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Original Article

Assessment of Serum Biochemical Changes in Hepatic Encephalopathy

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ABSTRACT

Objective: To analyze the association of various biochemical changes with different grades of hepatic encephalopathy among patients of hepatitis C-related decompensated liver disease presenting at Pak Emirates Military Hospital. Rawalpindi, Pakistan.

***Study Design*:** Comparative cross-sectional study.

***Place and Duration of Study*:** Medicine and Gastroenterology Department of Pak Emirates Military Hospital (PEMH), Rawalpindi Pakistan, from Mar 2020 to Feb 2021.

Methodology: This study was conducted on 100 patients with hepatitis C-related decompensated liver. A consultant medical specialist or gastroenterologist graded hepatic encephalopathy according to the West Haven criteria. Serum urea, creatinine, albumin and international normalized ratio were performed in all the patients at the time of grading of encephalopathy and derangement in the level of these parameters was analyzed with Grades of encephalopathy.

Results: Out of 100 patients, in the final analysis, 66 were males, and 44 were females. The commonest aetiology of hepatic encephalopathy was Infection (33%) followed by Constipation (29%). 15 patients had Grade-1 encephalopathy, 43 had Grade-2, 26 had Grade-3 while 16 had Grade-4 encephalopathy. Deranged serum creatinine, international normalized ratio and albumin levels were significantly associated with a higher grade of hepatic encephalopathy (p-value<0.05) in our study participants.

Conclusion: Biochemical markers studied in patients with hepatic encephalopathy secondary to hepatitis C-related decompensated chronic liver disease were deranged. In addition, creatinine, albumin and International normalized ratio were found to be more deranged in higher grades of encephalopathy.

Keywords: Albumin; Creatinine, Hepatic encephalopathy; International normalized ratio, Urea.

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INTRODUCTION

The liver is one of the most important organs of the human body. However, it is prone to various infective, and non-infective pathological processes.[1] Diseases of the liver and whole hepatobiliary system may lead to temporary or permanent damage to the parenchyma of this vital organ of the human body.[2] Relationship of biochemical findings with clinical findings has always been an area of interest for clinicians and researchers to use these changes as predictors of clinical complications.[3] Prevalence of Hepatitis C infection varies globally, but it is alarmingly high in our part of the world, making it a leading cause of chronic liver disease.[4] Burden of disease decompensated chronic liver disease is also quite high in Pakistan, consuming a big chunk of the health care budget.[5] Decompensated liver disease may present with several complications, including hepatic encephalopathy, not only compromising the patient's quality of life and making the long-term prognosis poor.[6]

Study by Bai *et al*. concluded that deficiency of albumin might lead to overt hepatic encephalopathy, and administration of albumin may improve the severity of overt hepatic encephalopathy.[7] Slack *et al*. proposed various mechanisms for that, including direct renal damage by chronic hepatitis C infection.[8] Bohra *et al*. concluded that serum urea, creatinine, bilirubin, and INR deranged at baseline predicted a high grade of encephalopathy and poor outcome among their study participants.[9]

The burden of cirrhosis and chronic liver disease is alarming in our setup.[4] Salamat *et al*. evaluated the patients based on MELD score, which incorporates the bilirubin, creatinine and INR.[10] Lmited local data has been available to establish any association of biochemical parameters with Grades of hepatic encephalopathy. We, therefore, designed this study with the rationale of looking for an association of various biochemical changes with different grades of hepatic encephalopathy among patients of hepatitis C-related decompensated liver disease presenting at Pak Emirates Military Hospital.

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METHODOLOGY

This comparative cross-sectional study was conducted at the Medicine and Gastroenterology Unit of Pak Emirates Military Hospital, Rawalpindi Pakistan from March 2020 to February 2021. Ethical approval (A/28/EC/30/19) was taken from the Ethical Review Board Committee of Pak Emirates Military Hospital Rawalpindi before the start of this study.The sample was gathered by using the non-probability consecutive sampling technique. The sample size was calculated using the WHO calculator taking population prevalence of hepatitis C-related hepatic encephalopathy as 4.4%%.[11] Sample size turned out to be 65.

Inclusion Criteria: All the patients of 18 to 60 years, presenting at the Emergency Department, admitted in the Wards or ICU with hepatic encephalopathy secondary to hepatitis C-related decompensated chronic liver disease were included in the study.

Exclusion Criteria: Patients with unclear diagnosis regarding the cause of chronic liver disease were excluded from the study. Patients who were pregnant or active alcohol users were also not included. Patients with causes of liver disease other than hepatic C or those with encephalopathy secondary to acute liver failure were also excluded from the study. Patients diagnosed with metabolic, lung, heart, primary brain or renal disease before diagnosis of liver disease were also excluded from the study.

Patients referred from the public sector and private hospitals with the same diagnosis were also included in the analysis as the referrals from the other hospital wards. Diagnosis of hepatitis C-related decompensated liver disease and hepatic encephalopathy was made based on the consultant medical specialist or gastroenterologist's clinical, laboratory and radiological findings.[12,13] Hepatic encephalopathy was graded according to the West Haven criteria.[14] Normal values for biochemical parameters studied were: Creatinine: 0.6 to 1.2mg/dL and between 0.5 to 1.1mg/dL for women, Urea: 2.5–7.0mmol/L, Albumin: 3.5 to 5.0g/dl and International Normalized Ratio: 1.1 or below.[15]

After written informed consent from the primary caregivers of potential participants, patients presenting with hepatic encephalopathy secondary to hepatitis C-related decompensated chronic liver disease in the Medicine/Gastroenterology unit of PEMH RWP, fulfilling the inclusion criteria were included in the study. In addition, a mini-mental state examination was also done to confirm hepatic encephalopathy or other causes of delirium (to exclude) in these patients.

Basic investigations included a Complete Blood picture, liver function test, INR, renal function test, C-reactive protein, tumour markers etc. and ultrasound abdomen. Infections were diagnosed by a consultant medical specialist or gastroenterologist based on relevant clinical and laboratory parameters.

All statistical analysis was performed using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). The mean and standard deviation for the age and duration of decompensated chronic liver disease was calculated. Frequency and percentages for gender, grades of encephalopathy and etiological causes of hepatic encephalopathy were calculated. Pearson Chi-square test was applied to look for the association of deranged biochemical parameters with grades of hepatic encephalopathy by keeping *p*-values less than or equal to 0.05 as significant.

RESULTS

A total of 100 patients with hepatic encephalopathy secondary to hepatitis C-related decompensated chronic liver disease were included in the study. The mean age of patients included in our study was 45.86±8.55 years. Other characteristics of the study population have been summarized in Table-I.

Table-I: Characteristics of Patients Admitted With Hepatic Encephalopathy due to Hepatitis C Related Decompensated Chronic Liver Disease (n=100).

Study Parameters	Frequency
Age (years)	
Mean±SD	45.86±8.55 years
Range (min-max)	18 years-59 years
Mean duration of decompensated chronic liver disease	3.33 ±4.446 years
Gender	
Male	66
Female	44
Grade of Hepatic Encephalopathy	
I	15
II	43
III	26
IV	16
Causes of Hepatic Encephalopathy	
Infection	33
Constipation	29
Esophageal bleeding	19
Hypokalemia	12
Excessive protein in diet	05
Others	02

Out of 100 patients, in the final analysis, 66 were male, and 44 were female. The mean duration of decompensated liver failure in patients included in our study was 3.33±4.44 years. The commonest aetiology of

hepatic encephalopathy was Infection (33%) followed by Constipation (29%). Oesophagal bleeding was found in 19 patients, hypokalemia was found in 12, and excessive protein in the diet was found in 5 patients. Out of all the patients included in the study, 15 patients had Grade-1 encephalopathy, 43 had Grade-2, 26 had Grade-3, and 16 had Grade-4 encephalopathy.

Our study revealed that deranged serum creatinine, INR and albumin levels were significantly associated with a higher grade of hepatic encephalopathy (*p*-values-0.006, 0.003, 0.003, respectively) participants. In contrast, serum urea levels (*p*-value-0.144) showed no statistical association (Table-II).

Table-II: Association of Biochemical Parameters with Grades of Hepatic Encephalopathy (n=100).

Biochemical parameters	Grade-I (n=15)	Grade-II (n=43)	Grade-III (n=26)	Grade-IV (n=16)	*p*-value
Urea					
Within range	12 (80.0%)	20 (46.5%)	15 (57.7%)	09 (56.2%)	0.144
Raised	03 (20.0%)	23 (53.5%)	11 (42.3%)	07 (43.8%)	
Creatinine					
Within range	14 (93.3%)	31 (72.1%)	18 (69.3%)	06 (37.5%)	0.006
Deranged	01 (6.7%)	12 (27.9%)	08 (30.7%)	10 (62.5%)	
International Normalized Ratio (INR)					
Within range	11 (73.3%)	37 (86.1%)	16 (61.5%)	06 (37.5%)	0.003
Deranged	04 (26.7%)	06 (13.9%)	10 (38.5%)	10 (62.5%)	
Albumin					
Within range	13 (86.7%)	26 (60.1%)	13 (50%)	04 (25%)	0.003
Deranged	02 (13.3%)	17 (39.9%)	13 (50%)	12 (75%)	

DISCUSSION

Chronic liver disease has been an area of immense interest for researchers and medical professionals in the past two decades as there was no definitive treatment other than organ transplant to cure this vital organ once it has been fibrosed.[10] Hepatitis C leading to chronic liver disease has been one of the leading causes of mortality and morbidity in our set up.[4,12] Ascities, hematemesis and encephalopathy are hallmark complications of decompensated chronic liver disease. The association between these clinical complications and biochemical markers is an interesting phenomenon and enables clinicians to detect high-risk cases early and predict the course of illness. We, therefore, designed this study with the rationale of looking for the association of various biochemical changes with different grades of hepatic encephalopathy among patients of hepatitis C-related decompensated liver disease presenting at Pak Emirates Military Hospital, Rawalpindi, Pakistan.

Hypoalbuminemia emerged as a biochemical parameter statistically significantly associated with a high grade of hepatic encephalopathy in our study participants (*p*-value<0.05). Bai *et al*.[16] found that decreased serum albumin levels may be associated with a higher risk of overt hepatic encephalopathy and hepatic encephalopathy-associated mortality during hospitalizations among patients suffering from chronic liver disease.

Piano *et al*.[17] emphasized renal function assessment among chronic liver disease patients to refine prognosis and define transplant strategies. Creatinine was the most reliable and commonly used marker for this purpose. Our results also revealed that raised creatinine levels were associated with a higher grade of encephalopathy and may be used as a marker for advanced disease among patients suffering from hepatitis C-related decompensated chronic liver disease.

Duah *et al*.[18] concluded that raised serum creatinine and blood urea nitrogen levels were independent predictors of severe disease and overt hepatic encephalopathy in their patients. Our results were similar to their results in terms of serum creatinine levels. However, serum urea levels were not associated with high grades of encephalopathy in our study participants (*p*-value>0.05).

A local study from the same hospital setting published in Pakistan Armed Forces Medical Journal using the MELD score as criteria to look for the severity of chronic liver disease and prioritize patients for liver transplant concluded that the higher the MELD score, higher the chances of mortality among these patients.[10] MELD score included serum creatinine and INR as main constituents, which were also studied in our analysis and emerged as strong predictors of higher grades of encephalopathy.

LIMITATIONS OF STUDY

Grades of hepatic encephalopathy are clinically determined, and observer bias may occur if different clinicians are

involved. Duration of hepatitis C infection, genotype and comorbidities were not studied in our analysis, which were the main limitations of our study. Baseline levels of the biochemical parameters prior to the onset of hepatic encephalopathy were also unknown in these patients, so this could not be concluded that biochemical abnormalities were the cause or consequence of hepatic encephalopathy. Nutrition and activity status prior to the onset of encephalopathy was also not recorded, which may affect our studied parameters. Addressing these limitations and conducting studies in multiple centres with large sample sizes may generate generalizable results in this regard.

CONCLUSION

Biochemical markers studied in patients with hepatic encephalopathy secondary to hepatitis C-related decompensated chronic liver disease were found deranged in many patients. In addition, creatinine, albumin and INR were found to be more deranged in higher grades of encephalopathy.

Conflict of Intrest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AR: Conception, study design, data acquisition, drafting the manuscript, critical review, approval of the final version to be published.

SR: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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