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DETERMINATION OF PREVALENCE AND PREDICTORS FOR HEPATIC ENCEPHALOPATHY IN LIVER CIRRHOSIS POPULATION IN SOUTHERN RAJASTHAN: A CROSS-SECTIONAL STUDY (ORIGINAL ARTICLE)

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ABSTRACT

Introduction: Liver cirrhosis a chronic disease associated often leads to complications like hepatic encephalopathy (HE) which can be fatal if not diagnosed early. HE is a reversible and potentially cause multiple organ failure. Limited research on HE prevalence and predictors has been done in southern Rajasthan. This study aimed to determine the prevalence and predictors of HE patients at Geetanjali Medical College and Hospital, Udaipur. **Materials and Methods:** a prospective cross-sectional study was conducted from January 2024 to June 2024 involving 141 patients. Data on demographics and clinical features were collected after obtaining written consent. Various test including haematological, biochemical, serological and USG scan were performed. patients were evaluated using MELD-Na score, CTP score until discharge. **Results:** The study included 141 patients with mean age of 51.97±12.82 years with males (122, 86.52%) highest in number than females (19, 13.48%) in analysing social history observed that patients are more alcoholic 90 (63.83%) the prevalence of HE was found to be 69.5%.upon binary logistic regression identified age, alcohol and serum ammonia levels as independent predictor with OR of 0.953, 0.240 and 0.802 respectively with p-value of 0.006, 0.002 and <0.001. upon applying ROC analysis of serum ammonia showed AUC of 0.980 with specificity of 0.884

and sensitivity of 0.980 and cut-off value of >55.7 mcg/dl. **Conclusion:** HE was a prevalent complication among liver cirrhosis patients (69.5%), with high ammonia levels identified as a potential predictor due to impaired urea metabolism and increased ammonia accumulation in brain.

KEYWORDS: Serum ammonia, Predictors, Liver cirrhosis, Hepatic encephalopathy.

INTRODUCTION

Liver cirrhosis is a state where the liver undergoes scarring and enduring damage, resulting in the replacement of healthy liver tissue with scar tissue. This process hinders the livers ability to function properly, eventually leading to liver failure as the disease progresses.[1] Chronic liver disease (CLD) pose a significant global health burden, causing around 2 million deaths annually common causes includes viral hepatitis B (HBV), hepatitis C infection (HCV), alcoholic steatohepatitis, non-alcoholic fatty liver disease (NAFLD) autoimmune and genetic factors it contributes to 45% of global health mortality.[2] Early sign and symptoms of cirrhosis includes nausea, fatigue, malaise, right upper quadrant pain, spider angioma, palmar erythema, dilated veins on abdomen and clubbing.[3] There are various mechanisms underlying liver fibrosis regression including genetic markers genes like ABCB4, ASL, ALDOB, GBE1, SLC25A13 etc. are highly expressed in the liver and therefore mutation o these genes mainly affect liver causes fibrosis.[4] Severe symptoms observed are caput medusae radiating from umbilicus, Dupuytren contracture, terry nails, petechiae and testicular atrophy.[5] For staging of liver cirrhosis both scales like the child pugh score (CP) and model for end stage liver disease (MELD-Na) score has an paramount importance for staging in liver cirrhosis population.[6] A major complication of chronic liver disease is hepatic encephalopathy (HE). Hepatic encephalopathy is a condition that can be reversed and is commonly seen in individuals with CLD it involves various neuropsychiatric symptoms caused by the build up of harmful substances.[7] the HE is categorised into various categories like overt HE having neuro and cognitive symptoms and minimal HE having disease condition but no signs and symptoms[8] the sign and symptoms of HE includes decreased consciousness and alertness, hyperventilation, asterixis, fetor hepaticus , hyperreflexia , mood changes, personality changes, muscular rigidity etc.[9] three critical factors have been identified hyperammonaemia, systemic inflammation and oxidative stress by glutamine gene alternations plays the major role for ammonia accumulation in brain and glial cells.[10] Pathogenesis of HE depends on two major factors ammonia and glutamine both metabolism

got compromised in decompensated cirrhosis which leads to accumulation in brain and crossing of blood brain barrier.[11] For diagnosis of HE various psychometric test used like number connection test, serial dot joining test are used for determining attention, processing speed and response for neuroimaging MRI is done commonly to observe various regions of brain affected.[13] Mostly WHC criteria is been used for grading of HE it categorised into from grade 1 to grade 4. Grade 1 HE has decreased attention and personality changes in grade 2 HE has some other neurological symptoms and grade 4 includes patients in coma.[14] This study aimed to showed the underlying predictors of hepatic encephalopathy in CLD population and document the severity and mortality associated with the disease in southern Rajasthan no study has been done this study is aimed to share the valuable insights of hepatic encephalopathy in target population.

METHODOLOGY

Study design

The study was conducted at the Department of Gastroenterology, Geetanjali Medical College and Hospital, Udaipur, Rajasthan. This observational, prospective, cross-sectional study involved data collection from in- patient and ICU records. The study population included adult and elderly patients with liver cirrhosis, including those with complications. The study was conducted over six months from January 2024 to June 2024. The sample size was calculated using Cochran formula, based on an estimated liver cirrhosis prevalence of 10%[15] a 95% confidence level (Z= 1,96) and a precision of 5%. This resulted in a required sample size of 136 but 141 participants were enrolled due to a high attrition rate, informed consent was obtained from all participants. Inclusion criteria included patients aged 18 and above with a diagnosis of liver cirrhosis. Exclusion criteria included patients having age under 18, those with other co-morbid conditions and pregnant patients to minimize potential confounding factors.

MATERIALS AND METHODS

A structured data collection form was used to obtain sociodemographic details, laboratory results and diagnostic findings such as USG and endoscopy from in-patient (IPD) and ICU records in the Department of Gastroenterology. Informed consent was obtained from all participants in a language they understood. The study employed the model for end stage liver disease (MELD-Na) score, Child-Turcotte-Pugh (CTP) score to assess disease severity and

prognosis the CTP score classifies mortality risk categories into class A, B and C with class C indicating the highest risk.

Process of data collection

The data collection process included obtaining informed consent. Data were then gathered using designed patient data collection form covering sociodemographic details, medical and social histories, physical examination findings and results from biochemical, haematological, serological, USG and endoscopy details with MELD-Na score and CTP score were recorded. All patients were tested for HBsAg and HCV to determine the cause of CLD and abdominal USG was used for diagnosis and assessing complications severe esophageal varices were treated with esophageal varices ligation (EVL).

Data analysis

Data analysis was performed using IBM SPSS statistics (v27). Descriptive statistics were used to analyse sociodemographic details with categorical data presented as percentages and illustrated through tables and graphs where applicable. Continuous variables were expressed as mean with standard deviation. Prior to conducting statistical analysis all continuous variables were assessed for normality to determine their distribution within their sample population. The study employed several statistical tests including chi-square test, Fishers exact test, T-test, Mann Whiteny U test, regression analysis and receiver operating characteristic (ROC) cure analysis, a p-value less 0.05 was considered statistically significant.

Study approval

Prior to the study ethical approval was obtained from Human Research Ethics Committee (GU/HREC/EC/2023/2373)

RESULTS

1.) Analysis of sociodemographic details

In this study total 141 patients were recruited and screeded the mean age observed is 51.97± 12.82 years the highest number of individuals were in 40-49years and least number in 80-89 years of age group, Shapiro wilk test applied for normality and showed normal distribution (p value > 0.05). in this study males were higher in number and found to be 122 (86.52%) and females 19 (13.48%) furthermore. After analysing social history its observed that patients were more alcoholic and were found to be 90 (63.83%) and are daily drinkers 47 (33.33%)

further its described in table 1. The prevalence of HE in cirrhosis population in southern Rajasthan was found to be 69.5%.

Table 1: Patient characteristics.

Parameter	HE (present)	HE (absent)	p-value
Age (mean ± SD)	53.38± 12.87	48.77± 12.24	0.049*
Weight (mean ± SD)	61.94± 11.65	59.93± 11.79	0.350
Gender n (%)			
• Male	87 (88.8%)	11 (11.2%)	0.237
• Female	35 (81.4%)	8 (18.6%)	
Social history n (%)			
• Smoking	38 (38.8%)	15 (34.9%)	0.660
• Alcohol	70 (71.4%)	20 (46.5%)	0.005 *
1. Daily drinkers	35 (35.7%)	12 (27.9%)	0.365
2. Weekly drinkers	19 (19.4%)	7 (16.3%)	0.661
3. Monthly drinkers	13 (13.3%)	3 (7%)	0.391
4. Rarely drinkers	14 (14.3%)	2 (4.7%)	0.148
• Tobacco	37 (37.8%)	21 (48.8%)	0.218
• Substance abuse	6 (6.1%)	4 (9.3%)	0.493
Physical examination n (%)			
• Dilated veins	18 (18.4%)	3 (7%)	0.080
• Spider veins	3 (3.1%)	3 (7%)	0.369
• Clubbing	27 (27.6%)	12 (27.9%)	0.965
• Erythema	2 (2%)	5 (11.6%)	0.028*
• Yellow discoloration	71 (72.4%)	24 (55.8%)	0.101
• GIT (tenderness)	33 (33.7%)	20 (46.5%)	0.147
• Abdominal distension	90 (91.8%)	30 (69.8%)	0.001*
• Pedal oedema	36 (36.7%)	17 (39.5%)	0.752
Etiology n (%)			
• Hepatitis B	13 (13.3%)	9 (20.9%)	0.248
• Hepatitis C	2 (2%)	0 (0%)	1.000
• NAFLD	60 (61.2%)	27 (62.8%)	0.860
• Compensated cirrhosis	18 (18.4%)	8 (18.6%)	0.973
• Decompensated cirrhosis	80 (81.6%)	35 (81.4%)	0.973
USG findings n (%)			
• Nodularity	91 (92.9%)	40 (93%)	1.000
• Altered echotexture	97 (99%)	41 (95.3%)	0.220
• Hyper echogenicity	60 (61.2%)	26 (60.5%)	0.932
• Splenomegaly	87 (88.8%)	41 (95.3%)	0.344
Complications n (%)			
• Ascites	83 (84.7%)	37 (86%)	0.835
1. Mild ascites	28 (28.6%)	18 (41.9%)	0.121
2. Moderate ascites	29 (29.6%)	16 (37.2%)	0.372
3. Severe ascites	36 (36.7%)	11 (25.6%)	0.196
• PHTN	80 (81.6%)	30 (69.8%)	0.117
• Oesophageal varices	65 (66.3%)	25 (58.1%)	0.352
1. Grade 1	17 (17.3%)	11 (25.6%)	0.259

2. Grade 2	37 (37.8%)	13 (30.2%)	0.390
3. Grade 3	13 (13.3%)	4 (9.3%)	0.506
4. Grade 4	1 (1%)	1 (2.3%)	0.518
• Sarcopenia	77 (78.6%)	29 (67.4%)	0.159
• Infections	57 (58.2%)	23 (53.5%)	0.606
Severity score (mean ± SD)			
• MELD-Na score	21.35± 7.52	18.90± 6.77	0.067
• CTP score	10.59± 1.50	9.23± 1.79	<0.001*

*Statistically significant.

Abbreviations: NAFLD: non-alcoholic fatty liver disease, PHTN- portal hypertension, MELD-Na – model for end stage liver disease, CTP- child Turcotte score.

On Comparing both groups of HE present and HE absent its observed that patients having age are high in group of HE present than other group (p-value: 0.049). patients consuming alcohol was reported high in group having HE compared to HE absent (p-value :0.005). on comparing both groups, patients having erythema is most observed in second group (p-value: 0.028). on comparing two groups, patients having abdominal distension were reported in first group having HE (p-value: 0.001) on assessing CTP score in both groups its observed that CTP score in first group is high than second group (p-value: <0.005)

2.) Analysis of lab parameters

In this study CBC, liver function test, kidney function test, electrolytes and ABG were performed. Lab parameters were compared with HE present and HE absent and its observed that patients having less RBC count in first group (2.91 mcL in first group and 3.2 mcL in second group ; p-value: 0.031), high direct bilirubin in first group (1.48 mg/dl in first group and 1.19 mg/dl in second group ; p-value: 0.007) and very high ammonia levels in first group (135 mcg/dl in first group and 48 mcg/dl in second group; p-value: <0.05) and its described in table 2.

Table 2: Lab parameters of both groups.

Parameter	HE (present)	HE (absent)	p-value
CBC (mean ± SD)			
• Hb	8.31± 2.23	8.77± 2.48	0.275
• RBC	2.91± 0.71	3.20± 0.82	0.031*
• MCV	88.26± 14.11	86.03± 13.67	0.291
• WBC	9.43± 6.47	7.86± 4.85	0.307
• Neutrophil	70.40± 11.00	66.51± 10.86	0.056
• Pt. count	116.09± 71.42	111.19± 82.85	0.249
• RDW	17.21± 3.11	17.65± 3.53	0.428
LFT (mean ± SD)			

• AST [median (L-U)]	70.2 (45.6-132.7)	68.90 (44.6-110)	0.428
• ALT [median (L-U)]	36.3 (27.1-61.5)	36.1 (24.3-50.1)	0.234
• ALP	152.09± 101.02	176.52± 138.65	0.541
• Total bilirubin	2.44 (1.23-4.10)	1.76 (0.83-3.33)	0.068
• Direct bilirubin	1.48 (0.82-3.	1.19 (0.46-1.6)	0.007*
• Indirect bilirubin	0.68 (0.38-1.41)	0.52 (0.23-1.37)	0.154
• Albumin	2.14± 0.50	2.31± 0.72	0.589
• Globulin	4.43± 1.06	4.07± 1.08	0.057
• PT	20.30± 7.13	20.07± 3.98	0.518
• INR	1.67± 0.70	1.65± 0.44	0.596
ABG (mean ± SD)			
• Pco2	29.68± 6.11	29.87± 5.13	0.857
• Hco3-	20.36± 4.32	18.78± 3.81	
Electrolytes (mean ± SD)			
• Sodium	131.00± 6.10	133.45± 11.46	0.248
• Chloride	100.81± 6.92	101.30± 6.16	0.621
• Potassium	4.13± 0.81	4.12± 0.70	0.920
• Calcium	2.45± 2.39	2.22± 2.05	0.914
• magnesium	1.97± 0.17	2.01± 0.12	0.214
KFT (mean ± SD)			
• sr. creatinine	1.40± 0.83	1.33± 1.11	0.095
• BUN	24.27± 15.58	24.53± 20.64	0.361
• Sr. urea	48.74± 32.48	44.28± 36.64	0.152
• ammonia	135.53± 61.80	48.24± 7.55	<0.001*

*Statistically significant

Abbreviations: Hb: haemoglobin, RBC: red blood cell count, MCV: mean cell volume, WBC: white blood cell, RDW: red cell distribution width, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, PT: prothrombin time, INR: international normalised ratio, Pco2: partial pressure carbon di oxide, Hco3-: bicarbonates, BUN: blood urea nitrogen.

3.) Analysis of predictors of HE

All 141 participants are screened for determining predictors for HE binary logistic regression is applied on diverse population for determining predictors for HE.

From log regression table its observed that age, alcohol, RBC, direct bilirubin, serum ammonia levels, CTP score have p-value less than 0.05 and are statistically significant and were independent predictors of HE further described in table 3

Table 3: Predictors for HE in liver cirrhosis.

Variable	95% confidence interval		Odds ratio	p-value
	Lower limit	Upper limit		
Age	0,921	0.986	0.953	0.006*
Alcohol	0.098	0.585	0.240	0.002*
RBC	0.785	2.226	1.322	0.293
Direct bilirubin	0.751	1.053	0.889	0.172
Ammonia	0.708	0.909	0.802	<0.001*
CTP score	0.468	1.344	0.793	0.389

* Statistically significant

Abbreviations: RBC: red blood cell, CTP- child-Turcotte-Pugh score.

4.) Analysis by receiver operating characteristic curve (ROC analysis)

Receiver operating curve (ROC) was applied on age and ammonia to identifying age and serum ammonia levels concentration predicting hepatic encephalopathy. Described in figure 1.

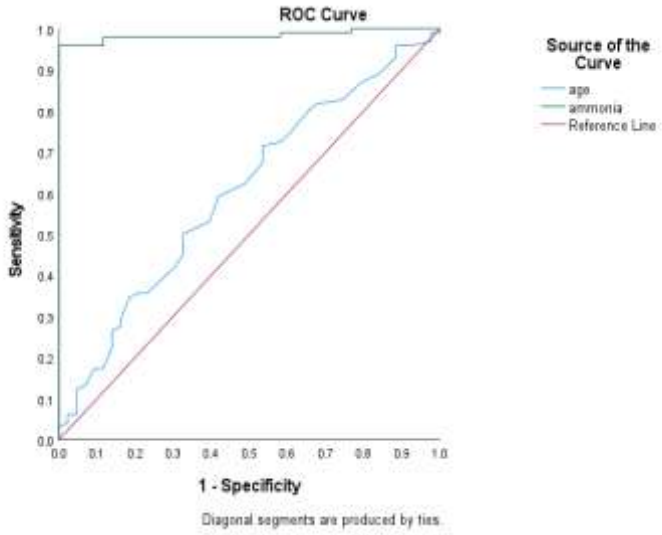

Figure 1: ROC curve showing the levels of serum ammonia and age for detecting hepatic encephalopathy.

1.) Serum ammonia

The area under curve (AUC) for serum ammonia levels was found to be 0.984 with specificity of 0.884 and sensitivity of 0.980 found to predict HE in liver cirrhosis population. The critical concentration of serum ammonia levels in patients who developed HE in liver cirrhosis population was >55.7 mcg/dl.

2.) Age

The area under curve (AUC) for age was found to be 0.604 with specificity of 0.419 and sensitivity of 0.592 found to predict HE in liver cirrhosis population. The critical age in patients who developed HE in liver cirrhosis population was >49.5 years.

DISCUSSION

Liver cirrhosis or chronic liver disease has many co mplications, hepatic encephalopathy (HE) is most fatal complication related with disease which decreases patient health related quality of life. The current study is conducted to determine prevalence and underlying risk factors of HE in liver cirrhosis population of southern Rajasthan the mean age of the participants in this study is found to be 51.97 years which is similar to the studies conducted in Ghana[15] and multicentric study[16] the reporting of the disease highly depends on the sociodemogra phic characteristics of patient, severity and etiology of the disease. In this study males are in high proportion (86.52%) than females (13.48%) and equal number of patients recruited in ICU and wards this study aimed therefore to determine the precipitating factors of hepatic encephalopathy admitted in Geetanjali hospital Udaipur Rajasthan in our center there is less mortality in hepatic encephalopathy patients because of good treatment outcomes in the patient and all facilities available for diagnosing and novel treatment options available for managing the patient. Majority of patients in this study belong to middle class status and weight of patients reported in highest category of 50-60kg mainly patients were reported with weight loss during admission in analysing social history of patients its revealed that alcohol is the most common social habit found similar to the studies conducted by Hudson M et al[17] and Huang DQ et al[18] the prevalence of HE in this study is found to be 69.5% similar to the study conducted by A Das et al[19] but on contrary is increased in compared to other studies conducted by Bale A et al[20] and Rathi S et al.[21]

Patients having HE in this study had lab values with low RBC count, high direct bilirubin and high ammonia levels in patients with HE present and absent were statistically significant similar to the study conducted by Butterworth RF et al[9] high direct bilirubin and high ammonia levels are being associated with increase incidence of covert HE and HE related complications and mortality during hospitalization. Study conducted by Bai Z et al[22] its observed that low albumin levels is significant predictor for overt HE though in this study its not statistically proven in this study observed that for the treatment of sever ascites large volume paracentesis was performed.

The independent predictors in the current study for HE observed are age, alcohol and ammonia levels were the independent predictors in this study the similar results also observed in study conducted by Tapper EB et al[23] in this study is being observed that patients being presented with moderate sarcopenia 106 (75%) due to the muscles involvement in ammonia metabolism sarcopenia is associated with higher reporting of HE. In normal healthy individual the ammonia metabolism is associated by liver, kidney and skeletal muscles which converts ammonia into urea by liver enzymes and excreted by kidney through urine but in cirrhotic patients this metabolic pathway is compromised due to hepatic decompensation which leads to ammonia accumulation in body parts crucially in brain hence it caused sarcopenia this similarity is also observed by study conducted by Jindal A et al.[24] information from other countries has not identified infections among the most occurring event study conducted by Lim YS et al[25] similar precipitating factors are also observed in the study conducted by Raphael KC et al[26] in the resources limited setting it also reflects the hygienic, nutritional and immune status in their patient. Given the current findings ROC analysis Is applied on serum ammonia levels which showed an AUC of 0.980 with specificity of 0.116 and sensitivity of 0.884 and cut-off value of >55.7 mcg/dl on contrary its lower than other study conducted by Chiriac S et al[27] and similar to the study conducted by Sharma P et al[28] ammonia as potential predictor for HE due to disease progression and severity which causes accumulation of ammonia in blood which causes penetration of ammonia in brain due to poor metabolism of urea and glutamate in body.in this study increase in age is also noted as potential predictor the possible explanation behind is that as the age progresses the severity of disease increases in chronic conditions and is associated with complications.

The present study was conducted is single centric and conducted on specific, single population for more and deep insightful results this present study recommends more large scale population study and multi-centric study to find out more potential predictors and to evaluate the role of serum ammonia and metabolic pathways in disease pathophysiology and evaluate age as potential predictor. The current study also recommends determination of prevalence of HE in other areas also for comparison of epidemiology of HE.

CONCLUSION

In conclusion, the present study patients with liver cirrhosis presented with many complications from these hepatic encephalopathy was the common complication observed in this study the prevalence of HE was found to be 69.5% and furthermore, it successfully

determined dependent and independent predictors of hepatic encephalopathy the results revealed significant information and its supported by logistic regression the potential predictors for HE observed are age and high ammonia levels as potential predictors of HE in this study. While, the present study has been taken into many efforts to reveal the results from many perspectives, but further research is recommended to perform the study on large population scale and multi-centric. Overall, the predictors of hepatic encephalopathy and liver cirrhosis in this study showed significant results and contributes to the field of gastroenterology, hepatology and healthcare of southern Rajasthan this study provides use full insights to improve the well being and quality of life of patients with hepatic encephalopathy.

Conflict of interest

There is no conflict of interest between the authors.

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REFERENCES

1. https://www.niddk.nih.gov/health-information/liver-disease/cirrhosis
2. Roehlen N, Crouchet E, Baumert TF. Liver Fibrosis: Mechanistic Concepts and Therapeutic Perspectives. Cells, 2020; 3, 9(4): 875. doi: 10.3390/cells9040875. PMID: 32260126; PMCID: PMC7226751.
3. U.S. Department of Veterans Affairs. Cirrhosis: A Patient's Guide (https://www.hepatitis.va.gov/cirrhosis/patient/index.asp). Accessed 7/26/2023.
4. Manuela Scorza, Ausilia Elce, Federica Zarrilli, Renato Liguori, Felice Amato, Giuseppe Castaldo, "Genetic Diseases That Predispose to Early Liver Cirrhosis", *International Journal of Hepatology*, 2014. Article ID 713754, 11 pages, 2014. https://doi.org/10.1155/2014/713754
5. Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician, 2019; 15, 100(12): 759-770. PMID: 31845776.
6. Fragaki M, Sifaki-Pistolla D, Orfanoudaki E, Kouroumalis E. Comparative evaluation of ALBI, MELD, and Child-Pugh scores in prognosis of cirrhosis: is ALBI the new alternative? Ann Gastroenterol, 2019; 32(6): 626-632. doi: 10.20524/aog.2019.0417. Epub 2019 Sep 26. PMID: 31700241; PMCID: PMC6826070.

7. Mandiga P, Foris LA, Bollu PC. Hepatic Encephalopathy. [Updated 2023 Mar 6]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430869/
8. Rose CF, Amodio P, Bajaj JS, Dhiman RK, Montagnese S, Taylor-Robinson SD, Vilstrup H, Jalan R. Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatol, 2020; 73(6): 1526-1547. doi: 10.1016/j.jhep.2020.07.013. Epub 2020 Oct 21. PMID: 33097308
9. Butterworth RF. Hepatic encephalopathy. Alcohol Res Health, 2003; 27(3): 240-6. PMID: 15535452; PMCID: PMC6668878
10. Vidal-Cevallos P, Chávez-Tapia NC, Uribe M. Current approaches to hepatic encephalopathy. Ann Hepatol, 2022; 27(6): 100757. doi: 10.1016/j.aohep.2022.100757. Epub 2022 Sep 14. PMID: 36115576.
11. Fallahzadeh MA, Rahimi RS. Hepatic Encephalopathy: Current and Emerging Treatment Modalities. Clin Gastroenterol Hepatol, 2022; 20(8S): S9-S19. doi: 10.1016/j.cgh.2022.04.034. PMID: 35940731.
12. McPhail MJ, Patel NR, Taylor-Robinson SD. Brain imaging and hepatic encephalopathy. Clin Liver Dis, 2012; 16(1): 57-72. doi: 10.1016/j.cld.2011.12.001. PMID: 22321465.
13. Ridola L, Faccioli J, Nardelli S, Gioia S, Riggio O. Hepatic Encephalopathy: Diagnosis and Management. J Transl Int Med, 2020; 31, 8(4): 210-219. doi: 10.2478/jtim-2020-0034. PMID: 33511048; PMCID: PMC7805282.
14. Puentes JCP, Rocha H, Nicolau S, Ferrão G. Effectiveness of the MELD/Na Score and the Child-Pugh Score for the Identification of Palliative Care Needs in Patients with Cirrhosis of the Liver. Indian J Palliat Care, 2018; 24(4): 526-528. doi: 10.4103/IJPC.IJPC_97_18. PMID: 30410269; PMCID: PMC6199842.
15. Duah A, Agyei-Nkansah A, Osei-Poku F, Duah F, Ampofo-Boobi D, Peprah B. The Prevalence, Predictors, and In-Hospital Mortality of Hepatic Encephalopathy in Patients with Liver Cirrhosis Admitted at St. Dominic Hospital in Akwatia, Ghana. Can J Gastroenterol Hepatol, 2020; 22, 2020: 8816522. doi: 10.1155/2020/8816522. PMID: 33425806; PMCID: PMC7772042.
16. Yang C, Zhu X, Liu J, Shi Q, Du H, Chen Y, Huang S, Zhou C, Wang Y, Li T, Bai Y, Xiong B. Development and Validation of Prognostic Models to Estimate the Risk of Overt Hepatic Encephalopathy After TIPS Creation: A Multicenter Study. Clin Transl Gastroenterol, 2022; 27, 13(3): e00461. doi: 10.14309/ctg.0000000000000461. PMID: 35093957; PMCID: PMC8963844.

17. Hudson M, Schuchmann M. Long-term management of hepatic encephalopathy with lactulose and/or rifaximin: a review of the evidence. Eur J Gastroenterol Hepatol, 2019; 31(4): 434-450. doi: 10.1097/MEG.0000000000001311. PMID: 30444745; PMCID: PMC6416096.
18. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, Loomba R. Global epidemiology of cirrhosis - aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol, 2023; 20(6): 388-398. doi: 10.1038/s41575-023-00759-2. Epub 2023 Mar 28. PMID: 36977794; PMCID: PMC10043867
19. Das A, Dhiman RK, Saraswat VA, Verma M, Naik SR. Prevalence and natural history of subclinical hepatic encephalopathy in cirrhosis. J Gastroenterol Hepatol, 2001; 16(5): 531-5. doi: 10.1046/j.1440-1746.2001.02487.x. PMID: 11350549.
20. Bale A, Pai CG, Shetty S, Balaraju G, Shetty A. Prevalence of and Factors Associated With Minimal Hepatic Encephalopathy in Patients With Cirrhosis of Liver. J Clin Exp Hepatol, 2018; 8(2): 156-161. doi: 10.1016/j.jceh.2017.06.005. Epub 2017 Jun 20. PMID: 29892178; PMCID: PMC5992259.
21. Rathi S, Chopra M, Chouduri G, Sharma P, Madan K, Chhabra M, Rai RR, Govil A, Konar A, Goenka M, Agarwal M, Mukherjee J, Thorat V, Salunkhe S, Abraham P, Nagral A, Jhaveri A, Bhat N, Varghese J, R S A, Ravishankar, Reddy DC, Dhiman RK. Prevalence of Minimal Hepatic Encephalopathy in Patients With Liver Cirrhosis: A Cross-Sectional, Clinicoepidemiological, Multicenter, Nationwide Study in India: The PREDICT Study. J Clin Exp Hepatol, 2019; 9(4): 476-483. doi: 10.1016/j.jceh.2018.09.009. Epub 2018 Oct 15. PMID: 31516264; PMCID: PMC6728606.
22. Bai Z, Bernardi M, Yoshida EM, Li H, Guo X, Méndez-Sánchez N, Li Y, Wang R, Deng J, Qi X. Albumin infusion may decrease the incidence and severity of overt hepatic encephalopathy in liver cirrhosis. Aging (Albany NY), 2019; 8, 11(19): 8502-8525. doi: 10.18632/aging.102335. Epub 2019 Oct 8. PMID: 31596729; PMCID: PMC6814610.
23. Tapper EB, Henderson JB, Parikh ND, Ioannou GN, Lok AS. Incidence of and Risk Factors for Hepatic Encephalopathy in a Population-Based Cohort of Americans With Cirrhosis. Hepatol Commun, 2019; 6, 3(11): 1510-1519. doi: 10.1002/hep4.1425. PMID: 31701074; PMCID: PMC6824059.
24. Jindal A, Jagdish RK. Sarcopenia: Ammonia metabolism and hepatic encephalopathy. Clin Mol Hepatol, 2019; 25(3): 270-279. doi: 10.3350/cmh.2019.0015. Epub 2019 Apr 22. PMID: 31006226; PMCID: PMC6759436.

25. Lim YS, Kim WR. The global impact of hepatic fibrosis and end-stage liver disease. Clin Liver Dis, 2008; 12(4): 733-46, vii. doi: 10.1016/j.cld.2008.07.007. PMID: 18984463.
26. Raphael K. C., Matuja S. S., Shen N. T., Liwa A. C., Jaka H. Hepatic encephalopathy; prevalence, precipitating factors and challenges of management in a resource-limited setting. *Journal of Gastrointestinal & Digestive System*, 2016; 6(3): 441. doi: 10.4172/2161-069x.1000441.
27. Chiriac S, Stanciu C, Cojocariu C, Singeap AM, Sfarti C, Cuciureanu T, Girleanu I, Igna RA, Trifan A. Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure. World J Clin Cases, 2021; 26, 9(3): 552-564. doi: 10.12998/wjcc.v9.i3.552. PMID: 33553393; PMCID: PMC7829715.
28. Sharma P, Sharma BC. Predictors of minimal hepatic encephalopathy in patients with cirrhosis. Saudi J Gastroenterol, 2010; 16(3): 181-7. doi: 10.4103/1319-3767.65189. PMID: 20616413; PMCID: PMC3003225.