 8.8% patients had gall bladder calculi and wall edema in 37.5% patients. Renal parenchymal changes were seen in 52 (5.2%) patients.

Most common UGI endoscopy findings were, Grade 2 and Grade3 oesophageal varices (41% and 31%) respectively, portal hypertensive gastropathy (93.2%), Duodenal ulcer (2.1%) and gastric ulcer in 0.95%. Only 59(5.9%) underwent liver biopsy due the fact that a majority of the patients were decompensated at presentation. Among the patients who underwent liver biopsy, 52.54% (31) had cryptogenic cirrhosis, NASH was diagnosed in 9 (15.25%), Autoimmune hepatitis in 5 (8.47%). NASH has been diagnosed from retrospective data and prior to development of complications. Majority had Grade A2 inflammation (61.01%) and F4 stage of fibrosis (66.10%) in our study. The most common complications in our study population were ascites (78.6%), variceal bleeding in 43.4%, hepatic encephalopathy in 21.6%, SBP in 4.2%, HRS in 2.7% HCC in 1.3%, Hypersplenism in 0.4% and sepsis in 12.8% of patients. (**Fig:4**) Comorbidities commonly observed were diabetes in 14% and tuberculosis in 3% patients.

Approximately 50% had Child C disease, 40.4% Child B cirrhosis and Child A was seen in only 9.8% patients. Mean MELD score was 17.80+ 7.51. 60% patients had MELD scores between 10-19, 23.1% had MELD between 20-29 and MELD of >30 was seen in 8.8% indicating advanced disease. APRI more than 1.5, was seen in 38.5% patients. All patients were followed up to 1 month and mortality was 7.8%. Most mortality was seen in ethanol related cirrhosis (6.8%). Complications associated with mortality were ascites 89.2% (66) patients, HE 63.5% (47) patients and variceal haemorrhage 58.1% (43). HRS and SBP was seen in 16 (21.6%) and 5 (6.8%) patients respectively. Multiple complications (>3) were seen in 18.4%. Mortality was higher in Grade C nutrition compared to patients with Grade 1 and 2 nutrition (p value: 0.002)

IV. Figures And Tables

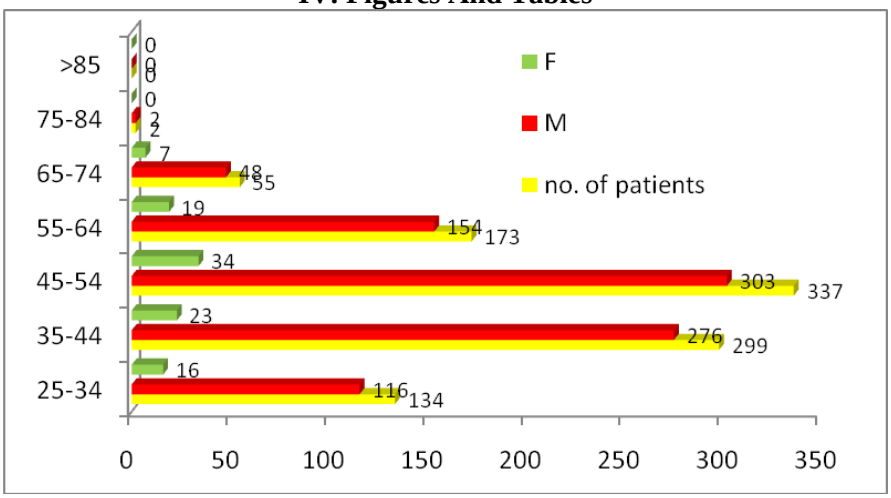

Figure 1 : Showing age distribution of the cases

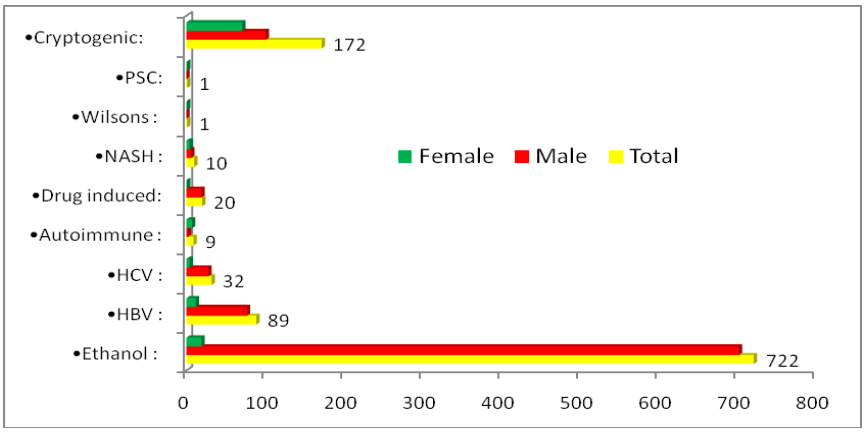

Figure 2 : Showing aetiological distribution of all cases

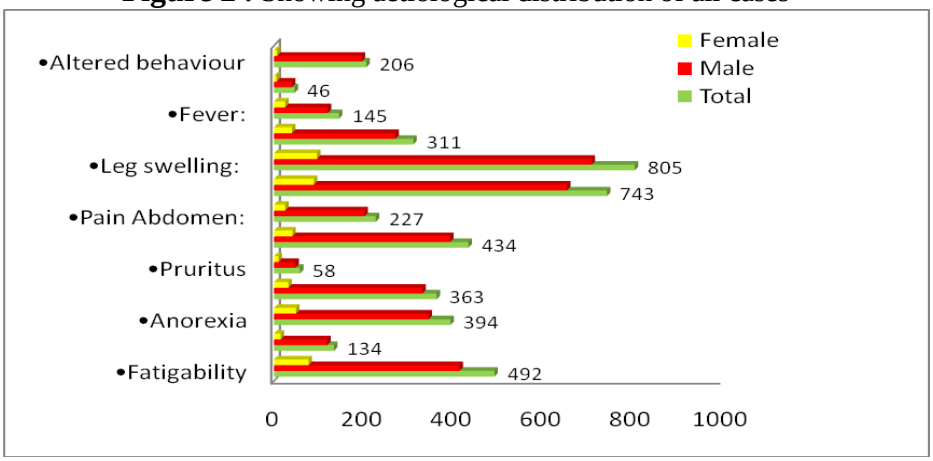

Figure 3: Showing clinical features in the cirrhosis patients

Table 1: Showing biochemistry findings in all cases :

Parameter	Total	Male	Female	P value
T/bilirubin(mg/dl)	4.25± 7.83	4.40± 8.15	3.10± 4.66	0.90
Conj.Bilirubin(mg/dl)	1.65± 3.61	1.70± 3.65	1.34±3.28	
AST (U/L)	117.7±128.79	122.4 ± 134.6	82.92 ± 59.5	0.002
ALT(U/L)	64.0±86.96	65.25 ± 91.0	54.56 ± 44.7	0.211
Alk Phos IU/ml	219.9± 173.69	220.9± 172.5	212.62 ± 183	0.62
T/Protein(g/dl)	7.22 ± 0.95	7.26± 0.952	6.94± 0.93	
Albumin(g/dl)	2.69± 0.64	2.71± 0.65	2.56± 0.60	0.019
Globulin(g/dl)	4.52± 0.84	4.54± 0.84	4.35± 0.83	
Albumin:Globulin	0.64± 0.33	0.64± 0.34	0.62± 0.23	
PT (sec)	19.19±7.67	19.28± 7.89	18.55± 5.76	
INR	1.74± 0.76	1.75± 0.78	1.67± 0.55	
GGT(U/L)	177.50± 333.7	188.89± 351.8	91.52± 98.5	0.003
S/Ammonia(mg/dl)	70.03±54.3	72.88±55.0	41.20± 36.1	
TLC per cub mm	7643.9±6161.6	7861.25±6409.6	6004.16±3393.1	
Haemoglobin(mg/dl)	8.69± 2.55	8.76± 2.28	8.13±4.03	0.013
RBC(per cubmm)	3.31±0.76	3.32±0.73	3.21±0.97	
Platelet count	1.30±0.52	1.30± 0.53	1.28± 0.46	
S/Sodium(meq/l)	134.55±8.7	134.4±9.05	135.3±6.18	
S/Pottasium(mg/dl)	4.18± 5	4.24±5.31	3.71± 0.82	
S/Urea(mg/dl)	35.59± 29.92	36.33±31.17	30.01±16.93	
S/creatinine(mg/dl)	1.37±2.10	1.41±2.22	1.03± 0.61	
FBS (mg/dl)	110.21±57.21	110.49±58.40	108.05±47.41	
PPBS(mg/dl)	139.69±66.91	140.05±67.62	137.03± 61.48	
S/Calcium(mg/dl)	7.84±0.53	7.85±0.53	7.83±0.51	
Magnesium(mg/dl)	1.70± 0.35	1.73±0.36	1.52±0.27	

Values were mean + standard deviation.AST: Aspartate transaminase, ALT: Alanine transaminase,PT: prothrombin time, INR: International Normalised ratio, GGT: Gamma Glutaryl Transaminase, TLC: Total Leukocyte count, RBC: Red Blood cell, FBS: Fasting Blood sugar, PPBS: Post Prandial Blood sugar

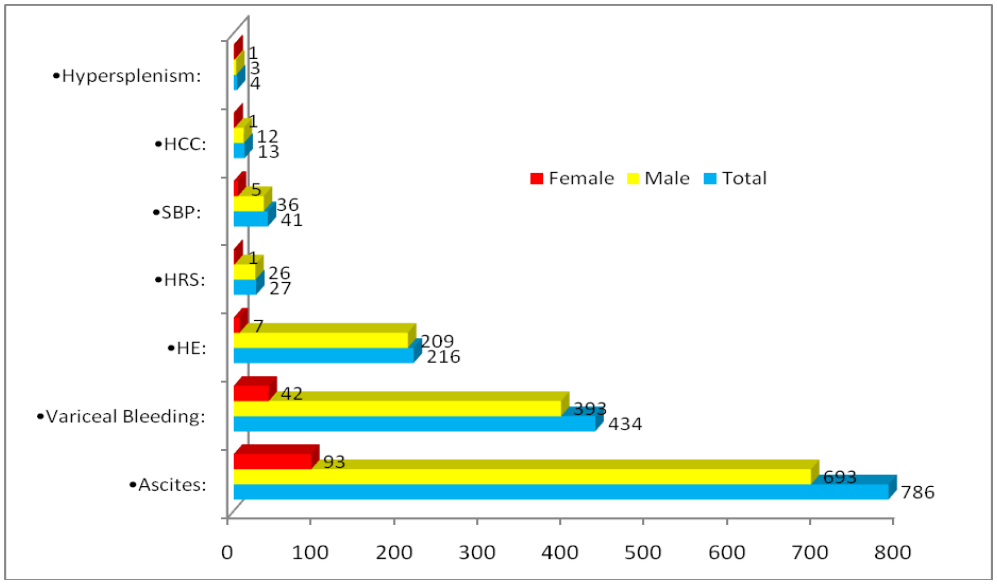

Figure: 4: Showing distribution of complications in all cases

V. Discussion

The clinical profile among the cirrhosis patients is largely unknown in this part of North East India. Male predominance was seen in our study with a M: F ratio of 7.4:1 and was similar to findings noted in a study by Pathak O.K et al 2009, where 80.7% among 181 patients were males.[21] Higher incidence was also reported by Paul SB et al 2007 with a M: F ratio of 6.1:1, among cirrhotics.[22] This difference is due to high incidence of ethanol intake among men compared to women, which is the major aetiology of chronic liver disease and also due to differences in the medical care seeking practice among both sexes. In our study, 63.6% cases were seen in the most productive age group 35-54 yrs age group (Mean age: 45.8 $\pm$ 10.45 years). Paul SB et al 2007,[22] found similar mean age of 45.1$\pm$ 13.1 years. Another study done among multiracial Asian population by Qua CS et al among 460 patients showed a mean age of 58.8 yrs range (15-87 yrs).[23] When cirrhosis occurs at a young age, it causes prolonged morbidity. Earlier reports from the West, reported that younger age group (<35yrs) consisted <5% of the cirrhotics.[25,26] In our study, 13.4% had cirrhosis < 35 yrs of age. Similarly, R Maskey et al 2011 observed 14.28%, <35 yrs of age.[24] However due to more and more young adults acquiring the habit of alcohol abuse, the number of young cirrhotics is likely to be high. In a study by Sarin SK et al 1988, 37% of the 169 patients analysed were <35 yrs of age.[27]

Studies have found an association between low socioeconomic status and increased cirrhosis incidence.[28,29,30] In our study however, majority were from middle class or lower middle class background 72.7% and 23.4% respectively. This could be because health care facilities at government hospitals are mostly availed by middle socioeconomic group. Similar findings were observed by Goel A et al, 2013 where majority belonged either to middle class (n=329; 70%) or lower class. [31] Protein Energy Malnutrition (PEM) is often observed in liver cirrhosis.[32] Western studies have documented malnutrition rates from 20% in compensated liver cirrhosis to 60% in decompensated disease. [33] Increased sepsis, reduced life span have been observed in cirrhotics with poor nutrition status compared to those without. [34] In a study in Malaysian patients (Tai et al 2010) [35], 66.7% had SGA GradeB and 33.3% ,Grade C nutritional status. In our study, 41% had moderate malnutrition and 37.1% had severe malnutrition and was similar to findings in other studies.

Most patients present late with advanced disease. Ascites (74.3%), UGI bleeding (43.4%), jaundice (36.3%) and altered behaviour (20.3%) were the commonest presentation in our study. Ascites and upper GI bleeding was the commonest complications in other studies too; Maskey R et al 2011[24] (ascites 84.4% and Upper GI bleeding in 35.5%) and Md Shahid Aziz et al 2009; (Ascites 53.8% and upper GI bleed 25.1%) too had similar findings.

While hepatitis B infection is more prevalent in the Asian and Sub Saharan Africa, in our study cirrhosis was mostly alcohol related (72.2%) as ethanol abuse is known to be very high in North East. Alcohol was the commonest aetiology in a study by R Maskey et al 2011. However, in other studies from Iran, where alcohol ingestion is not allowed by religious scriptures , the most common aetiologies observed were HBV

infection (42.4%), AIH (14%), HCV infection (9.1%), Wilson,s disease in 1.2% and Cryptogenic cirrhosis (33.3%), (Hajiani E et al). 38 In another study from Pakistan, the common aetiologies were due to HCV in 67.7%, HBV in 18%, Wilson's disease and AIH in 1.2% (Md Shahid Aziz et al).[36]

Liver cirrhosis is an immunodeficient state and with malnutrition may increase the risk of tuberculosis especially extrapulmonary cases. In our study, 3% patients had tuberculosis, (63.3% extrapulmonary) , majority were alcohol related (53.3%). A study from Western India too showed higher prevalence rate, in alcohol related cirrhotics. [37] In a Korean study, 31% cirrhotics had extrapulmonary TB.[39] In the Verona Diabetes study, prevalence of DM in cirrhosis was 12.3-57%.[40] In our study, Diabetes was seen in 15%.

Complications noted in our study population were similar to those observed in many other studies like Hamzullah Khan et al 2006 [41] that also showed ascites in 27.86 %, variceal bleeding in 18.03%, HRS in 3.27% and HCC in 1.63% patients. In another small study by Hajiani et al, [38] ascites was present in 32%, acute variceal haemorrhage was seen in 8%, HE in 1% and HCC in 6% of patients. These studies were however with lesser number of patients.

Around 50% patients had Child C disease suggesting advanced disease. Similar findings were seen by Hajiani E et al 2012, Child C cirrhosis (51%) patients. Some studies have however shown variable results perhaps due to differences in the time of presentation to the hospital. In a study by Muhammad Shah Aziz et al, 2009[36] Child A was seen in 39.5%, Child B in 35.3% patients, and Child C in 25.1% patients. Hamzullah Khan et al 2006, [41] too showed that majority were Child A category (83.3%). This could be due to predominant viral etiology and hence moderate disease whereas majority of our patients were alcohol related.
Compared with findings by R Maskey et al [24] our patients had slightly lower Hb% (8.69 versus 9.7+ 2.8 gm/dl) and lower platelet counts (1.30+ 0.52 vs 1.7+ 1.3 lakh/cubmm) because patients with Upper GI bleed was more in our study. Mean albumin levels were low and comparable in both studies (2.69+ 0.64 vs 2.32+ 0.50mg/dl). On Upper GI endoscopy, others showed similar findings to our study, however with lesser number of patients. In a study by Hajiani et al [38], moderate esophageal varices was seen in 38.2% patients, Sarin SK et al 27 showed Gd3 and Gd 4 varices in majority and Maskey et al, [24] showed grade 3 esophageal varices in 14.4%.

Mortality was low in our patients (7.4%) due to better treatment and also because follow up was for a short period and majority were related to ethanol abuse 68 (94.95%). In other studies, mortality varied according to the follow up periods and in the study by Sarin SK et al [27] the mortality was 44.3% in adults. In a small study by Maskey et al, mortality rate was 13.3%. Among the study population, patients with severe malnutrition had significantly lower BMI (p value: 0.000) and higher mortality than patients with mild to moderate malnutrition. (SGA A-B). Mortality in patients with Child C cirrhosis was significantly higher than Child A-B cirrhosis (p:<0.000). Similarly patients with higher MELD were associated with increased mortality.Patients with APRI score >1.5 was associated with significantly higher (p<0.000) mortality than patients with APRI <1.5.

VI. Conclusion

Cirrhosis of liver is a major health problem in North East India and affects males in the most productive years. Alcohol abuse is the major cause of cirrhosis in North East India that is entirely preventable through proper education and legislation. Malnutrition, widely prevalent among cirrhotics is associated with high mortality. Patients present in advanced stage of disease with complications. However, limitation of the study was that patients were not followed up for long and the effect of the various treatment options were not recorded.

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