Assessment of Clinical, Laboratory and Endoscopic Risk Factors for Hepatic Encephalopathy Development in Egyptian Cirrhotic Patients with Upper GIT Bleeding

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AIM: to assess risk factors for hepatic encephalopathy development in Egyptian patients with gastrointestinal bleeding.

MATERIAL AND METHODS: 120 cirrhotic patients with upper gastrointestinal bleeding were randomly assigned into: (group I) patients who complicated with hepatic encephalopathy (n = 60) versus (group II) patients not complicated with hepatic encephalopathy (n = 60). Clinical, laboratory and endoscopic features of all patients were explored and compared between the 2 groups.

RESULTS: Patients with Child’s class C, more ascites and spontaneous bacterial peritonitis were significantly more in group I (p < 0.001), also diabetic patients (p = 0.02). Total leucocytic count, total, direct bilirubin, INR, creatinine and blood urea nitrogen were significantly higher in group I (p < 0.001), also AST (p = 0.04), albumin was significantly lower (p < 0.001). Higher degrees of esophageal varices and portal hypertensive gastropathy were the significant cause of bleeding in group I (p= 0.001 and 0.02 respectively). Degree of ascites, Child’s score points, diabetes, and spontaneous bacterial peritonitis were significantly related to encephalopathy grade (p < 0.001, < 0.001, < 0.001, 0.016 respectively), also total, direct bilirubin, INR, blood urea nitrogen and Total leucocytic count (p = 0.005, 0.002, 0.001, 0.02, 0.018 respectively). Patients with advanced encephalopathy grades had significantly higher variceal and gastropathy grades (p = 0.002 and 0.038).

CONCLUSION: Hepatic encephalopathy following upper GIT bleeding in this study needed other cofactors to occur as advanced Child’s classes and score, presence of ascites, renal impairment, leucocytosis, diabetes, spontaneous bacterial peritonitis and higher variceal and gastropathy grades. Special monitoring and early prophylactic interventions are advised in patients with these factors.

Key words: Esophageal and gastric Varices; Liver cirrhosis; Peritonitis; Hepatic encephalopathy precipitating Factors

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Abbreviations
GIT: gastrointestinal tract
TIPS: transjugular intrahepatic portosystemic stent shunt
AST: aspartate transaminase
ALT: alanine transaminase
CBC: complete blood picture
PHG: portal hypertensive gastropathy.
AASLD: American association for the study of liver disease
TLC: total leucocytic count
INR: international normalizing ratio
BUN: blood urea nitrogen
HCC: hepatocellular carcinoma
SBP: spontaneous bacterial peritonitis
DM: diabetes mellitus
Upper gastrointestinal bleeding can be manifested with hematemesis, melena or hematochezia. Acute bleeding due to gastroesophageal varices in cirrhotic patients is associated with higher morbidity, mortality rates as well as development of life-threatening complications. This bleeding significantly increase protein concentration in the bowel which results in increased ammonia production by colonic bacteria and precipitation of hepatic encephalopathy[4].

Hepatic encephalopathy, a neurological dysfunction disorder including a wide spectrum of clinical symptoms and signs with different grades ranging from minimal abnormalities in neuropsychological function to coma[5].

Hyper ammonemia causes neurotransmitter abnormalities and injury to astrocytes, astrocyte swelling and brain edema, which appear to be the pathogenetic mechanisms of neurological manifestations of hepatic encephalopathy[6]. Studies shows that lactulose administration is highly effective prophylactic measure of hepatic encephalopathy development in patients presented with upper gastrointestinal bleeding[7].

However, recently, strong evidence that the kidneys have a role in pos GIT bleeding hyperammonemia was proved and these results have recently been confirmed in cirrhotic patients with a transjugular intrahepatic portosystemic stent shunt (TIPS)[8].

Despite use of lactulose and enemas in patients presented with gastrointestinal bleeding, many patients still develop hepatic encephalopathy and on contrary not all patients with GIT bleeding develop this complication indicating that other specific risk co factors play a role in development of this complication that carries a high morbidity and mortality.

In this study we aimed to asses clinical features, laboratory and endoscopic risk factors for hepatic encephalopathy development in patients presented with upper GIT bleeding in order for identification of this high risk group for early intervention and prophylactic measurements.

Subjects
All subjects of the study were recruited from gastroenterology and hepatology emergency and endoscopy unit, Internal Medicine department, Faculty of Medicine, Zagazig University, Egypt in the period between April 2016 and October 2016.

This case - control study included 120 cirrhotic patients presented to emergency unit by upper GIT bleeding and were randomly assigned into 2 groups: (group I) patients who complicated with hepatic encephalopathy (n = 60) and (group II) patients who were not complicated with hepatic encephalopathy (n = 60) with different severities of the liver disease that was assessed according to Child’s–Pugh classification[9].

Inclusion criteria
(1) All cirrhotic patients with different Child’s classes developed hepatic encephalopathy either at time of admission with bleeding or later on during follow up.

Exclusion criteria
(1) Patients with other precipitating factors for hepatic encephalopathy than gastrointestinal bleeding as constipation, electrolyte disturbances, protein intake, diarrhea, diuretic use paracentesis and severe sepsis.

(2) Non cirrhotic patients admitted with upper GIT bleeding.

(3) Patients refused to enter the study.

The ethical committee of Faculty of Medicine at Zagazig University approved our study protocol, a written consent was taken from all patients or their relatives and control subjects according to Helsinki declaration at recruitment.

METHODS
All subjects were subjected to complete history taking (including history of previous bleeding episode, encephalopathy episodes, upper GIT endoscopy, amount of blood loss, amount of blood transfusion units, hepatocellular carcinoma, DM, hypertension or other co morbidities) and thorough full clinical examination including assessment of hemodynamic status.

Grading of hepatic encephalopathy was according to West Haven Grading System[10]:

Grade 0 - Minimal hepatic encephalopathy (subclinical hepatic encephalopathy); minimal abnormalities in memory, concentration, coordination and intellectual function and absence of flapping tremors.

Grade 1 - minimal lack of awareness; defect in addition or subtraction; sleep abnormalities (hypersomnia or insomnia or inversion of sleep pattern); emotional abnormalities (euphoria or depression), irritability; mild confusion.

Grade 2- Lethargic or apathetic state; personality changes; disorientation of time; abnormal behavior; slurred speech; appearance of asterixis; drowsiness, major abnormalities in ability to do mental tasks.

Grade 3- Somnolence but patient can be aroused; marked confusion; inability to perform any mental tasks; disorientation for time and place; memory defect; occasional fits and incomprehensible speech.

Grade 4- Coma with or without response to painful stimuli.

Routine biochemical measurement
Liver function tests including total and direct bilirubin, albumin, AST, ALT, kidney function tests, CBC, coagulation profile, random blood glucose, total and differential leucocytic count in ascetic fluid samples and alpha fetoprotein for patients with focal lesions.

Radiological investigations
A) Pelvi-abdominal ultrasonography for confirmation of liver cirrhosis, detection of hepatic focal lesions and ascites.

B) Triphisic abdominal CT for diagnosis of hepatocellular carcinoma in suspected patients.

Upper GIT endoscopy
Pentax EPK- I 5000 videoscope was used for diagnostic and therapeutic management. Endoscopy was performed for patients with hepatic encephalopathy following regaining of conscious level.

Esophageal varices were graded according to Paquet system[11]; Grade 0: no varices. Grade I: varices which disappear on...
Portal hypertensive gastropathy (PHG) was graded according to Tanoue et al. classification: Grade 0: none. Grade I: mild PHG. Grade II: moderate PHG. Grade III: severe PHG.

Bleeding ulcer was classified according to Forrest classification:

- Acute hemorrhage (I): I a (Spurting bleeding); I b (Oozing bleeding).
- Stigmata of recent hemorrhage (II): II a (Visible vessel); II b (Adherent blood clot); II c (Flat pigmented haematin on ulcer base).
- Ulcers without active bleeding (III): (Lesions without stigmata of recent bleeding with clean ulcer base).

### Management

All patients with GIT bleeding with or without hepatic encephalopathy were treated according to recommended guidelines of American association for the study of liver disease (AASLD).

### Statistical analysis

The obtained data were checked, entered and analyzed statistically using SPSS program version 20. Data were expressed as means ± standard deviation for quantitative variables and frequency & percentages for qualitative variables. ANOVA (F test), t test or mann-whitney, Chi-Square tests ($\chi^2$) or fisher exact were used when appropriate. The results were considered statistically significant if the P value was <0.05.

## RESULTS

### Demographic and clinical characteristics of studied groups

Our patients were matched as regards age, sex, prevalence of hepatocellular carcinoma, number of blood units transfused and degree of hemodynamic stability ($p > 0.05$) (Table 1).

Patients complicated with hepatic encephalopathy had a significantly larger amount of ascitis than patients without encephalopathy ($p < 0.001$), also frequency and percentage of patients complicated with spontaneous bacterial peritonitis was statistically significantly higher in encephalopathy group when compared to group II ($p < 0.001$) (Table 1).

Patients with advanced Child’s class C and higher Child’s score points as well as mortality were significantly more in patients complicated with hepatic encephalopathy following upper GIT bleeding ($p < 0.001$) (Table 1 and Figure 1).

Frequency and percentage of diabetic patients was statistically significantly higher in group I patients complicated with hepatic encephalopathy ($p = 0.02$) (Table 1).

### Laboratory data of studied groups

Patients complicated with hepatic encephalopathy had a highly significant values of TLC, total bilirubin, direct bilirubin, INR, creatinine and BUN when compared to group II ($p < 0.001$), also AST was significantly higher ($p = 0.04$), however ALT values didn’t differ significantly between the 2 groups ($p > 0.05$) (Table 2).

Serum albumin levels were also highly significantly lower in hepatic encephalopathy patients ($p < 0.001$) (Table 2).

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**Table 1 demographic and clinical characteristics of studied groups**

|                      | Group I (patients with encephalopathy) N=60 | Group II (Patients without encephalopathy) N=60 | P     |
|----------------------|--------------------------------------------|-----------------------------------------------|-------|
| Age                  | 59.5±9.9                                   | 57.2±7.7                                      | 0.16  |
| Sex                  |                                            |                                               |       |
| Female               | 23 (38.3%)                                 | 19 (31.7%)                                    | 0.44  |
| Male                 | 37 (61.7%)                                 | 41 (68.3%)                                    |       |
| Hemodynamic stability|                                            |                                               |       |
| Stable               | 35 (58.3%)                                 | 44 (73.3%)                                    | 0.08  |
| Unstable             | 25 (41.7%)                                 | 16 (26.7%)                                    |       |
| No of blood units transfused | 1.27 ± 1                           | 1.4 ± 1.4                                     | 0.55  |
| HCC                  | 17 (28.3%)                                 | 4 (15%)                                       | 0.07  |
| S.B.P                | 11 (18.3%)                                 | 8 (15%)                                       | <0.001** |
| Ascites              |                                            |                                               |       |
| No                   | 8 (13.3%)                                  | 44 (73.3%)                                    | <0.001** |
| Mild                 | 11 (18.4%)                                 | 5 (5%)                                        |       |
| Moderate             | 22 (36.7%)                                 | 13 (21.7%)                                    |       |
| Marked               | 19 (31.7%)                                 | 9 (0%)                                        |       |
| Child’s class        |                                            |                                               |       |
| A                    | 3 (0%)                                      | 26 (43.3%)                                    | <0.001** |
| B                    | 11 (18.3%)                                 | 26 (43.3%)                                    |       |
| C                    | 49 (81.7%)                                 | 3 (13.4%)                                     |       |
| Point scores         | 11.2±2.41                                   | 7.1±1.6                                       | <0.001** |
| Encephalopathy grade |                                            |                                               |       |
| 1                    | 4 (6.7%)                                    |                                               |       |
| 2                    | 24 (40%)                                    |                                               |       |
| 3                    | 15 (25%)                                    |                                               |       |
| 4                    | 17 (28.3%)                                  |                                               |       |
| DM                   | 10 (50%)                                    | 8 (30%)                                       | 0.02* |
| Mortality            | 15 (25%)                                    | 1 (0%)                                        | <0.001** |

*: significant; **: highly significant; HCC: hepatocellular carcinoma; S.B.P: spontaneous bacterial peritonitis; DM: diabetes mellitus.

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**Figure 1** Percentage of distribution of different Child’s classes in studied groups: patients with hepatic encephalopathy (group I) were more of Child’s class C than patients without encephalopathy (group II).
Endoscopic features in studied groups

Percentages of higher degrees of esophageal varices and portal hypertensive gastropathy (grade III) were significantly higher as a cause of bleeding in patients complicated with hepatic encephalopathy as compared to group II \((p = 0.001\) and 0.02 respectively) but percentage of bleeding ulcer as an associated cause of bleeding was significantly higher in group II when compared to group I \((p = 0.02)\) (Table 3).

Percentage of fundal varix as a cause of bleeding didn’t significantly differ between groups \((p > 0.05)\) (Table 3).

Relation of different grades of encephalopathy to different demographic, clinical and laboratory data in group I

Regarding demographic and clinical data; age, sex, prevalence of hepatocellular carcinoma and degree of hemodynamic stability were not significantly related to encephalopathy grade \((p > 0.05)\), while degree of ascities, Child’s score points, DM, and spontaneous bacterial peritonitis were significantly related to encephalopathy grade \((p < 0.001, < 0.001, < 0.001, 0.016\) respectively) (Table 4).

Also patients with higher encephalopathy grades (grade 3 and 4) had significantly higher total and direct bilirubin, INR, BUN and TLC \((p = 0.005, 0.002, 0.001, 0.02, 0.018\) respectively), while no significant relation was found to albumin or creatinine \((p > 0.05)\) (Table 4).

Relation of different stages of encephalopathy to source of bleeding in group I

Patients with grad 3 and 4 encephalopathy had a higher percentages of variceal grade III \((p = 0.002)\), also patients with grade 3 encephalopathy had significantly higher grades of PHG \((p = 0.038)\), while prevalence of ulcers as an associated cause of bleeding was significantly higher in less encephalopathy grades \((p < 0.001)\) (Table 5).

DISCUSSION

Hepatic encephalopathy is a reversible neuropsychiatric disorder associated with chronic and acute liver dysfunction. It is characterized
by cognitive and motor abnormalities with different severities ranging from subtle psychological abnormalities to profound coma and death\(^\text{[10]}\).

Well-recognized factors, which tend for hepatic encephalopathy precipitation in patients with underlying liver cirrhosis, include an increased dietary protein load, constipation, and gastrointestinal bleeding and these factors also known as gut factors, and are consistent with the hypothesis that gut-derived nitrogenous constituents of portal venous blood contribute to hepatic encephalopathy development\(^\text{[11]}\). Use of sedative or hypnotic drugs and electrolyte imbalances also contribute to hepatic encephalopathy development in these patients\(^\text{[13]}\). The frequency of infection as precipitating factor appears to be declining and gastrointestinal bleeding appears to be increasing\(^\text{[8]}\).

Lactulose is effective in the management of hepatic encephalopathy\(^\text{[14]}\) and in the prevention of secondary episodes of encephalopathy\(^\text{[15]}\). Gut irritation with paromomycin plus lactulose had been found to be effective in the prevention of encephalopathy developmen after upper GIT bleed in previous trials\(^\text{[17]}\).

Despite use of lactulose and enemas in patients presented with gastrointestinal bleeding, many patients still develop hepatic encephalopathy and on contrary not all patients with GIT bleeding develop this complication indicating that other specific risk cofactors play a role in development of this complication so we aimed to assess clinical features, laboratory and endoscopic risk factors for hepatic encephalopathy development in these patients in order for identification of this high risk group.

In this study, exploring clinical features of patients complicated with hepatic encephalopathy, we found that advanced Child’s class (class C) and patients with larger amounts of ascites were the major constituent class in this group indicating that these patients are the most prone to develop this complication, also a significant difference between the two groups as regards mean and SD of Child’s score points, being higher in patients who complicated with hepatic encephalopathy was found.

These results were in agreement with Sharma et al\(^\text{[13]}\) 2011, study who found that patients who developed hepatic encephalopathy following upper GIT bleeding had significantly higher Child-Turcotte-Pugh (CTP) and MELD scores, arterial ammonia at baseline. CTP score in patients who develop hepatic encephalopathy was (11.8 ± 1.4 and 10.4 ± 2.3) in their study groups versus (7.1 ± 2.0 and 7.5 ± 1.3) with p value = 0.001, that was similar to our results for group I patients who develop hepatic encephalopathy (11.2 ± 2.41 versus 7.1 ± 1.6 in group II) and that score was significantly related to encephalopathy grade in this study (Table 4).

Also these results were in agreement with Wen et al, 2013\(^\text{[16]}\) who found that patients who had developed HE had a significantly higher baseline CTP score and on unconditional logistic regression analysis, patients who had developed hepatic encephalopathy were significantly associated with a higher baseline CTP score (OR 9.92, 95% CI 1.94-50.63, p < 0.05).

However in these studies, patients who developed hepatic encephalopathy were in group not receiving lactulose and were small in number in patients who received lactulose therapy and we can explain this difference from our study by that our study number of patients was larger than study of Sharma et al \((120 \ vs \ 70)\), also mean age of Sharma study was younger than patients of our study and were non diabetic beside that the main cause of cirrhosis was alcoholic cirrhosis in their study but we have the higher incidence of HCV related cirrhosis in our country.

Despite that frequency and percentages of hemodynamic unstable patients were higher in patients with hepatic encephalopathy, this didn’t reach a statistical significance in our study and was not in agreement with Sharma et al study who stated that patients who developed hepatic encephalopathy had significantly lower mean arterial pressure at baseline.

The present study found that percentage of diabetes mellitus (DM) in patients who developed hepatic encephalopathy was significantly higher and these percentages significantly related to grade of encephalopathy. Thuluvath\(^\text{[18]}\) has been suggested that DM may contribute to presence and severity of hepatic encephalopathy independent of liver disease severity in patients with HCV related cirrhosis. These patients especially with long standing DM complicated with autonomic neuropathy likely to develop hepatic encephalopathy because of longer intestinal transit time, resulting in small bowel bacterial overgrowth that leads to hyperammonemia from ingested blood and development of endotoxemia. Our results were also in agreement with El Soud et al\(^\text{[21]}\).

Mortality rate in group I was significantly higher than group II, Sheila Sherlock in their study \(^\text{[21]}\) reported that patients who did expire were mostly in Class C of Child’s classification who were the main constituent of hepatic encephalopathy patients in this study.

In sharma et al study serum creatinine levels were in normal range \((1.1 ± 0.3 \ and \ 0.9 ± 0.3 \ in \ both \ groups)\) but in our study patients presented with hepatic encephalopathy had a mean ± SD of creatinine \((1.7 ± 1 \ vs \ 0.76 ± 0.3 \ in \ group \ II)\) indicating that presence of renal impairment is an adding risk factor for encephalopathy in our patients. This was in accordance to Muntaz K., et al\(^\text{[13]}\) who confirmed that factors other than liver failure, such as uremia may also contribute to encephalopathy in such patients. Azotemia is an important pathogenic contributor to the onset of HE\(^\text{[22]}\); however blood urea nitrogen (BUN) but not creatinine was only significantly related to grade of encephalopathy in this study.

Kidney is a vital organ to clear bloodstream ammonia that increases the susceptibility to brain edema and encephalopathy\(^\text{[2]}\). Forms of renal function impairment occur in hepatic patient, including acute renal failure, end-stage renal disease (ESRD), chronic kidney disease, and hepatorenal syndrome\(^\text{[23]}\). In previous studies, acute renal failure carries unfavorable prognosis for mortality in hepatic encephalopathy patients. Hepatorenal syndrome patients had the worst outcome; hepatic encephalopathy patients with ESRD on regular hemodialysis had better survival than those with chronic kidney disease\(^\text{[24]}\).

Renal impairment in our patients occurred partially due dehydration secondary to previous use of diuretics in patients who have ascites due to decompensated liver disease who were the main

| Grade 1, N=4 | Grade 2, N=24 | Grade 3, N=15 | Grade 4, N=17 |
|-------------|-------------|-------------|-------------|
| Endoscopy   | Endoscopy   | Endoscopy   | Endoscopy   |
| No=4        | No=24       | No=15       | No=17       |
| Varices grade | 0.002* | 1 (0%)       | 1 (33.3%)   | 2 (20%)   |

| Ulcer grade |
|-------------|
| 0 (0%) |

Table 5 Relation of different stages of encephalopathy to source of bleeding.
component of group I or due to lack of oral intake due to anorexia. Therefore, caution must be taken and these patients need to be monitored vigilantly. Other cases of renal impairment were due to hepatorenal syndrome or chronic kidney disease secondary to diabetic nephropathy.

In this study we found that patients complicated with hepatic encephalopathy had a significantly higher total leucocytic count than group II and level of leucocytosis was significantly related to encephalopathy grades. Also sharma et al., in their study found on univariate analysis, patients with hepatic encephalopathy had significantly higher total leucocytes count. There is increasing evidence that infection/inflammation play a pathogenic role in episodes of hepatic encephalopathy. Systemic inflammatory response syndrome (SIRS) adding to poor outcome of cirrhotic patients.[24]

Leucocytosis in our patients in group I can be explained by that they are usually severely malnourished not only because of their disease but also because of food faddism and taboos regarding their diet.[25] Strict dietary restrictions especially protein diet for these patients lead to anorexia and malnutrition, and lowering their immunity and making them more susceptible to infections.[25] Spontaneous bacterial peritonitis episodes were comparable between the two groups and similar results were observed in sharma et al. study. In patients with ascites, the development of spontaneous bacterial peritonitis (SBP) is a well-recognized complication among cirrhotic patients who present with gastrointestinal bleeding.[26] Other sources of infections was chest infection due to coma and aspiration in some patients.

Therefore, patients with increased number of precipitants as in our patients in group I secondary to advanced Child’s class tend to have a worse outcome.

In our study we found that, patients in group I had significantly higher total bilirubin, direct bilirubin, INR levels, AST and lower serum albumin than group II patients with no significant difference between the 2 groups as regards ALT values. Similar results obtained by Wen et al. 2013, who found that patients who had developed HE had significant difference in total bilirubin, serum albumin and plasma prothrombin time values as compared to patients who did not develop hepatic encephalopathy. also Sharma et al. documented that total bilirubin in patients with encephalopathy was (3.4 ± 1.3 vs 2.1 ± 1.8 mg%, p = 0.008) as compared to patients who did not develop HE and we studied relation of these different laboratory data to different encephalopathy grades and we found that total and direct bilirubin, INR, BUN levels were significantly related to it, which all reflects that advanced Child’s class is the main significant and important factor for development and severity of this complication following GIT bleeding because of more decrease in hepatic clearance.

Regarding endoscopic finding, higher degrees of esophageal varices and portal hypertensive gastropathy (PHG) (grade III) was found as a cause of bleeding in patients complicated with hepatic encephalopathy as compared to group I (p = 0.001 and 0.02 respectively) but percentage of bleeding ulcer as an associated cause of bleeding was significantly higher in group II when compared to group I (p = 0.02). The grades of esophageal varices and severity of PHG often positively correlate with the severity of portal hypertension which correlates with severity of liver disease evaluated according to Child’s classification.[27,28] The severity of encephalopathy is related to Child’s class and score as documented in this study therefore, such mutual correlations may explain why patients with encephalopathy and higher grades had higher esophageal varices and PHG grades making them more prone for more blood loss and more hyperammonemia.

However percentage of bleeding ulcer as an associated cause of bleeding was significantly higher in group II when compared to group I and this may be explained by that smaller number (37/60) of patients in group I who did upper endoscopy and this was attributed to death of some cases and refuse to perform endoscopic management in others.

**Strength and limitation of study**

The strength of this study was that it strictly followed the guidelines of ASSLD for management of upper GIT bleeding and hepatic encephalopathy patients, limited for evaluation of effect of lag time between admission to upper GIT endoscopy performance on hepatic encephalopathy development, also it was not possible to do endoscopic evaluation for all patients either due to death or refuse to perform endoscopy.

**CONCLUSION**

Upper GIT bleeding as a precipitating factor for hepatic encephalopathy development in this study is not the main factor alone. This complication need other cofactors as advanced Child’s classes and score, presence of marked ascites, higher AST values, renal impairment, leucocytosis, DM, spontaneous bacterial peritonitis and higher variceal and PHG grades (all or some of them) to make these patients more prone to encephalopathy.

**RECOMMENDATIONS**

Upper GIT bleeding patients with advanced Child’s classes and score, larger amount of ascites, higher AST values, renal impairment, leucocytosis, DM, spontaneous bacterial peritonitis and higher variceal and PHG grades need special monitoring and care with early prophylactic interventions to avoid encephalopathy development.

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