


# Clinical Aspects and Precipitating Factors of Hepatic Encephalopathy Associated with Cirrhosis in a Cameroonian Population

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## Abstract

**Background:** Hepatic Encephalopathy (HE), a common complication of cirrhosis, is associated with a pejorative prognosis. This study aims to describe the clinical presentation, precipitating factors and outcome of HE. **Methods:** This was a cross-sectional multicenter inpatient study in cirrhotic patients admitted for HE in four tertiary hospitals in Yaoundé (Cameroon) from December 2016 to May 2017. The diagnosis of HE was based on West Haven clinical criteria. The diagnosis of cirrhosis was made using clinical and/or biological, endoscopic and/or ultrasonography signs. **Results:** A total of 53 patients with HE (mean age:  $49.9 \pm 18.9$  years, 35 Males) were included. The frequency of hospital admission for HE was 4.9%. HE grade III was the most common (37.7%), followed by grades I and II (26.4% and 26.4%, respectively). Grade IV was present in 9.4% of cases. According to the Child-Pugh score, 72.1% of the patients were at stage C and 27.9% at stage B. The main precipitating factors found were: constipation (38.5%), hyponatremia (35.9%), hepatocellular carcinoma (HCC) (31.7%), herbal medicine (28.3%), hypokalemia (25.6%), gastrointestinal bleeding (22.6%) and ascitic fluid infection (spontaneous bacterial peritonitis) (13.8%). In 5.7% of cases, no factor was identified. Mortality rate during hospitalization was 45.3% and was significantly associated with stage III (RR = 11.1; 95% CI: 1.9 -

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64.5;  $p = 0.003$ ) and IV (RR = 24; 95% CI: 1.6 - 40.9;  $p = 0.01$ ) of HE; Child-Pugh C score (RR = 15.2; 95% CI: 1.7 - 30.1;  $p = 0.003$ ) and hypokalemia (RR = 12.2; 95% CI: 1.3 - 19;  $p = 0.01$ ). **Conclusion:** HE is a common complication during cirrhosis with a poor prognosis. In the majority of cases, a precipitating factor could be determined.

## Keywords

Hepatic Encephalopathy, Liver Cirrhosis, West Haven Criteria, Child-Pugh, Cameroon

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## 1. Introduction

Hepatic encephalopathy (HE) associated with cirrhosis is a spectrum of neurological or neuropsychiatric manifestations occurring in patients with hepatic cirrhosis [1]. The symptoms of HE can range from simple neurological disorders detectable only by psychometric tests to coma [2]. The prevalence of overt HE at the time of diagnosis of cirrhosis varies from 10% to 50% depending on whether cirrhosis is compensated or decompensated and/or the presence of transjugular intrahepatic porto-systemic shunt (TIPS) [2]. The positive diagnosis of HE is based on a bundle of arguments in association with a particular clinical context. There are no specific clinical signs associated with HE. This disorder is classified into 4 stages according to the classification of the West Haven Criteria (WHC), ranging from simple neurological disorders detectable by psychometric tests to coma [3]. The onset of HE must be investigated for a precipitating factor, especially an infectious episode, gastrointestinal bleeding, electrolyte imbalance, constipation, diuretic use [4] [5]. HE in liver cirrhosis is disabling and associated with poor prognosis and high mortality without liver transplantation [6] [7] [8]. In Cameroon, due to the high prevalence of chronic viral hepatitis B and C both in general population and in high-risk group population [9] [10], there is a high incidence of cirrhosis and its complications, including HE. Data on HE during cirrhosis is scarce. We therefore, sought to describe the clinical presentation, precipitating factors and outcome of HE among cirrhotic patients.

## 2. Methods

### 2.1. Study Population

This was a cross-sectional multicenter inpatient study on cirrhotic admitted for HE in the internal medicine departments of the Yaounde Teaching Hospital, the Yaounde General Hospital, the Yaounde Military Hospital and the gastroenterology department of Yaounde Central Hospital. This study was conducted over a period of 6 months, from December 2016 to May 2017.

All patients with hepatic cirrhosis complicated by HE and hospitalized in the study sites were included. Patients with chronic liver disease other than cirrhosis, acute liver disease and neurological impairment other than HE associated to

cirrhosis were excluded.

## 2.2. Diagnosis of Cirrhosis and of HE

The diagnosis of cirrhosis was based on clinical and/or biological (including signs of liver failure and portal hypertension) and/or ultrasonographic signs of cirrhosis (irregular aspect of the liver surface, liver parenchymal texture heterogeneous, dilatation of the portal venous system vessels) and/or endoscopic signs of portal hypertension. HE was diagnosed based on clinical signs and they were classified using the WHC classification [3].

## 2.3. Data Collection

Participants in the study were conveniently recruited. Data collected included age, gender, symptoms of HE, signs and symptoms of cirrhosis, signs and symptoms of infection. Laboratory investigations requested included: serum electrolytes, random blood glucose, renal function tests, hepatitis B surface antigen, and hepatitis C antibodies. Ascitic tap was done and sent for analysis in order to diagnose spontaneous bacterial peritonitis (SBP). The diagnosis of SBP was made in presence of more than 250 of polymorphonuclear cells per ml. Any identified HE precipitating factor was recorded and during hospitalization, clinical outcome was also recorded.

## 2.4. Statistical Analysis

Data was registered using CsPro 6.3 software and analyzed using SPSS 23.0 software (SPSS Inc., Chicago, IL). Relative risk (RR) and the 95% confidence interval (95% CI) were calculated to assess associations between mortality and stage of HE, severity of cirrhosis and precipitating factors of HE in univariate analysis. A *p* value of <0.05 was considered significant.

## 3. Ethical Considerations

Ethical clearance was obtained from the Institutional Research Ethical Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaoundé I. The administrative authorizations were received from directors of the various hospitals involved in the study and written consent were obtained from all patients included or from their guardians.

## 4. Results

### Characteristics of the study population

During the study period, 53 (4.9%) patients with cirrhosis associated HE were enrolled out of 1081 hospitalized patients. The mean age was  $49.9 \pm 18.9$  years (minimum: 17 and maximum: 85 years). The sex ratio was 2.3.

### Etiologies of cirrhosis

The most frequent cause of cirrhosis was chronic hepatitis B virus alone (60%), followed by chronic hepatitis C virus alone (22.6%), hepatitis B virus as-

sociated to hepatitis D virus (7.5%) and alcohol consumption alone (3.8%). In 5.7% of cases the etiology of cirrhosis was unknown. The characteristics of patients are summarized in **Table 1**.

#### Description of the different clinical aspects of HE

According to the WHC, stage III of HE was the most represented (37.7%), followed by grades I and II, respectively in 26.4% and 26.4% of cases. Grade IV

**Table 1.** Baseline characteristics of the study population.

Variables	Number	Percentage (%)
<b>Gender</b>		
Male	37	69.8
Female	16	30.2
<b>Age groups</b>		
<b>Mean <math>\pm</math> SD (49.9 <math>\pm</math> 18.9)</b>		
<20	1	1.9
20 - 40	21	39.6
41 - 60	12	22.6
>60	19	35.8
<b>Comorbidities</b>		
Diabetes	8	15.1
HIV	5	10
Hypertension	8	15.1
Alcohol	11	20.8
HCC	7	13.2
<b>Etiologies of cirrhosis</b>		
HBV	32	60
HCV	12	22.6
Alcohol	2	3.8
Not identified	3	5.7
<b>Child Pugh score</b>		
Child B	12	27.9
Child C	31	72.1
<b>Outcome</b>		
Alive	29	54.7
Dead	24	45.3
<b>Biological parameters (Mean <math>\pm</math> SD)</b>		
Bilirubin (mg/l)		57.2 $\pm$ 80
Albumin (g/l)		20.3 $\pm$ 14.4
TP (%)		46.9 $\pm$ 27.4
Glycemia (g/l)		0.8 $\pm$ 0.6
Creatinemia (mg/l)		13.6 $\pm$ 16.5
Natremia (mEq/l)		103.5 $\pm$ 59.9
Kalemia (mEq/l)		3.02 $\pm$ 1.9
<b>Duration of hospitalization (days)</b>		8.7 $\pm$ 6

was present in 9.4% of cases. Distribution of the grade of HE is show in **Table 2**.

Child-Pugh classification could be performed in 43 patients. According to this score, 31 patients (72.1%) and 12 patients (27.9%) were classified Child C and Child B respectively.

#### Precipitating factors

The main precipitating factors found were: constipation (37.7%), herbal medicine (28.3%), hyponatremia (26.4%), HCC (24.5%), gastrointestinal bleeding (22.6%), hypokalemia (15%), and ascitic fluid infection (7.5%). No factor was identified in 5.7% of participants. The precipitating factors are detailed in **Table 3**.

#### Outcome:

The mortality rate during hospitalization was 45.3%. The average admission duration was  $8.7 \pm 6$  days. Mortality was significantly associated with stages III [RR = 11.1; 95% CI: 1.9 - 64.5;  $p = 0.003$ ] and IV [RR = 24; 95% CI: 1.6 - 40.9;  $p = 0.01$ ] of HE, Child C score of cirrhosis [RR = 15.2; 95% CI: 1.7 - 30.1;  $p = 0.003$ ] and Hypokaliemia [RR = 12.2; 95% CI: 1.3 - 19;  $p = 0.01$ ] (**Table 4**).

**Table 2.** Grades of HE according to the WHC classification.

Stages	Number	Percentage (%)
Stage I	14	26.4
Stage II	14	26.4
Stage III	20	37.7
Stage IV	5	9.4
Total	53	100

**Table 3.** The precipitating factors of HE.

Variables	Number	Percentage (%)
SBP	4	7.5
Gastrointestinal bleeding	12	22.6
Constipation	20	37.7
Hypokaliemia	8	15
Hyponatremia	14	26.4
Herbal medicine	15	28.3
Diuretics overdose	6	11.3
Paracentesis	2	3.8
Diarrhoea	8	15
HCC	13	24.5
Sedative drugs intake	1	1.9
Unidentified	3	5.7
Cutaneous infection	3	5.7
Lower respiratory tract infection	3	5.7
Urinary tract infection	2	3.8
Malaria	1	1.9
Vomiting	1	1.9

**Table 4.** Factors associated to mortality of HE.

Factors	Mortality n (%)	RR	IC à 95%	P
<b>Precipitating factors</b>				
Gastrointestinal bleeding	6 (25.0)	1.2	0.3 - 4.6	0.7
Constipation	8 (34.8)	0.7	0.2 - 2.3	0.6
Hyponatremia	6 (35.3)	0.9	0.25 - 3.5	0.9
Hypokaliemia	7 (36.8)	12.2	1.3 - 19	0.01
Diuretics overdose	4 (18.2)	3.0	0.4 - 18.1	0.3
Diarrhoea	6 (25.0)	4.5	0.8 - 24.8	0.1
Paracentesis	1 (4.2)	1.2	0.07 - 20.5	1.0
HCC	7 (41.2)	2.1	0.5 - 7.9	0.2
Herbal medicine	5 (20.8)	0.5	0.1 - 1.7	0.2
Urinary tract infection	2 (8.3)	1.2	0.1 - 9.4	1.0
Cutaneous infection	2 (8.3)	2.5	0.2 - 29.9	0.5
Lower respiratory tract infection	3 (12.5)	2.3	1.7 - 3.2	0.08
Vomiting	1 (4.2)	2,2	1.7- 3.1	0.4
<b>Grades of HE</b>				
Grade I	2 (8.3)	1	-	-
Grade II	5 (20.8)	3.3	0.5 - 21.7	0.3
Grade III	13 (54.2)	11.1	1.9 - 64.5	0.003
Grade IV	4 (16.7)	24	1.6 - 40.9	0.01
<b>Severity of cirrhosis</b>				
Child B	1 (2.3)	1	-	-
Child C	18 (41.9)	15.2	1.7 - 30.1	0.003

RR: Relative Risk; CI: Confidence Interval; HCC: Hepatocellular Carcinoma.

## 5. Discussion

This study aimed to describe the clinical profile of cirrhosis associated HE, specifically to describe the clinical aspects of HE, determine precipitating factors, and the outcome of cirrhotic related HE in Cameroon.

### 5.1. Age and Sex

The mean age of patients with HE was  $49.9 \pm 18.9$  years old. The relatively young age of these patients could be explained by the etiology of cirrhosis. Indeed, the most common cause of cirrhosis in Cameroon is chronic HBV infection, which affects mostly young people [9]. In this area of high endemicity for HBV infection, high prevalence of the HBV infection has mainly been attributed to HBV transmission occurring predominantly early in the life either through mother to child transmission or horizontal transmission [11] [12].

HE was most common in men (69.8%). The reason for this finding is not clear but similar results have been reported by some other studies. In the study on

precipitating factors and treatment outcomes of hepatic encephalopathy in Liver Cirrhosis in Nepal by Poudyal *et al.*, 78% of patients included were male [5]. In another study by Gad *et al.* in Egypt 63.3% of patients with HE in liver cirrhosis were male [13]. This could be as the result of men being more exposed to various risk factors of cirrhosis.

## 5.2. Etiologies of Cirrhosis

Chronic HBV was found to be the main etiology of cirrhosis in our study. HBV infection is frequent in Cameroon which is considered as one of most affected countries in the world with an overall pooled prevalence of 11.2% [9]. The predominance of hepatitis B as the etiology of cirrhosis could be explained by the high prevalence of HBV in Cameroonian population. Chronic HCV was found in 22.6% of patients. The high prevalence of HCV reported by several studies in the Cameroonian population [14] [15] might explained this finding.

## 5.3. Description of the Different Clinical Aspects of HE

Grade III of HE was the most represented type in this study. Gad Y *et al.* in Egypt [13] and Devrajani *et al.* in Pakistan [16] respectively reported a 54.0% (128/237) and 80% (70/87) prevalence of grade III and grade IV HE among admitted patients presenting with signs and symptoms of HE. Most patients in resource limited settings usually present with advanced disease due to late consultations and this might explain the above finding.

## 5.4. Precipitating Factors

Constipation, herbal medicine, hyponatremia, HCC and gastrointestinal bleeding were the most frequent precipitating factors of HE in our study population. These findings are consistent with those reported by several authors in Pakistan, Egypt and United States of America [4] [13] [17]. In our study, constipation appears to be the most frequent precipitating factor of HE (37.7%). In fact, gastrointestinal symptoms are common in cirrhotics and constipation has been reported in 8% of cases [18]. The underlying mechanisms are complex and involve abnormalities in gut motility such as delayed gastric emptying, altered intestinal permeability [19]. Patients with advance cirrhosis are more at risk of developing gut dysfunctions symptoms [19]. In this study 72% of patients were stage C of Child-Pugh classification and hence justifying constipation as the most common precipitating factor of HE.

The frequency of electrolytes imbalance was high (hyponatremia: 26.4%; Hypokaliemia: 15%) and could be partly explained by the effect of diuretics on one hand and secondary hyperaldosteronism on the other hand. Diarrhea found in 15% of cases could also contribute to electrolytes abnormalities in this study. Spontaneous bacterial peritonitis was found in 4 patients (7.4%). Increase intestinal permeability, bacterial translocation and decrease in host immunity have been associated with SBP in advanced liver cirrhosis [20]. Therapeutic ascitic tap

done in dubious conditions in some cases could also explain some cases of ascitic fluid infections. In some patients (5.7%), no precipitating factor was identified.

## 6. Outcome

The mortality rate associated with HE was 45.3% and significantly associated with stages III ( $p = 0.003$ ) and IV ( $p = 0.01$ ) of HE, Child C score of cirrhosis ( $p = 0.003$ ) and Hypokaliemia ( $p = 0.01$ ). Similar high mortality rates have been reported by studies in Africa. In 2016, Ntagirabiri *et al.* found a 56% HE mortality rate among cirrhotic patients [7]. In Nigeria, Onyek were reported a mortality rate of 48% [21]. This high mortality rate could be explained firstly by the severity of cirrhosis because the majority of patients usually consult in advanced stage of the disease and secondly by the various complications associated with cirrhosis. More so the absence of optimal treatment for certain complications and of liver transplantation in our setting could also explain this high mortality rate. Electrolyte imbalance is common in cirrhotic patients with hyponatremia being most frequently associated with hepatic encephalopathy [22]. In our study, only hypokalemia was found to be significantly associated with mortality among Cameroonian patients with cirrhosis related hepatic encephalopathy. Hypokalemia has been shown to induce hepatic encephalopathy and this is modulated by the kidneys. As less potassium enters the collecting tubules, more hydrogen ions are moved into the cells leading to increase intracellular acidosis. This triggers the conversion of glutamine to ammonia and bicarbonate. The ammonia is selectively either excreted in urine or returned to venous circulation. Ammonia that subsequently enters portal circulation is not metabolized by the cirrhotic patient likely therefore to precipitate hepatic encephalopathy [23].

## Limitations of the Study

One of the limitations of this study is that electroencephalography and brain scan were not done in certain cases to exclude central nervous system involvement. The retrospective nature of the study reduced the number of included files because of their incomplete nature.

## 7. Conclusion

HE is a frequent complication during cirrhosis with a high mortality. The main precipitating factors were constipation, herbal medicine, electrolyte imbalance, gastrointestinal bleeding and HCC.

## Data Availability

All the data used to support the findings of this study are available from the corresponding author upon request.

## Authors Contributions

This work was jointly carried out by all the authors.



Author MK contributed in collection of data, analysis and editing the article; Author FA contributed in study conception and editing the article. Author EKY wrote the protocol and the first draft of the manuscript. Authors AWNN, BJ, SFEB, POG, ETL, DNN contributed in collection of data and follow-up of the patients. Author ON supervised all the activities and approved the final version to be submitted for publication. All authors read and approved the final manuscript.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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